THYROID DISEASE IN CLINICAL PRACTICE

I. Ross McDougall

Thyroid Disease in Clinical Practice

Thyroid Disease in Clinical Practice

I. Ross McDougall
MB, CHB, PhD, FACP, FRCP (Glas)
Professor of Radiology and Medicine,
Stanford University School of Medicine,
California

Springer-Science+Business Media, B.V.

First edition 1992

Originally published by Chapman & Hall in 1992.
Softcover reprint of the hardcover 1st edition 1992

Typeset in 10/12pt Palatino by Graphicraft Typesetters Ltd., Hong Kong

ISBN 978-0-19-520936-5 ISBN 978-1-4899-2881-8 (eBook)
DOI 10.1007/978-1-4899-2881-8

A catalogue record for this book is available from the British Library

To Liz, Shona and Stewart

Contents

Preface

Thyroid diseases are common. They include hyper- and hypothyroidism, enlargement of the gland both diffuse and nodular, solitary nodules both benign and malignant, inflammatory diseases, rare congenital defects in structure and inborn errors in function. Many are simple to diagnose and treat, others are not. The literature often complicates rather than simplifies issues. My intention is to use personal experience, the teaching of others and distillation of the literature as the basis for a text which will allow the physician to deal with specific, patient-related problems. The first four chapters are general. There are short chapters on the structure and function of the thyroid followed by a review of tests. The fourth chapter is an outline of clinical evaluation, but this is no way substitutes for personal experience at the bedside or in the clinic.

The chapters on hyper- and hypothyroidism should help define the specific cause and management of patients with these problems. Evaluation and treatment of thyroid nodules and thyroid cancer cause considerable differences of opinion. These differences are reviewed and specific recommendations are outlined. Thyroiditides, although not related causally, symptomatically or therapeutically, are placed in Chapter 9 for convenience. Simple enlargement of the thyroid (Chapter 10) and iodine deficiency disorders (Chapter 11) receive less coverage than their clinical importance worldwide merits, but the key issues are covered. One of the most disconcerting aspects of thyroidology is how non-thyroidal illnesses both physical and mental can distort thyroid function tests so that thyroid dysfunction is diagnosed inappropriately. This is addressed in Chapter 12 with advice that should decrease this occurrence. Because radiation to the thyroid can cause clinically relevant thyroid disease and because some of the diagnostic tests and treatments involve administration of radioactive iodine to the patient, Chapter 13 brings together some aspects of radiation biology in relation the the thyroid.

The author has been lucky to be associated with academic and practising physicians and basic scientists whose main interest was 'the thyroid'. Early in my training I had the great fortune of working in Professor Edward McGirr's department at Glasgow Royal Infirmary. There I worked most closely with the late Bill Greig on the interface of thyroid and nuclear medicine. Subsequently, I had a fellowship to work with the late Joe Kriss at Stanford University Medical Center where we were colleagues for 15 years. In both of these institutes I worked with, and learned from, many fine clinicians and scientists. However, I have to pay a special tribute to Joe Kriss, who embodied all the characteristics patients hope for in their physician with the creative mind of a researcher and the ability to transmit his thoughts with precision and clarity.

It is possible the book may be of value to medical students and physicians in training, but it is aimed primarily at practising physicians. I hope it meets this goal.

I. Ross McDougall

CHAPTER ONE

Thyroid structure, development and developmental abnormalities

1.1 GROSS STRUCTURE

The thyroid is situated in the anterior neck. It consists of two somewhat pear-shaped lobes which lie to the sides of the trachea, and a smaller isthmus joining the medial aspects of the lobes lies over the second to fourth tracheal rings (Figure 1.1). The lobes are about 5 cm long, 3 cm across at the widest part, and 2 cm thick at the broader lower pole. The inferior poles of the lobes extend to the sixth tracheal ring, and the superior poles to the thyroid cartilage. In adults the thyroid weighs approximately 20 g. In the newborn it is about 1.5 g and it increases progressively with age and size [1]. There is some debate about whether a normal thyroid is palpable or not. Certainly in well-built men it is not, due to development of the anterior neck muscles. On the other hand, the normal thyroid can be palpated in many normal women. This will be discussed in more detail in Chapter 4.

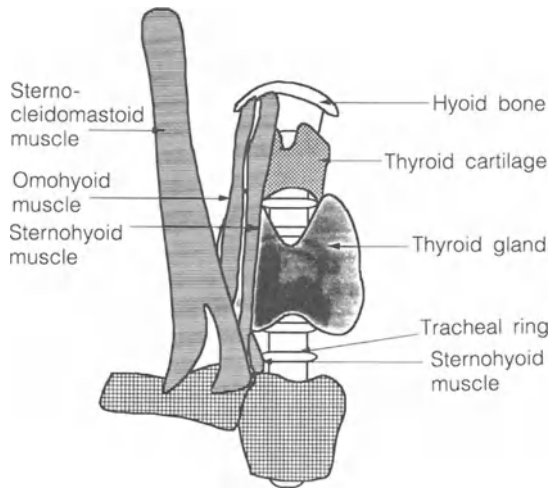


Figure 1.1 Diagram showing the relation of the thyroid to trachea, neck muscles and manubrium.

The thyroid is covered by the pretracheal fascia which is attached to the larynx, trachea and oesophagus, and since the isthmus is fixed to the tracheal rings, the gland moves upward with these structures on swallowing. This is a valuable manoeuvre when the clinician is trying to locate the inferior aspect of the lobes or the isthmus because these can be sensed to slide under, or bump against, the examining fingers when the patient swallows. A thyroid nodule also moves when the patient swallows. Because the pretracheal fascia is densest anteriorly, enlargement of the gland can extend posteriorly and inferiorly and the findings on palpation give an underestimate of the gland's size.

A pyramidal lobe which is the remnant of the thyroglossal duct (see below) projects up from the isthmus, or medial aspect of one of the lobes, more often from the left. It is the author's opinion that a pyramidal lobe is found almost entirely in patients with autoimmune thyroid diseases, such as **Graves' hyperthyroidism**, or **Hashimoto's thyroiditis** (Figure 1.2). This has been substantiated

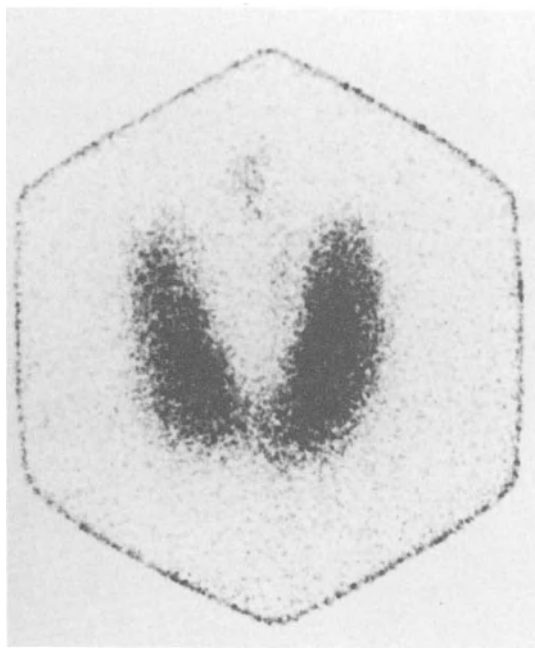


Figure 1.2 Thyroid scintigram using ^{123}I showing the lobes of the gland and pyramidal lobe. The scan was made 3 hours after an oral dose of 200 μCi ^{123}I.

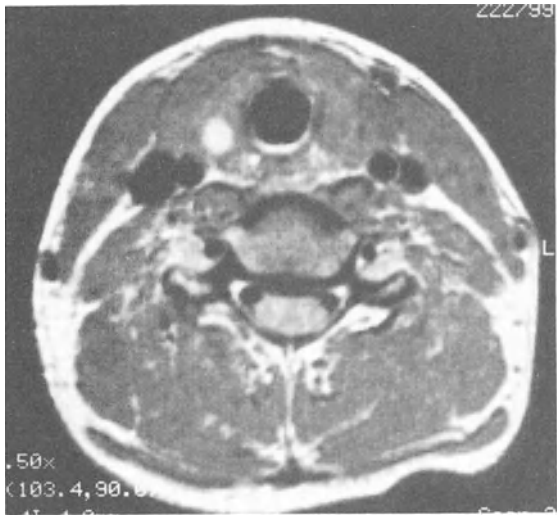


Figure 1.3 Nuclear magnetic resonance image of the neck, showing in cross-section the thyroid (with a small, incidental right-sided cyst seen as a white spot). Compare this which Figure 1.4, which is an anatomical diagrammatic representation of the structures.

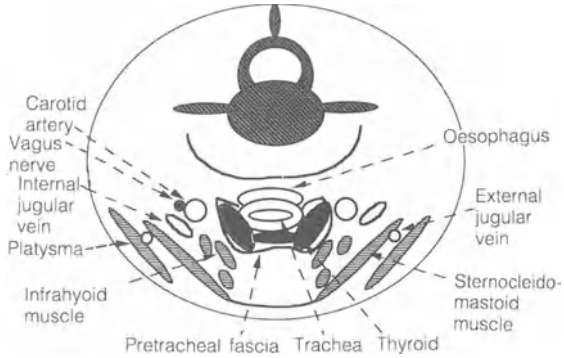


Figure 1.4 Cross-section of the neck at the level of the thyroid showing its relationship to the trachea, muscles, spine, etc.

by a study by Levy *et al.* [2] and is probably best explained by the glands being under constant stimulation either by **thyroid stimulating hormone** (TSH) or **thyroid receptor antibodies** (TRAb), which stimulate small rests of cells to divide and grow sufficiently to be seen on thyroid scintiscan. Alternatively, patients with autoimmune thyroid diseases are more likely to have imaging studies which would lead to discovery of this finding. The relationship of the thyroid to other structures in the neck is shown well by computed tomography (CT), or nuclear magnetic resonances (NMR) imaging (Figure 1.3). Figure 1.4 provides a diagrammatic representation. The thyroid is among the most vascular organs gram for gram. A euthyroid gland has a flow rate of about 5 ml/g/min. In Graves' hyperthyroidism this can increase to a litre/min and is clinically apparent by a palpable thrill and a bruit. There are four main arteries. Paired superior thyroid arteries arise as the first branch of the external carotid artery and descend to the upper poles. Paired inferior arteries arise from the thyrocervical trunk which is a branch of the first part of the subclavian artery (Figure 1.5). Less constant is the thyroidea ima artery which can arise from the aorta, innominate, subclavian or even the common

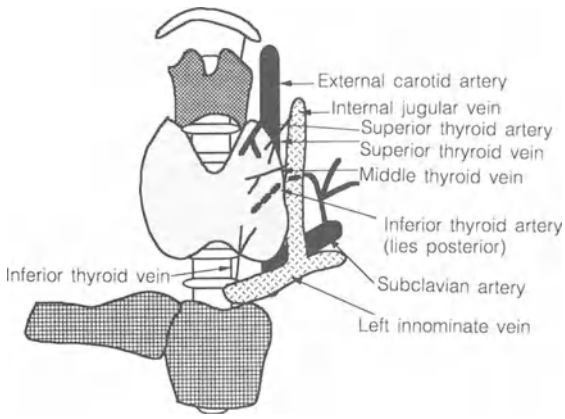


Figure 1.5 Arteries and veins of the thyroid.

carotid arteries. It supplies the inferior isthmus and hence is in a position of risk during tracheostomy. It is found in about 10% of the population. Small unnamed arteries communicate from the trachea to the posterior aspect of the thyroid; as a result the cut gland can bleed even after the major vessels are ligated. There is a rich anastamosis between superior and inferior vessels as well as between the lobes. The arteries divide into lobar and then lobular branches. The latter are small end arteries supplying a lobule consisting of some 20–50 follicles [3].

A plexus of veins on the surface of the thyroid drain into superior and middle thyroid veins, which in turn drain into the internal jugular veins. The inferior jugular vein, or veins, drain into the innominate veins.

There is a rich lymphatic supply which follows the veins. Within the thyroid, the lymphatics communicate between the lobes. The lymphatics drain into the internal jugular, pretracheal and anterosuperior mediastinal nodes. From the posterior aspect there is drainage into retropharyngeal nodes. Lymphatic drainage can be demonstrated in vivo by scintigraphy by injecting ^{99m}Tc sulphur colloid directly into the gland and imaging for several hours [4]. Likewise radiological imaging of lymph drainage has been demonstrated by several group [5–7].

The recurrent laryngeal nerves run inferiorly to the thyroid. Behind the lower third of the gland they lie about 1 cm lateral to the trachea in close relation to the interior artery. As many as 28 types of relationships between these two structures have been described. The motor branch of the nerve innervates the laryngeal muscles and damage to that nerve causes ipsilateral paralysis of the vocal cord and a hoarse voice. The superior laryngeal nerve is a branch of the vagus which arises close to the base of the skull. It has an internal sensory branch and an external motor branch to the cricothyroid muscle. This nerve is in close proximity to the superior thyroid artery and is at risk during surgery when this artery is being ligated. The main nerve supply to the thyroid itself is sympathetic. It arises from the middle cervical ganglion and travels with the inferior thyroid artery. Some sympathetic fibres from the superior cervical ganglion reach the thyroid along with the superior thyroid artery. These nerves are vasoconstrictors. Some patients with enlarged thyroids notice rapid fluctuations in the size of their glands and this is likely to be a vascular phenomenon mediated by the autonomic nervous system. These nerves are not important in the formation and release of thyroid hormones.

1.2 MICROSCOPIC STRUCTURE

The epithelial cells of the thyroid which produce and secrete thyroid hormones are arranged in spherical structures called follicles [8]. The cells are therefore called follicular cells. A single layer of follicular cells surrounds colloidal material containing stores of hormone incorporated into a protein called thyroglobulin, which is the main constituent of the colloid material. The dimensions of the follicle, the follicular cells and the colloid material vary considerably

depending on the availability of iodine, the effect of physiological and pathological stimulators, the presence of goitrogens, including medications, as well as thyroid suppressors. The diameter of follicles, even in physiological conditions, varies from 100 to 1000 μm (average 200–300 μm). Smaller follicles appear to be more active. When there is excessive prolonged stimulation the quantity of colloid material decreases reflecting release of stored hormone from thyroglobulin. The follicular cells are cuboidal with a length of about 10 μm. Under stimulation, they become progressively more columnar and can be as tall as 20 μm. This appearance is characteristic of Graves' hyperthyroidism which has not been treated, however, a similar appearance is found if the thyroid is lacking iodine and the gland is stimulated to make as much hormone as possible by pituitary thyroid stimulating hormone, TSH. In the former, the patient is hyperthyroid, in the latter hypothyroid, or euthyroid. Therefore, it is not possible to judge the thyroid status by looking at histology alone. Groups of 20–50 follicles form lobules which have a fine covering of connective tissue, which is continuous with the capsule of the gland. Each follicle is surrounded by delicate capillaries, but on standard staining these are not well demonstrated because they collapse. The rich lymphatic system is also difficult to demonstrate in specimens from normal glands, but lymphatics are well seen when carcinoma invades them.

The internal structure of the follicular cells reflects their active involvement in protein formation and secretion. The cytoplasm is rich in mitochondria, rough endoplastic reticulum, Golgi apparatus and secretory droplets. The nucleus is round or oval and is central in cuboidal cells, but more basal in columnar ones. Numerous microvilli project from the apical end of the cells into the colloid. Figure 1.6 illustrates these features.

Parafollicular cells (C cells) which produce and secrete calcitonin lie between follicles. They are difficult to see in sections of normal thyroid.

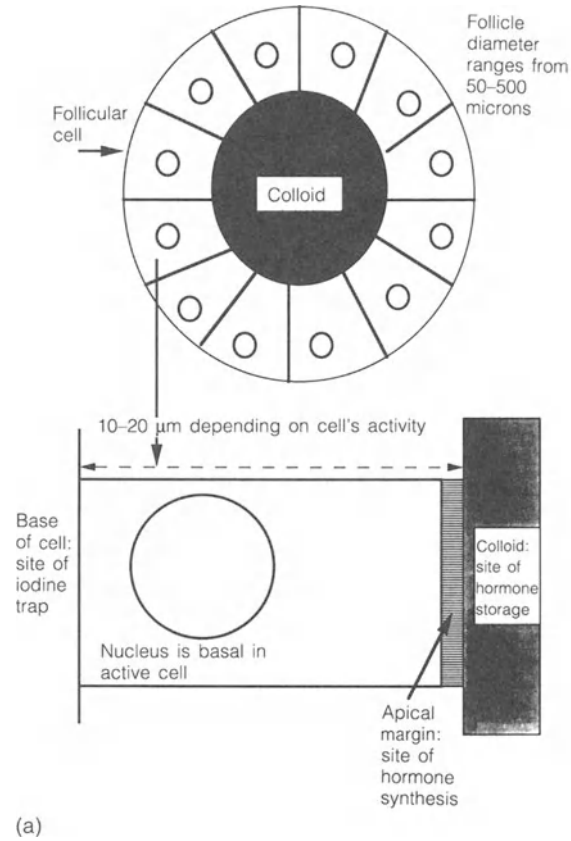
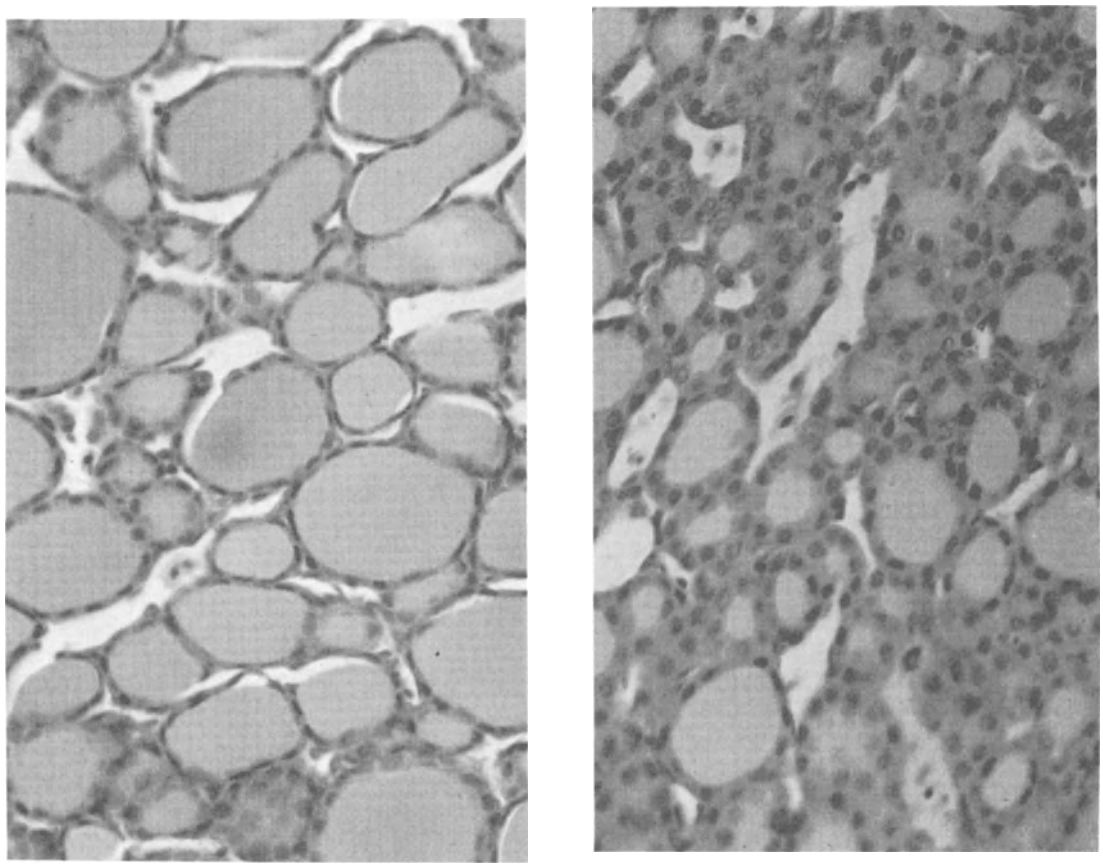


Figure 1.6 (*a*) diagrammatic representation of a follicle (the functional unit) and follicular cell showing briefly the subcellular components.

1.3 DEVELOPMENT

A brief description of the embryological development of the thyroid is necessary to explain the rare developmental abnormalities which can be encountered (Figure 1.7). The thyroid develops from the foregut and descends by a circuitous route to its normal cervical position. Its original position is



(b)

(*b*) Histology of follicles showing normal resting state on the left panel. The cells are low cuboidal and the follicles are of varying diameters. The panel on the right shows follicular cells that are stimulated, and these are more columnar and the follicles are smaller with less colloid. This could be produced by thyroid-stimulating hormone.

marked by the foramen caecum at the junction of the anterior two-thirds and posterior one-third of the tongue. The first evidence of its presence occurs at about 4 weeks as an evagination between the first and second pharyngeal pouches. This evagination lenghthens to form a tube and descends inferiorly and anteriorly to pass anteriorly to the hyoid bone. It then loops round and behind the hyoid before continuing its descent in the neck. Two lateral buds form. These will become the lateral lobes. They fuse with the ultimobranchial body which supplies cells that will become the parafollicular cells. Thus the follicular and parafollicular cells have different lineage. The pathway from pharynx to anterior neck is marked by the thyroglossal duct. It loses its tubular structure and by the sixth week atrophies. The follicular cells are able to trap iodine by the twelth week and hormone production occurs soon after that.

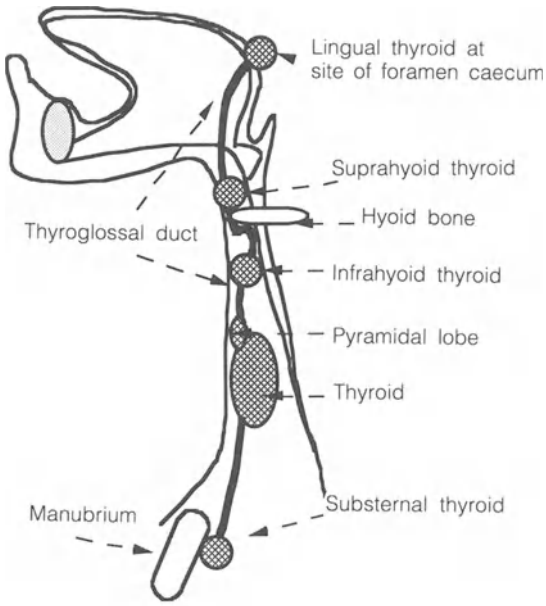


Figure 1.7 Pathway of the thyroglossal duct and sites of ectopic thyroid.

Table 1.1 Developmental abnormalities

Agenesis	
Dysgenesis:	ectopic
	lingual
	perihyoid
	intratracheal
	intraoesophageal
	mediastinal
	cardiac
Hemiagenesis	
Persistent thyroglossal duct	
Thyroglossal cysts	

1.4 DEVELOPMENTAL ABNORMALITIES

Developmental abnormalities fall into three major groups (Table 1.1). Firstly, **agenesis of the gland**. This is an important cause of neonatal hypothyroidism and is discussed in full in that section in Chapter 6. Secondly, defects due to persistence of the thyroglossal duct. These fall into two categories: recurrent infections due to persistence of a patent duct, and cyst formation along the course of the duct. Thirdly there is **dysgenesis of the gland** with ectopic thyroid occurring at any point in the descent of the gland. Failure of one lobe to develop is included, as is pyramidal lobe which can be important especially to the surgeon. Biochemical abnormalities of the formation of thyroid hormones are not discussed here.

With the exception of goitre, **thyroglossal duct cysts** are among the commonest midline swellings in the anterior neck. Knight *et al.* [9] found that 52% of 146 children with anterior neck swelling had this disorder. The cyst can be asymptomatic, it can be noted as a simple swelling, or it can get infected and present like a swollen lymph node. These cysts are usually perihyoid and found by the second decade. In the series described by Hawkin's *et al.* [10], 68% were in children less than 10 years of age and 94% in patients less than 20 years of age. The swellings are round, non-tender if uninfected, and cyst-like to pressure. They contain mucinous material and the lining epithelium is cuboidal or columnar and often ciliated. Repeated infection of the cyst alters the histological appearances. Reports of the frequency of follicular cells in association with these cysts give quite divergent results. Okstad *et al.* [11] found some in 41% of their cases, whereas Deane and Telander [12] found this in only 6%. There is not enough thyroid tissue to be imaged on radionuclide scintigraphy, thus differentiating a cyst from ectopic thyroid. Ultrasound is valuable to define that the swelling is cystic and to define its relationships to other structures in the neck [13]. Thyroglossal cysts move when the patient protrudes the tongue and sometimes, but not always, they move with swallowing. If the cyst is small and asymptomatic it can be left alone. Those which are large and cosmetically unpleasing should be removed, as should those which have been infected. Aspiration will frequently lead to

sinus formation and chronic drainage, if not, the cyst will usually reaccumulate. Aspiration is not advised for treatment, but can be used to establish a diagnosis preoperatively, when there is doubt about the nature of the mass. The principles of the operation were defined by Sistrunk in 1920 [14]. The cyst is removed with the thyroglossal duct, including the central portion of the hyoid, *en bloc*. A central core of tissue up to the foramen caecum should also be removed. No effort should be made to close the defect in the hyoid and no physiological disturbance is encountered. Only by doing this will the recurrence rate be low. Several surgeons report a recurrence rate of 2–3%; this contrasts with 40–59% if ductal structures are left.

Thyroid tissue can occur at any point from the foramen caecum to the cervical position. In addition, because the truncus arteriosus develops in close proximity to the thyroid and then passes inferior to it, thyroid tissue can be pulled into an ectopic position in the mediastinum, including inside the heart. The sites in which **ectopic thyroid** can be found are listed in Table 1.2. **Lingual thyroid** is by far the most common. The anomalies are found because the patients have symptoms listed in Table 1.2. Lingual thyroid is visible as a red or purple swelling at the back of the tongue (Figure 1.8). In 70% of cases, it is the only functioning thyroid, and often it is unable to make enough hormone to keep the patient euthyroid. The ectopic thyroid is then stimulated by pituitary TSH to grow in an effort to produce more hormone. Growth is accompanied by symptoms of dysphagia, dysphonia and dyspnoea [15]. Because the surface is vascular it can bleed. The appearance and position of a mass like this should prompt an ^{123}I scan (Chapter 3) to determine whether this is functioning thyroid and, if so, whether there is also a cervical thyroid (Figure 1.9). Biopsy or surgical treatment are seldom necessary. The patient should be treated with sufficient thyroid hormone to suppress TSH. This will almost invariably cause the mass to shrink.

Table 1.2 Symptoms and signs of ectopic thyroid

Site of ectopic thyroid	*Symptoms/signs*
Lingual	Dysphagia Dysphonia Dyspnoea Bleeding
Perihyoid	None Swelling
Intratracheal	None Dyspnoea
Intraoesophageal	None Dysphagia
Cardiac	None Murmur Cardiac failure

A **perihyoid mass** should also be evaluated by ^{123}I scintigraphy to determine if it is ectopic thyroid, but most will be thyroglossal duct cysts. Knight *et al.* [9] found only 2 patients with ectopic thyroids out of 146 patients with anterior midline neck swellings. Okstad *et al.* [11] found 5 out of 46 masses were ectopic thyroid, and 41 were thyroglossal cysts. If the mass concentrates radioiodine it is thyroid, and treatment with thyroxine should cause the lump to disappear and keep the patient euthyroid. Reports of surgery to split the midline tissue and implant the halves into the lateral neck are becoming rare and usually result from incomplete preoperative evaluation. If the intact tissue is not able to provide enough hormone, it is unlikely that after it has been cut and moved it will be able to do so.

Ectopic thyroid in the trachea or oesophagus is extremely rare and only found if the appropriate symptoms are present. Endoscopic biopsy proves, much to the surprise of the clinician, that there is thyroid inside the lumen. The most important differential

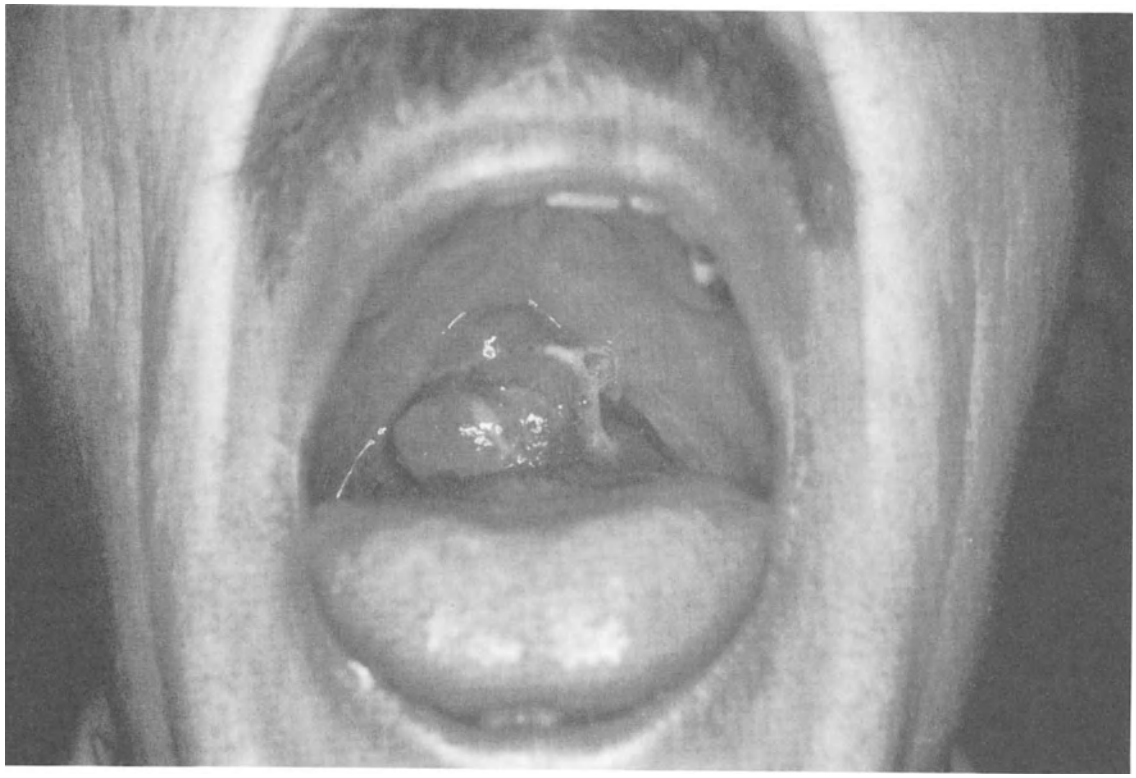


Figure 1.8 Typical appearance of lingual thyroid.

diagnosis is cancer of the thyroid which has invaded these structures. To make this differential requires careful examination of the biopsy, looking for criteria of malignancy, plus palpation of the thyroid to determine if a primary lesion can be felt. Treatment includes surgical removal of as much of the mass as possible by endoscopy, plus thyroxine for life [16].

Thyroid in the heart, **struma cordis**, is extraordinarily rare. Only 10 cases have been described in the literature. Nine of these involved the right ventricle [17]. They are found on imaging studies such as ultrasound and angiography, which have been ordered to investigate a murmur [18]. A mass is found which on biopsy is thyroid. The cervical thyroid is usually normal and this can be shown on radionuclide scan, which should be obtained if struma cordis is diagnosed. Treatment is thyroxine for life. Once again it is important to ensure the patient does not have metastatic thyroid cancer.

Ectopic thyroid is in the midline. Older texts describe a condition, 'lateral aberrant thyroid', and include this as a developmental defect. This is now recognized to be **metastatic well-differentiated thyroid cancer**, which can remain in regional lymph nodes for years without growth, hence its confusion with an aberrant benign rest. Stru-

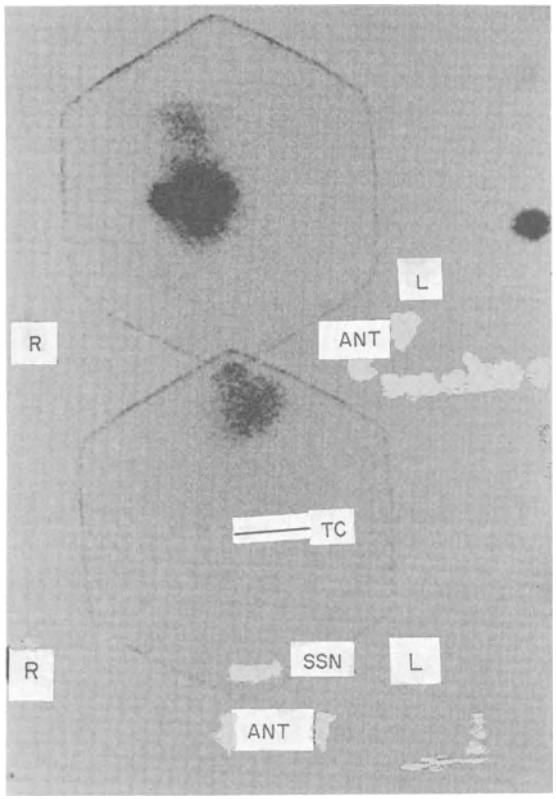


Figure 1.9 Iodine-123 scintigram of an ectopic thyroid in the region of the hyoid. The top panel shows the lesion with a radioactive cobalt marker placed at the side of the palpable midline swelling, showing that what is felt is indeed functioning thyroid which traps iodine. The lower panel shows the ectopic thyroid at the top of the image, thyroid cartilage (TC) and sternal notch (SN) are marked, showing thare is no cervical thyroid.

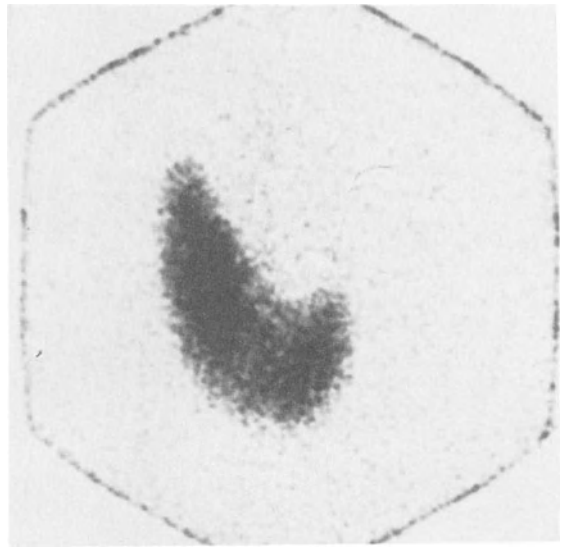


Figure 1.10 Iodine-123 scan in hemiagenesis where the remaining lobe and isthmus are seen. This has been called the 'hockey-stick' sign.

ma ovarii is not a developmental error, but is thyroid in an ovarian teratoma. This is described briefly in Chapters 5 and 8.

Absence of a lobe of the thyroid is rare in clinical practice, and there are few good statistics about its true frequency. Hamburger and Hamburger [19] describe 4 cases out of 7000 (0.057%) who had thyroid scintiscans. An almost identical frequency was presented by Harada *et al.* [20] in patients having thyroid surgery, 7 out of 12 456 (0.056%). In both of these reports, the patients had an underlying problem that prompted thyroid scintigraphy or surgery, and a significant proportion of reported cases have hyperthyroidism [21] including T_3 toxicosis [22] or unilateral goitre. One of the first reports of this defect was by Gow [23], who also in a different context provided evidence that myxoedema is caused by atrophy of the thyroid. Melnick and Stemkovoski [24] reviewed the literature and found a total of 90 cases. The defect is three times more common in women and in 80% the left lobe is missing, though there are well-documented reports of the right being absent [25]. There is no known aetiological factor.

If one lobe is seen on scintiscan, it is important to prove that the condition is indeed hemiagenesis. The scan appearance can be like a hockey-stick when one lobe and isthmus are present (Figure 1.10). The most likely differential is a functional nodule with suppression of the remainder of the gland

(see section on autonomous nodule in Chapter 5). Inflammation of the opposite lobe which can have no uptake of radioiodine in one lobe is easy to diagnose clinically because the non-visualized lobe is swollen and tender. To separate hemiagenesis from autonomous nodule requires either ultrasound which will show whether the contralateral lobe is present or not [26] or, alternatively, scintigraphy can be repeated after giving the patient injections of TSH. Other methods of differentiating these two conditions include thallium 201 (^{201}Tl) scintigraphy which shows suppressed tissue, or imaging with ^{123}I with a lead shield over the hot tissue. Even suppressed thyroid will take up some ^{123}I and can be seen if imaged sufficiently long. These tests are discussed in Chapter 3. If the patient with hemiagenesis is euthyroid and has no goitre, no treatment is required. Pathological problems are treated exactly as they would be in patients with both lobes intact.

KEY FACTS

- Developmentally the thyroid arises from the back of the tongue and migrates to the cervical position.
- Ectopic thyroid tissue can be found from the region of the foramen caecum, throughout the thyroglossal tract, and even inferior to the thyroid due to altered migration.
- Total agenesis is rare, but hemiagenesis is found in about 0.06% of patients.
- An enlarged thyroid is the commonest midline swelling in the neck.
- A thyroglossal cyst is the second most common midline swelling in the neck.
- In adults the normal thyroid is about 20 g.
- There are two lobes, the right is more often the bigger.
- The follicle is the functional unit which makes up the structure of the thyroid.
- The follicular cell is the most important and common cell in the gland.
- A single layer of follicular cells surrounds a central core of colloid, which contains thyroglobulin, the prehormone for thyroid hormones.
- The thyroid is very vascular.
- Knowledge of the close association of the recurrent laryngeal nerves and parathyroids are important for the surgeon.

REFERENCES

1 Spencer, R.P. and Banever, C. (1970) Human thyroid growth: a scan study. *Invest. Radiol.*, **5**, 111–16.

2 Levy, H.A., Sziklas, J.J., Rosenberg, R.J. *et al.* (1987) Incidence of a pyramidal lobe on thyroid scans. *Clin. Nucl. Med.*, **12**, 560–61.

3 Johnson, N. (1955) The blood-supply of the human thyroid gland under normal and abnormal conditions. *Br. J. Surg.*, **42**, 587–94.

4 Kriss, J.P. (1970) Radioisotopic thyroidolymphography in patients with Graves' disease. *J. Clin. Endocrinol. Metab.*, **31**, 315–24.

5 Beales, J.S.M., Nundy, S. and Taylor, S. (1971) Thyroid lymphography. *Br. J. Surg.*, **58**, 168–71.

6 Ram, M.D., Archer, B.T. and Brown, H.W. (1974) Thyroidography and thyroidolymphography. *Surg. Gynecol. Obstet.*, **138**, 417–20.

7 Gandhi, G.M. and Shanker, S. (1976) Thyroid lymphography. *Am. J. Surg.*, **131**, 563–5.

8 Klinck, G.H., Oertel, J.E. and Winship, T. (1970) Ultrastructure of normal human thyroid. *Lab. Invest.*, **22**, 2–22.

9 Knight, P.J., Hamoudi, A.B. and Vassy, L. E. (1983) The diagnosis and treatment of midline neck masses in children. *Surgery*, **93**, 603–11.

10 Hawkins, D.B., Jacobsen, B.E. and Klatt, E.C. (1982) Cysts of the thyroglossal duct. *Laryngoscope*, **92**, 1254–8.

11 Okstad, S., Mair, I.W.S., Sundsfjord, J.A. *et al.* (1986) Ectopic thyroid tissue in the head and neck. *J. Otolaryngol.*, **15**, 52–5.

12 Deane, S.A. and Telander, R.L. (1978) Surgery for thyroglossal duct and branchial cleft anomalies. *Am. J. Surg.*, **136**, 348–53.

13 Noyek, A.M. and Friedberg, J. (1981) Thyroglossal duct and ectopic thyroid disorders. *Otolaryngol, Clin. N. Amer.*, **14**, 187–201.

14 Sistrunk, W.E. (1920) The surgical treatment

of cysts of the thyroglossal tract. *Ann. Surg.*, **71**, 121–2.
15 Katz, A.D. and Zager, W.J. (1971) The lingual thyroid: its diagnosis and treatment. *Arch. Surg.*, **102**, 582–5.
16 Postlethwait, R.W. and Detmer, D.E. (1975) Ectopic thyroid nodules in the esophagus. *Ann. Thorac. Surg.*, **19**, 98–100.
17 Shemin, R.J., Marsh, J.D. and Schoen, F.J. (1985) Benign intracardiac thyroid mass causing right ventricular outflow tract obstruction. *Am. J. Cardiol.*, **56**, 828–9.
18 Rieser, G.D., Ober, K.P., Cowan, R.J. and Cordell, A.R. (1988) Radioiodine imaging of struma cordis. *Clin. Nucl. Med.*, **13**, 421–2.
19 Hamburger, J.I. and Hamburger, S.W. (1970) Thyroid hemiagenesis. *Arch. Surg.*, **100**, 319–20.
20 Harada, T., Nishikawa, Y. and Ito, K. (1972) Aplasia of one thyroid lobe. *Am. J. Surg.*, **124**, 617–19.
21 Avramides, A., Vichayanrat, A., Solomon, N. *et al.* (1977) Thyroid hemiagenesis. *Clin. Nucl. Med.*, **2**, 310–14.
22 Matsumura, L.K., Russo, E.M.K., Dib, S.A. *et al.* (1982) Hemiagenesis of the thyroid gland and T3 hyperthyroidism. *Postgrad. Med. J.*, **58**, 244–6.
23 Gow, W.J. (1883) Total absence of the left lobe of the thyroid body. *J. Anat. Physiol.*, **18**, 118.
24 Melnick, J.C. and Stemkowski, P.E. (1981) Thyroid hemiagenesis (hockey stick sign): a review of the world literature and a report of four cases. *J. Clin. Endocrinol. Metab.*, **52**, 247–51.
25 Russotto, J.A. and Boyar, R.M. (1971) Thyroid hemiagenesis. *J. Nucl. Med.*, **12**, 186–7.
26 Cornelius, E.A. (1987) Combined nuclear medicine and ultrasound studies in the evaluation of suppressed thyroid tissue. *Clin. Nucl. Med.*, **12**, 8–9.

CHAPTER TWO

Thyroid physiology

2.1 INTRODUCTION

This chapter deals with the control of thyroid function, the formation and secretion of thyroid hormones, their transport in the blood, their action at the cellular level and their metabolism. There are two physiological important thyroid hormones: **L triiodothyronine** and **L thyroxine**. L triiodothyronine is the more important hormone at the cellular level, but L thyroxine is the more abundant in the circulation. Thyroxine and triiodothyronine are designated T_4 and T_3 because they contain 4 and 3 iodine atoms per molecule respectively. Throughout the text, I have used T_4 and T_3 to indicate serum hormones, and L thyroxine or L triiodothyronine when these compounds are used for treatment. Aspects of iodine intake and excretion are discussed after the formation and metabolism of thyroid hormones. **Thyrocalcitonin** (calcitonin), a hormone produced, albeit not exclusively, by the thyroid is discussed separately at the end of the chapter. In general, physiology as it applies to man is discussed, although in certain areas, knowledge from animal experiments has to suffice. I have tried to introduce clinical relevance in each section. I have not discussed testing of thyroid function in this chapter, but have provided a basis on which the reader can understand investigations as described in Chapter 3.

2.2 REGULATION OF THYROID FUNCTION

2.2.1 INTRODUCTION

The formation and secretion of T_3 and T_4 are largely controlled by thyroid stimulation hormone (thyrotropin in the USA; thyrotrophin in the UK.) designated TSH. TSH is produced in, and secreted from, specific cells in the anterior pituitary. There are two main factors controlling formation and release of TSH. **Thyrotrophin releasing hormone** (TRH) from the hypothalamus is a positive stimulus, and increased level of T_3 and/or T_4 in the circulation a negative one. Several other hormones, neurotransmitters, drugs and clinical conditions modulate this control. The hypothalamus is under less well defined control from higher centres. Finally, the thyroid is able to 'autoregulate' all steps of synthesis and release of hormones [1] although this is much less important than the TSH control mechanism. Autoregulation is described after the formation of thyroid hormones, because an understanding of the synthesis is necessary to understand autoregulation. Figure 2.1 shows the overall control in its simplest form. As each step is discussed, additional control mechanisms are added.

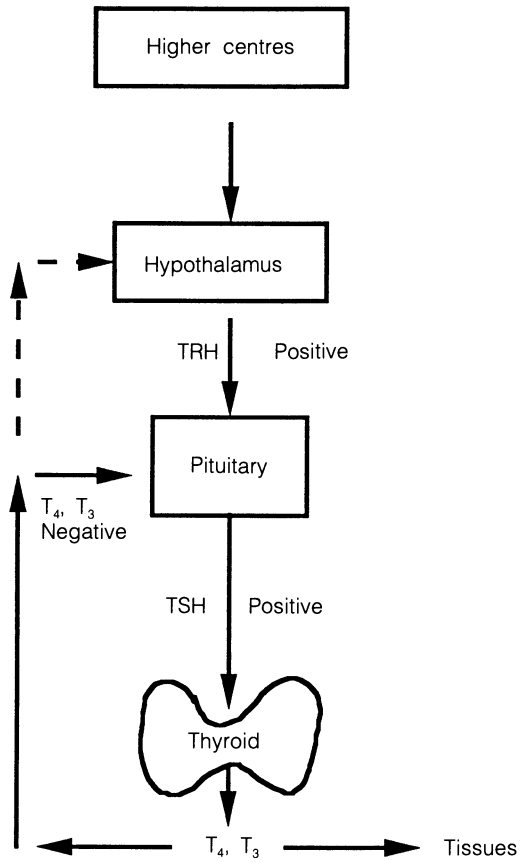


Figure 2.1 Simplified diagram of the control of thyroid function.

2.2.2 HYPOTHALAMUS AND THYROTROPHIN RELEASING HORMONE

The existence of hypothalamic factors, or hormones which control the anterior pituitary and subsequently peripheral endocrine glands, was proposed for more than 40 years [2, 3]. The hypothesis was based on the knowledge that lesions in the hypothalamus could cause end organ failure; damage to the portal vessels between the hypothalamus and anterior pituitary could also cause end organ failure, and electrical stimulation of specific sites in the hypothalamus caused the release of pituitary hormones. The hypothesis was proven in 1968, when TRH was isolated, characterized, synthesized and shown to act *in vitro* and *in vivo* by releasing TSH from pituitaries [4, 5]. Guillemin processed 50 tons of sheep hypothalami from 5 million sheep, and obtained 1 mg of pure TRH. Schally working with pigs isolated an equivalent substance. Both isolates were shown to be the tripeptide, L-pyroglutamyl-L-histidyl-L-prolinamide, molecular weight 362. These workers' contributions are well described in their Nobel lectures [6, 7].

TRH is formed in the hypothalamic cells as a precursor consisting of five copies of the active molecule; the tripeptide is formed post-translationally [8]. It is synthesized in the median eminence and specific hypothalamic nuclei. In addition, TRH is produced in many other sites in the brain, spinal cord, retina, gastrointestinal tract, pancreas and prostate [9]. Its purported roles in these sites is discussed at the end of this section. TRH formed in neurone bodies of hypothalamic neurones travels in the axons to the primary vascular plexus of the portal system where it gains access to the blood and is transported to the anterior pituitary. There it interacts with high-affinity, specific receptors on the thyrotrophes, specific cells designated to produce TSH. TRH causes a rapid release and a slower formation of TSH from these cells.

Much of our understanding of the physiology of TRH comes from studies of the effects of pharmacological quantities in normal people and in those with hyperthyroidism, or hypothyroidism [10–13]. The usual dose is 200–400 μg given by intravenous injection. In normal people, it causes a brisk rise in serum TSH (normal basal range approximately 0.4–5.0 μU/ml or 0.4–5.0 mU/l), which reaches a peak at 20–30 min and falls towards normal by 60–90 min (Figure 2.2). One to 4 hours after injection of TRH, there is a rise in serum T_3 of up to 70%, and a

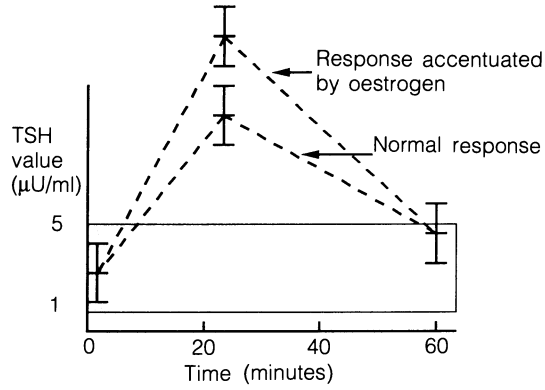


Figure 2.2 TRH test showing normal response to intravenous injection of 400 μg TRH on serum TSH in normal men and in women or men pretreated with oestrogen.

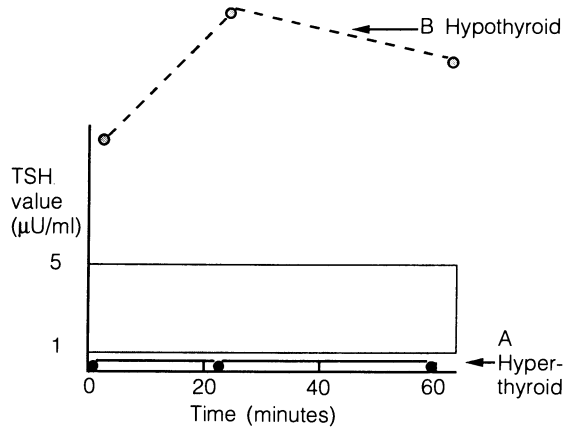


Figure 2.3 TRH test showing normal response to intravenous injection of 400 μg TRH on serum TSH in hyperthyroidism (A) and hypothyroidism (B).

15–20% rise in T_4. This shows the sequence, hypothalamus to pituitary to thyroid. In patients who are hyperthyroid, irrespective of the cause, injection of TRH fails to produce a surge in serum TSH (Figure 2.3(A)). Therefore, high levels of T_4 or T_3, or both, inhibit the effect of TRH on the pituitary. In contrast, in primary hypothyroidism where the thyroid is failing and the levels of T_4 and T_3 low, TSH is high and TRH causes a dramatic increase in serum TSH which falls to baseline slowly, (Figure 2.3(B)).

TRH is thought to cause release of TSH by the following sequence. When TRH interacts with the receptor, there is subsequent hydrolysis of phosphatidylinositol 4,5–biphosphate to inositol triphosphate [14]. This causes a rise in intracellular calcium, either by release from an intracellular pool, or by rapid entry of extracellular calcium. Calcium forms a calcium–calmodulin complex which activates protein bound kinases. These produce fusion of vesicles containing TSH with the plasma membrane through an intermediary phosphorylation step, releasing TSH into the circulation.

TRH has a half-life of about 5 minutes, it is degraded by peptidases and some is excreted intact in the urine. When injected intravenously, only about 1–2% crosses the blood–brain barrier.

In addition to releasing TSH, TRH causes a brisk rise in serum prolactin in normals and hypothyroid patients [15]. There is no rise in the already high levels in patients with prolactinomas (tumours of the pituitary which secrete prolactin and can cause amenorrhoea, infertility and galactorrhoea). TRH causes a rise in growth hormone in children, but not in adults or patients with acromegaly.

Because TRH is present in diverse areas of the brain, brain stem and spinal cord, its role as a neurotransmitter has been proposed. It has been found to reverse spinal cord injury in cats [16] and improve shock [17]. There has been considerable interest in TRH in diagnosing and treating psychiatric diseases, and this is discussed in Chapter 12. Interested readers are referred to excellent reviews by Vagenakis [18], Jackson [19] and Utiger [20] which deal mostly with the hypothalamic–pituitary–thyroid axis and Griffiths [9] which covers the central nervous system effects.

2.2.3 CLINICAL

TRH has been very valuable in our understanding of physiology and pathophysiology of the hypothalamic–pituitary thyroid axis. The TRH test was important in defining subtle degrees of hyperthyroidism and hypothyroidism; however, as measurements of T_4, T_3 and TSH have become more refined, they alone fulfil this role. TRH still has a role in differentiating hypothalamic from pituitary lesions. These aspects are discussed in Chapter 3, which deals with tests.

2.2.4 ANTERIOR PITUITARY AND THYROTROPHIN

About 5% of anterior pituitary cells secrete TSH. The cells, called thyrotrophes, are predominantly located in the anteromedial aspect of the gland. TSH is a glycoprotein of molecular weight 28 000 which is constituted from two non-covalently bound polypeptide chains designated alpha and beta [21, 22]. The alpha subunit is identical to those of **luteotrophin** (LH), **follitrophin** (FSH) and **chorionic gonadotrophin** (HCG). It has 96 amino acids and is called the common subunit. It is encoded by a single gene. The beta unit of 110 amino acids confers biological and immunological properties. The gene which encodes this subunit is on a different chromosome. Chin and his colleagues [23, 24, 26] have isolated the genes for both subunits. Alpha chain mRNA is approximately 800 bases in length, beta mRNA about 700 bases. The thyrotrophe produces an excess of alpha units and therefore the production of the beta subunit is the rate limiting step. Carbohydrate moieties are added at a post-translational step [27, 28]. As discussed above, TRH is the main stimulus for release of TSH. TSH can be measured in serum with precision by immunoradiometric assay (Chapter 3). The hormone has a half-life of about 1 hour in the circulation. In normal man about 165 mU are secreted daily. Peripheral tissues, in particular liver and kidney, metabolize TSH and the thyroid plays almost no role in this regard. The main negative feedback control for production and secretion of TSH is the level of free thyroid hormones in the blood. There are nuclear receptors for T_4 and T_3 in the thyrotrophe, the affinity for T_3 is about 10–20 times greater than for T_4. In addition, the thyrotrophe is rich in enzymes which deiodinate T_4 to T_3 (5′ deiodinase, type II) [25]. About 50% of T_3 in the thyrotrophe is formed in the cell by this mechanism. Therefore, intrathyrotrophe T_3, but not serum T_3, is the more important regulator. Chin *et al.* [26] have shown in a mouse model that T_3 in higher than physiological amounts lowers the level of messenger RNAs which control formation of the TSH subunits, in particular the beta subunit. It appears that T_3 has a direct action at the chromosomal level. As is discussed under action of thyroid hormones, the nuclear receptor is usually 50% occupied by T_3 in normal circumstances, but as occupancy in thyrotrophes increases there is progressive inhibition of mRNA synthesis of the TSH peptides which at 90% occupancy is complete. High levels of thyroid hormones also reduce the number of TRH receptors on the thyrotrophe and T_3 might have a minor inhibitory role on the hypothalamus.

Somatostatin and dopamine have an inhibitory action at the level of the pituitary. Oestrogen augments the action of TRH. This has been shown *in vitro* on cultured thyrotrophes and in men who were subjected to TRH tests before and after oestrogen administration. Norepinephrine has a positive role and glucocorticosteroids an inhibitory role at this level (Figure 2.4). Each of these is of considerably less importance than TRH and free thyroid hormone levels.

TSH levels show diurnal variation, peak levels are from about 12 midnight to 3 or 4 am; the nadir is about 11 am till noon. The diurnal range is about 1 μU/ml (normal range of TSH in healthy people is 0.4–5.0

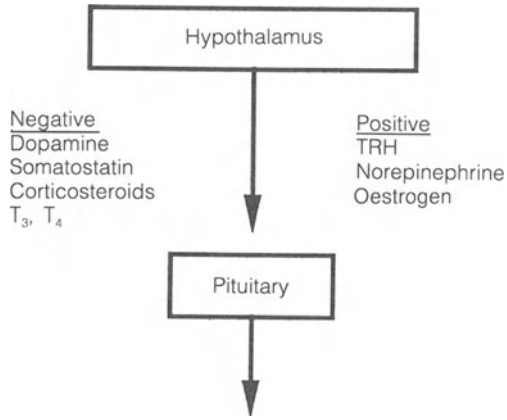


Figure 2.4 Additional factors modulating the action of TRH on TSH secretion by the thyrotrophe.

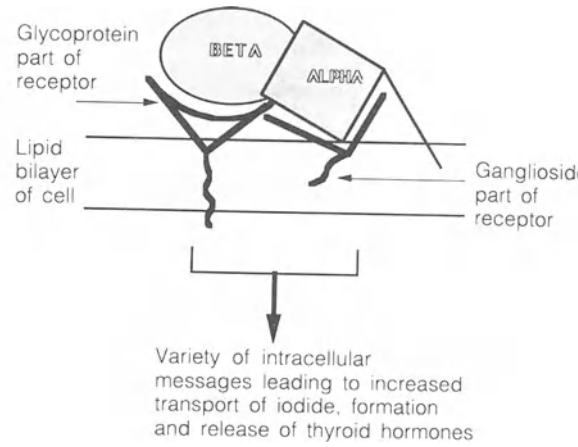


Figure 2.5 Diagrammatic representation of the TSH receptor and its interaction with subunits of TSH. Adapted from Chan *et al.* [31].

μU/ml or mU/l). The secretion is pulsatile with peaks every 10 minutes which are on average 50% greater than basal values [29]. Immediately after birth, there is a brisk rise in TSH which subsides in 24–48 hours. This is followed by a rise in total and free thyroid hormone levels, and is thought to be teleologically sound, by protecting the newborn from the cold, harsh world by a surge in hormones which 'produce heat'. Cold exposure causes a rise in TSH in newborn, but not adult experimental animals or man, although extreme cold can produce very minor changes in adults.

TSH combines with a specific transmembrane receptor in the follicular cells. The receptor has two components: one a glycoprotein, the other a ganglioside. the two units of TSH interact with these as shown diagrammatically in Figure 2.5. The alpha subunit attaches to the cell membrane and the ganglioside part, the beta subunit with the glycoprotein. This interaction produces several important intracellular signals. There is an increase in cyclic AMP, which has been attributed to the alpha subunit/ganglioside interaction. This most probably controls iodide uptake into the follicular cell. The interaction of the beta subunit/glycoprotein receptor causes an increase in phosphatidyl inositol and produces changes in microtubules which result in increased iodide transport into the follicular lumen and increased iodination of thyroglobulin.

Much of the current knowledge of the structure and function of the TSH receptor comes from development of families of monoclonal antibodies against parts of the receptor [30, 31]. Experiments with these antibodies have also demonstrated that different antibodies can have disparate effects on the cell. Some simply block the action of TSH, and the expected rise in cyclic AMP does not occur. Others cause an increase in cyclic AMP and in thyroid function. Others cause an increase in cell growth, rather than function.

2.3 FORMATION OF THYROID HORMONES

The functional unit of the thyroid is the follicle. Follicles consist of an outer layer of follicular cells surrounding the central mass of colloid. The follicular cells are critical for the production and secretion of thyroid hor-

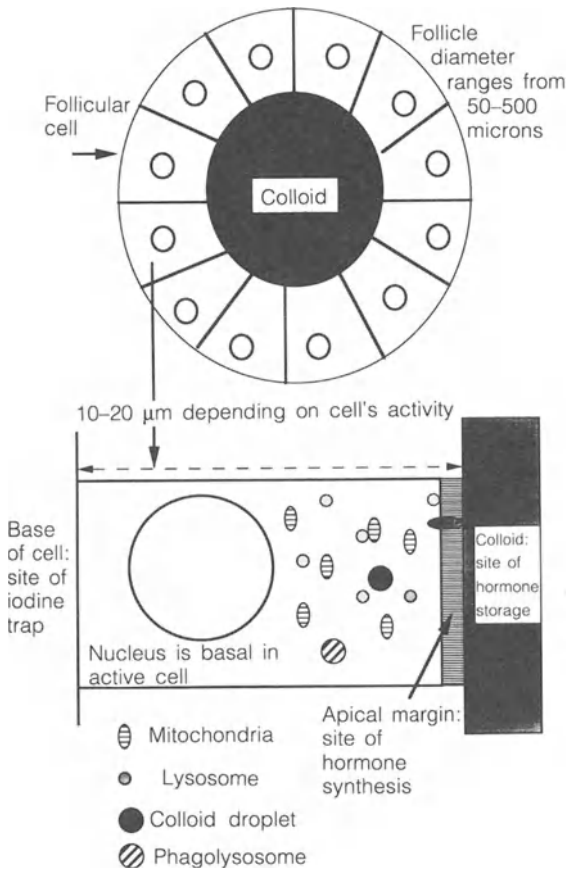


Figure 2.6 Follicle and follicular cell showing more detail than Figure 1.6.

mones, although some of the synthetic steps occur at the interface of the apex of the cell and the colloid. Figure 2.6 is a diagram of the structure of a follicle and a follicular cell. Iodide is transported into the cell and combines with tyrosine to form iodotyrosines. These are coupled to form thyroid hormones, thyroxine and triiodothyronine (iodothyronines) which are stored in the colloid on molecules of thyroglobulin from which they are released as required. Thyroxine structure was determined by Harrington and Barger in 1927 [32] and triiodothyronine by Gross and Pitt-Rivers and Roche *et al.* in 1952 [33, 34].

2.3.1 IODIDE TRANSPORT (IODIDE TRAP, IODIDE PUMP)

Iodide in the serum is actively transported into into the follicular cell by an active mechanism situated at the base of the cell. Wolff [35] has proved this is an active transport mechanism which concentrates iodide against a chemical and electrical gradient. The concentration of iodide inside the cell is 20–40 times that in the extracellular fluid, and this ratio can be increased (several hundredfold) when the thyroid is under TSH stimulation. Experimentally, thyroid cells have to be intact to trap iodide and the mechanism can be saturated by excess iodide, or inhibited by other anions such as bromide, thiocyanate (SCN^-), perchlorate (ClO_4^-) and pertechnetate (TcO_4^-) [36]. The transport requires oxidative metabolism and phosphorylation and is increased by high levels of TSH. It is inhibited *in vitro* by ouabain, but this has no clinical implication for patients on digitoxin or derivatives. Normally trapped iodide is rapidly transported across the follicular cell and organified. In certain thyroid diseases – including a specific inborn error of hormone synthesis and Hashimoto' thyroiditis, and in patients on antithyroid drugs, such as methimazole and propylthiouracil, and excess inorganic iodine – there is a defect in this mechanism and free iodide remains inside the follicular cell. This can be demonstrated using a tracer of radioactive iodine followed by perchlorate to block further trapping of iodide. In these clinical situations, the radioactive iodine leaks out of the thyroid and this can be detected by scintillation counting over the thyroid. This is described in more detail in Chapter 3.

Iodide is also trapped by parietal cells of the gastric mucosa, and glandular epithelium in mammary glands, salivary glands and choroid plexus. The non-thyroidal tissues which trap iodide are unable to produce thyroid hormones. Uptake in these

sites is seen on whole-body scintiscans of the distribution of radioiodine, and should not be misinterpreted as abnormal or metastatic thyroid cancer.

Loss of the ability to trap iodide by the thyroid is a rare cause of hereditary goitrous hypothyroidism [37, 38]. The defect is also present in other tissues, therefore, it is easy to diagnose by finding low uptake of a tracer dose of radioiodine by the thyroid and low salivary to serum iodide ratio. Because the anions described above are trapped by the thyroid they have, or have had, clinical relevance. $^{99m}TcO_4^-$ is radioactive with a short half-life of 6 hours, and it has been used for thyroid scintigraphy [39, 40], although I prefer ^{123}I for reasons that are presented in Chapter 3. $KClO_4$ and NaSCN were used as antithyroid drugs. However, both are toxic, the former causing aplastic anaemia, and they are not used [41, 42].

As the concentration of plasma iodide increases, the percentage of iodide trapped by the thyroid decreases (although the absolute uptake remains constant). This is very important clinically, since iodine can be given unknowingly to patients in medications and radiographic contrast media. This makes quantitative measurement of thyroid function with radioiodine impossible.

2.3.2 ORGANIFICATION OF IODINE (IODINATION OF TYROSINE)

All subsequent steps in formation and storage of thyroid hormones take place in the colloid. Iodide which has been trapped is rapidly transferred to the lumen of the follicle where it combines with tyrosine which has been incorporated into thyroglobulin molecules. Iodide must be oxidised to I^o for this to occur. If one wishes to attach iodine to proteins *in vitro*, this step is also essential. *In vivo*, this is achieved by an enzyme, thyroid peroxidase in the presence of H_2O_2 [43]. The peroxidase is found in microsomes and is the antigen against which antimicrosomal antibodies are directed. This enzyme has molecular weight of approximately 100 000 [44].

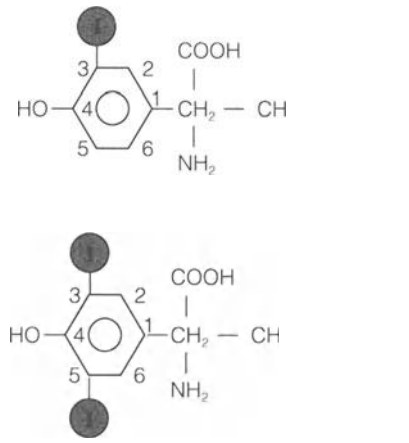


Figure 2.7 Structure of monoiodotyrosine and diiodotyrosine. Numbers designate appropriate position of carbon atoms in benzene ring. In tyrosines, these are numbered 1 to 6. In thyronines the inner ring carbons are numbered 1 to 6, the outer ring 1′ to 6′.

One iodine atom combining with tyrosine produces monoiodotyrosine (MIT), two atoms diiodotyrosine (DIT) (Figure 2.7). Thyroglobulin is discussed in more detail below, but suffice it to say here that there are about 120 tyrosine molecules per molecule of thyroglobulin; of these about 30 can be iodinated and about 6–8 are available for formation of thyroid hormone. The most important action of standard antithyroid drugs such as propylthiouracil and methimazole is to interfere with this synthetic step. Thus iodide is not organified. Hereditary deficiency of this enzyme is a cause of goitrous cretinism. In this disorder, the uptake of iodine into the thyroid is increased, but the iodine is not organified [45, 46]. Diagnosis is established by demonstration that the trapped iodide can be 'washed out' using the perchlorate discharge test [47]. The association of deaf-mutism and goitrous hypothyroidism from this defect is called **Pendred's syndrome** [48].

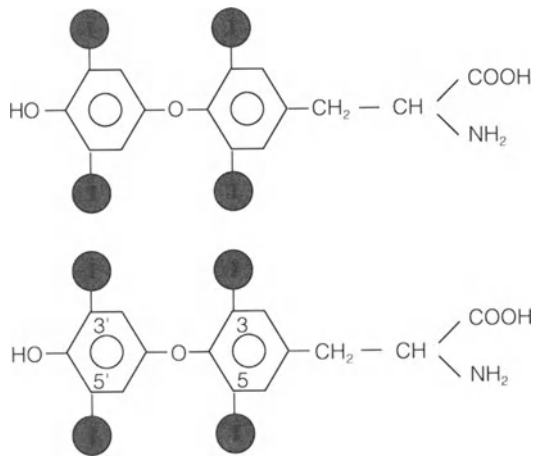


Figure 2.8 Structure of L thyroxine (T_4) and L triiodothyronine (T_3).

2.3.3 COUPLING OF TYROSINES TO FORM THYRONINES

Two iodotyrosines combine to form iodothyronine, two DIT molecules produce T_4 and one MIT plus one DIT produce T_3. The structures of T_4 and T_3 are shown in Figure 2.8. The tertiary structure of thyroglobulin brings the precursor DIT molecules into apposition, which is thought to involve formation of a diphenylether ring. Alternative theories are presented in references 49 and 50. The coupling step is catalysed by the same peroxidase enzyme which is involved in oxidation of iodide and organification of tyrosine.

2.3.4 THYROGLOBULIN

Thyroglobulin makes up the majority of the colloid. It is a large glycoprotein of molecular weight 660 000, made from two dimers of 330 000 [51]. It contains approximately 5170 amino acid molecules, of which 120–30 are tyrosine and about 10% of the total weight is carbohydrate. The human thyroglobulin gene is on chromosome 8. Its amino acid sequence is known, as is the DNA sequence [51]. Thyroglobulin is synthesized in large membrane-bound polyribosomes found in the rough endoplasmic reticulum [52]. Glycosylation occurs post-translationally. It is transported through the smooth endoplasmic reticulum to the Golgi apparatus where glycosylation occurs. Glycosylated thyroglobulin is packaged in vesicles and delivered into the colloid space by fusion of the vesicle and apical cell membranes [53]. Iodination is a post-translational step which takes place at the interface of the cell and colloid. When there is adequate iodine in the diet and the patient is euthyroid it has been determined that each thyroglobulin molecule has approximately 7–10 MIT, 5–10 DIT, 2 T_4 molecules and there is 1 T_3 for every 2 or 3 thyroglobulin molecules [54]. The review of thyroglobulin synthesis and secretion by Van Herle *et al.* is recommended [55].

Thyroglobulin is a repositary for thyroid hormones and their precursors. Normally there is a supply of about 100 days of hormone stored in the colloid. Thus the thyroid differs from other endocrine glands in this regard, since hormones are usually produced and secreted on demand. Thyroglobulin is important clinically, since it is an antigen characteristic for the thyroid. It can be detected in the serum in a variety of thyroid diseases, but most importantly it is a marker for persistent, or recurrent, thyroid cancer. This is discussed in the next chapter.

The potential for abnormal thyroglobulin is considerable due to its high molecular weight. It has been shown that some cases of goitre, and/or goitre plus hypothyroidism are due to abnormal thyroglobulin structure which cannot be iodinated efficiently, or which cannot form the necessary configuration for coupling [56].

2.3.5 SECRETION OF THYROID HORMONES

Before thyroid hormones are secreted, thyroglobulin has to be taken into the follicular cell and hydrolysed to release the active hormones. Droplets of thyroglobulin are

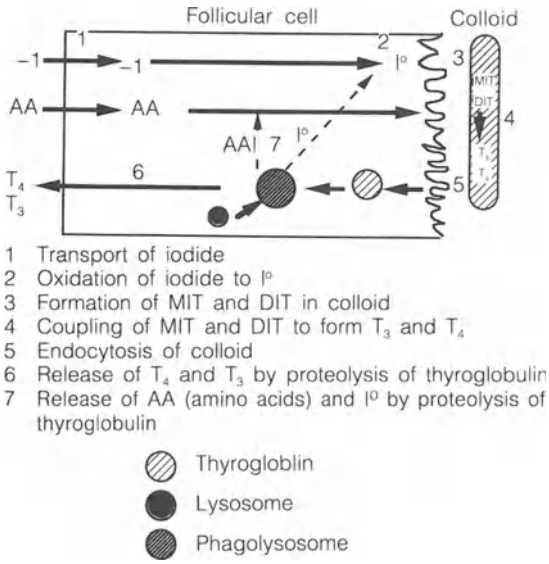


Figure 2.9 Formation of thyroid hormones.

engulfed by pseudopods from the apex of the cell [57]. Colloid droplets enclosed in apical membranes are taken into the cytoplasm of the follicular cell, and lysosomes containing proteolytic enzymes migrate towards and fuse with them producing phagolysosomes [58]. Migration of these organelles is regulated by intracellular microtubules and microfilaments [59]. Enzymatic degradation of thyroglobulin produces T_4, T_3, MIT, DIT and amino acids [60, 61]. The first two are secreted into the circulation, the iodotyrosines are deiodinated by intracellular deiodinases and iodide used again for iodination of tyrosine bound to thyroglobulin (Figure 2.9). A small proportion of iodine is lost from the thyroid.

There is a rare inborn error where function of the deiodinase enzyme is absent and MIT and DIT are secreted. Since these iodotyrosines are metabolically inactive, their release from the thyroid is equivalent to loss of iodine and eventually causes iodine deficiency [62–64]. This defect can be diagnosed by injecting radiolabelled MIT or DIT intravenously into the patient, and showing these intact molecules to be present unaltered in the urine by radiochromatography. Normally the molecules would be deiodinated and free radioiodine found in the urine.

2.4 AUTOREGULATION OF THE THYROID

The control mechanisms described above, although exquisitively sensitive to alterations in thyroid hormone levels, do not work instantaneously. In addition, they fail to account for potential changes in thyroid hormone levels brought about by rapid changes in plasma inorganic iodine. The amount of iodine in the diet varies considerably; also there are sources of iodine such as medications (amiodarone), antiseptics, and radiographic contrast agents which suddenly provide many orders of magnitude the amount of iodine required for normal function. The thyroid has several well-recognized mechanisms independent of the hypothalamic–pituitary axis which help preserve normality. The term autoregulation was introduced in this context by Ingbar [1]. These mechanisms can be demonstrated to be active in the absence of TSH in experimental animals, or when TSH is kept constant.

A rise in plasma inorganic iodide is followed by reduced uptake of iodide into the follicular cells. This does not occur immediately and the mechanism is not understood. Clearly, it results in less iodide being available for hormone synthesis. If trapping were to remains constant, a large excess of plasma iodide would result in more iodide entering the cell than normal, but as the intracellular concentration of iodine increases, a second control mechanism prevents excess hormone formation. The second mechanism decreases the organification of tyrosine. This is called the **Wolff–Chaikoff effect** [65]. It is transient and in normals usually only lasts for several days. Break-through from this protective mechan-

ism in patients is almost certainly due to the first protective mechanism reducing the amount of iodide entering the cell. Therefore, there is no longer an excess of intracellular iodine and the iodination can return to a normal rate of hormone production. In a number of clinical situations, the Wolff–Chaikoff effect continues as long as there is excess iodine. These include Hashimoto's thyroiditis and Graves' disease, which has been treated by radioiodine or partial thyroidectomy.

Large doses of iodide reduce secretion of stored hormones. The mechanism is not fully understood. Changes in reducing release of hormones are subtle in euthyroid normals, but are dramatic in hyperthyroid patients with Graves' disease.

When there is a deficiency of iodide, the transport of iodide into follicular cells increases. In man the other changes are not easy to separate from those of increased TSH and, indeed, iodide deficiency probably augments the TSH effects. There is an increase in formation of MIT and T_3; therefore, the more active hormone which contains less iodine is produced preferentially.

2.5 TRANSPORT OF HORMONES IN SERUM

Almost all thyroid hormone in the circulation is reversibly bound [66] to carrier proteins. The small proportion of unbound, or free hormone dictates the metabolic condition. The protein-bound hormone is metabolically inert, although it supplies a potential sources of hormone. It acts as a buffer, so that sudden changes in levels of hormones in the blood do not cause sudden alternations in thyroid function. There has been debate whether protein-bound hormone enters some tissues [67], but there is little experimental data to support this concept [68]. In serum only 3 molecules out of 10 000 of T_4 and 3 out of 1000 of T_3 are free. Conversely 99.97% of T_4 and 99.7% of T_3 are protein bound. Because of the protein binding, thyroid hormones are not lost in the urine unless there is severe proteinuria. Knowledge of the protein binding is very important in understanding serum thyroid function tests and the effect of drugs and non-thyroidal illnesses on thyroid function test results.

Three plasma proteins are important in transport, **thyroid binding globulin** (TBG), **thyroxine binding prealbumin** (TBPA) also called transthyretin, and albumin. These can be demonstrated by adding tracer quantities of radioactive T_4 and T_3 to serum and running an electrophoretic strip and demonstrating the distribution of radioactivity in relation to the protein classes. Alternatively, electrophoresis of the serum of a patient treated several days previously with radioiodine provides the same information, the thyroid having produced T_4 and T_3 as described previously, although some radioiodine has been incorporated into the thyroid hormones by *in vivo* labelling.

TBG is a single-chain glycoprotein produced by the liver [69]. It should not be confused with thyroglobulin. It migrates as an interalphaglobulin, has a molecular weight of 55 000 and is present in the lowest concentration of the three, approximately 1–2 mg/dl. The affinity of TBG for T_4 and T_3 is the highest of the transport proteins and although present in the lowest concentration, it carries approximately 70% of both hormones. There is one binding site for T_3 and T_4 on each molecule. When TBG is fully saturated, it can carry 12–28 μg T_4/dl (150–360 nmol/l). Since the normal range for T_4 is 5–11 μg/dl, TBG is about one-third saturated; in other words one out of three or four TBG molecules carries a T_4 molecule. TBG has a half-life of about 5–6 days and is produced by the liver, which is also a major site for its metabolism. Reference 69 is a comprehensive review of this protein. The gene responsible for TBG production is on the X chromosome and there are X-linked associated increases and decreases of TBG [70–73].

Table 2.1 Summary of important features of TBG, TBPA and albumin

	TBG	*TBPA*	*Albumin*
Plasma concentration (mg/dl)	1–2	15–20	3000–4500
% T_4 bound	60–80	10–20	5–15
% T_3 bound	50–70	0–1	30–50
T_4 binding capacity (μg/dl)	12–28	250–300	considerable
Molecular weight	55 000	54 000	66 000

Thyroxine binding prealbumin was discovered by Ingbar in 1958 [74]. It is present in approximately 15–20 mg/dl and has the capacity to bind 300 μg T_4. However, it has a lower affinity than TBG for T_4 and normally carries about 10–20% of this hormone [75]. It consists of four identical polypeptide chains which are arranged so there is a central channel containing two T_4 binding sites [76]. Usually only the first site is occupied and only one out of 300 TBPA molecules carries T_4 [77]. TBPA transports no (or very little) T_3. TBPA is associated with retinol-binding-protein, which is the major transport protein for vitamin A. TBPA is produced in the liver, has a half-life of about 1–2 days and it is very sensitive to illness and malnutrition, which cause the level to fall as a direct result of lowered synthesis. It contains no carbohydrate and is stable *in vitro*.

Albumin has the largest capacity for binding thyroid hormones. However, because it has the lowest affinity, it carries only 5–15% of T_4 and about 30–50% of T_3. Table 2.1 summarizes important features of these proteins.

The amount of free hormone is proportional to the amount of binding proteins and the total hormone level. This can be expressed simply by the following relationship:

$$FT_4 \text{ is proportional to } \frac{T_4}{TBG} + \frac{T_4}{TBPA} + \frac{T_4}{Albumin}$$

Therefore, if total thyroid hormone levels are used to define thyroid status, it is important to know the thyroid binding capacity,

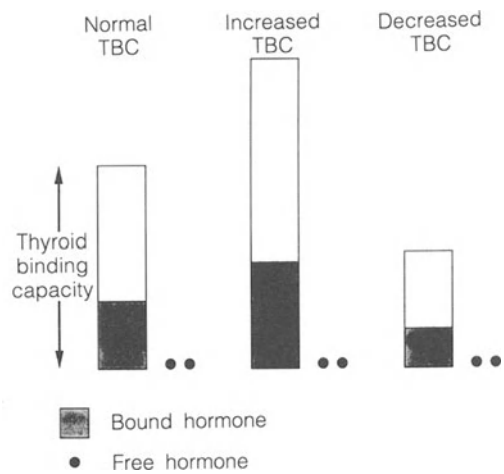


Figure 2.10 Effect of alterations in the amout of thyroid transport proteins on total thyroid hormone levels. Under normal circumstances, every effort is made to keep the level of free hormone normal. Therefore, an increase or decrease in transport protein levels results in a corresponding change in level of bound hormone so that the amount of free hormone remains the same.

$$FT_4 = K \times \frac{T_4}{TBC}.$$

otherwise the total hormone results cannot be interpreted correctly. The levels of the transport proteins are altered by genetic, physiological, pharmacological and pathological conditions, and any change in the amount or affinity of these proteins, alters the measurement of total thyroid hormones. This is shown diagrammatically in Figure 2.10. Table 2.2 gives a list of some of the

Table 2.2 Factors that cause an increase in thyroid binding proteins

TBG	Inherited Oestrogens Pregnancy Hepatitis Porphyria Drugs
TBPA	Inherited
Albumin	Familial dysalbuminaemic hyperthyroxinaemia

Table 2.3 Factors that cause a decrease in thyroid binding proteins

TBG	Inherited Androgens Steroids Severe nephrosis Chronic liver disease
Binding inhibitors	Drugs: Dilantin (diphenylhydantain; hydantain), aspirin Severe illness

factors that increase the amount of binding proteins and Table 2.3 lists factors that reduce the levels. Numerically, the most important is the effect of oestrogen in increasing binding capacity. This topic is expanded in Chapter 3, in the section dealing with thyroid function tests, and in Chapter 12 on the effects of non-thyroidal illness on thyroid function and testing.

The free hormone enters the cell and dictates thyroid function. This applies to all cells including thyrotrophes in the anterior pituitary. The control mechanisms discussed above strive to keep the free hormone levels normal. Therefore, an increase in thyroid binding proteins for any reason will cause a corresponding fall in FT_4 because the denominator of the equation increases, but the numerator remains constant. This is recognized at the pituitary level, resulting in a rise in TSH which causes an increase in thyroid function with release of the proportionately correct amount of T_4 to bring FT_4 back to normal. These changes continuously modulate thyroid function to keep FT_4 within physiological range.

Abnormally high total thyroid hormone levels have been attributed to a albumin-like carrier protein in several families [78, 79]. This has been called **familial dysalbuminaemic hyperthyroxinaemia**, and should be considered when total T_4 is high, but TSH and FT_4 normal and there is no evidence of high TBG or oestrogen use.

2.6 METABOLISM OF THYROID HORMONES

T_4 is the most abundant thyroid hormone. It is also a prehormone and is converted to T_3 for its major activity [80–84]. This involves removal of an outer ring I^- by the enzyme 5′ deiodinase. There are two forms of this enzyme: one is found in liver, kidney and muscle cells, the other form in pituitary and in brown fat cells [85]. An alternative breakdown pathway is through formation of rT_3 by enzymatic removal of an inner ring I^-. The enzyme is a 5 deiodinase. This is shown in Figure 2.11. The same enzymes metabolize triiodothyronines to diiodothyronines, which is shown diagrammatically in Figure 2.12. Normally about 80% of T_4 is broken down by 10 deiodination, the remainder by alternative pathways. Of the deiodinated T_4, about 50% forms T_3 and 50% rT_3. The outer ring deiodination is reduced in severe illness, starvation, and by medications such as propylthiouracil, ipodate, steroids and propranolol [83]. These factors inhibit the 5′ deiodinase enzyme, type I, which also is involved in deiodination of rT_3; therefore, the level of T_3 is lower and rT_3 higher under these circumstances. Table 2.4 gives a comprehensive list of conditions that inhibit this enzyme.

The remaining 20% of the hormones are conjugated with glucuronide, or sulphate in

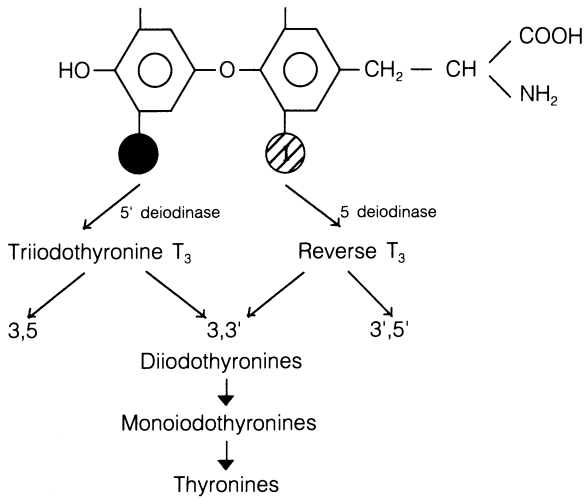


Figure 2.11 Metabolism of thyroid hormones by deiodination.

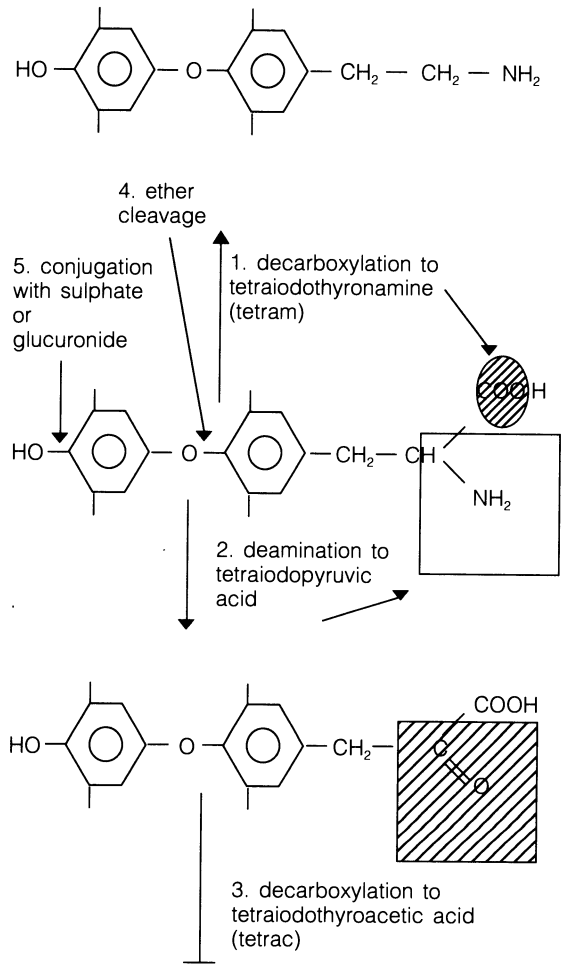


Figure 2.12 Alternative pathways for degradation of thyroid hormones.

the liver, deaminated, decarboxylated, or subjected to ether cleavage. The net result is formation of metabolically inert compounds, although deaminated T_4 (tetrac) and T_3 (triac) do retain activity. These compounds are also subject to deiodination which removes all activity. Figure 2.12 shows these diagrammatically and reference 86 is a comprehensive, well-referenced review.

2.7 IODIDE CYCLE

Discussion of the iodide cycle has been introduced at this point because it depends not only on intake of iodine, but also on iodide released during metabolism of thyroid hormones. The amount of iodine in the diet varies considerably, but normal homeostasis is maintained over a range of about 75 μg to several thousand μg/day. The recommended range is 80–150 μg/day [87], and from 50–1000 μg is considered safe [88]. In the USA, the average amount of dietary iodine increased from 150 μg/day in the early 1960s, to approximately 500 μg/day by the 1970s. Recent data shows the intake is currently falling, and is in the range of 200–300

Table 2.4 Some of the factors that impair conversion of T_4 to T_3 by inhibiting type I 5′ deiodinase

1 Systemic illness	Chronic ill health Calorie deprivation Acute illness: e.g. surgery, myocardial infarct
2 Drugs	Propylthiouracil Ipodate Amiodarone Propranolol High-dose steroids
3 Age	Fetus and early neonate ? old age – probably due to chronic illness

Table 2.5 Sources and quantities of dietary iodine in the USA in 1978. Adapted from [90]

Source	*μg/day**	%
Dairy	535	56
Grain	153	16
Meat/fish/poultry	103	11
Sugars	102	11
Beverages	40	4
Potatoes	4	0.4
Legumes	2	0.2
Leafy vegetables	1	0.1
Miscellaneous	12	1.3
Total	952	100

* Based on 3900 kcal: 2580 kcal provides 700 μg iodine.

μg/day. In the UK, two recent surveys found intakes of 100 and 250 μg/day [89]. As intake falls below 50 μg/day there is an increase in the incidence of goitre, and at values less than 20 μg/day, goitre is almost universal and cretinism occurs in offspring [88]. This is discussed in Chapter 11.

Sources of dietary iodine are shown in Table 2.5. Measurements have been made on sample foodbaskets in different regions of the USA [90] and the results presented are taken from that reference. The main sources are food and drink, although air, especially in sea-coastal areas, can provide 14–20 μg/day [91]. Seawater contains 50 μg/l and iodine is volatilized by sunlight. Marine fish and shellfish provide about 800 μg/kg but there is wide variation. Plants take up iodine in the concentration it is present in the soil. This depends on the distance from the sea, and in areas where the topsoil has been removed by glaciers, the iodine content is low. Old soil is considerably richer in iodine than new. Thus, in general mountainous areas far from the sea, where the topsoil has been removed by glaciers or other natural forces, are low in iodine and their inhabitants are at risk of iodine deficiency, unless they have access to alternative sources of iodine. In the developed world, foodstuffs are transported considerable distances and, as a result, knowledge of the local iodine content of soil can be misleading in predicting iodine status of the population. Meat and animal products, such as milk, contain iodine in proportion to that in fodder, although sources such as antiseptics used to cleanse teats can add substantial amounts of iodine to milk. Seaweed is very rich in iodine with up to 4 or 5 mg/kg. Cattle fed on seaweed produce milk which is very rich in iodine; normally milk contains 35–55 μg/kg. Too much iodine can cause goitrous hypothyroidism in particular in people with autoimmune thyroid disease, and one of the culprits is seaweed.

There are medicinal sources which are extremely potent [92], e.g. amiodarone contains 75 mg iodide per 200 mg tablet, and 6 mg is released daily, thus a patient taking 600–800 mg amiodarone daily is 'ingesting' 18–24 mg iodine. Radiographic contrast agents contain 300–500 mg iodine/ml. Usually 50–150 ml of contrast is injected giving 1.5–7.5 g iodine to the patient (1 500 000–7 500 000 μg). It should be remembered that contrast is frequently used for CT scanning. There is in the USA great pressure from advertisements to ingest multivitamins, many of which contain approximately 150 μg iodine per pill. There is also considerable intake of kelp for poorly defined reasons. Other sources of increased iodine intake can be subtle. Erythrosine, a dye used widely to colour foodstuffs and pills, contains 58% iodine [93]. Iodide is lost by cooking, in particular boiling [94].

I have taken three situations each in steady state, with dietary intakes of 100, 300 and 500 μg daily and tabulated expected distributions as shown in Table 2.6, and illustrated in more detail the cycle for intake of 300 μg in Figure 2.13.

Dietary iodine is converted to iodide in the stomach and absorbed in the stomach and upper small intestine. It is absorbed rapidly and after 3 hours there is no difference between fasting and non-fasting [94]. Iodide enters the extracellular water and is called

Table 2.6 Effect of the amount of iodine in the diet on the iodine cycle

Dietary iodine	100 μg	300 μg	500 μg
Endogenous iodide	50 μg	50 μg	50 μg
Thyroid transport	70 μg	70 μg	70 μg
Thyroid uptake	47 %	20 %	13 %
Urinary iodide	80 μg	280 μg	480 μg
Faecal iodide	15 μg	15 μg	15 μg

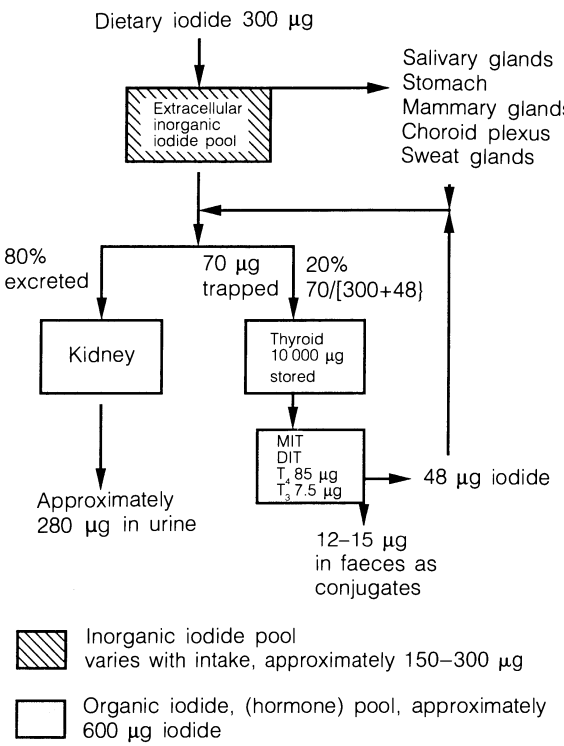


Figure 2.13 Iodide cycle.

the extracellular inorganic iodide pool. To this pool, iodide is added from the breakdown of thyroid hormones. Inorganic iodide in the circulation is called plasma inorganic iodide, and usual concentrations are between 0.1–1.0 μg/dl. Values less than 0.1 μg/dl are associated with goitre. The average range of T_4 produced by the thyroid is 70–100 μg/day (90–129 nmol/day) and of T_3 5–10 μg/day (7.5–15 nmol/day). If we accept mean values of T_4 and T_3 production of 85 and 7.5 μg respectively, and accept that 80% of these are subsequently deiodinated, T_4 produces 44 μg iodide (65% of [80 × 85]/100), and T_3 gives 3.5 μg iodide (58% of [7.5 × 80]/100). Therefore, 47.5 μg iodide from endogenous sources is added to the dietary iodide. (In Table 2.6, 47.5 μg has been approximated to 50 μg.)

The thyroid and the kidney account for almost all iodide clearance. It is true that salivary glands, parietal cells, mammary glands, and choroid plexus trap iodide but, of these, lactation is the only one which loses iodide from the body. Milk can contain 20 times the concentration of plasma inorganic iodide. The thyroid produces 85 μg T_4 and 7.5 μg T_3 and small amounts of rT_3 and other inactive iodinated tyrosines and thyronines daily; therefore, it requires about 60 μg of iodide every 24 hours. Due to leakage of some iodide from the gland, the amount necessary for normal hormone synthesis is 70 μg/day. With an intake of 300 μg plus 47.5 μg from endogenous sources, the thyroid transports approximately 20% of the extrathyroidal inorganic iodide, 70/347.5. The remainder is excreted by the kidneys. There must be a small positive balance of iodide, since the thyroid is the main repository in the body containing from 5000–10 000 μg. It is now possible using fluorescent scanning to determine this with accuracy (Chapter 3).

Twenty per cent of the hormones are conjugated and they are secreted in the bile into faeces. The organic iodide pool is approximately 600 μg.

In cases of severe iodine deficiency, the thyroid preferentially produces T_3, therefore balanced equations have to take this into consideration. If T_3 alone is secreted, approximately 40 μg/day (61 nmol/day) would be adequate and this requires only 23 μg iodide.

2.8 ACTION OF THYROID HORMONES

Thyroid hormones in excess or deficiency have dramatic effects on whole animals and on organ systems. Thyroid hormone is essential for metamorphosis of a tadpole to a frog and in the developmment of the salamander. In humans, fetal brain and skeletal development are greatly impaired by lack of thyroid hormones. The oxygen consumption of almost all tissues increases with increasing levels of thyroid hormones, the exceptions being the spleen, testis and adult brain. There has been debate about how these occur, but the consensus of opinion is that the main action is a nuclear one [95–97], lesser actions occur at the cell membrane and mitochondria.

2.8.1 NUCLEAR ACTIONS

Thyroid hormones have to be internalized to have an effect. This may be partly by diffusion, but recent evidence points to a receptor being of importance. Once inside the cell, thyroid hormones bind to a nuclear receptor. The receptor has highest affinity for triac, then L T_3, L T_4 and reverse T_3, and this is consistent with the metabolic effects of these hormones [97, 98]. The receptor is a non-histone protein of approximately 50 000–60 000 molecular weight, which is bound to chromatin [99]. There are two genes encoding thyroid receptor proteins, one on chromosome 3, the other on chromosome 17. These are designated C–erb–A beta and C–erb–A alpha respectively. Although the two receptors are minimally different structurally, they have the same affinities for thyroid hormones. The receptor has been found in all thyroid hormone responsive cells, and there is good correlation between the amount of receptor in a tissue and the effect of thyroid hormones on that tissue. Under normal conditions about 50% of the receptor sites are occupied by thyroid hormones; therefore, the receptor capacity is low. There is also good correlation between the number of receptor sites occupied by T_3 and the thyromimetic effects. Of the sites occupied, about 80% contain T_3 and 10–15% contain T_4.

T_3 by attaching to its receptor modulates gene expression. In most cases, the response is positive with formation of new or more protein but, in some cases, the effect is inhibitory. After addition of T_3 to responsive cells *in vitro*, it is possible to demonstrate an increase in RNA polymerase I, ribosomal RNA, RNA polymerase II and messenger RNA. This sequence is followed by creation of new protein. Therefore thyroid hormones, in particular T_3, can increase protein formation. Many proteins are known to be produced in increased amounts by increase in thyroid hormone receptor occupancy. They include growth hormone, malic enzyme which is important in lipid synthesis, acetylcoenzyme A carboxylase, fatty acid synthetase, glucose–6–phosphate dehydrogenase, plus several others [100]. Somewhat paradoxically, thyroid hormone decreases formation of TSH in thyrotrophes as discussed previously. It would appear that the major physiological functions of thyroid hormones result from production, or inhibition, of biologically important proteins, some of which are enzymes, others hormones and hormone receptors.

2.8.2 EXTRANUCLEAR EFFECTS OF THYROID HORMONES

Thyroid hormone causes an increase in transport of glucose into cells within minutes. The time course is not consistent with a nuclear effect causing translation, or transcription, of proteins which would facilitate this. In contrast, a similar increase in transport of amino acids is delayed for many hours and probably is due to a nuclear action of T_3, rather than an action on plasma membranes.

For several years there was a bitter debate,

whether the primary action was at the level of the mitochondria [101] rather than the nucleus, but at this time most of the evidence points to the mitochondrial changes such as morphological alterations, increased transport of ADP, and production of ATP in hyperthyroidism as secondary to nuclear actions.

2.9 CALCITONIN

Calcitonin is made and secreted from parafollicular cells, also called C cells. The concept of a calcium-lowering hormone was proposed by Copp *et al.* in 1962 [102], and investigations by several groups confirmed the theory and determined that the main source of the material is the thyroid [103, 104]. Calcitonin is a peptide of 32 amino acids. There are two genes, alpha and beta, responsible for formation of calcitonin. Both are on the eleventh chromosome. They also encode two closely related proteins, calcitonin gene related protein and katacalcin. Calcitonin lowers serum calcium and its action is largely through inhibition of osteoclasts [105]. Very quickly it causes reversal of the structural changes of osteoclasts which are characteristic of bone resorption [106]. When calcitonin is given chronically in large doses, it reduces the number of osteoclasts; this might be secondary to inhibition of function of these cells. Calcitonin also increases renal excretion of calcium, sodium and phosphate and possibly stimulates formation of 1, 25-dihydroxycholecalciferol. The major stimulus to calcitonin secretion is a rise in serum ionized calcium. Other stimuli are gastrin and secretin. The last two are thought to aid conservation and storage of calcium after a meal. Calcitonin levels fall in patients after thyroidectomy. They also fall concomitantly with oestrogen at and after the menopause. It is believed that this is one factor in causing osteoporosis. The physiological importance of calcitonin is not great since there is no disturbance in calcium homeostasis after thyroidectomy, provided the parathyroids are intact and patients with consistently elevated calcitonin levels (medullary cancer) are not hypocalcaemic.

Calcitonin is a sensitive marker for the presence of medullary cancer, and can be used to monitor the course of this cancer. Testing is usually combined with a stimulus for its secretion such as pentagastrin or calcium. These tests are described in Chapters 3 and 8. Cacitonin has a role in treatment of Paget's disease of bone. There is increasing evidence that it is as active when given by nasal spray. This is outside the scope of the text, but reference 107 covers the topic comprehensively.

Cacitonin gene related protein is produced and secreted mainly at nerve terminals and has a similar, but considerably weaker, effect on lowering calcium, at least an order of magnitude less than calcitonin. In contrast, it has a profound action on blood vessels and is the most potent vasodilator known [108]. No physiological function has been ascribed to katacalcin.

KEY FACTS

- The functional unit of the thyroid is the follicle.
- The follicle is made up of a single layer of cuboidal (follicular) cells surrounding a central store of colloid.
- The basal end of the follicular cell traps iodine from the plasma and synthesizes thyroid hormones from iodine and tyrosine.
- The synthesis involves the trapping of iodine, its oxidation and attachment of one atom to tyrosine (monoiodotyrosine MIT), followed by a second atom to produce diiodotyrosine (DIT), coupling of the iodotyrosines to produce iodothyronines, triiodothyronine (T_3) and tetraiodothyronine (T_4).
- The synthesis occurs at the apex of the follicular cell.

- The iodotyrosines and iodothyronines are stored as part of thyroglobulin in the colloid.
- Thyroglobulin is taken up into the follicular cells by pinocytosis.
- Pinocytotic vesicles fuse with lysosomes containing proteolytic and other enzymes.
- Thyroid hormones are released from the breakdown of thyroglobulin and released into the extracellular space and plasma.
- All steps of thyroid hormone formation and release are controlled by TSH.
- There is a less important autoregulation which depends on the amount of iodine in the follicular cell; too much inhibits synthesis, too little speeds synthesis and augments TSH actions.
- Iodine comes from the diet, in particular seafood, preservatives and red dyes.
- 100 μg iodine is adequate for normal hormonogenesis.
- TSH is a glycoprotein with two peptide chains.
- TSH is produced in, and secreted from, specific cells in the anterior pituitary.
- There is a receptor for TSH on follicular cells.
- TRH is the most important positive stimulus to TSH secretion; thyroid hormones the most important inhibitory stimulus.
- TRH is a tripeptide which is produced in, and secreted from, the hypothalamus.
- Thyroid hormones secreted from the thyroid are largely bound to three transport proteins in the plasma.
- 99.97% of T_4 and 99.7% of T_3 in plasma are protein bound: the unbound fraction is called free hormone.
- The free hormones enter cells and dictate thyroid function.
- The three transport proteins are thyroxine binding globulin, thyroxine binding prealbumin and albumin.
- T_4 is 70% bound to TBG, 10% to TBPA and 20% to albumin.
- T_3 is about 50% bound to both TBG and albumin.
- Medications, hormones and hereditary defects can increase and decrease the amount of binding proteins.
- Altered amounts of binding proteins change the amount of total hormone in the plasma, but the free hormone remains constant.
- The main action of thyroid hormones is at the nucleus.
- T_3 is more important than T_4 for thyroid activity.
- However, the relationship of FT_4 and TSH levels in the blood are more closely related than T_3 and TSH levels.
- Most cells have 5′ deiodinase enzymes, which convert T_4 to T_3 intracellularly.
- The main role of thyroid hormones is to increase transcription of proteins, including structural and functional proteins.
- Extranuclear actions of thyroid hormones on cell membranes and mitochondria are much less important.

REFERENCES

1 Ingbar, S.H. (1972) Autoregulation of the thyroid: response to iodide excess and depletion. *Mayo Clin. Proc.*, **47**, 814–23.

2 Green, J.D. and Harris, G.W. (1947) The neurovascular link between the neurohypophysis and adenohypophysis. *J. Endocrinol.*, **5**, 136–46.

3 Harris, G.W. (1955) *Neural Control of the Pituitary Gland*, Edward Arnold, London.

4 Burgus, R., Dunn, T.F., Desidiro, D. *et al.* (1970) Characterisation of ovine hypothalamic hypophysiotropic TSH-releasing factor. *Nature*, **226**, 321–5.

5 Nair, R.M.G., Barrett, J.F., Bowers, C.Y. *et al.* (1970) Structure of porcine thyrotropin releasing hormone. *Biochemistry*, **9**, 1103–6.

6 Guillemin, R. (1978) Peptides in the brain: the new endocrinology of the neuron. *Science*, **202**, 390–402.

7 Schally, A.V. (1978) Aspects of hypothalamic regulation of the pituitary gland: its implication for the control of reproductive processes. *Science*, **202**, 18–28.

8 Lechan, R.M., Wu, P. and Jackson, I.M.D. (1986) Immunolocalization of the thyrotropin-releasing hormone prohormone in the rat central nervous system. *Endocrinol.*, **119**, 1210–16.

9 Griffiths, E.C. (1987) Clinical applications of thyrotrophin-releasing hormone. *Clin. Sci.*, **73**, 449–57.

10 Ormston, B.J., Garry, R., Cryer, R.J. *et al.* (1971) Thyrotropin-releasing hormone as a thyroid function test. *Lancet*, **2**, 10–14.

11 Hershman, J.M. (1974) Clinical application of thyrotropin-releasing hormone. *N. Engl. J. Med.*, **290**, 886–90.

12 Foley, T.P. Jr., Owings, J., Hayford, J.T. *et al.* (1972) Serum thyrotropin responses to synthetic thyrotropin-releasing hormone in normal children and hypopituitary patients. *J. Clin. Invest.*, **51**, 431–6.

13 Okerlund, M.D. and Greenspan, F.S. (1977) Clinical studies of thyrotropin and thyrotropin-releasing-hormone. *Pharmacol. Ther. C.*, **2**, 79–94.

14 Kolesnick, R.N. and Gershengorn, M.C. (1985) Thyrotropin-releasing hormone and the pituitary: new insights into the mechanisms of stimulated secretion and clinical usage. *Am. J. Med.*, **79**, 729–39.

15 L'Hermite, M., Vanhaelst, L., Gopinischi, G. *et al.* (1972) Prolactin release after injection of thyrotrophin-releasing hormone in man. *Lancet*, **1**, 763–5.

16 Faden, A.I. (1986) Neuropeptides and central nervous system injury: clinical implications. *Arch. Neurol.*, **43**, 501–4.

17 Macintosh, T.K. and Faden, A.I. (1986) Thyrotropin-releasing hormone (TRH) and circulatory shock. *Circ. Shock*, **18**, 241–58.

18 Vagenakis, A.G. (1979) Regulation of TSH secretion, in *Clinical Neuroendocrinology: A Pathophysiological Approach*, (eds G. Tolis *et al.*) Raven Press, New York, pp. 329–43.

19 Jackson, I.M.D. (1982) Thyrotropin-releasing hormone. *N. Engl. J. Med.*, **306**, 145–55.

20 Utiger, R.D. (1987) Thyrotropin-releasing hormone and thyrotropin secretion. *J. Lab. Clin. Med.*, **109**, 327–35.

21 Pierce, J.G. (1971) The subunits of pituitary thyrotropin – their relationship to other glycoprotein hormones. *Endocrinol.*, **89**, 1054–6.

22 Pierce, J.P. and Parsons, T.F. (1981) Glycoprotein hormones: structure and function. *Ann. Rev. Biochem.*, **50**, 465–95.

23 Chin, W.W. (1987) Glycoprotein hormone genes, in *Molecular Cloning of Hormone Genes*, (ed. J.F. Habener), Humana, Clifton N.J., pp. 137–72.

24 Chin, W.W. (1988) Hormonal regulation of thyrotropin and gonadotropin gene expression. *Clin. Res.*, **20**, 484–93.

25 Larsen, P.R. (1982) Thyroid-pituitary interaction. *N. Engl. J. Med.*, **306**, 23–32.

26 Chin, W.W., Shupnik, M.A. and Ross, D.A. (1985) Regulation of the alpha and thyrotropin beta-subunit messenger ribonucleic acids by thyroid hormones. *Endocrinol.*, **116**, 873–8.

27 Weintraub, B.D., Stannard, B.S., Magner, J.S. *et al.* (1985) Glycosylation and posttranslational processing of thyroid-stimulating hormone: clinical implications. *Rec. Prog. Horm. Res.*, **41**, 577–606.

28 Gesundheit, N. and Weintraub, B.D. (1988) Thyroid-stimulating hormone synthesis and glycosylation: clinical implications *Thyroid Today*, **10** (**1**), 1–11.

29 Greenspan, S.I., Klibanski, A., Schoenfeld, D. *et al.* (1986) Pulsatile secretion of thyrotropin in man. *J. Clin. Endocrinol. Metabol.*, **63**, 661–8.

30 Kohn, L.D., Valente, W.A., Cheng, A. *et al.* (1986) Monoclonal antibodies to the TSH receptor in the study of Graves' disease, in *Serono Symposium on Monoclonal Antibodies*, (eds G. Forti. M. Serio and M.B. Lipsett), Raven Press, New York, p. 232.

31 Chan, J., DeLuca, M., Santisteban, P., *et al.* (1987) Nature of thyroid autoantigens: the TSH receptor, in *Thyroid Autoimmunity* (eds A. Pinchera, S.H. Ingbar, J.M. McKenzie and G.F. Fenzi) Plenum Press, New York and London. pp. 11–26.

32 Harington, C.R. and Barger, G. (1927) Chemistry of thyroxine. III. Constitution and synthesis of thyroxine. *Biochem. J.*, **21**, 169–81.

33 Gross, J. and Pitt-Rivers, R. (1952) The identification of 3,5,3'-triiodothyronine in plasma. *Lancet*, **1**, 439–40.

34 Roche, J., Lissitzky, S. and Michel, R. (1952) Sur la presence de triiodothyronine dans la thyroglobuline. *Cr. Hebd. Seance Acad. Sci. Paris*, **234**, 1228–30.

35 Wolff, J. (1964) Transport of iodide and other anions by the thyroid gland. *Physiol. Rev.*, **44**, 45–90.

36 Halmi, N.S. (1961) Thyroidal iodide transport. *Vitam. Horm.*, **19**, 133–63.

37 Stanbury, J.B. and Chapman, E.M. (1960) Congenital hypothyroidism with goitre. Absence of an iodide concentrating mechanism *Lancet*, **1**, 1162–5.

38 Wolff, J. (1983) Congenital goiter with defective iodide transport. *Endocrin. Rev.*, **4**, 240–54.

39 Dodds, W.J. and Powell, M.R. (1968) Thyroid scanning with technetium 99m pertechnetate. *Radiol.*, **91**, 27–31.
40 Strauss, H.W., Hurley, P.J. and Wagner, H.J. Jr. (1970) Advantages of ^{99m}Tc pertechnetate for thyroid scanning in patients with decreased radioiodine uptake. *Radiol.*, **97**, 307–10.
41 Editorial (1961) Potassium perchlorate and aplastic anaemia. *Br. Med. J.*, **1**, 1520.
42 Hobson, A.J. (1961) Aplastic anaemia due to treatment with potassium perchlorate. *Br. Med. J.*, **1**, 1368.
43 Taurog, A. (1970) Thyroid peroxidase and thyroxine biosynthesis. *Rec. Prog. Horm. Res.*, **26**, 189–247.
44 Kimura, S., Kotani, T., McBride, O.W. *et al.* (1987) Human thyroid peroxidase: complete cDNA and protein sequence, chromosome mapping, and identification of two alternatively spliced mRNA's. *Proc. Natl. Acad. Sci. USA*, **8**, 5555–9.
45 Parker, R.H. and Beierwaltes, W.H. (1961) Inheritance of defective organification of iodine in familial goitrous cretinism. *J. Clin. Endocrinol. Metab.*, **21**, 21–30.
46 Stanbury, J.B. and Hedge, A.N. (1950) A study of a family of goitrous cretins. *J. Clin. Endocrinol. Metab.*, **10**, 1471–84.
47 Stanbury, J.B. and Talley, D. (1979) The inherited errors of the thyroid system, in *The Thyroid Physiology and Treatment of Disease*, (eds J.M. Hershman and G.A. Bray), Pergamon Press, Oxford, pp. 349–58.
48 Pendred, V. (1896) Deaf-mutism and goitre. *Lancet*, **2**, 532.
49 Lissitzky, S. (1989) Physiology of the thyroid. Iodine metabolism in the thyroid, thyroid hormone formation, and the biosynthesis and structure-function relationship of thyroglobulin, in *Endocrinology*, Vol. 1, 2nd edn, (eds L.J. De Groot *et al.*), WB Saunders Company, Philadelphia, pp. 512–22.
50 Green, W.L. (1987) Physiology of the thyroid and its hormones, in *The Thyroid*, (eds J.H. Ingbar and L.E. Braverman) Elsevier Science Publishing Company Inc., New York, pp. 1–46.
51 Malthiery, Y. and Lissitzky, S. (1987) Primary structure of human thyroglobulin deduced from the sequence of its 8468-base complementary DNA. *Eur. J. Biochem.*, **165**, 691–8.
52 Davies, E., Dumont, J.E. and Vassart, G. (1975) Improved technique for the isolation of intact thyroglobulin-producing polyribosomes. *Anal. Biochem.*, **80**, 289–97.
53 Godelaine, D., Spiro, M.J. and Spiro, R.G. (1981) Processing of the carbohydrate units of thyroglobulin. *J. Biol. Chem.*, **256**, 10161–8.
54 Robbins, J., Rall, J.E. and Gorden, P. (1980) The thyroid and iodine metabolism, in *Metabolic Control and Disease*, (eds P.K. Bondy and L.E. Rosenberg), W.B. Saunders, Philadelphia, pp. 1325–425.
55 Van Herle, A.J., Vassart, G. and Dumont, J.E. (1979) Control of thyroglobulin synthesis and secretion (first of two parts). *N. Engl. J. Med.*, **301**, 239–49.
56 Torresani, J. and Lissitzky, S. (1976) Further studies on abnormal thyroglobulin from congenital goiters likely related to defective thyroglobulin export, in *Advances in Thyroid Research*, (eds J. Robbins and L.E. Braverman), Excerpta Medica, Elsevier, New York, pp. 453–6.
57 Erickson, L.E. (1981) Exocytosis and endocytosis in the thyroid follicle cell. *Moll. Cell. Endocrinol.*, **22**, 1–24.
58 Herzog, V. (1984) Pathways of endocytosis in thyroid follicle cells, *Int. Rev. Cytol.*, **94**, 107–39.
59 Wolff, J. and Bhattacharyya, B. (1975) Microtubules and thyroid hormone mobilization. *Ann. NY. Acad. Sci.*, **253**, 763–70.
60 Dunn, A.D. and Dunn, J.T. (1982) Thyroglobulin degradation by thyroidal proteases: action of purified cathepsin. *Endocrinol.*, **111**, 280–9.
61 Dunn, A.D. and Dunn, J.T. (1982) Thyroglobulin degradation by thyroidal proteases: action of thiol endopeptidases *in vitro*. *Endocrinol.*, **111**, 290–8.
62 McGirr, E.M., Hutchison, J.H. and Clement, W.E. (1959) Sporadic goitrous cretinism. Dehalogenase deficiency in the thyroid gland of a goitrous cretin and in heterozygous carriers. *Lancet*, **2**, 823–6.
63 McGirr, E.M., Clement, W.E., Currie, A.R. *et al.* (1959) Impaired dehalogenase activity as a cause of goitre with malignant changes. *Scot. Med. J.*, **4**, 232–41.
64 Choufoer, J.C., Kassenaar, A.A.H. and Querido, A. (1960) The syndrome of congenital hypothyroidism with defective dehalogenation of iodotyrosines. Further observation and discussion of the pathophysiology. *J. Clin. Endocrinol. Metab.*, **20**, 983–1003.
65 Wolff, J. and Chaikoff, I.L. (1948) The inhibitory action of excessive iodide upon the synthesis of diiodotyrosine and thyroxine in the thyroid gland of normal rat. *Endocrinol.*, **43**, 174–9.
66 Robbins, J., Cheng, S-Y., Gershengorn, M.C.

et al. (1978) Thyroxine transport proteins of plasma: molecular properties and biosynthesis. *Rec. Prog. Horm. Res.*, **34**, 477–519.
67 Krenning, E.P., Docter, R., Visser, T.J. *et al.* (1983) Plasma membrane transport of thyroid hormone: its possible pathological significance. *J. Endocrinol. Invest.*, **6**, 59–66.
68 Mendel, C.M., Cavalieri, R.R. and Weisiger, R.A. (1988) Uptake of thyroxine by the perfused rat liver: implications for the free hormone hypothesis. *Am. J. Physiol.*, **255**, E110–19.
69 Hocman, G. (1981) Human thyroxine-binding globulin. *Rev. Physiol. Biochem. Pharmacol.*, **91**, 45–89.
70 Beierwaltes, W.H. and Robbins, J. (1959) Familial increase in the thyroxine-binding sites in serum alpha globulin. *J. Clin. Invest.*, **38**, 1683–8.
71 Hodgson, S.F. and Wahner, H.W. (1972) Hereditary increased thyroxine-binding-globulin capacity. *Mayo. Clin. Proc.*, **47**, 720–4.
72 Ingbar, S.H. (1961) Clinical and physiological observations in a patient with idiopathic decrease in the thyroxine-binding globulin of plasma. *J. Clin. Invest.*, **40**, 2053–63.
73 Nikolai, T.F. and Seal, U.S. (1967) X-chromosome linked inheritance of thyroxine-binding globulin deficiency. *J. Clin. Endocrinol. Metab.*, **27**, 1515–20.
74 Ingbar, S.H. (1958) Pre-albumin: a thyroxine binding protein of human plasma. *Endocrinol.*, **63**, 256–9.
75 Woebar, K.A. and Ingbar, S.H. (1968) The contribution of thyroxine-binding prealbumin to the binding of thyroxine in human serum, as assessed by immunoadsorption. *J. Clin. Invest.*, **47**, 1710–21.
76 Hoffenberg, R. and Ramsden, D.B. (1983) The transport of thyroid hormones. *Clin. Sci.*, **65** 337–42.
77 Robbins, J. and Edeloch, H. (1986) Hormone transport in blood: thyroid hormone transport proteins: their nature, biosynthesis, and metabolism, in *Werner's The Thyroid*, 5th edn, (eds S.H. Ingbar and L.E. Braverman), J.B. Lippincott Company. Philadelphia, pp. 116–27.
78 Ruiz, M., Rajatavanin, R., Young, R.A. *et al.* (1982) Familial dysalbuminemic hyperthyroxinemia: a syndrome that can be confused with thyrotoxicosis. *N. Engl. J. Med.*, **306**, 635–9.
79 Moses, A.C., Lawlor, J., Haddow, J. *et al.* (1982) Familial euthyroid hyperthyroxinemia resulting from increased thyroxine binding to thyroxine-binding prealbumin. *N. Engl. J. Med.*, **306**, 966–9.
80 Cavalieri, R.R. (1980) Peripheral metabolism of thyroid hormones, in *Thyroid Today*, **3** (7).
81 Sterling, K., Brenner, M.A. and Newman, E.S. (1970) Conversion of thyroxine to triiodothyronine in normal human subjects. *Science*, **169**, 1099–100.
82 Balsam, A. and Ingbar, S.H. (1979) Observations on the factors that control the generation of triiodothyronine from thyroxine in rat liver and the nature of the defect induced by fasting. *J. Clin. Invest.*, **63**, 1145–56.
83 Cavalieri, R.R. and Pitt-Rivers, R. (1981) The effect of drugs on the distribution and metabolism of thyroid hormones. *Pharmacol. Rev.*, **33**, 55–80.
84 Chopra, I.J., Solomon, D.H., Chopra, U. *et al.* (1978) Pathways of metabolism of thyroid hormones. *Rec. Prog. Horm. Res.*, **34**, 521–67.
85 Silva, J.E. and Larsen, P.R. (1984) The potential of brown adipose tissue (BAT)-type II T_4–5′-deiodinase (5′-D II) as a local and systemic source of T_3 in rats. *Annales D'endocrinol.*, **45**, 60, (abstract).
86 Engler, D. and Burger, A.G. (1984) The deiodination of the iodothyronines and of their derivatives in man *Endocrine Rev.*, **5**, 151–84.
87 Food and Nutrition Board (1974) *Iodine nutrition in the United States*, National Academy of Sciences, Washington D.C.
88 Ermans, A.M. (1986) Endemic goiter, in *Werner's The Thyroid*, 5th edn, (eds S.H. Ingbar and L.E. Braverman), J.B. Lippincott Company, Philadelphia, pp. 705–21.
89 Hall, R. and Lazarus, J.H. (1987) Changing iodine intake and the effect on thyroid disease. *Br. Med. J.*, **294**, 721–2.
90 Park, Y.K., Harland, B.F., Vanderveen, J.E. *et al.* (1981) Estimation of dietary iodine intake of Americans in recent years. *J. Am. Diet. Ass.*, **79**, 17–24.
91 Koutras, D.A., Matovinovic, J. and Vought, R. (1980) The ecology of iodine, in *Endemic Goiter and Endemic Cretinism*, (eds J.B. Stanbury and B.S. Hetzel) John Wiley and Sons Inc, New York, pp. 185–95.
92 Braverman, L.E. (1986) Iodine-induced thyroid disease, in *Werner's The Thyroid*, 5th edn, (eds S.H. Ingbar and L.E. Braverman) J.B. Lippincott Company, Philadelphia, pp. 735–46.
93 Vought, R.L., Brown, F.A. and Wolff, J.

(1972) Erythrosine: an adventitious source of iodine. *J. Clin. Endocrinol. Metab.*, **34**, 747–52.
94 Wayne, E.J., Koutras, D.A. and Alexander, W.D. (1964) Metabolism of inorganic iodine, in *Clinical Aspects of Iodine Metabolism* F.A. Davis Company, Philadelphia, pp. 3–37.
95 Lavin, T.N. (1989) Mechanism of action of thyroid hormone, in *Endocrinology*, Vol. 1, 2nd edn, (eds L.J. De Groot *et al.*) W.B. Saunders Company, Philadelphia, pp. 562–73).
96 Surks, M.I., Koerner, D., Dillman, W. *et al.* (1973) Limited capacity binding sites for L-triiodothyronine in rat liver nuclei. *J. Biol. Chem.*, **248**, 7066–72.
97 Samuels, H.H. and Tsai, J.S. (1974) Thyroid hormone action: demonstration of similar receptors in isolated nuclei of rat liver and cultured GH_1 cells. *J. Clin. Invest.*, **53**, 656–9.
98 Oppenheimer, J.H., Schwartz, H.L. and Surks, M.I. (1974) Tissue differences in the concentration of triiodothyronine nuclear binding sites in rat: liver, kidney, pituitary, heart, brain, spleen and testis. *Endocrinol.*, **95**, 897–903.
99 Gruol, D.J. and Kempner, E. (1982) The size of the thyroid hormone receptor in chromatin. *J. Biol. Chem.*, **257**, 708–13.
100 Weinberger, C., Thompson, C.C., Ong, E.S. *et al.* (1986) The c-erb-A gene encodes a thyroid hormone receptor. *Nature*, **324**, 641–6.
101 Sterling, K. (1979) Thyroid hormone action at the cell level. *N. Engl. J. Med.*, **300**, 117–23.
102 Copp, D.H., Cameron, E.C., Cheney, B.A. *et al.* (1962) Evidence for calcitonin: a new hormone from parathyroid that lowers blood calcium. *Endocrinol.*, **70**, 638–49.
103 Hirsch, P.F., Gauthier, G.F. and Munson, P.L. (1963) Thyroid hypocalcemic principle and recurrent laryngeal nerve injury as factors affecting the response to parathyroidectomy in man. *Endocrinol.*, **73**, 244–52.
104 Foster, G.V., Baghdiantz, A., Kumar, M.A. *et al.* (1964) Thyroid origin of calcitonin. *Nature*, **202**, 1303–5.
105 Macintyre, I., Alevizaki, M., Bevis, P.J.R. *et al.* (1987) Calcitonin and the peptides from calcitonin gene. *Clin. Orthopaedics Rel. Res.*, **217**, 45–55.
106 Chambers, T.J., Fuller, K., McSheeny, P.M.J. *et al.* (1985) The effect of calcium regulating hormones on bone resorption by isolated human osteoclastoma cells. *J. Pathol.*, **145**, 297–305.
107 De Deuxchaisnes, C.N., Devogelaer, J.P. Huaux, J.P. *et al.* (1987) New modes of administration of salmon calcitonin in Paget's disease. Nasal spray and suppository. *Clin. Orthopaedic Rel. Res.*, **217**, 56–71.
108 Struthers, A.D., Brown, M.J., Macdonald, D.W.R. *et al.* (1986) Human CGRP: the most potent endogenous vasodilator in man. *Clin. Sci.*, **70** 389–93.
109 McDermott, M.T. and Kidd, G.S. (1987) The role of calcitonin in the development and treatment of osteoporosis. *Endocrin. Rev.*, **8**, 377–90.

CHAPTER THREE

Tests of thyroid function

3.1 INTRODUCTION

Thyroid disorders are common. At least 5% of the adult population in Western countries have hypothyroidism, hyperthyroidism, goitre or a nodule in the thyroid. Most of those with a goitre or nodule are euthyroid, but laboratory confirmation of this is required. Laboratory documentation of abnormal thyroid function is very important, because treatment, whether for hyperthyroidism or hypothyroidism, is often lifelong and therefore should not be based on clinical opinion alone. Suspected thyroid disease is more common than true dysfunction. The tired, depressed, overweight, nervous, infertile, irritable, thin and comatose are all at risk of having their thyroid function tested. Therefore, whatever tests are used they should have high sensitivity (almost all patients with disease should be detected by the test in question), and high specificity (normal people should have normal results with the test). Figure 3.1 shows how sensitivity, specificity and predictive values are calculated. Many of the tests of thyroid function do not fufil these basic requirements.

$$\text{Sensitivity} = \frac{TP}{TP + FN}$$

$$\text{Specificity} = \frac{TN}{TN + FP}$$

Example: In a study of thyroid function in 100 hyperthyroid patients, 95 have a serum free T_4 value above normal and 5 have normal values. In 900 euthyroid controls, 45 have results that are high and 855 results are normal.

Sensitivity = 95% (95/{95+5})
Specificity = 95% (855/{855+45})

From the data it is possible to calculate:

The positive predictive value = TP/{TP+FP}
= 95/{95+45} = 70%

The negative predictive value = TN/{TN+FN}
= 855/{855+5} = 99%

TP = True positive TN = True negative

FP = False positive FN = False negative

Figure 3.1 Tests of thyroid function. Interpretation of test results.

The tests should also function reliably in as wide a range of pathological conditions as possible, and should not be influenced by ill-health unrelated to thyroid, or to alterations in the plasma proteins, or by medications. They should be cost-effective. To a large extent newer methods of measuring thyroid stimulating hormone (TSH) and some of the methods for measuring free T_4 (FT_4) achieve these goals, and since they are the ones which best allow both ends of the pituitary–thyroid axis to be evaluated, they will be discussed in most detail. Figure 3.2 is a diagram of the hypothalamic–pituitary–thyroid–tissue interactions and shows what tests can be conducted to study each level. In this chapter, the individual tests are described with supporting data on their strengths and weaknesses. There is a brief

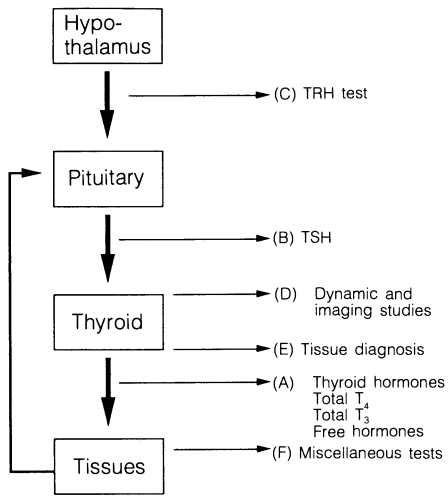


Figure 3.2 Diagrammatic representation of hypothalamic-pituitary-thyroid relations, showing what levels can be investigated by laboratory tests.

description of which tests should be ordered to diagnose or exclude various thyroid disorders. Algorithms to diagnose specific thyroid dysfunctions are introduced and described in greater detail in appropriate chapters.

3.2 TOTAL THYROID HORMONES

Total T_4 and total T_3 are designated T_4 and T_3 respectively. These are measured by specific radioimmunoassays. Normal values are listed in Table 3.1. T_4 in the serum is 99.96% protein bound and T_3 about 99.7%. Measurement of these hormones is dependent not only on the amount of hormone secreted and its rate of degradation and excretion, but also on the levels of binding proteins in the serum. The three major binding proteins, thyroid binding globulin (TBG), thyroid binding prealbumin (TBPA) and albumin are described in detail in Chapter 2. Most healthy euthyroid individuals have normal levels of T_4 and T_3 and normal binding proteins. Most patients with hyperthyroidism, irrespective of its cause, have high levels of these hormones, but normal or near normal levels of binding proteins. Less commonly, only T_3 is high (T_3 toxicosis) and this is more characteristic of hyperthyroidism due to a functioning autonomous nodule [1, 2] in patients with early Graves' hyperthyroidism [3, 4], or those relapsing after stopping antithyroid drugs [5]. High levels of T_3 are found in patients taking oral triidothyronine (cytomel), and very rarely it is due to metastatic thyroid cancer [6]. The corollary, high T_4 with normal or low T_3, is found in patients with hyperthyroidism and coexistent non-thyroidal illness [7–9]. From these data, it would appear that T_4 and T_3 would be sensitive and specific for diagnosing hyperthyroidism from euthyroidism. This is not so. The most important problem is that high T_4 and T_3 values are found in patients with increased levels of binding proteins. This is most often due to oestrogens (pregnancy or contraceptive pill) which induce increased production of TBG by the liver. Table 3.2 lists the causes of increased T_4, many of which are due to increased binding proteins. As was discussed in Chapter 2, the unbound or free hormone dictates thyroid status; protein-bound hormone is functionally inert. Therefore, it is essential to prove that a high T_4 is not simply due to increased binding proteins.

Low levels of T_4 and T_3 are found in severe hypothyroidism. In mild hypothyroidism, T_4 and T_3 values are of no diagnostic value because they are frequently in the low-normal range; this applies to T_3 in particular [10]. Just as high levels of T_4 and T_3 do not implicitly define hyperthyroidism, neither do low levels define hypothyroidism. Low or absent levels of binding proteins can be the cause. Table 3.3 lists the causes of low T_4 and low T_3.

To add further to the limitations of measuring T_4 and T_3, it is recognized that systemic illness can produce low results even when there is no thyroid disorder. No

Table 3.1 Thyroid function test results: standard, Système Internationale (SI) and conversion factors

Test	*Standard reference intervals*	*Units*	*SI reference intervals*	*Units*	*Conversion factor*
T_4	5–11	μg/dl	64–142	nmol/l	12.87
T_3	70–200	ng/dl	1.1–3.1	nmol/l	0.01536
rT_3	20–40	ng/dl	0.3–0.6	nmol/l	0.01536
FT_4	0.8–2.0	ng/dl	10–26	pmol/l	12.87
T_3RU	25–35	%	0.25–0.35		0.01
TSH RIA	<6	μU/ml	<6	mU/l	1
TSH IRMA	0.4–4.0	μU/ml	0.4–4.0	mU/l	1
24-hour uptake					
USA	10–30%				
UK	15–45%				
Thyroglobulin					
Athyreotic	<5	ng/ml	<5	μg/l	1
Normal	<20	ng/ml	<20	μg/l	1

Table 3.2 Tests of thyroid function: causes of high levels of thyroid hormones (total)

- Hyperthyroidism
- Increased binding proteins
  - pregnancy
  - oral contraceptives
  - newborn
  - acute hepatitis
  - porphyria
  - fluoruracil
  - marijuana
  - hereditary increase
  - abnormal binding protein
- Acute psychiatric illness
- Acute medical illness (rare)
- Pituitary resistance to thyroid hormone
- Antibodies to thyroid hormones

Table 3.3 Tests of thyroid function: causes of low levels of thyroid hormones (total)

- Hypothyroidism
- Decreased binding proteins
  - androgens
  - glucocorticosteroids
  - nephrotic syndrome
  - cirrhosis
  - L–asparaginase
  - hereditary
- Non-thyroidal illness
  - low T_3 syndrome
  - low T_3 and low T_4 (sick euthyroid)

single unifying theory explains all of the abnormalities in thyroid tests found in the sick. The topic is discussed separately in Chapter 12 and only important generalizations are presented here. In most euthyroid sick patients, T_3 levels are low [11–13]. This is termed the **low T_3 syndrome**. In a significant proportion of patients with more severe or protracted illness, T_4 and calculated FT_4I (this is discussed below) are low [14, 15]. We found that approximately 50% of sick patients who had a low T_3 also had a low T_4 and low FT_4I [16]. This is called the **euthyroid sick syndrome**. To further confuse matters, a small proportion of sick patients have high T_4 values, in particular those with acute liver disease and acute psychotic illnesses [17–19].

Because reverse T_3 levels are high in sick patients, some investigators have recom-

mended measurement of this to help in diagnosis [12, 14]. The fact that the patient is sick is apparent from clinical examination, and I have rarely found this test to be useful.

In summary, high values of T_4 and T_3 are characteristic of hyperthyroidism, but are found in euthyroid patients with excessive or abnormal binding proteins. Low T_4 and T_3 are characteristic of severe hypothyroidism, but are also found in euthyroid patients with low levels of binding proteins, or with systemic illness. Hyperthyroid patients with coexisting systemic illness can have normal T_4 and T_3. Patients with mild hypothyroidism can also have normal results. As a result, the sensitivity of these tests is moderate and their specificity poor. It is necessary to have information of the binding proteins to interpret T_4 and T_3 values.

3.2.1 TESTS OF THYROID BINDING PROTEINS

Most of the 'falsely' abnormal total hormone results are due to abnormalities of the binding proteins, and with knowledge of the thyroid binding capacity of the plasma it is possible to correct for these. There are specific radioimmunoassays for TBG and TBPA. Because TBG is the most important binding protein carrying 70–80% of the hormones, it is usually measured alone [20]. Thyroid binding capacity (this is shortened to TBC and is largely due to TBG, and readers should look at reports carefully since these abbreviations TBC and TBG are sometimes used interchangeably, although they are somewhat different) can be measured indirectly by quantitating the capacity of binding sites in serum which are not carrying hormone. This is done using the T_3 **resin uptake test** (T_3RU). T_3RU does NOT meausre T_3. In this test, serum from the patient, plus a resin which binds T_3 and a tracer of radioactive ^{125}I–T_3, are incubated together under conditions defined for each commercial kit. The ^{125}I–T_3 equilibrates between the resin and unoccupied sites on the binding proteins in the serum. The resin is removed and radioactivity counted. The proportion of added radioactivity which is present in the resin is the T_3RU, and usually it is in the range 25–35%. If there are a lot of unoccupied binding sites on the proteins, the tracer will bind there and the T_3RU is low and vice versa. Figures 3.3 and 3.4 show the basis for the test and the findings in euthyroid, hyperthyroid and hypothyroid patients who have normal binding proteins. Figure 3.5 shows the results when the levels of binding proteins are increased or

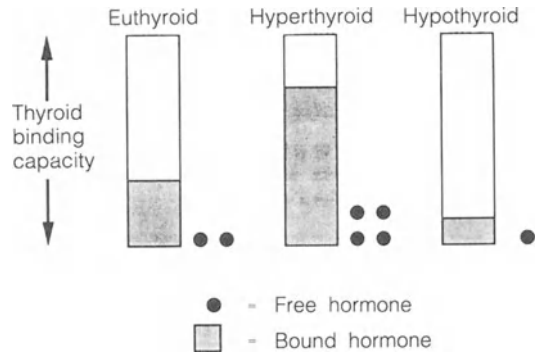


Figure 3.3 Relation of bound hormone to free hormone and binding capacity.

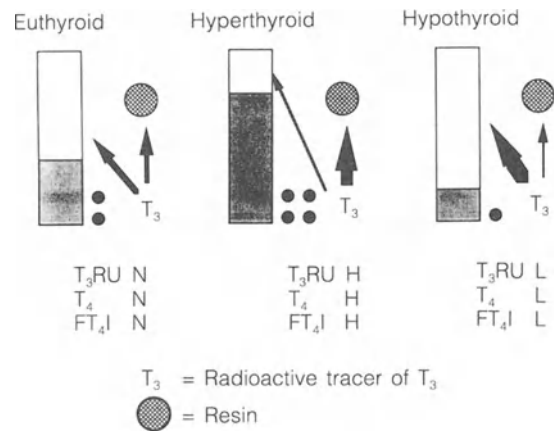


Figure 3.4 T_3 resin uptake test.

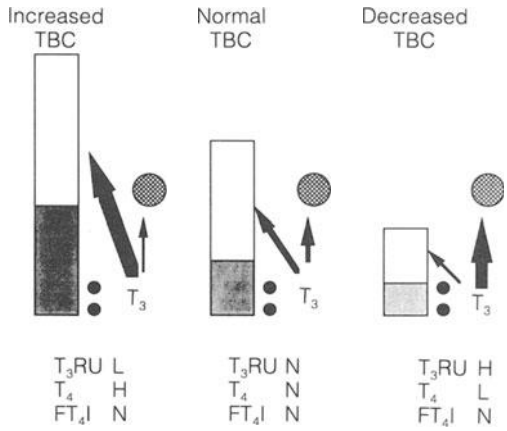


Figure 3.5 T_3 resin uptake test: effect of changes in thyroid binding capacity.

decreased. Knowledge of T_4, (T_3) and T_3RU values makes it possible to determine if the problem is due to thyroid disease, or to a binding protein abnormality. If both tests are abnormal in the same direction, the thyroid is at fault, e.g. if T_4 and T_3RU are both high, hyperthyroidism is diagnosed; in hypothyroidism both tests are low. In contrast, if one test is high and the other low, the defect is due to the carrier proteins.

3.2.2 FREE THYROID HORMONE INDICES (BY CALCULATION)

Many clinical laboratories provide a measure of free thyroxine which is obtained from the formula $\{ T_4 \times T_3RU \}/100$. The mathematical derivation for this is provided in Figure 3.6. This is called the **free thyroxine index** (FT_4I), which has also been given the term T_7 since it is derived from T_4 and T_3RU. This test has gained widespread acceptance in practice because the two tests used for its derivation are simple to perform and are robust. In addition, it gives clinically valuable results in healthy outpatients [21]. Unfortunately, the test gives low results in sick euthyroid patients [14, 16]. Table 3.4 shows

$$FT_4 \propto \frac{\text{total } T_4}{TBC} = \text{total } T_4 \times \frac{1}{TBC}$$

$$T_3RU \propto \frac{1}{TBC}$$

$$FT_4 \propto \text{total } T_4 \times T_3RU$$

$$FT_4I = [\text{total } T_4 \times T_3RU]/100$$

Figure 3.6 Theoretical derivation of free thyroxine index (FT_4I).

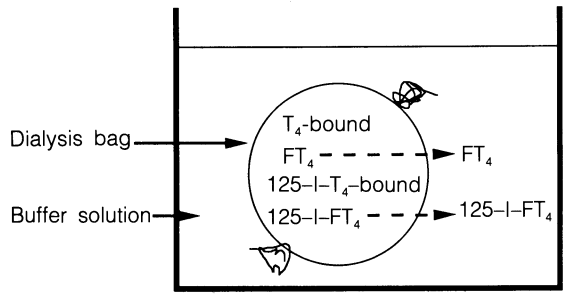
Table 3.4 Thyroid function tests in various clinical situations

Clinical status	*T_4*	*T_3RU*	*FT_4I*	*FT_4*	*T_3*
Euthyroid	N	N	N	N	N
Hyperthyroid	H	H	H	H	H
Hypothyroid	L	L	L	L	L
Euthyroid High TBC	H	L	N	N	H
Euthyroid Low TBC	L	H	N	N	L
Euthyroid Sick	L	N	L	N	L

the expected results of T_4, T_3, T_3RU and FT_4I in a variety of thyroidal and non-thyroidal conditions. FT_3I can be calculated using the formula $\{ T_3 \times T_3RU \}/100$, however, this has less practical value.

3.2.3 FREE THYROID HORMONE MEASUREMENTS

FT_4 can be measured by two methods: equilibrium dialysis, or radioimmunoassay [22, 23]. It is generally accepted that the dialysis method is the 'gold standard', however, it is restricted to research laboratories because the method is time consuming, requires meticulous attention to detail, and only a small number of samples can be processed simultaneously. The basis of the test is shown diagrammatically in Figure 3.7.



$$\frac{FT_4}{\text{Total } T_4} = \frac{125\text{-I-}FT_4}{125\text{-I-total } T_4}$$

and total T_4 = bound T_4 + FT_4

Figure 3.7 Diagrammatic representation of the measurement of free thyroxine (FT_4) by dialysis. A tracer amount of ^{125}I–T_4 is added to the serum, and the mixture is placed in the dialysis bag. The radioactive hormone distributes like the natural hormone. The free hormone can leak out of the bag. The radioactivity that leaks out is counted and the percentage free hormone is calculated by dividing this by the amount placed in the bag. The free T_4 is calculated by multiplying the total T_4 by this percentage.

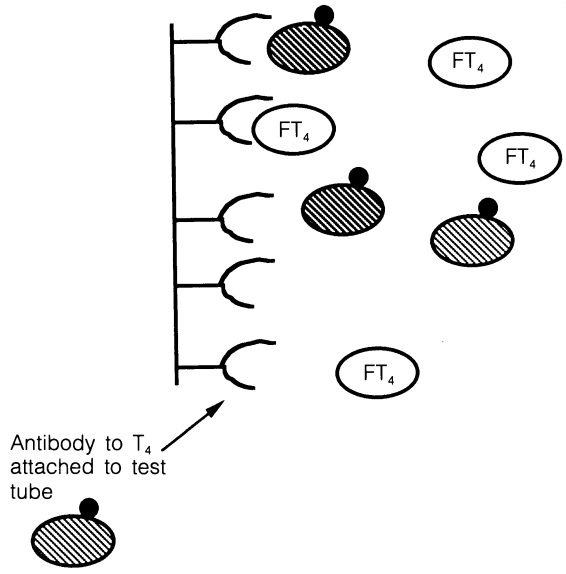


Figure 3.8 Diagram of the basis for a one-step free thyoxine (FT_4) assay. Represents radioactive analogue of thyroxine which competes with FT_4 for antibody binding sites. The higher the FT_4 the lower the amount of analogue binding to antibody. The test depends on the analogue not binding to plasma proteins. However in practice protein (albumin) binding does occur.

FT_4 measurements by RIA have been both valuable and perplexing. Not all commercial FT_4 kits actually assay FT_4. As a result, the same specimen assayed by different kits appears to have disparate amounts of FT_4 [24 – 27]. Those kits which include a derivative of T_4 to be used in the method (so called one-step methods) measure albumin-bound T_4, not FT_4 [28]. The two-step techniques provide reproducible, clinically valuable results in patients with thyroid dysfunction, in healthy euthyroid controls and also in euthyroid patients with severe systemic illness [16, 29]. The two-step assays are sensitive and specific. The results closely match those obtained by equilibrium dialysis [30]. The theoretical basis for these tests are shown in Figures 3.8 and 3.9. The one-step assays are simple but give falsely low results in sick patients, and they are not recommended. Accuracy should not be sacrificed for simplicity [31].

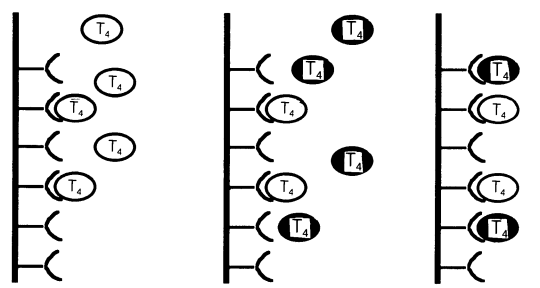


Figure 3.9 Diagram showing the basis for a two-step free thyroxine (FT_4) assay.

The two-step assays will be referred to as FT_4 measurements. FT_4 measurements

provide an excellent index of thyroid status in almost any clinical situation, but there are several limitations, which fortunately are not common in clinical practice. It has been known for two decades that FT_4 by equilibrium dialysis gives high results in patients who are heparinized [32, 33]. This has also been demonstrated when measurements are made with the two-step assay [34]. Unpublished research has shown that heparin cleaves serum triglycerides into free fatty acids (FFA) and glycerol. The FFA binds to albumin and displaces T_4. Therefore FT_4 rises. Our studies have shown that the heparin only has this effect when given parenterally to the patient, it does not produce a rise in FT_4 when added to serum *in vitro*. Also the rise in FT_4 occurs in the test tube after heparinized blood is withdrawn from the patient. The FT_4 *in vivo* is normal and the patient euthyroid. If thyroid function is required in a patient who needs heparin, draw the serum sample first, or wait several days until after heparin is stopped.

We have also found FT_4 values to be high in some patients with acute psychiatric illness [19]. The mechanism has not been defined and this topic is discussed in more detail in Chapter 12. FT_4 values are usually normal in sick patients but in *very sick* euthyroid patients the values can be low. This is a bad prognostic finding. A comprehensive discussion of changes in thyroid function in sickness is presented in Chapter 12. Clinicians should be cautious when they interpret thyroid function tests in critically ill patients but, fortunately, testing is not often required in this setting.

In summary, FT_4 is the active fraction of the main circulating hormone. Knowledge of this value is a very important indicator of the thyroid status of any patient. The two-step methods give an accurate, precise result which can be trusted in differentiating hyperthyroidism and hypothyroidism from normal. The test is not influenced by abnormalities in the thyroid binding proteins, by medications (except heparin), or by non-thyroidal illnesses. I find it indispensable in work-up of patients.

3.3 PITUITARY–THYROID AXIS: TSH (NEW AND OLD TECHNOLOGIES)

The anterior pituitary is the organ most sensitive to changes in thyroid hormone levels. TSH radioimmunoassays became available in 1965 [34, 35]. Ridgway [36] has recently written about the development of these assays and the sequence of advances to the new, highly sensitive methods which are described below. With the old technology, most laboratories report an upper limit of 5–6 μU/ml (mU/l). In primary hypothyroidism, TSH is high and this is the most sensitive single test to diagnose mild hypothyroidism. Because of the sensitivity of the pituitary to minor fluctuations in thyroid hormones, it is possible to have a TSH result which is above the normal range in association with normal T_4 and T_3 (FT_4 can be normal but is usually at the low end of the range). This is called **subclinical hypothyroidism**. In the past, it was understood theoretically that TSH should be low in patients with hyperthyroidism, since high levels of T_4 and T_3 suppress the pituitary. But older assays could only differentiate TSH levels of 1, or 2 μU/ml, and since many euthyroid individuals have TSH levels of 0.5–2.0 μU/ml the assay could not separate suppressed from normal values (Figure 3.10). There have been remarkable advances in technology, and sensitive TSH assays have been developed using two antibodies against different epitopes of TSH and the assay technique is a non-competitive sandwich. If a radionuclide is used, the assay is termed an **immunoradiometric assay** (IRMA), but **amplified enzyme-linked immunoassays** (AEIA) give the same precision. Figure 3.11 shows the difference between convential TSH RIA and IRMA. Using one of

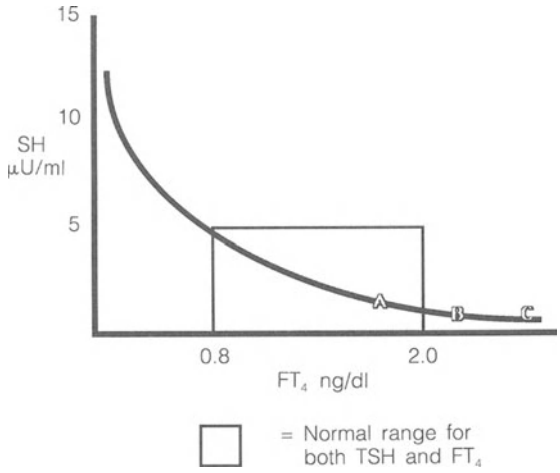


Figure 3.10 Diagram showing the relationship of free thyroxine (FT_4) with TSH measured by radioimmunoassay. A, B and C have different FT_4 values but TSH RIA results are not different. A is euthyroid; B is mildly hyperthyroid; C is moderately hyperthyroid.

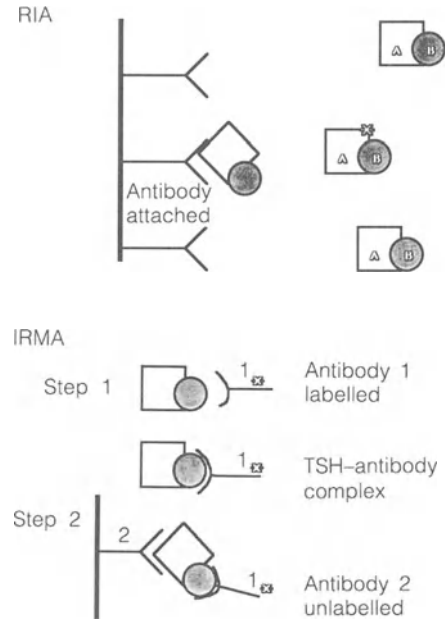


Figure 3.11 Diagram showing the basis for the measurement of TSH by immunoradiometric assay (IRMA). Antibody competes for unlabelled and labelled antigen. A and B are chains of TSH and * is labelled antigen. Sandwich of antigen between labelled antibody 1 and unlabelled antibody 2 makes the assay extremely sensitive.

the earlier TSH IRMA kits with some minor modifications which could detect <0.3 μU/ml, we reported a sensitivity of 97% for hyperthyroidism; only 1 out of 30 hyperthyroid patients had a measureable TSH [37]. The specificity was 100% in 62 controls. More recent assays can detect <0.05 μU/ml or lower, and several investigators have reported even better statistics. Toft [38] found all hyperthyroid patients had suppressed TSH, and all normal controls had normal results, therefore the test had perfect sensitivity and specificity. This contrasted with results of conventional assay in the same samples where sensitivity and specificity were both 93%. Hershman *et al.* [39] evaluated five new TSH kits and all gave undetectable levels in 51 hyperthyroid patients. Klee and Hay [40] recommend that any new-technology TSH assay must have sensitivity and specificity above 95%, and this appears to be met by most. TSH is an extremely valuable diagnostic aid: hypothyroid patients have high levels and hyperthyroid patients low levels. Because there appears to be clear separation form normal, some have recommended this as the first test of thyroid function [41]. Figure 3.12 shows diagrammatically how this is possible and should be contrasted with Figure 3.10. When the result is normal the patient is euthyroid. When TSH is low, the patient is hyperthyroid provided pituitary insufficiency is excluded. When TSH is high, the patient is hypothyroid provided a pituitary tumour secreting TSH is excluded. The evidence supports that TSH measurement can replace the TRH test for mild hyperthyroidism. Blunt *el al.* [42] recommend that TRH test be retained in work-up of hypopituitary patients to differentiate hypothalamic from hypopituitary

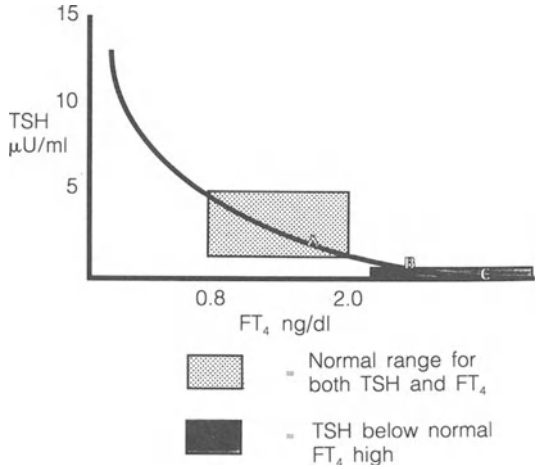


Figure 3.12 Graph of the relationship of free thyroxine (FT_4) with TSH as measured by IRMA. A, B and C have different FT_4 values and TSH IRMA results are different.

hypothyroidism. Unfortunately, there are borderline situations where thyroid hormone levels are normal but TSH is undetectable. This is subclinical hyperthyroidism, analogous to subclinical hypothyroidism. Utiger [43] is concerned that patients who fall into this category will receive unnecessary treatment for hyperthyroidism. We and others have shown that critically sick patients occasionally have low TSH values which do not signify hyperthyroidism [44, 45] and this is discussed in Chapter 12.

3.4 HYPOTHALAMIC-PITUITARY AXIS: (TRH TEST)

Thyrotrophin releasing hormone (TRH) was isolated, characterized and synthesized in 1968 [46, 47] and soon after became available for clinical use [48, 49]. The test involves injecting TRH intravenously and evaluating the response of the pituitary to secrete TSH. The patient should be fasted, relaxed and recumbent. An intravenous line is in place and a blood sample drawn immediately before the TRH is injected. Most patients

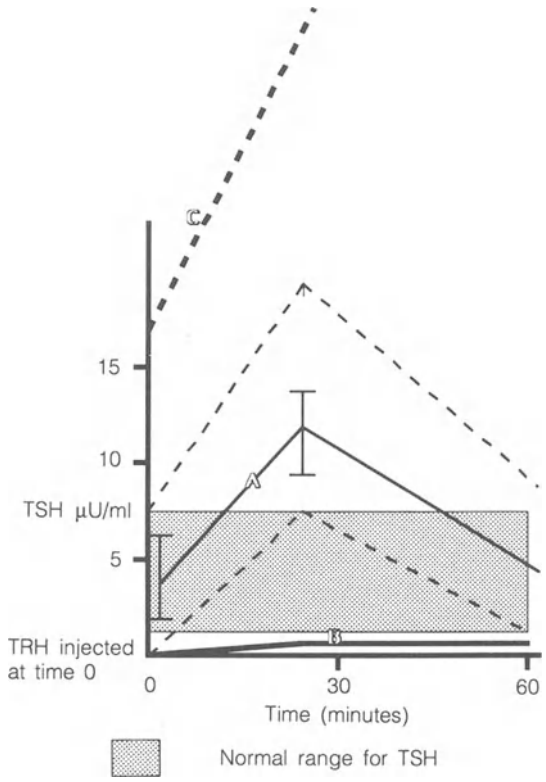


Figure 3.13 TRH test showing normal response, and results in primary hypothyroidism and hyperthyroidism. A is the normal response in euthyroid patients; B is the response in hyperthyroid patients (blunted); C is the response in hypothyroidism.

notice a strange taste and have a feeling in the perineum not unlike the urge to micturate. Venous blood samples are drawn at 20 and 60 minutes (some investigators include a 40 minute sample as well). TSH measurements are obtained on the samples and the results plotted against time. A normal response is a rise in TSH which is maximal at 20–30 minutes with return to normal by 60–90 minutes. Figure 3.13 shows the normal range of results and the response in hypo- and hyperthyroidism. In hyperthyroidism, the pituitary is suppressed by thyroid hormone and there is no rise in TSH after injection of TRH.

Table 3.5 Radionuclides for thyroid uptake and scintigraphy

				Approximate radiation dose	
Radionuclide	*T1/2*	*Energy*	*Dose μCi*	*thyroid*	*whole body*
Iodine 123	13.3H	159 Kev	100–200	1–3R	3–6mR
Iodine 131	8.05D	365 Kev	5–10 uptake	5–10R	3–6mR
			50–100 scan	50–100R	30–60mR
Technetium 99m	6.0H	140 Kev	1000–2000	0.4–2.0R	10–50mR

The test was of great value in understanding the physiology and pathophysiology of the hypothalamic–pituitary–thyroid interactions, and it was valuable clinically in the diagnosis of borderline hyperthyroidism [50]. Because of the development of sensitive TSH measurements which show suppressed levels in hyperthyroidism, the TRH test is superfluous in this role. Patients with primary hypothyroidism have an elevated TSH by definition; therefore, the TRH test is also superfluous in this situation. When it was done, a very exuberant rise in TSH was found and its return to normal was delayed. Sometimes this test is used in research to study patients with subclinical thyroid dysfunction.

The TRH test can give false positive results in elderly men, with flat responses being recorded in patients who have no clinical, or laboratory evidence of hyperthyroidism [51]. There are reports of the injection causing hypertension and complications have been reported [52]. However, these are uncommon.

TRH testing is being recommended to help differentiate subtypes of affective disorders [53]. At times, the test is even difficult to interpret in relation to thyroid disorders, and it is my perception that its use in diagnosing psychiatric illness should not be accepted until controlled blinded trials show it is of value. This is discussed in more detail in Chapter 12.

In summary, the TRH test in diagnosis of thyroid dysfunction has been replaced by sensitive TSH assay and will seldom be used in practice. TRH testing still has a role in work-up of hypothalamic-pituitary lesions [42].

3.5 DYNAMIC AND IMAGING STUDIES OF THE THYROID

3.5.1 RADIOIODINE UPTAKE (RAIU)

In this test, a known amount of radioactive iodine is given to the patient and the percentage taken into the thyroid measured by an external counting device. The radionuclide of choice is ^{123}I, although historically ^{125}I, ^{130}I, ^{131}I and ^{132}I have been used. ^{125}I and ^{131}I give a significant radiation dose to the gland, and are not recommended for routine use. Table 3.5 lists the important physical characteristics of these radionuclides and the doses used for uptake and scintigraphy which is discussed in the next section. The radionuclide is usually given by mouth, ^{123}I is supplied in capsule form, but all the radionuclides can be given as liquids. The measurement is made at a known time after ingestion. The 24 hour uptake is most useful, but this can be coupled with an early measurement between 3–6 hours. When early measurements are used, the patient should be fasted, but this is not important for the 24 hour study. Uptake is often done in coordination with scintigraphy. However, the clinician may need one rather than the other, so time and money can be saved by thoughtful ordering. For uptake measurement, the external

Iodine-123 sample counted using same probe that is used for patient.
Sample should be in same position in neck phantom.
Measure room background.

Give iodine-123 sample to patient

Patient measurements made at predetermined times.*
Measure counts over thyroid.
Measure counts over thigh as patient background.+

$$\text{Thyroid uptake} = \frac{(\text{thyroid} - \text{patient background counts}) \times 100}{(\text{sample} - \text{room background counts}) \times \text{decay factor}}$$

* In general uptake measurements are made at 6 and/or 24 hours.
For iodine-123 decay factor for 6 hour uptake = 0.73 and decay factor for 24 hour uptake = 0.284.

+ Some measure background over the neck with a lead block over the thyroid.

Figure 3.14 The steps involved in measuring radioiodine uptake of the thyroid.

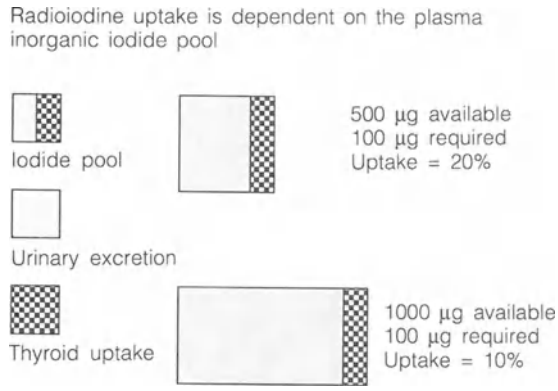


Figure 3.15 Diagram showing the effect of an iodine pool on radioiodine uptake measurement.

detecting device is usually a simple probe dedicated to this purpose. It has one sodium iodide crystal and one photomultiplier tube. A radioactive incident in the crystal causes a tiny flash of light, which causes an electrical pulse which is in turn multiplied up to 10^6 and is detected as an electrical pulse. The number of pulses are proportional to the number of radioactive emissions which, in turn, are proportional to the amount of radioactivity.

The test was very important in our understanding of normal physiology and pathophysiology, and interested readers can read references 54–57 which are of historic interest. Figure 3.14 shows the calculations used to make the measurement. It requires attention to detail. The capsule is counted prior to administering it to the patient. Counts are made over the thyroid at a specific time, and are corrected for background by subtracting thigh counts. Correction is necessary for temporal decay of the radionuclide, over the time between its administration and the uptake measurement.

The uptake measurement depends on the function of the thyroid and the size of the iodine pool or, more precisely, the plasma inorganic iodine. Figure 3.15 shows how the uptake can vary significantly in normal people because of differences in the amount of inorganic iodine in the serum.

Originally, the test was important in differentiating normal people from hyperthyroid and hypothyroid patients. There is significant overlap between these groups, and so the test is not recommended for this purpose. In the USA there has been a progressive fall in uptake measurements in normal people. Pittman *et al.* [58] noted a decrease from 28.5 ± 6.5% in 1959 to 15.4 ± 6.8% in 1967–8. Bernard *et al.* [59] in California found the 24 hour uptake was almost identical to that described by Pittman *et al.*: the average in 116 euthyroid patients was 15.6% ± 4.5%. Even lower values were recorded by Caplan and Kujak [60] (12.1 ± 6.1%), and their lower limit was 0; therefore hypothyroid patients could not be separated from normals. The same group of investigators, in a subsequent study, found that 14% of patients with Graves' disease and 80% with toxic nodular goitre had normal uptake measurements. Therefore, the uptake test has poor sensitivity and specificity.

The two main indications for this test are, firstly, to differentiate those patients with

Table 3.6 Tests of thyroid function: causes of increased radioiodine uptake

Hyperthyroidism: Graves' disease
toxic adenoma
toxic multinodular goitre
Iodine deficiency
Recovery from thyroiditis: silent
subacute
Neonate
Dyshormonogenesis except trapping defect
Hashimoto's thyroiditis (some cases)
After stopping antithyroid drugs
Technical error

Table 3.7 Tests of thyroid function: causes of decreased radioiodine uptake

Iodine load: dietary
radiographic contrast agents
medicinal with inorganic iodine
amiodarone
Thyroxine or other thyroid medications: factitious
Thyroiditis: acute phase
silent
subacute
Hypothyroidism
Ectopic thyroid
Capsule not ingested or digested
After surgery or radioiodine
Lower results in elderly
After severe exercise
Technical error

hyperthyroidism and high uptake, from, those with low uptake. Secondly, the test is a prerequisite to treating a patient with radioiodine. High radioiodine uptake can be due to many causes apart from Graves' disease (Table 3.6). There are many conditions associated with low uptake of radioiodine (Table 3.7) and the patient can be clinically hyperthyroid, euthyroid, or hypothyroid; therefore the uptake cannot be used to determine thyroid status. Thyroid status has to be defined clinically and by measurement of thyroid hormone, preferably FT_4 and TSH levels.

Prior to making an uptake measurement, it is important to ensure the patient is not taking any thyroid or antithyroid preparation, and that there has been no recent radiographic contrast injections, or intake of iodine-containing medications. Thyroxine has to be stopped for 4 weeks and triiodothyronine for 2 weeks before doing this test. Water-soluble contrast studies require a delay of 4 weeks and lipid-soluble agents, e.g. for lymphangiography of up to a year before an accurate measurement can be obtained. Clearly, it is important to ensure a patient who is to be treated with radioiodine does not have an injection of radiographic contrast before the treatment since radioiodine therapy has to be delayed for the same length of time. However, in the situation where it is important to reduce thyroidal uptake of iodine, e.g. an atomic accident with release of large amounts of ^{131}I, this can be achieved with inorganic iodine. Ten milligrams iodine reduces uptake to less than 1.5%, 130 mg potassium iodide (100 mg iodide) reduces thyroidal uptake to less than 1%.

Because the uptake is so dependent on plasma inorganic iodine, PII, some workers have used the **absolute iodine uptake** (AIU).

$$\text{AIU} = \text{PII} \times \text{thyroid clearance rate}$$

Normally, this ranges from 1–6 μg/hour. Very few laboratories offer this test although theoretically it is superior to the RAIU.

Because ^{99m}Tc is trapped by the follicular cells and is readily available in sterile form for intravenous injection, it has been used for thyroid uptake measurement. The uptake is usually calculated by counting over the thyroid and thigh 20–130 minutes after injection of 1–2 mCi (37–74 MBq) ^{99m}Tc as pertechnetate, and expressing the result as the percentage of the administered dose. The normal range is 0.2–3.0%. There is no good separation of hypothyroid patients from euthyroid controls. Hyperthyroid patients with Graves' disease usually have high results, but since the radioiodine uptake is used to determine how much therapy

to prescribe, technetium uptake is of limited use. In the situation where it is essential to establish the diagnosis of hyperthyroidism with great urgency, technetium uptake or scintiscan can confirm this in minutes. The clinical problem could be severe toxicity, fever, tachycardia, confusion and obtundation in a patient with a goitre. There is concern that the patient has thyroid storm and blood test results cannot be obtained for several hours. I should stress that appropriate treatment for thyroid storm should be started promptly, but technetium uptake greater than 4.0% would confirm the need for this. Uptake of technetium is also lowered by a high iodine pool, and the measurement should be made prior to treatment with inorganic iodine or infusion of radiographic contrast (refer to section on thyroid storm in Chapter 5).

In summary, the RAIU is valuable to differentiate hyperthyroidism with high uptake from low uptake. This differentiation is important because treatment is quite different. As a corollary, the uptake is necessary prior to treatment with radioiodine because it will determine that the gland is capable of trapping iodine and the uptake result is usually incorporated into a formula which determines what dose is prescribed.

(a) TSH stimulation test

The basis of this test is to determine if the thyroid can trap more iodine after stimulation with parenteral TSH [63]. In primary hypothyroidism, the gland is incapable of responding, but in central hypothyroidism an increase is found when the measurement after TSH is compared with the baseline measurement. The test involves a standard 24 hour RAIU, then the patient is given three daily doses of 10 IU of TSH intramuscularly. RAIU is repeated after the third injection. If the second measurement is double the first, or if it is increased by 15%, the patient has central, not primary hypothyroidism. This test was important but is of historic interest only because the differentiation is possible with measurement of FT_4, TSH and TRH test. It is not without risk because patients can have reactions to the TSH [64].

This test has also been used to demonstrate suppressed thyroid in patients with autonomous nodules. The diagnosis can be made simply by shielding the hot nodule with a strip of lead and scanning for a few more minutes [65]. Alternatively, ultrasound or ^{201}Tl scintigraphy can show the presence of the suppressed lobe.

(b) T_3 suppression test

This test is also of historic interest; it will be used very infrequently in practice. The test differentiated autonomous non-suppressible thyroid function from normal [66]. It was used to diagnose mild hyperthyroidism, whether due to Graves' disease or autonomous nodule, from normal thyroid function. The rationale is, if the thyroid is autonomous, the uptake will not be decreased by giving the patient thyroid hormone, in particular, T_3. In contrast, in normal people, T_3 will inhibit pituitary TSH secretion, and subsequent thyroid uptake of radioactivity is decreased. Traditionally, T_3 was used because of its rapid effects, and 75–100 μg was prescribed daily (25 μg 3 or 4 times) for 7–10 days. Some investigators used T_4 [67] or thyroid extract [68], but T_3 is recommended provided there is a specific reason to do the test. Twenty-four hour uptake of radioiodine is obtained first, then T_3 is prescribed in the dose range described and a repeat 24 hour uptake obtained on the last day of the T_3 treatment. Currently, ^{123}I would be used for the measurements. In the past, ^{131}I was used and it was important to make counts over the thyroid prior to administering the second uptake dose because of the long half-life of that radionuclide.

The T_3 suppression test is not without risk, because the additional thyroid hormone can add to that secreted by an autonomous

gland and make the patient more hyperthyroid, and even cause complications such as arrhythmias. This is important when the test does not contribute much clinically. The reason for its low clinical utility is that *in vitro* tests define the thyroid status precisely, and borderline hyperthyroidism is determined by a suppressed TSH and high, or high-normal, FT_4 and T_3. The test was important in defining pathophysiology by actually showing non-suppressibility of thyroid, and before accurate *in vitro* tests were available it was used diagnostically. One situation where it is still used is to show whether the thyroid in a patient with Graves' disease treated with antithyroid medications has lost its autonomous function [69]. This would imply that the gland has returned to normal and spontaneous remission occurred. Unfortunately, the test is not sufficiently predictive to recommend its use in practice.

(c) Perchlorate discharge test

Iodine which is trapped by the follicular cell is rapidly bound to tyrosyl molecules in thyroglobulin in the normal thyroid. There is almost no free iodine in the follicular cells. The organification step is inhibited in several clinical situations, and these lead to an accumulation of unbound iodine in the cell. These conditions include Hashimoto's thyroiditis [70] and the rare inborn error of the peroxidase enzyme necessary for the organification of iodine biochemically [71]. Antithyroid drugs, such as propylthiouracil and methimazole, act by inhibiting this enzyme leaving free iodine in the cell [72, 73], as does iodine in pharmacological doses [74]. The perchlorate ion competes with iodine for the trapping mechanism, and if a pharmacological dose of perchlorate is prescribed no further iodine is trapped. No iodine is added to that already inside the cell. Because the iodine in the cell is free, it leaks out into the circulation due to there being a higher concentration inside compared with outside the cell. It is more correct to call the test perchlorate leak, or perchlorate wash-out, because the iodine is not actively discharged. The conventional wash-out test involves giving a tracer dose of ^{123}I (100–200 μCi to an adult) and making thyroid and thigh measurements at timed intervals for 2–3 hours. An oral dose of 400 mg of potassium perchlorate is prescribed and thyroid and thigh counts continued for 2–3 hours. Slight variations in the procedure have been described, but the theory is the same (75–77). Figure 3.16 shows diagrammatically a normal (negative) and abnormal (positive) response. A positive result is usually easy to determine, and Trotter [78] requires a drop of 15% before he accepts it to be abnormal. Gray *et al.* [79]

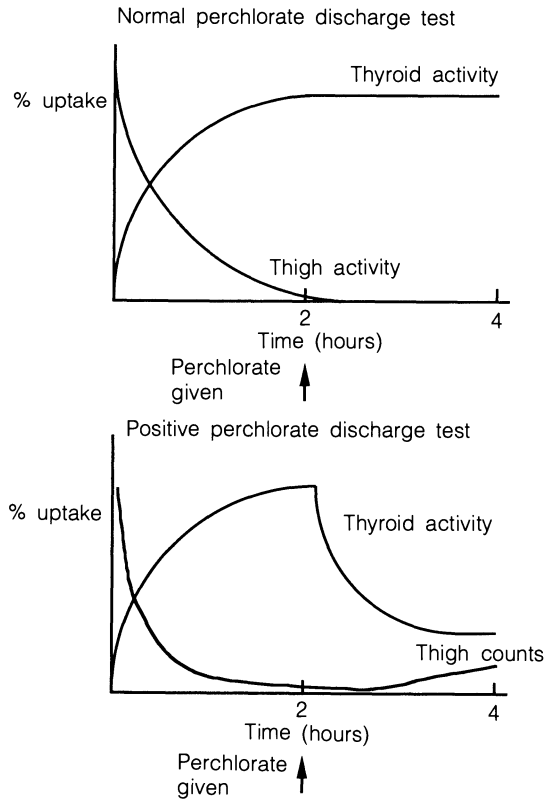


Figure 3.16 Diagram of perchlorate 'washout'. The top graph shows a normal response, the lower shows an abnormal or positive discharge.

developed a short perchlorate discharge test using sterile ^{131}I given intravenously with continuous monitoring over the thyroid for 10 minutes, at which time 200 mg sterile potassium perchlorate is injected intravenously with counting over the thyroid continued for a further 10 minutes. A positive discharge by this technique is greater than 0.5% of the administered dose.

The only reason for doing this test is to diagnose they very uncommon inborn defect in organification. The other conditions causing a positive result are easily diagnosed by history, examination and *in vitro* tests.

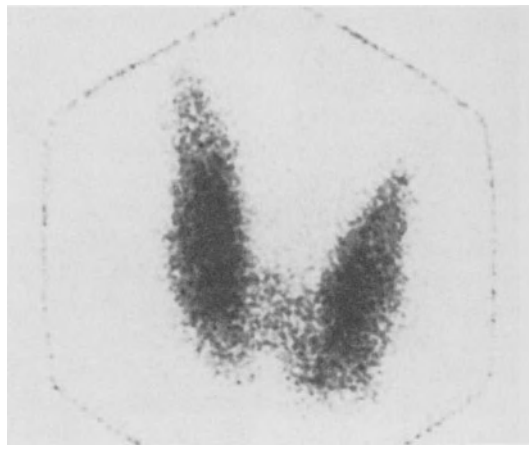


Figure 3.17 A normal thyroid scintigram made 3 hours after an oral dose of 200 μCi ^{123}I. The lobes are fairly symmetrical and the isthmus is not seen well.

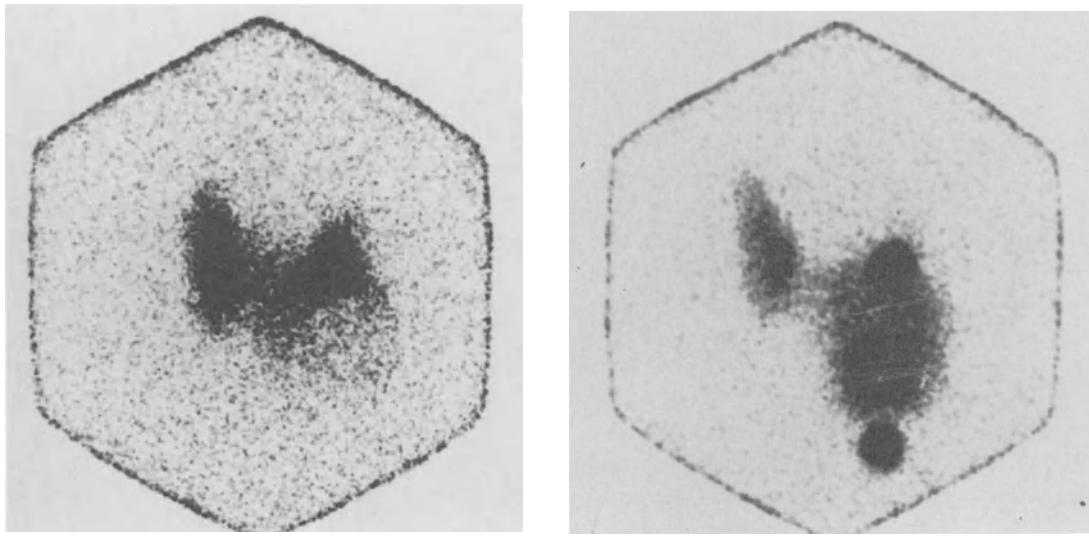
3.5.1 THYROID SCINTIGRAPHY

(a) Routine scintigraphy

Thyroid scintigraphy as a routine test became possible with the development of the rectilinear scanner by Cassen. Interested readers are referred to early landmark papers by Cassen *et al.* [80], Allen and Goodwin [81] and Bauer *et al.* [82]. Thyroid imaging is now done using an Anger camera with a pinhole collimator, rather than rectilinear scanner because the former gives better resolution [83, 84]. A pinhole collimator with a 4 mm aperture can resolve non-functioning lesions smaller than 1 cm, provided the lesion is not surrounded by normal thyroid, or sitting in front of the full thickness of the normal lobe. The best radionuclide is ^{123}I [85], which is given by mouth as a capsule and scintigrams are obtained 3–6 hours later. Imaging is done with the patient lying supine, and it is advantageous to place a pillow under their shoulders to push the neck and thyroid anteriorly. The collimator should be placed at the correct distance, usually 4–5 cm above the anterior neck, and the thyroid centred in the field of view. Many thyroidologists and nuclear physicians use 1–2 mCi (37–74 MBq) ^{99m}Tc pertechnetate given by intravenous injection and image after 5–10 minutes. If speed is important, this is recommended; however, ^{99m}Tc is trapped and not organified and there are many reports of this radiopharmaceutical giving different results from radioiodine (see below). The indications for scan have been:

1. Determining the size of the thyroid.
2. Determining if a nodule concentrates radioiodine (hot nodule), or not (cold nodule). Figure 3.17 shows a normal scan and Figure 3.18 shows a cold nodule (a) and a hot nodule (b).
3. Determining if a retrosternal shadow on a chest radiograph is a thyroid.
4. Determining if a lump in the tongue or track of thyroglossal duct contains a functioning thyroid.
5. Evaluation of a multinodular goitre.

It is not necessary to obtain a thyroid scintiscan to determine the size of the gland, this can be judged by clinical examination. In addition, Ripley *et al.* [86] have shown that routine scintigraphy in work-up of patients with Graves' disease who are to be treated with radioiodine gave no additional information over clinical examination and uptake measurement.



(a) (b)

Figure 3.18 (*a*) and (*b*) are both made 3 hours after 200 μCi ^{123}I. (*a*) A cold nodule in the left lower pole (compare with Figure 3.19 showing a marker over the nodule). (*b*) A hot nodule in the left lower pole in a different patient. In this case, cobalt markers have been placed at the upper and lower margins of the nodule, thus ensuring what is felt and imaged are the same.

Probably more thyroid scans are obtained to determine if a nodule is hot or cold than for any other reason. This is because malignancy is extremely rare in a hot nodule, and thyroid cancers are often cold on scan. Based on these statements, the rationale for obtaining a scan would appear sound. However, there are several problems. First and most important, although a cancerous nodule is usually cold, most cold nodules are not cancerous. The average incidence of cold nodules being cancerous is quoted to be 10–20% [87]. Other pathological conditions which produce cold nodules on scintiscan include adenoma, adenomatous hyperplasia, colloid cyst, haemorrhagic cyst, Hashimoto's thyroiditis, subacute thyroiditis, and a large parathyroid adenoma. Datz [88] has listed rare causes such as abscess, artifact, fibrosis after radiation and amyloidosis. There is general agreement that only 10–20% of palpable thyroid nodules are hot by scanning. The incidence is greater in countries where multinodular goitres are common.

If we assume that a hot nodule is never malignant and that all cancers are cold nodules; and accept that 20% of nodules are hot (and therefore are benign); and that 10% of patients with a single palpable nodule have a cancer in that nodule; and that 100 patients who have a thyroid nodule are investigated using radioiodine scintigraphy; 80 will have a cold nodule and 10 of these will be malignant, so the scan has increased the probability of a nodule being malignant from 1:10 (10 out of 100) to 1:8 (10 out of 80). The sensitivity is 100%, but the specificity only 30%, the positive predictive value of a cold nodule being malignant is 12.5%, and the negative predictive value of finding a cancer in a hot nodule 100%. Several of the assumptions can be

questioned. In many series, the incidence of cancer in solitary nodules is lower than 10%. The incidence of hot nodules is often reported to be 6–10% [89, 90]. Not all hot nodules are benign, but almost all are. Inserting these numbers makes the test even less useful clinically. The assumption that all cancers are cold is not correct, as shown by Nelson *et al.* [90]. These investigators reviewed rectilinear scans in 67 patients who had proven thyroid cancer: only 54% of the cancers were cold, in 40% the scan was normal and in the remainder the scan had a patchy appearance. It is probable that more cancers would have been cold if imaging had been done with a gamma camera. I agree with the concept that a normal scintigram does not exclude cancer. In a different report, only one-half of lesions subsequently proven to be cancer were cold on preoperative scintigram [91]. There is further difficulty in the interpretation of the scan by what is meant by a hot or cold nodule. Some report warm, or lukewarm nodules, and this leaves the clinician in doubt about how to proceed. I try to be as dogmatic as possible. If the nodule has less radioactivity than surrounding normal thyroid, it is cold, even if the difference is minimal. If the nodule has more radioactivity it is hot. The nodule should be palpated while scanning is done and radioactive markers, which will be seen on the images, positioned carefully at the edges of the lesion. This leaves no doubt that the palpable nodule and the scan findings relate to the same area (Figure 3.19). This technique is not simple and requires practice and attention to detail. Suitable markers are a dedicated cobalt source, or a few μCi of ^{99m}Tc at the tip of a Q-tip which is covered with Sellotape.

In certain cases, it is valuable to obtain oblique [92] and/or lateral images because passage of radioactivity through the cold nodule from normal thyroid behind it can lead to the wrong impression. The half-value layer of ^{123}I in tissues is 4.7 cm. This means

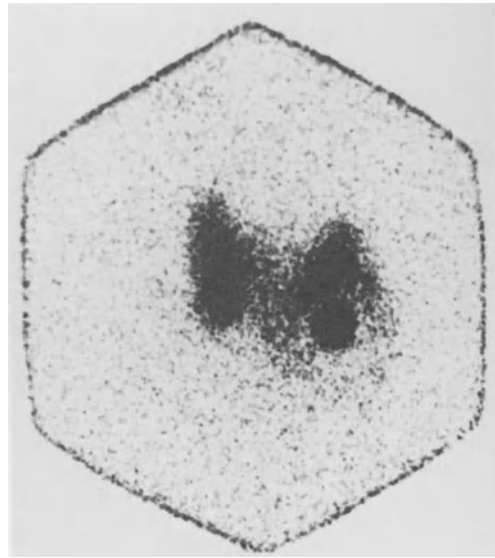


Figure 3.19 A Scan in same patient as 3.18 (*a*) with a cobalt marker placed over the centre of the left-sided nodule. This proves the palpable lesion is a cold nodule.

that one-half of the gamma emissions from normal thyroid are attenuated by a nodule of diameter 4.7 cm, but, more important, if the nodule is 1–1.5 cm in diameter approximately 90% of the emissions from normal thyroid behind will be detected. This accounts for many of the false negative reports. By imaging the nodule at an angle which places it clear of normal thyroid, the 'true' result is obtained. These concepts are shown diagrammatically in Figure 3.20. When the nodule lies within normal thyroid it can be impossible to image. The concept that hot nodules are never malignant is based on pathological correlation with the results of radioiodine scintigraphy. There are a few case reports of malignant hot nodules [93–95] and this topic is expanded in Chapters 5 and 7. This data does not apply to the results of a pertechnetate scan. Pertechnetate is trapped by the follicular cell but is not organified and leaks out fairly quickly. As a result, it is to be expected that the scan finding 10–20 minutes after injection of this

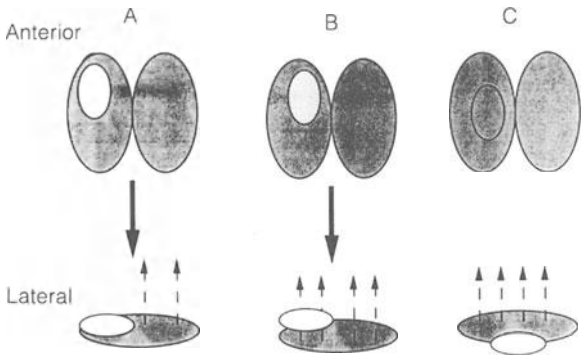


Figure 3.20 Schematic representation of scintigraphy of the thyroid nodules. A, B and C are thyroids of identical size with cold nodules of similar dimensions in the right lobes. The nodule in A appears cold, but the ones in B and C do not, due to gamma rays from ^{123}I from the normal thyroid penetrating the nodule (B), or arising from in front of it (C).

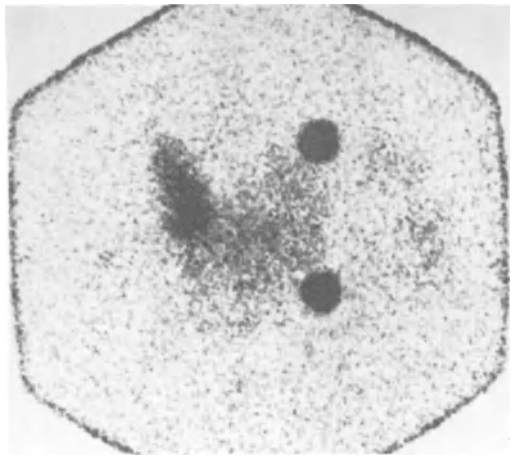


Figure 3.21 Thyroid scan 3 hours after 200 μCi ^{123}I, showing an abnormal thyroid with reduced uptake in the left lobe as well as a faint uptake lateral to the left lobe. This is rare, but found in functioning metastases from thyroid cancer in the cervical nodes. Usually, the function of the metastases is not great enough for them to be imaged until normal thyroid has been removed.

radiopharmaceutical could differ from the findings several hours after administration of radioiodine. There are many reports of disparate findings, and a hot nodule on a pertechnetate scan can be cold with radioiodine and vice versa [88, 96–100]. Therefore, if there is uncertainly whether a nodule really is hot when pertechnetetate is used, why not always use ^{123}I [85, 101, 102]?

Uptake of radioiodine or pertechnetate in the neck outside of the thyroid is virtually diagnostic of metastases [103, 104]. Figure 3.21 shows a proven example of this.

In summary, thyroid scintigraphy is not recommended as the primary routine test in the work-up of a solitary thyroid nodule. Any palpable nodule in the region of the thyroglossal tract could contain functioning thyroid, and in that situation the cervical thyroid is often not present. ^{123}I scintigram defines exactly what and where there is thyroid tissue. Most thyroglossal duct cysts do not contain enough follicular cells to be imaged, and normal cervical thyroid is present. A scan is recommended in this situation.

The best way of proving whether a superior mediastinal mass is a retrosternal thyroid is by scintigraphy with ^{123}I. ^{99m}Tc should not be used, because there is so much background activity from the surrounding cardiac and vascular tissues that it is impossible to delineate thyroid tissue at that site. It has been stated that the energy of the gamma rays of ^{99m}Tc are not high enough to penetrate the sternum, and that is why this radiopharmaceutical is not used. This is incorrect since the same agent is used successfully to image the cardiac blood pool and obtain important functional informational about the ventricles. The reason why ^{99m}Tc should not be used in diagnosis of a substernal goitre is the high background activity in blood pool and vessels which makes distinction of substernal goitre impossible. Although ^{131}I emits gamma rays with a higher energy than ^{123}I, there is no need to use the former and the higher absorbed

radiation dose is a disadvantage. Tomographic imaging of ^{123}I (single photon emission tomography – SPECT) can occasionally help to delineate the extent of a multinodular goitre [105].

A thyroid scintigram of a goitre sometimes provides information which is different from the clinical impression. This applies in a multinodular goitre where there is no way of knowing if the nodules are functioning or not without the scan. A dominant nodule which is cold should be investigated further by needle aspiration (Chapter 7).

(b) Whole body scintigraphy for thyroid metastases

This test is designed to provide information about the presence, or absence, of functioning metastases from differentiated thyroid cancer. The test is of no value in anaplastic or medullary cancer. It should only be done after thyroidectomy, which removes the primary cancer and a proportion of normal thyroid tissue. The extent of surgery is controversial and is discussed in full in Chapter 8. If the scan is done when there is a significant amount of normal thyroid present, the radioiodine localizes preferentially in that site and metastases are not visualized. Autoradiographic studies have shown that cancers have about 1% of the uptake of normal thyroid. The test uses ^{131}I and doses from 0.5–10 mCi (18.5–370 MBq) have been recommended with most nuclear physicians using 1 or 2 mCi (I use 2 mCi (74 MBq)). When whole-body scintigraphy is done after thyroidectomy, it should be delayed for about 4 weeks from the time of operation to allow endogenously secreted thyroid hormones to be metabolized and TSH to rise. This will only occur when a significant amount of thyroid has been removed. If the operation was a lobectomy and isthmusectomy, there is sufficient residual thyroid to maintain euthyroidism, and the scan will usually only demonstrate the residual lobe. When thyroxine has been started postoperatively, it should be discontinued for 4 weeks prior to scanning and triiodothyronine should be stopped for 2 weeks [106]. Blood is drawn for TSH and thyroglobulin measurement before the dose of ^{131}I is administered. The TSH gives information about the metabolic condition under which scanning is done, and thyroglobulin is an independent marker for thyroid cancer which is discussed below.

A whole-body scan is obtained 48–72 hours after the dose is administered. This delay allows background activity to fall to very low levels, and it allows sufficient time for metastases to trap radioiodine. I routinely obtain anterior and posterior whole-body images as well as pin-hole images of the thyroid area. Normal uptake is expected in residual thyroid, salivary glands, stomach and colon and bladder. The last two are routes of excretion of iodine. Late scans (5–10 days after the dose is administered) can demonstrate diffuse hepatic uptake of radioiodine, which is due to the liver metabolizing radioiodinated thyroid hormones [107]. There has to be functioning thyroid tissue producing hormone for this to occur, and the appearance should not be misinterpreted as metastases. The main drawback about this scan is that about 10% of differentiated cancers do not concentrate iodine. Recently, Hoschl *et al.* [108] described a false-positive result in the lungs caused by bronchiectasis. I have seen positive uptake in the lungs in a patient who had bronchitis at the time of scanning. There was no other clinical or laboratory evidence of metastases (radiographs, thyroglobulin and a thallium scan were negative). No therapy was advised, and a repeat scan when the patient had no lung problem was negative. Fortunately, I read the aforementioned article. Another cause of a false-positive result was ^{131}I accumulating in a renal cyst [109].

Lakshmanan *et al.* [110] recommend a simplified low-iodine diet to augment uptake in lesions. Several aspects of this are provided

Table 3.8 Simplified low-iodine diet used in the preparation of a patient with thyroid cancer for whole-body scintigraphy

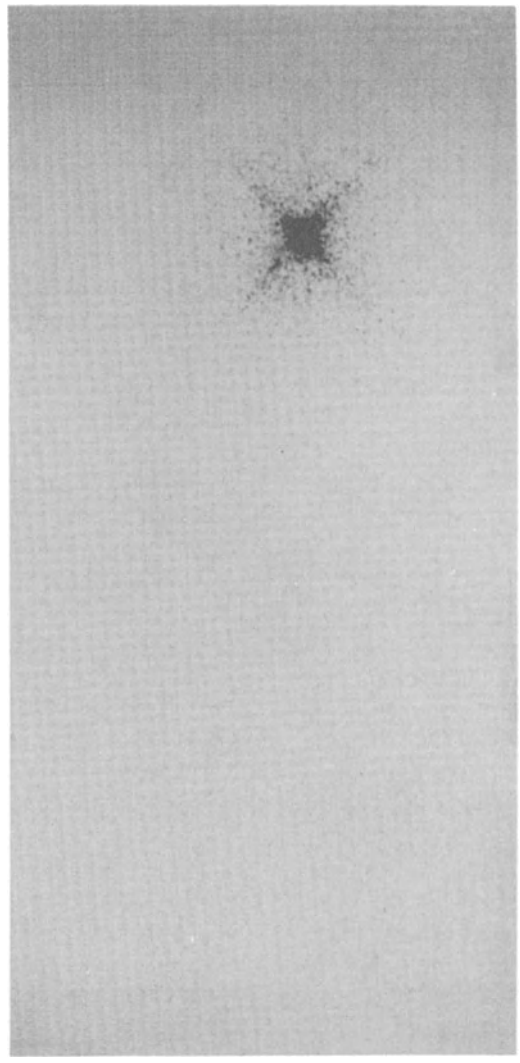
A low-iodine diet is recommended for 2 weeks before a ^{131}I scan and continued until therapy has been prescribed. The following should be avoided:

Iodized salt and sea salt
Milk and dairy products
Eggs
Seafood
Kelp
Breads with iodate dough conditioners
Red food dyes
Restaurant foods

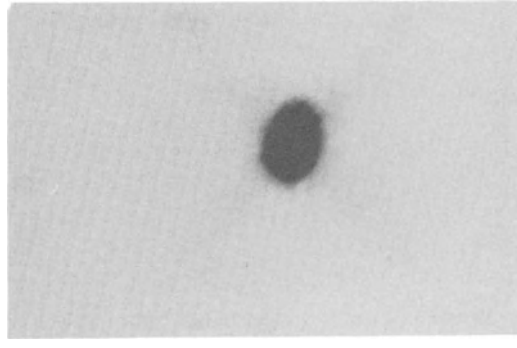
This successfully reduces urinary iodide to 50 μg/day [110].

in Table 3.8. I ensure there is no obvious increased source of iodine such as radiographic contrast/or kelp tablets. There is no good way of doing a controlled study of normal and low-iodine diets in the same patients, since any lesion seen on the first scan would be treated.

It is valuable to calculate uptake in lesions so that a decision about treatment can be made. Figure 3.22 (a and b) shows a whole-body scan with only thyroid uptake and Figure 3.23 one with widespread metastases. More examples are given in Chapter 8. Technetium whole-body scintigram is inferior to ^{131}I [111], and since it does not predict whether therapy can be given I do not recommend this.



(a)



(b)

Figure 3.22 (*a*) Whole-body radioiodine scan made 48 hours after 2 mCi ^{131}I, showing residual thyroid in the cervical area but no metastases in regional nodes, or distant sites. (*b*) Spot over thyroid.

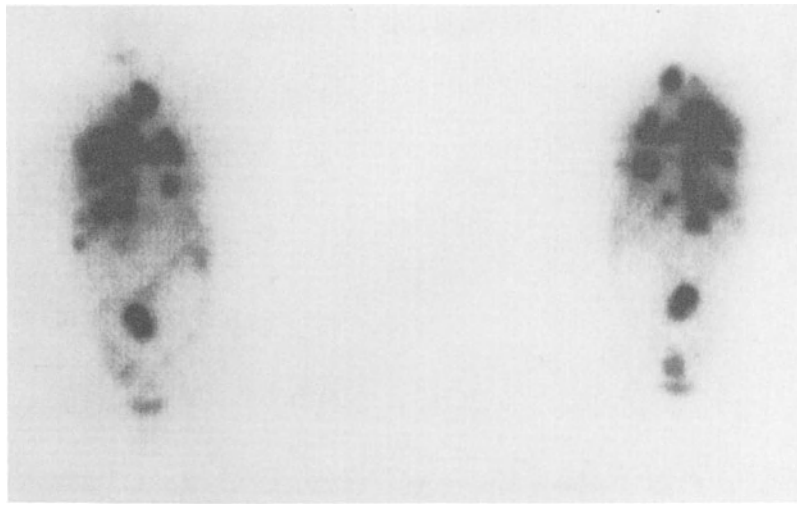


Figure 3.23 Whole-body scan made 72 hours after 2 mCi ^{131}I, showing multiple areas of abnormal uptake due to functioning metastases of follicular cancer.

3.5.3 MISCELLANEOUS RADIONUCLIDE IMAGING TESTS

(a) Gallium

Gallium citrate [^{67}Ga] is used to detect inflammatory disease and metastases. It was introduced as a bone scanning agent in the 1960s and found to localize in non-skeletal primary cancers and their metastases. The cancers include lung, melanoma, hepatoma and lymphoma. The radiopharmaceutical was also found to localize in abscesses and other acute and chronic inflammatory processes. The mechanism of uptake in these lesions is multifactorial and includes the labelling of transferrin, the uptake in inflammatory cells, increased capillary permeability in the lesion, and the labelling of bacteria and others not well defined [112–114]. Gallium has a minor role in diagnosing thyroid diseases. As might be expected there are reports of it showing positive uptake in anaplastic cancer [115], lymphoma [115], subacute thyroiditis [116, 117], Hashimoto's thyroiditis [118], amiodarone thyroiditis [119], and sarcoidosis of the thyroid [120, 121]. There is one report of positive uptake in the thyroid in Graves' disease [122]. Because both cancer and inflammation are imaged, the test cannot have good specificity and there are not enough publications to allow us to determine the sensitivity. Since most of the diseases in which this test is positive are diagnosed by other simpler and more accurate methods, the role for ^{67}Ga scintigraphy is very limited. It might be considered in a patient with a fever of unknown origin, who is borderline hyperthyroid to diagnose thyroiditis and it has a small role in staging of lymphoma.

^{67}Ga emits gamma rays with energies of 93, 184, 295 and 394 Kev, it has a half-life of 78 hours, and the usual dose is 3–5 mCi (111–185 MBq) by intravenous injection. Imaging for inflammatory pathology is done from 6–24 hours after the injection, and for cancer the image should be delayed up to 48 hours after injection.

(b) Thallium

Thallium 201 decays by electron capture and emits low-energy X-rays with energies of 70–80 Kev. It has a half life of 64 hours. The standard dose is 2.0 mCi by intravenous injection, and imaging is started at 5 minutes. Thallous chloride (^{201}Tl) is used commonly

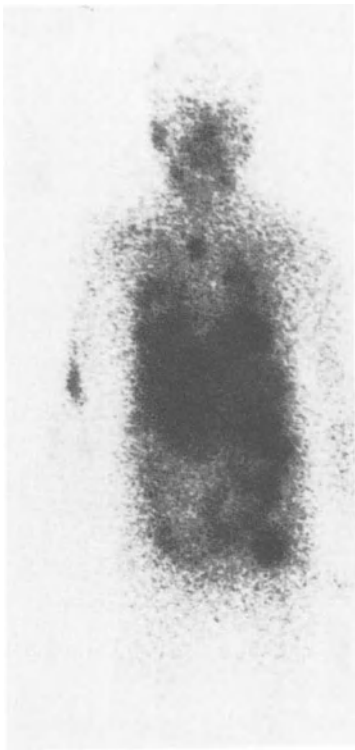


Figure 3.24 Whole-body ^{201}Tl scan in a patient with metastatic follicular cancer (not the patient whose scan is shown in Figure 3.25). ^{201}Tl is normally seen in the heart, salivary glands, liver and intestines. The uptake in the lungs, neck and pelvis are metastases.

to image the myocardium. In addition, it has been shown to localize in certain cancers including thyroid cancer [123, 124]. Why and how the radionuclide is taken up by cancer are not known. Whole-body thallium scintigram searching for metastases has good sensitivity, and this test has the great benefit that thyroid medications do not have to be stopped prior to imaging. Figure 3.24 Shows whole-body ^{201}Tl scan in a patient with metastatic follicular cancer. The reason for whole-body ^{131}I scan described above is to define whether there is uptake in cancer that could subsequently be treated with the same radionuclide. A positive ^{131}I scan means that therapy can be considered, a positive thallium scan means that cancer is present and that some other test is necessary before determining how the cancer can be treated. Usually a ^{131}I scan has to be done. Therefore, I prefer to obtain a standard ^{131}I whole-body scintigram first. Thallium has a role in searching for suspected disease when the ^{131}I scan is negative in a patient with persistently high thyroglobulin. If ^{201}Tl is shown to be as sensitive as ^{131}I in detecting cancer, it is probable that it will become the first test looking for metastases. A negative ^{201}Tl study would mean there is no need to stop the patient's thyroid. Brendel *et al.* [125] found a low sensitivity for thallium [43%]; therefore, there is insufficient published data to support this approach at present.

A recent report shows that ^{201}Tl demonstrates suppressed thyroid in patients with autonomous hyperfunctioning nodules, thus differentiating a hot nodule from hemiagenesis [126].

(c) Other radiopharmaceuticals

^{99m}Tc pentavalent dimercaptosuccinate (DMSA) has been used to image medullary cancer with varied results. Images are made 2 hours after intravenous injection of 10 mCi (370 MBq) of the radiopharmaceutical. It should be considered in patients with high values of calcitonin, but no evidence of its source [127]. Alternatively, radioiodinated metaiodobenzyl guanidine (MIBG) has been used in this clinical setting [128].

3.5.4 THYROID ULTRASOUND (SONOGRAPHY)

Ultrasound is a simple rapid, relatively cheap and non-invasive method to study the structure of the thyroid. It requires no patient preparation. The study is done with the patient recumbent and the neck extended. A very high frequency sound wave (5–10 MHz) is pulsed into the area of interest and the echoes detected by the transmitter and reproduced as an image. Because fluid has no internal structures it does not produce an echo; in contrast, solid tissue produces many

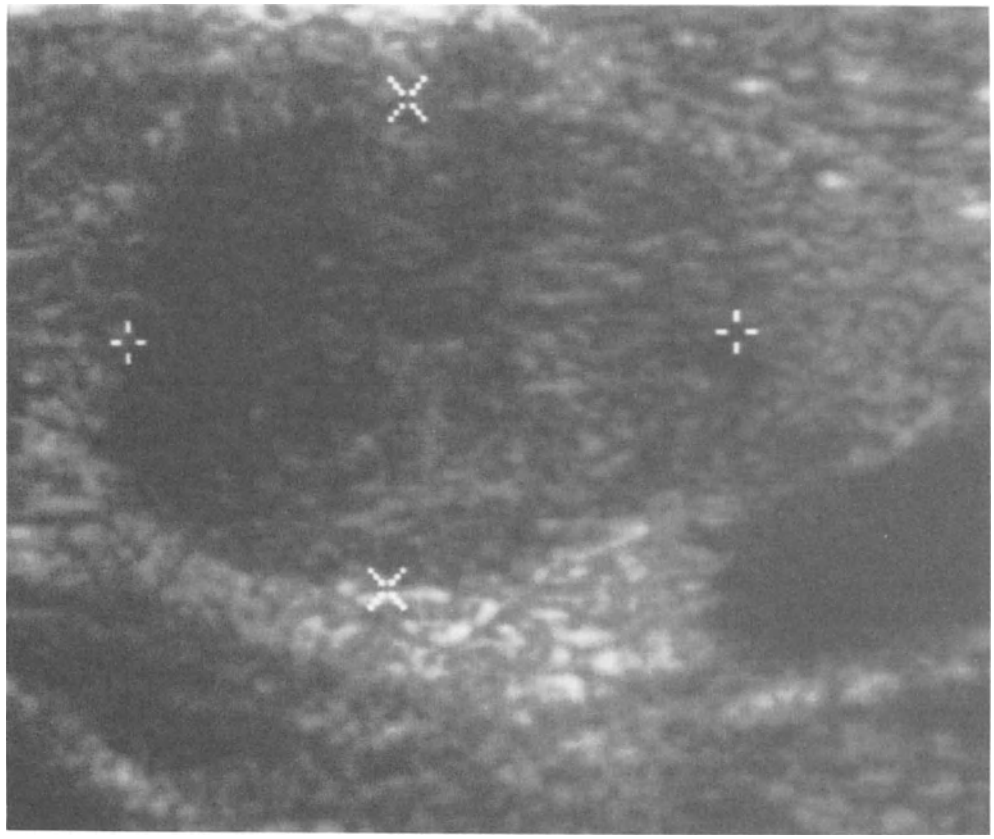


Figure 3.25 Ultrasound of a right-sided thyroid nodule. This is solid. Ultrasound does not give tissue characteristics that allow cancer to be differentiated from benign tissue. This nodule was shown to be benign on fine-needle aspiration.

echoes at tissue interfaces (Figure 3.25). Modern, 'state of the art', small-parts equipment provide marvellous resolution, of <0.5 mm in the axial direction and <1 mm transversely [129]. In spite of this, the hope that ultrasound would provide different tissue characteristics in cancers compared to benign lesions has been realized. As a result, I find this test less useful than some investigators in work-up of the solitary nodule. It is possible to differentiate a solid from a pure cystic nodule with more than 95% confidence [130], however, pure cysts in the thyroid are not common; in one report only 1 out of 146 single nodules met the criteria of a single, fluid-filled lesion, with a well-defined capsule and increased passage of echoes through the posterior wall of the cyst [131]. There is one article which stands out in contrast. Hammer *et al.* [132] studied 341 patients who had thyroid surgery and in whom the pathology was known. Forty-eight patients had cancer (14%), and 94 had pathological evidence of a cyst (35%). Thyroid ultrasound was available in 64 patients, and it correctly predicted cysts in only 15 of 27 cases (sensitivity 56%), and it showed 7 of 37 solid lesions to be cystic (specificity 83%). Details of the imaging in this study are not provided, but the results are disquieting.

Differentiation of the cystic lesion is important because pure cysts are seldom malignant. However, in the series described [132],

27% of the benign and 33% of the malignant lesions were cystic. The cancer could be in the cyst, or the cyst was the result of central necrosis of the cancer. Some clinicians find the results of ultrasound help them decide if surgery is necessary. Walker *et al.* [133] compared the results from operation with preoperative ultrasound results in 200 patients with a solitary nodule on clinical examination. One hundred and one of the series subsequently had a thyroid operation. Forty-nine solitary solid nodules were diagnosed by ultrasound, and 8 (16%) were cancers. The ultrasound did not prevent operation on the 41 with benign nodules. Fifty-two patients had complex or cystic lesions on ultrasound, and all were histologically benign. Thirty were removed for clinical indications. The authors have followed the remaining 99 patients who were found to have cystic, multinodular or diffuse lesions. They state 'nearly 50% of patients with a clinically solitary thyroid nodule have avoided surgery'. This begs the questions of who palpated the thyroids, why were some asymptomatic multinodular goitres removed, and how do they know the remainder are benign?

Ultrasound has been recommended as a screening test to find nodules in patients who have had head and neck irradiation. There is no unanimity of opinion but undoubtedly the test will find non-palpable nodules in 10–25% of patients [134] and cause a dilemma for the clinican and concern for the patient. This finding almost always results in a nuclear scintigram being obtained and this can be normal. Then the questions of biopsy or even surgery of an impalpable nodule arise. As a result, in this clinical setting I prefer to rely on palpation which is repeated annually.

In spite of these negative comments, I find ultrasound helpful in several clinical setting. Firstly, in obtaining accurate measurement of the size of a nodule. If a patient is put on suppressive therapy in an effort to shrink a nodule, it is reassuring to have measurements at intervals (annually) proving the nodule is not growing. The rationale and expected results from suppression are presented in Chapter 7. Blum [130] states that knowledge of the dimensions of the thyroid allow accurate calculation of its volume, which can be used in determining how much radioiodine treatment to prescribe in cases of Graves' hyperthyroidism or 'hot' nodule. Secondly, on occasion the clinical impression can be that of a dominant nodule, but there is a hint of smaller subclinical nodules. Ultrasound will differentiate a solitary nodule from a multinodular goitre. Ultrasound can demonstrate unequivocally that the problem is multinodular goitre. If one nodule is dominant, I recommend evaluating it as if it were solitary, and this will usually involve fine-needle aspiration. Thirdly, those who are skilled ultrasonographers state that the test aids needle aspiration. I have virtually no experience of combining the two procedures, and usually do aspirations using touch, holding the nodule with the forefinger and thumb of my left hand and aspirating with the right hand using a syringe holder. This is described in detail in section 3.6.

3.5.5 FLUORESCENT SCANNING

This test images the distribution of inorganic iodine in the thyroid. The principle was proposed by Hoffer *et al.* in 1968 [135], and early results presented by Hoffer and Gottschalk [136]. If a photon (either a gamma ray or X-ray), whose energy is greater than the binding energy of an inner K shell electron of non-radioactive iodine (^{127}I), strikes the electron, the latter is ejected from its orbit with an energy equal to the difference of the incident photon and the electron's binding energy. The gap created by loss of the K shell electron is filled by an electron from the next orbit, the L shell, falling into that spot. The second electron has a higher binding energy than the first, and as it moves into the K shell the difference in energy is given off. This can take one of two forms, either a

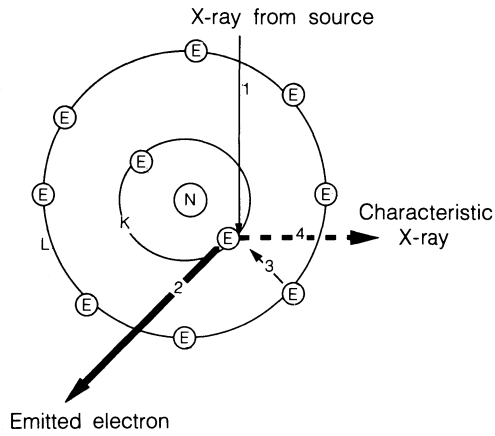


Figure 3.26 This shows the theoretical basis for fluorescent scintigraphy. N = nucleus; E = electron; K = inner shell; L = second shell; 1 = incident X-ray; 2 = emitted electron, 3 = L–K electron; 4 = characteristic X-ray.

low-energy electron (Auger electron), or a characteristic X-ray which has an energy of 28.5 Kev that is suited to imaging. Figure 3.26 shows the sequence diagrammatically. The equipment for fluorescent scanning has a source of photons, usually americium (Am-241), which emits 59.6 Kev gamma rays, and a high-resolution detector capable of imaging the low energy X-rays.

Because the equipment is expensive and limited in use to thyroid investigations, the test is not widely available. The patient requires no preparation and one benefit of the study is that it can be done after the patient has received a large dose of iodine. The number of photons given off are proportional to the amount of iodine in the gland, and therefore it is possible to quantitate the iodine content. Patton and Sandler [137] found in 33 normal controls an average of 10.7 ± 4.8 mg (M ± SD). The result in primary hypothyroidism was only 1.5 ± 0.9 mg and in untreated hyperthyroidism 36.5 ± 19.4 mg. In subacute thyroiditis, there was normal content at the onset of symptoms, but thyroidal iodine decreased dramatically, and this corresponds with the course of the illness described in Chapter 9. Similar results have been described by other investigators in the USA, but Meignan and Gall [138] in France found considerably lower normal values (5 ± 2.5 mg) most probably the result of less dietary iodine. These results are interesting in relation to our knowledge of physiology of thyroidal iodine, but do not help in practice.

It was hoped that malignant nodules could be differentiated from benign on the basis of their iodine content. Although early investigations were encouraging with lower iodine content found in maligancy [139], current data indicate that the iodine content cannot be used to discriminate in an individual case. In a study of 150 nodules, 38 of which were subsequently shown to be malignant, a ratio of iodine content in the nodule compared to the content of the opposite lobe of <0.6 correctly identified 37 cancers, but incorrectly put 41 of the 112 benign lesions into the same category (sensitivity 97%, specificity 65%).

The test gives an extremely low radiation dose to the thyroid (approx 20–40 mrad) [140], no radiation has to be administered and the whole-body dose is negligible.

3.5.6 MISCELLANEOUS RADIOLOGICAL STUDIES

(c) Computerized tomography (CT)

There is no place for CT scanning in routine evaluation of patients with thyroid diseases. There are a few situations where this test contributes clinical information which is not available from other simpler and cheaper approaches (140–142). Although CT can diagnose substernal goitre, this condition is diagnosed more specifically by ^{123}I. In the rare patient with thyroid cancer who has a spinal metastasis, this test gives excellent anatomical information of the relationship of the spinal cord. It sometimes is useful in

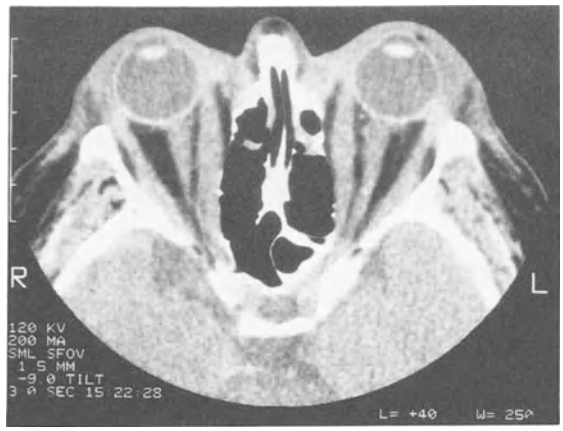


Figure 3.27 CT of orbits in a patient with advanced Graves' ophthalmopathy. The extraocular muscles are considerably enlarged.

patients with recurrent cancer in the neck when there is no uptake of radioiodine. If the scan shows localized lesions which are known not to concentrate iodine, then surgery can be recommended. Whenever CT is ordered, the physcian must anticipate that contrast material containing inorganic iodine will be given; therefore, scintigraphy or therapy with radioiodine must be done first, or be delayed for 4–6 weeks.

We have found that CT scan of the orbits valuable in evaluating Graves' ophthalmopathy [144]. No contrast is required and the scan gives excellent resolution of the extraocular muscles and the optic nerve. The test should not be ordered routinely in patients with mild disease, but should be used when treatment of the ophthalmopathy by radiation or surgery is planned. Figure 3.27 shows characteristic findings of bulky extraocular muscles in a patient with clinically advanced Graves' ophthalmopathy.

(b) Nuclear magnetic resonance imaging (NMRI)

When NMRI was introduced in clinical medicine, there was the hope that neoplastic tissue would have tissue spectroscopic characteristic that would allow it to be differentiated from normal and benign pathology. As a corollary, it was hoped that malignant nodules would show a different signal from benign ones. This is not so. NMRI has no place in routine work-up of thyroid disease [145, 146]. It is valuable in evaluating the spinal cord in cases with metastases to the spine, and is better than CT in the diagnosis of compression and has the benefit that no contrast is given. It allows the extent of cancers which do not trap radioiodine to be evaluated. In contrast, the test can show unexpected abnormalities as is shown in Figure 1.3. The scan was done to evaluate the cervical spine in a young woman with radicular symptoms in the neck and arm. A thyroid nodule was found, and this engendered concern in the patient and her internist. No lesion was palpable, but an ultrasound was necessary to prove that the problem was a 5 mm cyst. No additional tests or treatment were advised or have been necessary.

3.6 TISSUE DIAGNOSIS

There has been a remarkable change in the approach to diagnosing thyroid nodules in the last 10 years. This involves establishing a tissue diagnosis by needle biopsy. The approach had been used in Scandanavia [147], and by a small number of clinicians in the USA [148, 149] for many years prior to its general acceptance in the USA and Europe. Reasons for biopsy results not being accepted earlier include fear that malignancy would be tracked along the course of the needle, that the tissue obtained would not be representative of the nodule as a whole, and concern about false-positive and false-negative results. There is no data to support that this test spreads cancer; the other concerns are discussed in more detail below.

There are several methods of obtaining tissue. Firstly, using a large-bore (14 or 15 gauge) dedicated biopsy needle, such as Trucut, or Vim Silverman [150]. This

approach requires a small incision in the skin overlying the nodule, and it provides a core of tissue which is evaluated by standard pathological techniques. This is fairly traumatic and can cause complications, such as perforation of the trachea, damage to the recurrent laryngeal nerve and haematoma [150]. The most common approach is to use a smaller regular needle [gauge 23–25], and 10–20 ml syringe. This technique provides tissue for cytological rather than histological interpretation, and because it has gained widespread acceptance it is described in more depth below. One of my colleagues uses a compromise between these extremes with an 18–19 gauge needle. He obtains a small core of tissue which is large enough to be sectioned for histological interpretation. No skin incision is required.

Fine-needle aspiration is promoted as the primary test for evaluation of a solitary thyroid nodule by Van Herle *et al.* [151]. Their detailed analysis demonstrates that it is the most cost-effective first test. Blum [152] raises a concern, which I echo, that cost-effectiveness is easier to apply to a population than to a patient. As with any test, the reason for proceeding with fine-needle aspiration should be carefully considered, and it should not be done by rote. For example, if a patient has had previous neck irradiation and now presents with a hard, fixed thyroid nodule, should the biopsy be obtained? I would argue no. A negative result would not alter my recommendation to have the nodule removed. Some believe knowledge of the pathology preoperatively helps the surgeon plan the procedure. However, if the clinical suspicion is so strongly in favour of cancer, I believe the procedure would be the same without the biopsy result. When a decision is reached to do an aspirate, there should be a full discussion with the patient of the procedure, the possible results and the steps taken to treat each of these (see below). The patient lies supine with a pillow under the shoulders to push the thyroid and nodule more anteriorly. The skin should be anaesthetized with 1% Xylocaine. When a 23–25 gauge needle is used for aspiration, the instillation of the anaesthetic is about as painful as a single aspirate, but several aspirates are usually necessary and this aspiration is tolerated better after local anaesthesia. The nodule is immobilized between the fingers and thumb of one hand, and the needle inserted using firm pressure with the other hand. To help stabilize the syringe and needle, it is very helpful to use a dedicated syringe holder such as the Cameco syringe pistol. Suction can be obtained in the syringe with one hand, the other hand ensuring the nodule remains immobilized. The needle is moved back and forth in the nodule while pressure is maintained in the syringe. As soon as material is seen in the barrel of the syringe, the procedure is stopped. The best specimens are obtained by first removing the syringe from the needle, leaving the needle *in situ* for a second or two, before the syringe is reattached to the needle and then removed with the needle. A tissue drop is gently expressed onto a glass slide. The drop is smeared with the edge of a second slide in the same fashion as a blood smear. If the syringe and needle are pulled out together, without releasing the negative pressure, there is a risk of sucking the specimen into the barrel of the syringe from which it is difficult to remove. One half of the slides are placed as quickly as possible in 95% alcohol fixative, the remainder are dried in air. The former are stained using Papanicolaou, or an equivalent stain, the latter with Wright's stain which demonstrates colloid.

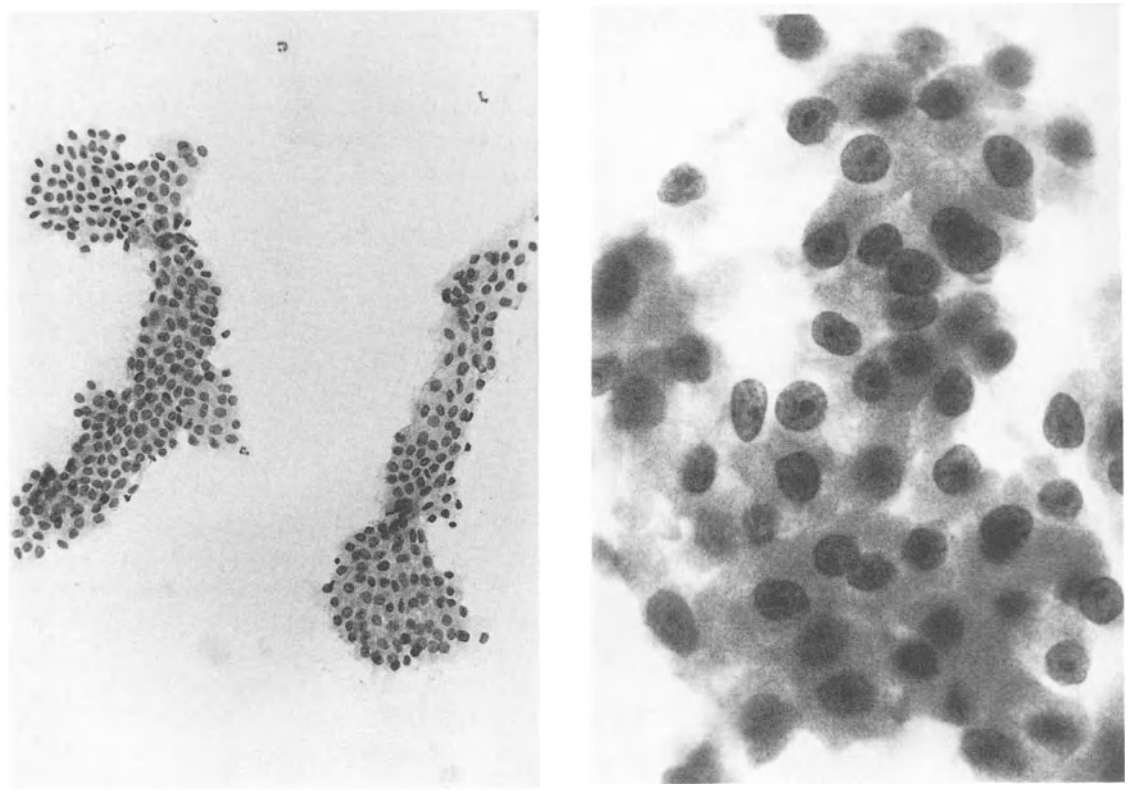
When fluid is obtained, the aspirator should try to remove it all. The colour can vary from serous, through bloody to black. Clear liquid, like water, establishes that a parathyroid cyst has been drained [153]. The fluid is put into a plain sterile tube and the contents spun down so that the any cells can be stuided microscopically. If a mass is

still palpable after the fluid is drained, it should be aspirated. Blum [152] states that ultrasound-assisted aspiration is helpful in this situation because it allows the operator to determine where the biopsy needle is positioned. This was discussed above under ultrasound, and I admit I do not use this combination of procedures. Gentle pressure should be applied to the puncture site for 5 minutes, and the patient kept under observation for 15–20 minutes. Those clinicians who get immediate feed-back of the result are in an enviable position. I consider myself fortunate in obtaining the result in 24 hours, so there is very little delay in discussing them with the patient. It is prudent to have everything ready before doing the procedure, including having the slides prepared with the identifying features of the patient. (Ball-point and regular ink are dissolved by the fixative, and so a pencil is recommended for recording details.)

Two alternative approaches for aspiration have been described. Burch [154] uses a 21 gauge butterfly needle attached to a 20 ml syringe, and he stands behind the patient palpating the nodule as most clinicians do in routine practice. Having defined the nodule, he inserts the needle and a colleague standing in front of the patient does the aspiration. The patient does not see the needle. I ask patients if they would like a cover over their eyes and can only recall one who did. Zajdela *et al.* (155) use a needle alone without negative pressure from a syringe. They insert a 23 or 25 gauge needle and move it back and forth in different directions in the tumour. Cells are drawn into the barrel of the needle by capillary action. They have used this technique to aspirate successfully both thyroid and breast lesions.

Complications are uncommon. Occassionally, there is bleeding into the lesion, but his responds to pressure and I have used an ice pack and pressure with apparent resolution. Pressure alone might have been sufficient. Blum [152] recommends not aspirating the thyroid if there is a bleeding disorder and I agree. However, I do not request coagulation studies before aspiration and know of no-one who does. He also recommends not aspirating a nodule in a patient with Graves' disease because the gland is so vascular. I have done so several times. One patient had Graves' disease plus a nodule, coexisting severe cardiac and joint disease. I wished to treat her with radioiodine and try to prevent referral for thyroid surgery. There was no bleeding from the aspirate, the cytology was benign, radioiodine was successful (one dose made her hypothyroid) and, to my surprise and her pleasure, the nodule disappeared after the radioiodine treatment.

There are four broad categories into which the results fall: malignant, benign, suspicious, and inadequate. In the last case, the aspirate should be repeated. Papillary cancer, which is the commonest thyroid cancer, has characteristic features shown in Figure 3.28. Ashcraft and Van Herle [156] in an extensive review of the literature, found the overall accuracy of the procedure was 90%. There are numerous reports of hundreds [154–165] or even thousands of patients being studied [166–168]. It is generally agreed that there are few false-positive results. Boey *et al.* [164] in a review of 14 publications calculated that the false-positive rate was 3.8%. There are exceptions to this. Khalifa *et al.* [169] report a false-positive rate of 56%, but the small number of patients studied probably is responsible for their results. Similarly, the incidence of false negatives is small, averaging about 5%. These figures conceal an important fact, namely, that suspicious lesions are not included in the statistical calculations. In many series, 10–20% of the results fall into a suspicious or indeterminate category. The most frequent and troublesome cause of this is the microfollicular neoplasm (Figure 3.29), because it is impossible by cytological analysis to differentiate a follicular adenoma from a follicular carcinoma. This is because the



(a) (b)

Figure 3.28 Fine-needle aspirate of a thyroid nodule made with a 23 gauge needle. Two papillary fronds of cells are seen on low power (*a*). (*b*) High power of same tissue; the papillary configuration is noted. The nuclei are prominent and have a ground glass appearance, with prominent nucleoli. Nuclear inclusions, which are characteristic, are not seen in this example but are seen in Figure 8.2.

diagnosis of carcinoma depends on vascular and capsular invasion, which is only seen on histological specimen. As an example Gharib *et al.* [168] did fine-needle aspiration on 1970 patients, and 330 (17%) had indeterminate pathology. Of the 330, 253 had surgery and 60 were found to have cancer. In their series, 98 patients were diagnosed to have cancer by biopsy. In the total group, only 8% had cancer ([98 + 60]/1970), but 38% of the cancers were in the suspicious group. Planimetric evaluation of the cells does not help [170].

Thyroid aspirate is helpful in diagnosing inflammatory disease of the thyroid [171]. Aspiration should not be used indiscriminately but only if it will add information to the clinical and standard laboratory findings. I do not think it should be used routinely in diffuse goitre. The test has aided in determining the presence of metastases to the thyroid [172]. Since most of the published reports are from academic thyroid units, there is concern that the test is not applicable to routine community or district hospitals. Asp *et al.* [173] in a non-academic institute had a sensitivity and specificity of 100% for papillary cancer, but the results of their

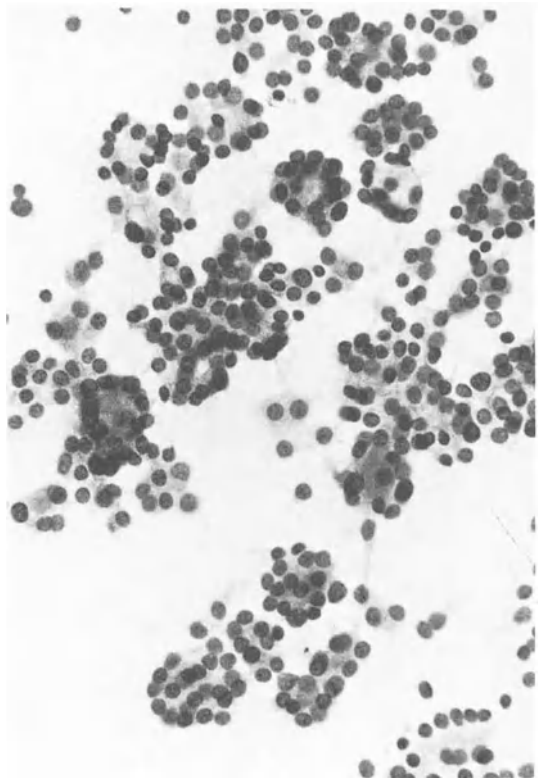


Figure 3.29 Fine-needle aspirate of a thyroid nodule with a 23 gauge needle. The aspirate shows a 'microfollicular' appearance. With this appearance, it is not possible to differentiate well-differentiated thyroid cancer from follicular adenoma. This turned out to be a follicular cancer.

entire series were sensitivity 100% and specificity 47%. Like most practitioners who use this test, they found that it increased the likelihood of finding cancer when the patient is referred to surgery. In their study, 64% of patients who had a needle aspirate and were referred to surgery had cancer, compared to only 26% of those who did not have preoperative aspiration during the same time period.

In summary, fine-needle aspiration has become accepted as a standard test in the diagnosis of dominant thyroid nodules. The published results indicate that the test has good sensitivity and specificity, but the problem of the indeterminate pathology is not resolved. The number of patients with a nodule who are referred to surgery should be less than when scintigraphy and ultrasound are used, and the proportion of patients found to have cancer at operation should be increased. Additional discussion of this topic is presented in Chapter 5 in the section on autonomous nodule, and Chapter 7 on management of thyroid nodules.

3.7 MISCELLANEOUS TESTS

3.7.1 THYROGLOBULIN

Measurement of thyroglobulin in the serum provides very important clinical information about patients who have had surgical and/or additional radioiodine therapy for differentiated thyroid cancer. If there is no functioning thyroid tissue (normal/or malignant), there should be no thyroglobulin in the circulation. Based on this measurement, it would appear straightforward to define whether a patient is free of differentiated thyroid cancer. However, a substantial proportion of patients with papillary cancer, which is the most common thyroid cancer, have in their circulation antibodies to thyroglobulin. We found this in 40% of the first group of patients we studied [174]. Conventional radioimmunoassays for thyroglobulin cannot function with accuracy in the presence of the antibody against the antigen that is being measured. We use a sandwich-type immunoradiometric assay to overcome this problem [175, 176]. Not all commercially available assays are of this type, and the differences in the assays result in important clinical implications [177].

There are many publications attesting to the value of thyroglobulin in excluding or diagnosing the presence of metastatic differentiated cancer [178–189]. In our original study comparing thyroglobulin measurements with whole-body radioiodine 131

scintiscans, the blood test had a sensitivity of 100% and a specificity of 83% [174]. In this situation, the patients had discontinued suppressive thyroxine for 4 weeks and had elevated TSH values, which are known to increase thyroglobulin levels if there is any functioning thyroid tissue. Therefore, whether the patient is taking thyroxine should be recorded. Black *et al.* [183] evaluated thyroglobulin measurements in 274 patients, 266 of whom had thyroid surgery and 183 also had postoperative radioiodine treatment. With the patients taking thyroxine, thyroglobulin predicted correctly the presence or absence of disease in 97.5%; when the patients were off thyroxine this figure fell to 84%. The results have to be interpreted in relation to the amount of residual thyroid tissue left postoperatively. We accept as normal values up to and equal to 10 ng/ml in those who have one lobe. However, if all thyroid has been ablated thyroglobulin should be undetectable [184]. Using these criteria, sensitivity and specificity for patients who had had ablation and were on thyroxine were 97% and 96% respectively; for those with residual thyroid the results were 97% and 87%. When thyroxine was stopped for 4 weeks, the statistics were lower. The sensitivity and specificity for those with no thyroid tissue were 79% and 95% respectively, and in those with residual thyroid 94% and 71%. Somewhat against these overall favourable results. Coakley *et al.* [185] found the test to be of little use, with 5 of 10 patients having false-negative results. Similarly, Moser *et al.* [186] found 30 out of 158 patients had a positive ^{131}I scan but undetectable thyroglobulin, and they recommend that thyroglobulin should not be substituted for a ^{131}I scan until a negative scan is obtained. In spite of these negative results, it is very unusual for thyroglobulin to be undetectable in the presence of widespread metastases [187]. I find this test extremely valuable. It gives an independent index of the status of patients with differentiated thyroid cancer which can be evaluated along with a whole-body ^{131}I scan. In many patients it reduces the number of follow-up scans. However, it should only be used as the sole method of follow-up when a ^{131}I scan is negative.

Thyroglobulin levels are high in many benign thyroid conditions, including non-toxic goitre [188] and benign nodules [189]. It cannot be used as a screening test for the presence of cancer. Similarly, Schneider *et al.* [190] did not find any difference in thyroglobulin levels in patients with benign or malignant thyroid nodules after external neck irradiation.

3.7.2 CALCITONIN

Calcitonin is a valuable serum marker for medullary cancer [200]. It is analogous to thyroglobulin. If the patient has had a total thyroidectomy, there should be no calcitonin, and serum values rise when there is a recurrence. Unfortunately, there is no single radionuclide like ^{131}I which can be used to diagnose and treat medullary cancer. The test is important in screening relatives of a patient with known medullary cancer [201], and there are provocative tests using calcium and pentagastrin which increase the sensitivity of the measurement [202]. This is expanded under medullary cancer in Chapter 8.

3.7.2 ANTITHYROID ANTIBODIES

There is abundant evidence that several of the common and important thyroid diseases are autoimmune. These include Graves' disease; Hashimoto's throiditis, primary hypothyroidism and simple non-toxic goitre. Antithyroid antibodies are found in the circulation of patients with these disorders. The antibodies cause the pathophysiology in some instances, such as thyroid receptor antibody (TRAb) in Graves' disease; others appear to be simply markers of the presence

of autoimmunity. The antibodies which are of diagnostic importance are antithyroglobulin (antiTg), antimicrosomal (antiM), TRAb, and thyroid growth antibodies or immunoglobulins (TGI). There are different methods of measuring each of these. AntiTg was originally measured by tanned red cell agglutination [191], but solid-phase radioimmunoassay is more sensitive [192, 193]. Using the latter, positive results are found in more than 90% of patients with Graves' disease and Hashimoto's thyroiditis, and many with primary hypothyroidism. AntiM, which is thought to be an antibody against thyroid peroxidase, was originally detected by complement fixation, but is also detected with more sensitivity using solid-phase radioimmunoassay. More than 90% of patients with Graves' disease and Hashimoto's thyroiditis have this in their circulation. These tests are not specific, since from 15–20% of apparently normal people have circulating thyroid antibodies, albeit at low titres. It is not clear if they have a forme fruste of autoimmune thyroiditis, or not. These assays are of value in the diagnosis of Hashimoto's thyroiditis. High titres of these antibodies in a euthyroid patient with a diffuse goitre establish this diagnosis. I seldom use these measurements in the diagnosis of Graves' disease since the clinical features of hyperthyroidism, diffuse goitre and ophthalmopathy, define that disease. There are some clinicians who believe that the presence of high levels of antibodies predict subsequent hypothyroidism and, therefore, they alter the therapeutic approach, e.g. they treat with antithyroid drugs or remove less thyroid at operation [194]. I do not subscribe to this philosophy.

TRAb was originally discovered by Adams and Purves [195], and because it has a longer time-activity course than TSH, it was called long-acting thyroid stimulator (LATS). This topic is expanded in Chapter 5. Two recent excellent, well-referenced, reviews are recommended [196, 197]. Although the evolution of knowledge of these antibodies has given us remarkable insight into the pathophysiology of Graves' hyperthyroidism, they are of less diagnostic relevance because the diagnosis can be made without them and treatment is not influenced by the result. One exception to this is in the pregnant woman with Graves' disease, in whom high titres of TRAb should alert the clinicians to the possibility of neonatal hyperthroidism due to transplacental passage of this immunoglobulin. Growth-promoting antibodies have been discovered more recently, and have provided us with the concept that goitrous conditions associated with euthyroidism and negative antiTg and antiM are caused by other anti-TSH receptor antibodies which produce cell hyperplasia [198]. Their role in clinical thyroidology is not defined. The topic of thyroid autoimmunity is discussed in relevant chapters in more detail. Those readers interested in the historical background of the discoveries of thyroid autoimmunity are referred to *Autoimmunity* [199].

3.7.4 TESTS OF THYROID ACTION ON PERIPHERAL TISSUES

One of the most important thyroid tests from the 1920s for three decades was the basal metabolic rate [203]. Basal metabolism is increased in hyperthyroidism and decreased in hypothyroidism, but there is significant overlap with normal results, logistic difficulties in conducting the test, and several non-thyroidal conditions which increase the result (polycythaemia, leukaemia, pregnancy, cardiac failure and phaeochromocytoma) and decrease the result (adrenal insufficiency, nephrotic syndrome and cachexia), so that it is of no value. The last time I wanted to do this test for a research project, the equipment could not be located!

Thyroid hormones affect almost every tissue and organ, and excess or insufficiency produce secondary changes, such as high

Table 3.9 Tests of thyroid function in various uncomplicated thyroid conditions

To prove suspected condition	*First tests*	*Secondary*
Euthyroidism	TSH FT_4	
Hyperthyroidism	TSH FT_4	T_3
Hypothyroidism	TSH FT_4	
Hashimoto's	TSH FT_4 antiTg+M	
Non-toxic goitre	TSH FT_4	
Single nodule	FNA	Scintigram/sonogram
Multinodular goitre	TSH FT_4	Scintigram
Subacute thyroiditis	TSH FT_4	Uptake
Silent thyroiditis	TSH FT_4 antiTg+M	Uptake
Sick euthyroid*	TSH FT_4	

* Only if suspicion of thyroid disease is high.

cholesterol in hypothyroidism and shortened systolic time intervals in hyperthyroidism. However, none of the tests of peripheral effect of thyroid hormones has sufficiently good sensitivity and specificity to recommend their use diagnostically. The corollary, however, is that a high cholesterol without any explanation should prompt measurement of FT_4 and TSH to ensure that hypothyroidism is not overlooked.

Table 3.9 lists the tests which are recommended in uncomplicated common thyroid conditions. More detailed approaches are presented in each of the chapters dealing with specific diseases.

KEY FACTS

- Because thyroid dysfunction is common and suspected thyroid dysfunction very common, laboratory testing is necessary in many patients.
- Testing can evaluate plasma thyroid hormones, the pituitary thyroid axis and the hypothalamic-pituitary thyroid axis.
- Imaging of thyroid can give excellent anatomic details (ultrasound and CT) or functional information (radionuclide).
- Total thyroid hormone levels are altered, not only by changes in thyroid status, but also by changes in binding proteins.
- In general, hyperthyroidism and increased levels of binding proteins cause high levels of total T_4 and T_3.
- In general, hypothyroidism and low levels of binding proteins cause low levels of total T_4 and T_3.
- Ill-health and starvation can produce inappropriately low total hormone values.
- There are mathematical methods of determining free thyroid hormone levels, but they are not truly measuring free hormone.
- The commonest mathematical derivation is $(T_4 \times T_3RU)/100$.
- There are several methods for measuring FT_4, the gold standard is dialysis, the most cost and time effective is a two-step radioimmunoassay.
- One-step FT_4 measurements should not be relied on, especially in ill patients.
- New methods for measuring TSH using two antibodies against the alpha and beta chains of TSH respectively, allow both low and high values to be differentiated from normal values.
- Low TSH values are characteristic of hyperthyroidism.
- High TSH values are characteristic of hypothyroidism.
- The best combination of tests is FT_4 and TSH.
- The amount of rise in TSH after an in-

travenous injection of TRH is useful in differentiating hypothalamic from pituitary disease.

- TRH test has been largely replaced by TSH measurement in diagnosing thyroid dysfunction.
- Measurement of thyroid trapping of ^{123}I is valuable in diagnosing and planning therapy in hyperthyroidism.
- Scintigraphy with ^{123}I can be useful in some patients with nodules (to determine their function) and in patients with suspected substernal thyroid.
- Whole-body scintigraphy with ^{131}I is valuable in determining the extent of differentiated thyroid cancer in patients who have had surgical thyroidectomy.
- Other radionuclides such as ^{201}Tl and ^{67}Ga have a small role in defining extent of thyroid cancer.
- In differentiated thyroid cancer, the serum thyroglobulin (Tg) level is very valuable to determine the extent of the disease and response to therapy.
- In medullary cancer, the serum calcitonin level is a useful indicator of the extent of the disease and response to treatment.
- Several imaging techniques, such as ultrasound, CT and NMRI, give excellent anatomic detail of the thyroid, neck and mediastinum.
- These tests do not show function and do not differentiate benign from malignant disease.
- Fluorescent imaging is a method for determining the inorganic iodine content of the thyroid.

REFERENCES

1 Shimaoka, K. (1973) Toxic adenoma of the thyroid with triiodothyronine as the principal circulating thyroid hormone. *Acta Endocrinol.*, **43**, 285–93.

2 Popma, B.H,. Cloutier, M.D. and Hayles, A.B. (1973) Thyroid nodule producing T_3 toxicosis in a child. *Mayo Clin. Proc.*, **48**, 273–5.

3 Hollander, C.S., Shenkman, L., Mitsuma, T. *et al.* (1971) Hypertriiodothyroninaemia as a premonitary manifestation of thyrotoxicosis. *Lancet*, **2**, 731–3.

4 Hollander, C.S., Mitsuma, T., Nihei, N. *et al.* (1971) Clinical and laboratory observations in cases of triiodothyronine toxicosis confirmed by radioimmunoassay. *Lancet*, **1**, 731–3.

5 Shenkman, L., Mitsuma, T., Blum, M. *et al.* (1972) Recurrent hyperthyroidism presenting as triiodothyronine toxicosis. *Ann. Intern. Med.*, **77**, 410–13.

6 Sung, L.C. and Cavalieri, R.R. (1973) T_3 toxicosis due to metastatic thyroid carcinoma. *J. Clin. Endocrinol. Metab.*, **36**, 215–17.

7 Engler, D., Donaldson, E.B., Stockigt, J.R. *et al.* (1978) Hyperthyroidism without triiodothyronine excess: an effect of severe non-thyroidal illness. *J. Clin. Endocrinol, Metab.*, **46**, 77–82.

8 Caplan, R.H., Pagliara, A.S. and Wickus, G. (1980) Thyroxine toxicosis. A common variant of hyperthyroidism. *JAMA*, **244**, 1934–8.

9 Ogbuawa, O. and Johnson, R. (1980) T_4-toxicosis storm in pernicious anemia. *Arch. Intern. Med.*, **140**, 1245–6.

10 Evered, D., Ormston, B.J., Smith, P.A. *et al.* (1973) Grades of hypothyroidism. *Br. Med. J.*, **1**, 657–62.

11 Bermudez, F., Surks, M.I. and Oppenheimer, J.H. (1975) High incidence of decreased serum triiodothyronine concentration in patients with nonthyroidal disease. *J. Clin. Endocrinol. Metab.*, **41**, 27–40.

12 Chopra, I.J., Chopra, U., Smith, S.R. *et al.* (1975) Reciprocal changes in serum concentrations of 3,3′,5′-triiodothyronine (reverse T_3) and 3,3′,5-triiodothyronine (T_3) in systemic illness. *J. Clin. Endocrinol. Metab.*, **41**, 27–40.

13 Croxon, M.S. and Ibbertson, H.K. (1977) Low serum triiodothyronine (T_3) and hypothyroidism in anorexia nervosa. *J. Clin. Endocrinol. Metab.*, **44**, 167–74.

14 Chopra, I.J., Solomon, D.H., Hepner, G.W. *et al.* (1979) Misleadingly low free thyroxine index and usefulness of reverse triiodothyronine measurement in nonthyroidal illness. *Ann. Intern. Med.*, **90**, 905–12.

15 Wood, D.G., Cyrus, J. and Samols, E. (1980) Low T_4 and low FT_4I in seriously ill patients: concise communication. *J. Nucl. Med.*, **21**, 432–5.

16 Bayer, M.F. and McDougall, I.R. (1982) Free thyroxine by solid phase radioimmunoassay: improvement in the laboratory diagnosis of thyroid status in severely ill patients. *Clin. Chim. Acta*, **118**, 209–18.

17 Gavin, L.A., Rosenthal, M. and Cavalieri, R.R. (1979) The diagnostic dilemma of isolated hyperthyroxinemia in acute illness. *JAMA*, **242**, 251–3.
18 Cohen, K.L. and Swigar, M.E. (1979) Thyroid function screening in psychiatric patients. *JAMA*, **242**, 254–7.
19 Spratt, D.I., Pont, A., Miller, M. *et al.* (1982) Hyperthyroxinemia in patients with acute psychiatric disease. *Am. J. Med.*, **73**, 41–8.
20 Burr, W.A., Ramsden, D.B., Evans, S.E. *et al.* (1977) Concentration of thyroxine-binding globulin: value of direct assay. *Br. Med. J.*, **1**, 485–8.
21 Dos Remedios, L.V., Weber, P.M., Feldman, R. *et al.* (1980) Detecting unsuspected thyroid dysfunction by the free thyroxine index. *Arch. Intern. Med.*, **140**, 1045–9.
22 Ingbar, S.H., Braverman, L.E., Dawber, N.A. *et al.* (1965) A new method for measuring the free thyroxine hormone in human serum and an analysis of the factors that influence its concentration. *J. Clin. Invest.*, **44**, 1679–89.
23 Sterling, K. and Brenner, M.A. (1966) Free throxine in human serum; simplified measurement with the aid of magnesium precipitation. *J. Clin, Invest.*, **45**, 153–63.
24 Kaptein, E.M., Macintyre, S.S., Weiner, J.M. *et al.* (1981) Free thyroxine estimates in nonthyroidal illnesses: comparison of eight methods. *J. Clin, Endocrinol. Metab.*, **52**, 1073–7.
25 Szpunar, W.E., Block, M., Bernarz, M.N. *et al.* (1980) Clinical evaluation of three free-thyroxine assays. *J. Nucl. Med.*, **21**, 576–8.
26 Witherspoon, L.R., Shuler, S.E., Garcia, M.M. *et al.* (1980) An assessment of methods for the estimation of free thyroxine. J. Nucl. Med., 21; 529–39.
27 Melmed, S., Geola, F.L., Reed, A.W. *et al.* (1982) A comparison of methods for assessing thyroid function in nonthyroidal illness. *J. Clin, Endocrinol. Metab.*, **54**, 300–6.
28 Bayer, M.F. (1983) Free thyroxine results are affected by albumin concentrations and nonthyroidal illness. *Clin. Chim. Acta*, **130**, 391–6.
29 Bayer, M.F. and McDougall, I.R. (1980) Radioimmunoassay of free thyroxine in serum. Comparison with clinical findings and results of conventional thyroid function tests. *Clin. Chem.*, **26**, 1186–92.
30 Mcdougall, I.R., Bayer, M.F., Nierenberg, D. *et al.* (1982) Disparate effects of heparin on free thyroxine measured by two different radioimmunoassays. *J. Nucl. Med.*, **23**, 507–10.
31 Bayer, M.F. and McDougall, I.R. (1984) Clinical assessment of a radioimmunoassay for free thyroxine using a modified tracer. *J. Nucl. Med.*, **25**, 402–5.
32 Chopra, I.J., Van Herle, A.J., Teco, G.N.C. *et al.* (1980) Serum free thyroxine in thyroidal and non-thyroidal illnesses: comparison of measurements by radioimmunoassay, equilibrium dialysis and free thyroxine index. *J. Clin. Endocrinol, Metab.*, **51**, 135–43.
33 Hershman, J.M., Jones, C.M. and Bailey, A.L. (1972) Reciprocal changes in thyrotropin and free thyroxine produced by heparin. *J. Clin. Endocrinol, Metab.*, **34**, 574–9.
34 Utiger, R.D. (1965) Radioimmunoassay of plasma thyrotropin. *J. Clin. Invest*, **44**, 1277–86.
35 Odell, W.D., Wilber, J.F. and Paul, W.E. (1965) Radioimmunoassay of thyrotropin in human serum. *J. Clin. Endocrinol. Metab.*, **25**, 1179–88.
36 Ridgway, E.C. (1988) Thyrotropin radioimmunoassay: birth, life and demise. *Mayo Clin. Proc.*, **63**, 1028–34.
37 Bayer, M.F., Kriss, J.P. and McDougall, I.R. (1985) Clinical experience with sensitive thyrotropin measurements. Diagnostic and therapeutic implications. *J. Nucl. Med.*, **26**, 1248–56.
38 Toft, A.D. (1988) Use of sensitive immunoradiometric assay for thyrotropin in clinical practice. *Mayo Clin. Proc.*, **63**, 1035–42.
39 Hershman, J.M., Pekary, A.E., Smith, V.P. *et al.* (1988) Evaluation of five high-sensitivity American thyrotropin assays. *Mayo Clin. Proc.*, **63**, 1133–9.
40 Klee, G.G. and Hay, I.D. (1988) Sensitive thyrotropin assays: analytic and clinical performance criteria. *Mayo Clin. Proc.*, **63**, 1123–32.
41 Caldwell, G., Kellett, H.A., Gow, S.M. *et al.* (1985) A new strategy for thyroid function testing. *Lancet*, **1**, 1117–19.
42 Blunt, S., Woods, C.A., Joplin, G.F. *et al.* (1988) The role of a highly sensitive amplified enzyme immunoassay for thyrotropin in the evaluation of thyrotroph function in hypopituitary patients. *Clin. Endocrinol.*, **29**, 387–93.
43 Utiger, R.D. (1988) Thyrotropin measurments: past, present and future. *Mayo Clin. Proc.*, **63**, 1053–6.
44 Makoviak, J.A., McDougall, I.R., Bayer, M.F. *et al.* (1987) Significance of thyroid dysfunction in human cardiac allograft procurement. *Transplantation*, **43**, 824–6.

45 Bayer, M.F., Makoviak, J.A., McDougall, I.R. (1987) Diagnostic performance of sensitive measurements of thyrotropin during severe non-thyroidal illness: their role in the diagnosis of hyperthyroidism,. *Clin. Chem.*, **33**; 2178–84.
46 Schally, A.V. (1978) Aspects of hypothalamic regulation of the pituitary gland (Nobel Prize lecture December 1977). *Science*, **202**, 18–28.
47 Guillemin, R. (1978) Peptides in the brain: the new endocrinol of the neurone (Nobel Prize lecture December 1977). *Science*, **202**; 390–402.
48 Ormston, B.J. Garry, R., Cryer, R.J. *et al.* (1971) Thyrotrophin-releasing hormone as a thyroid-function test. *Lancet*, **2**, 10–14.
49 Fleischer, N., Lorente, M., Kirkland, J. *et al.* (1972) Synthetic thyrotropin releasing factor as a test of pituitary thyrotropin reserve. *J. Clin. Endocrinol. Metab.*, **34**, 617–24.
50 Jackson, I.M.D. (1982) Thyrotropin-releasing hormone. *N. Engl. J. Med.*, **306**, 145–55.
51 Snyder, P.J. and Utiger, R.D. (1972) Response to thyrotropin-releasing hormone (TRH) in normal man. *J. Clin. Endocrinol. Metab.*, **34**, 380–5.
52 Borowski, G.D., Garofano, C.D., Rose, L.I. *et al.* (1984) Blood pressure response to thyrotropin releasing hormone in euthyroid subjects. *J. Clin. Endocrinol. Metab.*, **58**, 197–200.
53 Loosen, P.T. (1988) Thyroid function in affective disorders and alcoholism. *Neurol. Clinics*, **6**, 55–82.
54 Hamilton, J.G. and Soley, M.H. (1939) Studies in iodine metabolism by use of a new radioactive isotope of iodine. *Am. J. Physiol.*, **127**; 557–72.
55 Hamilton, J.G. and Soley, M.H. (1940) Studies in iodine metabolism of the thyroid gland *in situ* by use of radioiodine in normal subjects and in patients with various types of goiters. *Am. J. Physiol.*, **131**, 135–43.
56 Jaffe, H.I. and Ottoman, R.E. (1950) Evaluation of radioiodine test for thyroid function. *JAMA*, **143**, 515–19.
57 Vanderlaan, W.P. (1957) Accumulation of radioactive iodine. *N. Engl. J. Med.*, **257**, 752–6.
58 Pittman, J.A., Dailey, G.E. and Beschi, R.J. (1969) Changing normal values for thyroidal radioiodine uptake. *N. Engl. J. Med.*, **280**, 1431–4.
59 Bernard, J.D., McDonald, R.A. and Nesmith, J.A. (1970) New normal ranges for the radioiodine uptake study. *J. Nucl. Med.*, **11**, 449–51.
60 Caplan, R.H. and Kujak, R. (1971) Thyroid uptake of radioactive iodine: a re-evaluation. *JAMA*, **215**, 916–18.
61 Hooper, P.L. and Caplan, R.H. (1977) Thyroid uptake of radioactive iodine in hyperthyroidism. *JAMA*, **238**, 411–13.
62 Atkins, H.L. (1971) Technetium-99m pertechnetate uptake and scanning in the evaluation of thyroid function. *Semin. Nucl. Med.*, **1**, 345–55.
63 Querido, A. and Stanbury, J.B. (1950) The response of the thyroid to thyrotropic hormone as an aid in the differential diagnosis of primary and secondary hypothyroidism. *J. Clin. Endocrinol, Metab.*, **10**, 1192–201.
64 Krishnamurthy, G.T. (1978) Human reaction to bovine TSH: concise communication. *J. Nucl. Med.*, **19**, 284–6.
65 Al-Aid, M.A., Al-Attar, R.A. and Al Hindawi Ay (1987) Clinical utility of a simple physical technique in thyroid scintigraphy. *Eur. J. Nucl. Med.*, **13**, 443–5.
66 Werner, S.C. and Spooner, M. (1955) A new and simple test for hyperthyroidism employing L-triiodothyronine and the 24 hour I-131 uptake method. *Bull. New York Acad. Med.*, **31**, 137–45.
67 Oddie, T.H., Rundle, F.F., Thomas, I.D. *et al.* (1960) Quantitative observations with the thyroxine suppression test of thyroid function. *J. Clin. Endocrinol. Metab.*, **20**, 1146–57.
68 Greer, M.A. and Smith, G.E. (1954) Method for increasing the accuracy of the radioiodine uptake as a test for thyroid function by the use of dessicated thyroid. *J. Clin. Endocrinol. Metab.*, **14**, 1374–84.
69 Alexander, W.D., Harden, R. McG., Schimmins, J. *et al.* (1967) Treatment of thyrotoxicosis based on thyroidal suppressibility. *Lancet*, **2**, 681–8.
70 Morgans, M.E. and Trotter, W.R. (1957) Defective organic binding of iodine by the thyroid in Hashimoto's thyroiditis. *Lancet*, **1**, 553–5.
71 McGirr, E.M. and Greig, W.R. (1968) Genetics and the thyroid. *Medicine Today*, **2**, 21–8.
72 Silver, S. (1968) The thyroid gland and ^{131}I, in *Radioactive Nuclides in Medicine and Biology*, Lea and Febiger, Philadelphia, pp. 1–143.
73 Klopowitz, J.M. and Solomon, D.H. (1971) Tests of thyroid function, in *Nuclear Medicine*, (2nd edn), (ed. W.H. Blahd), McGraw Hill, New York, pp. 175–226.
74 Wolff, J. (1969) Iodide goiter and the pharmacological effects of excess iodide. *Am. J. Med.*, **47**, 101–24.

75 Floyd, S.C., Beierwaltes, W.H., Odoson, V.N. *et al.* (1960) Defective iodination of tyrosine a cause of nodular goiter? *J. Clin. Endocrinol. Metab.*, **20**, 881–8.
76 Baschieri, L., Benedetti, G., De Luca, F. *et al.* (1963) Evaluation and limitations of the perchlorate test in the study of thyroid function. *J. Clin. Endocrinol. Metab.*, **23**, 786–91.
77 Stewart, R.D.H. and Murray, I.P.C. (1966) An evaluation of the perchlorate discharge test. *J. Clin. Endocrinol. Metab.*, **26**, 1050–8.
78 Trotter, W.R. (1962) *Diseases of the Thyroid*, 1st edn, F.A. Davis Co, Philadelphia, pp. 168–70.
79 Gray, H.W., Hooper, L.A. and Greig, W.R. (1973) An evaluation of the twenty-minute perchlorate discharge test. *J. Clin. Endocrinol. Metab.*, **37**, 351–5.
80 Cassen, B., Curtis, L., Reed, C. *et al.* (1951) Instrumentation for I^{131} use in medical studies. *Nucleonics*, **9**, 46–50.
81 Allen, H.C. Jr., Goodwin, W.E. (1952) The scintillation counter as an instrument for the *in vivo* determination of thyroid weight. *Radiology*, **58**, 68–79.
82 Bauer, F.K., Goodwin, W.E., Barrett, T.F. *et al.* (1952) Scintigrams of the thyroid gland. *Calif. Med.*, **77**, 380–2.
83 Hurley, P.J., Strauss, H.W., Pavoni, P. *et al.* (1971) The scintillation camera with pinhole collimator in thyroid imaging. *Radiology*, **101**, 133–4.
84 Sostre, S., Ashare, A.B., Quinones, J.D. *et al.* (1978) Thyroid scintigraphy: pinhole images versus rectilinear scan. *Radiology*, **129**, 759–62.
85 McDougall, I.R. and Kriss, J.P. (1976) Which radioisotope for diagnosis of thyroid disorders? *Clin. Nucl. Med.*, **2**, 235–8.
86 Ripley, S.D., Freitas, J.E. and Nagle, C.E. (1984) Is thyroid scintigraphy necessary before I-131 therapy for hyperthyroidism? Concise communication. *J. Nucl. Med.*, **25**, 664–7.
87 Ashkar, F.S. (1981) Thyroid imaging and function studies. *Clin. Nucl. Med.*, **6**, 77–86.
88 Datz, F.L. (1987) *Gamuts in Nuclear Medicine*, Appleton & Large, Norwalk.
89 Freitas, J.E., Gross, M.D. and Ripley, S. (1985) Radionuclide diagnosis and therapy of thyroid cancer: current status report. *Semin. Nucl. Med.*, **15**, 106–31.
90 Nelson, R.L., Wahner, H.W. and Gorman, C.A. (1978) Rectilinear thyroid scanning as a predictor of malignancy. *Ann. Intern. Med.*, **88**, 41–4.
91 O'Holleran, L.W., O'Holleran, T.P., Mills, G.Q. *et al.* (1982) Use of thyroid scans in the selection of surgical patients. *Am. J. Surg.*, **144**, 639–40.
92 Karelitz, J.R. and Richards, J.B. (1974) Necessity of oblique views in evaluating functional status of a thyroid nodule. *J. Nucl. Med.*, **15**, 782–5.
93 Nagai, G.R., Pitts, W., Basso, L. *et al.* (1987) Scintigraphic 'hot nodules' and thyroid cancer. *Clin. Nucl. Med.*, **12**, 123–7.
94 Fukata, S., Tamai, W., Matsubayashi, S. *et al.* (1987) Thyroid cancer and hot nodule. *Eur. J. Nucl. Med.*, **13**, 313–14.
95 Sandler, M.P., Fellmeth, B., Salhany, K.E. *et al.* (1988) Thyroid carcinoma masquerading as a benign hyperfunctioning nodule. *Clin. Nucl. Med.*, **13**, 410–15.
96 Shambaugh, G.E., Quinn, J.L., Oyasu, R. *et al.* (1974) Disparate thyroid imaging. *JAMA*, **228**, 866–9.
97 Erjavec, M., Movrin, T., Auerspere, M. *et al.* (1977) Comparative accumulation of ^{99m}TC and ^{131}I in thyroid nodules: case report. *J. Nucl. Med.*, **18**, 346–7.
98 Barth, J.D., Bakker, W.H., Henneman, G. *et al.* (1978) Discrepancies between iodine and technetium thyroid scintigraphy. *JAMA*, **240**, 463–4.
99 Hirabayashi, S., Koga, Y., Kitahara, T. *et al.* (1975) Inconsistent images of thyroid nodule scintigrams made with iodine and pertechnate: case report. *J. Nucl. Med.*, **16**, 918.
100 Turner, J.W. and Spencer, R.P. (1976) Thyroid carcinoma presenting as a pertechnetate 'hot' nodule, but without ^{131}I uptake: case report. *J. Nucl. Med.*, **17**, 22–3.
101 Wellman, H.N. and Anger, R.T. Jr. (1971) Radioiodine dosimetry and the use of radioiodines other then ^{131}I in thyroid diagnosis. *Semin. Nucl. Med.*, **1**, 356–78.
102 Task force on short-lived radionuclides for medical applications. Evaluation of diseases of the thyroid gland with the *in vivo* use of radionuclides. *J. Nucl. Med.*, **19**, 107–12.
103 Vieras, F. (1983) Preoperative scintigraphic detection of cervical metastasis from thyroid carcinoma with technetium-99m pertechnetate. *Clin. Nucl. Med.*, **10**, 567–9.
104 Nakayama, A.C., Nakaja, H., Zeze, F. *et al.* (1987) Thyroid cancer with a high ^{123}I-NaI uptake in primary and metastatic foci with euthyroidism. *Eur. J. Nucl. Med.*, **13**, 480–1.
105 Chen, J.S., La France, N.D., Rippin, R. *et al.* (1988) Iodine-123 SPECT of the thyroid in multinodular goiter. *J. Nucl. Med.*, **29**, 110–13.

106 Goldman, J.M., Line, B.R., Aamodt, R.L. *et al.* (1980) Influence of triiodothyronine withdrawal time on ^{131}I uptake postthyroidectomy for thyroid cancer. *J. Clin. Endocrinol. Metab.*, **50**, 734–9.
107 Rosenbaum, R.C., Johnston, G.S., Valente, W.A. (1988) Frequency of hepatic visualisation during I–131 imaging for metastatic thyroid cancer. *Clin. Nucl. Med.*, **13**, 657–60.
108 Hoschl, R., Choy, D., H-L. and Gandevia, B. (1988) Iodine-131 uptake in inflammatory lung disease: a pitfall in treatment of thyroid carcinoma. *J. Nucl. Med.*, **29**, 701–6.
109 Brachman, M.B., Rothman, B.J., Ramanna, L. *et al.* (1988) False-positive iodine-131 body scan caused by a large renal cyst. *Clin. Nucl. Med.*, **13**, 416–18.
110 Lakshmanan, M., Schaffer, A., Robbins, J. *et al.* (1988) A simplified low iodine diet in I–131 scanning and therapy of thyroid cancer. *Clin. Nucl. Med.*, **12**, 866–8.
111 Khammash, N.F., Halkar, R.K., Abdel-Dayem, H.M. (1988) The use of technetium-99m pertechnetate in postoperative thyroid carcinoma. A comparative study with iodine-131. *Clin. Nucl. Med.*, **16**, 17–22.
112 Hoffer, P. (1980) Gallium mechanisms. *J. Nucl. Med.*, **21**, 282–5.
113 Hoffer, P. (1980) Gallium and infection. *J. Nucl. Med.*, **21**, 484–8.
114 Tsan, M-F. (1985) Mechanism of gallium-67 accumulation in inflammatory lesions. *J. Nucl. Med.*, **26**, 88.
115 Higashi, T., Ito, K., Mimura, T. *et al.* (1987) Clinical evaluation of ^{67}Ga scanning in the diagnosis of anaplastic carcinoma and malignant lymphoma. *Radiology*, **141**, 491–7.
116 Seder, J., Shimshak, R. and Williams, R. (1979) Reversible ^{67}Ga citrate uptake in the thyroid with subacute thyroiditis. *Clin. Nucl. Med.*, **4**, 158–60.
117 Machac, J., Nejatheim, M. and Goldsmith, S.J. (1985) Gallium citrate uptake in crytococcal thyroiditis in a homosexual man. *J. Nucl. Med. All. Sci.*, **29**, 283–5.
118 Soin, J.S. (1987) Quantitative estimation of ^{67}Ga citrate in hypofunctioning thyroid nodules. *Radiology*, **122**, 243–5.
119 Ling, M.C.C., Dake, M.D. and Okerlund, M.D. (1988) Gallium uptake in the thyroid gland in amiodarone-induced hyperthyroidism. *Clin. Nucl. Med.*, **13**, 258–9.
120 Moreno, A.J., Brown, J.M., Salinas, J.A *et al.* (1984) Ga-67 positivity in sarcoidosis of the skin with coincident thyroid uptake of uncertain etiology. *Clin. Nucl. Med.*, **9**, 165–6.
121 Moreno, A.J., Brown, J.M., Spicer, M.J. *et al.* (1985) Thyroid localization of Ga-67 citrate. *Semin. Nucl. Med.*, **15**, 224–5.
122 Allard, J.C., Lee, V.W. and Franklin, P. (1988) Thyroid uptake of gallium in Graves' disease. *Clin. Nucl. Med.*, **16**, 663–6.
123 Fukuchi, M., Tachibana, K., Nishikawa, A. *et al.* (1978) Thallium-imaging in thyroid carcinoma – appearance of a lymph-node metastasis. *J. Nucl. Med.*, **19**, 195–6.
124 Tonami, N. and Hisada, K. (1980) ^{201}Tl scintigraphy in post operative detection of thyroid cancer: comparative study with ^{131}I. *Radiology*, **136**, 461–4.
125 Brendel, A.J. Guyot, M., Lefort, G. *et al.* (1988) Thallium-201 imaging in the follow-up of differentiated thyroid carcinoma. *J. Nucl. Med.*, **29**, 1515–20.
126 Corstens, F., Huysmans, D. and Kloppenberg, P. (1988) Thalium-201 scintigraphy of the suppressed thyroid: an alternative for iodine-123 scanning after TSH stimulation. *J. Nucl. Med.*, **29**, 1360–3.
127 Hoefnagel, C.A., Delprat, C.C., Zanin, D. *et al.* (1988) New radionuclide tracers for the diagnosis and therapy of medullary thyroid carcinoma. *Clin. Nucl. Med.*, **16**, 159–65.
128 Keeling, C.A. and Basso, L.V. (1988) Iodine-131 MIBG uptake in metastatic medullary carcinoma of the thyroid. *Clin. Nucl. Med.*, **16**, 260–3.
129 James, E.M. and Charboneau, J.W. (1985) High-frequency (10 MHz) thyroid ultrasonography. *Semin. Ultrasound CT MR*, **6**, 294–309.
130 Blum, M. (1986) Ultrasonography and computed tomography of the thyroid gland, in *Werner's The Thyroid*, 5th edn, (eds S.H. Ingbar and L.E. Braverman) Lippincott Company, Philadelphia, pp. 576–91.
131 Simeone, J.F., Daniels, G.H., Mueller, P.R. *et al.* (1982) High-resolution real-time sonography of the thyroid, *Radiol.*, **145**, 431–5.
132 Hammer, M., Wortsman, J. and Folse, R. (1982) Cancer in cystic lesions of the thyroid. *Arch. Surg.*, **117**, 1020–3.
133 Walker, J., Findlay, D., Amar, S.S. *et al.* (1985) A prospective study of thyroid ultrasound scan in the clinically solitary thyroid nodule. *Br. J. Radiol.*, **58**, 617–19.
134 Carroll, B. (1980) Personal communication.
135 Hoffer, P.B., Jones, W.D., Crawford, R.B., *et al.* (1968) Fluorescent thyroid scanning. A new method of imaging the thyroid. *Radiology*, **90**, 342–4.
136 Hoffer, P.B. and Gottschalk, A. (1971)

Fluorescent thyroid scanning. Scanning without radioisotopes. Initial clinical results. *Radiology.*, **99**, 117–23.
137 Patton, J.A. and Sandler, M.P. (1986) X-ray fluorescent scanning, in *Thyroid and Parathyroid Imaging*, (eds M.P. Sandler, J.A., Patton and C.L. Partain), Appleton-Century-Crofts, Norwalk, Conn., pp. 247–74.
138 Meignan, M. and Galle, P. (1980) Principles and clinical application of thyroid scanning with x-ray fluorescence. *Clin. Nucl. Med.*, **5**, 71–80.
139 Patton, J.A., Hollifield, J.W., Brill, A.B. *et al.* (1976) Differentiation between malignant and benign solitary thyroid nodules by fluorescent scanning. *J. Nucl. Med.*, **17**, 17–21.
140 Johnson, P.M., Esser, P.D. and Lister, D.B. (1979) Fluorescent thyroid imaging. Clinical evaluation of an alternative instrument. *Radiology*, **130**, 219–22.
141 Silverman, P.M., Neuman, G.E., Korobkin, M. (1984) Computed tomography in the evaluation of thyroid disease. *AJR*, **142**, 897–902.
142 Binder, R.E., Pugatch, R.D. and Faling, L.J. (1980) Diagnosis of posterior mediastinal goiter by computed tomography. *J. Computer Assist. Tomograph.* **4**, 550–2.
143 Bashist, B., Ellis, K. and Gold, R.P. (1983) Computed tomography of intrathoracic goiters. *AJR*, **140**, 455–60.
144 Enzmann, D.R., Donaldson, S.S. and Kriss, J.P. (1979) Appearance of Graves' disease on orbital computed tomography. *J. Computer Assist. Tomograph*, **3**, 815–19.
145 Sandler, M.P., Patton, J.A., Sacks, G.A. *et al.* (1984) Evaluation of intrathoracic goiter with I-123 scintigraphy and nuclear magnetic resonance imaging. *J. Nucl. Med.*, **25**, 874–6.
146 Smith, F.W., Runge, V.M., Sandler, M.P. *et al.* (1986) Magnetic resonance imaging in thyroid disease, in *Thyroid and Parathyroid Imaging*, (eds M.P. Sandler, J.A. Patton and C.L. Partain), Appleton-Century-Crofts, Norwalk, Conn., pp. 333–49.
147 Einhorn, J. and Franzen, S. (1962) Thin-needle biopsy in the diagnosis of thyroid disease. *Acta Radiol.*, **58**, 321–5.
148 Crile, G.W. Jr and Hazard, J.B. (1951) Classification of thyroiditis with special reference to use of the needle biopsy. *J. Clin. Endocrinol. Metab.*, **11**, 1123–7.
149 Crile, G.W. Jr and Vickery, A.L. Jr (1952) Special uses of the Silverman needle in office practice and at operation. *Am. J. Surg.*, **83**, 83–5.
150 Wang, C-A. and Vickery, A.L. Jr (1976) Needle biopsy of the thyroid. *Surg. Gyn. Obstet.*, **143**, 365–8.
151 Van Herle, A.J., Rich, P., Ljung, B.M.E. *et al.* (1982) The thyroid nodule. *Ann. Intern. Med.*, **96**, 221–32.
152 Blum, M. (1984) The diagnosis of the thyroid nodule using aspiration biopsy and cytology. *Arch. Intern. Med.*, *144*, 1140–42.
153 Katz, A.D. and Dunkleman, D. (1984) Needle aspiration of non-functioning parathyroid cysts. *Arch. Surg.*, **119**, 307–8.
154 Burch, W. (1983) Fine-needle aspiration biopsy of the thyroid gland. *Ann. Intern. Med.*, **98**, 1024–5.
155 Zajdela, A., Zillhardt, P. and Voillemot, N. (1987) Cytological diagnosis by fine needle sampling without aspiration. *Cancer*, **59**, 1201–5.
156 Ashcraft, M.W. and Van Herle, A.J. (1981) Management of thyroid nodules II. Scanning techniques, thyroid suppressive therapy, and fine needle aspiration. *Head and Neck Surg.*, **3**, 297–322.
157 Walfish, P.G., Hazani, E., Strawbridge, H.T.G. *et al.* (1977) Combined ultrasound and needle aspiration cytology in the assessment and management of hypofunctioning thyroid nodule. *Ann. Intern. Med.*, **87**, 270–4.
158 Esselstyn, C.B. and Crile, G. Jr (1978) Needle aspiration and needle biopsy of the thyroid. *World J. Surg.*, **2**, 321–9.
159 Colacchio, T.A., LoGerfo, P. and Feind. C.R. (1980) Fine needle cytologic diagnosis of thyroid nodules. Review and report of 300 cases. *Am. J. Surg.*, **140**, 568–71.
160 Miller, T.R., Abele, J.S. and Greenspan, F.S. (1981) Fine-needle aspiration biopsy in the management of thyroid nodules. *West J. Med.*, **134**, 198–205.
161 Prinz, R.A., O'Morchoe, P.J., Barbato, A.L. *et al.* (1983) Fine needle aspiration biopsy of thyroid nodules. *Ann. Surg.*, **198**, 70–3.
162 Ramacciotti, C.E., Pretorius, H.T., Chu, E. *et al.* (1984) Diagnostic accuracy and use of aspiration biopsy in the management of thyroid nodules. *Arch. Intern. Med.*, **144**, 1169–73.
163 Al-Sayer, H.M., Krukowski, Z.H. Williams, V.M.M. *et al.* (1985) Fine needle aspiration cytology in isolated thyroid swellings: a prospective two year evaluation. *Br. Med. J.*, **290**, 1490–2.
164 Boey, J., Hsu, C., Collins, R.J. *et al.* (1986) False-negative errors in fine-needle aspiration biopsy of dominant thyroid nodules: a prospective follow-up study. *World J. Surg.*, **10**, 623–30.

165 Silverman, J.F., West, R.L., Larkin, E.W. *et al.* (1986) The role of fine-needle aspiration biopsy in the rapid diagnosis and management of thyroid neoplasm. *Cancer*, **57**, 1164–70.

166 Miller, J.M., Hamburger, J.I. and Kini, S.R. (1980) The impact of needle biopsy on the preoperative diagnosis of thyroid nodules. *Henry Ford Hosp. Med. J.*, **28**, 145–8.

167 Galvan, G. (1977) Thin needle aspiration biopsy and cytological examination of hypofunctional, 'cold' thyroid nodules in routine clinical work. *Clin. Nucl. Med.*, **2**, 413–21.

168 Gharib, H., Goellner, J.R., Zinsmeister, A.R. *et al.* (1984) Fine-needle aspiration biopsy of the thyroid. The problem of suspicious cytological findings. *Ann. Intern. Med.*, **101**, 25–8.

169 Khalifa, M.S., Nur, A., Al Sarrag, S. *et al.* (1988) Management of the solitary cold thyroid nodule: a prospective study. *Int. Surg.*, **73**, 99–101.

170 Boon, M.E., Lowhagen, T., Willems, J-S. (1980) Planimetric studies on fine needle aspirates of follicular adenoma and follicular carcinoma of the thyroid. *Acta Cytologica*, **24**, 145–8.

171 Guarda, L.A. and Baskin, H.J. (1987) Inflammatory and lymphoid lesions of the thyroid gland. Cytopathology by fine-needle aspiration. *Am. J. Clin. Pathol.*, **87**, 14–22.

172 Watts, N.B. (1987) Carcinoma metastatic to the thyroid: Prevalence and diagnosis by fine-needle aspiration cytology. *Am. J. Med. Sci.*, **293**, 13–17.

173 Asp, A.A., Georgitis, W., Waldron, E.J. *et al.* (1987) Fine needle aspiration of the thyroid. Use in an average health care facility. *Am. J. Med.*, **83**, 489–93.

174 Bayer, M.F. and McDougall, I.R. (1980) Follow-up of patients with differentiated thyroid cancer using thyroglobulin measured by an immunoradiometric assay. Comparison with I–131 total body scans. *J. Nucl. Med.*, **21**, 741–4.

175 Bayer, M.F. and Kriss, J.P. (1979) Immunoradiometric assay for serum thyroglobulin: semiquantitative measurement of thyroglobulin in antithyroglobulin-positive serum. *J. Clin. Endocrinol. Metab.*, **49**, 557–64.

176 Bayer, M.F. and Kriss, J.P. (1979) A solid phase, sandwish-type radioimmunoassay for antithyroglobulin: elimination of false positive results and semiquantitative measurement of antithyroglobulin in the presence of elevated thyroglobulin. *J. Clin. Endocrinol. Metab.*, **49**, 565–71.

177 Bayer, M.F., McDougall, I.R. (1984) Differences in radioimmunoassay results for thyroglobulin that affect management of patients with thyroid cancer. *Clin. Chem.*, **30**, 81–6.

178 Van Herle, A.J. and Uller, R.P. (1975) Elevated serum thyroglobulin: a marker of metastases in differentiated thyroid carcinomas. *J. Clin. Invest.*, **56**, 272–7.

179 Shlossberg, A.H., Jacobson, J.C.J. and Ibbertson, H.K. (1979) Serum thyroglobulin in the diagnosis and management of thyroid carcinoma. *Clin. Endocrinol.*, **10**, 17–27.

180 Tang Fui, S.C.N. Hoffenberg, R., Maisey, M.N. *et al.* (1979) Serum thyroglobulin concentrations and whole-body radioiodine scan in follow-up of differentiated thyroid cancer after thyroid ablation. *Br. Med. J.*, **2**, 298–300.

181 Charles, M.A., Dodson, L.E., Waldeck, N. *et al.* (1980) Serum thyroglobulin levels predict total body iodine scan findings in patients with treated well-differentiated thyroid carcinoma. *Am. J. Med.*, **69**, 401–7.

182 Blahd, W.H., Drickman, M.V., Porter, C.W. *et al.* (1984) Serum thyroglobulin, a monitor of differentiated thyroid carcinoma in patients receiving thyroid hormone suppression therapy: concise communication. *J. Nucl. Med.*, **25**, 673–7.

183 Black, E.G., Cassoni, A., Gimlette, T.M.D. *et al.* (1981) Serum thyroglobulin in thyroid cancer. *Lancet*, **2**, 443–5.

184 Bayer, M.F., McDougall, I.R. and Kriss, J.P. (1987) Retrospective study of serum thyroglobulin measurements performed in patients with differentiated thyroid carcinoma at the Standford University thyroid clinic between 1979 and 1985, in *Thyroglobulin and Thyroglobulin Antibodies in the Follow-up of Thyroid Cancer and Endemic Goiter*, (eds M. Hufner and C. Reiners), George Thieme Verlag, Stuttgart, pp. 104–11.

185 Coakley, A.J., Page, C.J., Gaunt, J. *et al.* (1982) Whole body counting and thyroglobulin levels in assessment of thyroid carcinoma, in *Nuclear Medicine and Biology: Proceedings of Third World Congress Nuclear Medicine and Biology, Paris*, (ed. C. Raynaud) Pergamon Press.

186 Moser, E., Fritsch, S. and Braun, S. (1988) Thyroglobulin and ^{131}I uptake of remaining thyroid tissue in patients with differentiated carcinoma after thyroidectomy. *Nucl. Med. Comm.*, **9**, 262–6.

187 Miller, J.H. and Marcus, C.S. (1988) Metastatic papillary thyroid carcinoma with normal serum thyroglobulin level. *Clin. Nucl. Med.*, **16**, 652–3.

188 Levine, G.A., Hershman, J.M., Van. Herle, A.J. *et al.* (1978) Thyroglobulin and calcitonin in patients with nontoxic goiter. *JAMA*, **240**, 2282–3.
189 Lo Gerfo, P., Colacchio, T., Colacchio, D. *et al.* (1979) Thyroglobulin in benign and malignant thyroid disease. *JAMA*, **241**, 923–5.
190 Schneider, A.B., Favus, M.J., Stachura, M.E. *et al.* (1977) Plasma thyroglobulin in detecting thyroid carcinoma after childhood head and neck irradiation. *Ann. Intern. Med.*, **86**, 29–34.
191 Roitt, I.M., Doniach, D., Campbell, P.N. *et al.* (1956) Autoantibodies in Hashimoto's disease (lymphadenoid goitre). *Lancet*, **2**, 820–1.
192 Mori, T. and Kriss, J.P. (1971) Measurement by competitive binding radioassay of serum anti-microsomal and anti-thyroglobulin antibodies in Graves' disease and other thyroid disorders. *J. Clin. Endocrinol. Metab.*, **33**, 688–98.
193 Mariotti, S., Russova, A., Pissani, S. *et al.* (1982) A new solid-phase immunoradiometric assay for anti-thyroglobulin autoantibody. *J. Endocrinol. Invest.*, **5**, 227–33.
194 Lundstrom, B., Hed, J., Johansson, K-E. *et al.* (1977) Thyroid function after subtotal thyroidectomy for hyperthyroidism related to some morphological and immunological features. *Acta Chir. Scand.*, **143**, 215–20.
195 Adams, D.D. and Purves, H.D. (1956) Abnormal responses in the assay of thyrotrophin. *Proc. Univ. Otago Med. School*, **34**, 11–12.
196 Rappaport, B. (1987) Autoimmune mechanisms in thyroid disease, in *The Thyroid*, (ed. W.L. Green), Elsevier, New York, pp. 47–106.
197 Rees-Smith B. (1988) Autoantibodies to the thyrotropin receptor. *Endocrine Review*, **9**, 106–21.
198 Dumont, J.E., Roger, P.P. and Ludgate, M. (1987) Assays for thyroid growth immunoglobulins and their clinical implications: methods, concepts and misconceptions. *Endocrine Reviews*, **8**, 448–52.
199 Multiple authors (1988) Various personal recollections of scientists reposible for important discoveries in the field of thyroid autoimmunity. *Autoimmunity, Volume 1*, Gordon and Breach Science Publishers Inc. Great Britain (Reprints available directly from the publisher.)
200 Tashjian, A.H. Jr. Howland, B.G., Melvin K.E.W. *et al.* (1970) Immunoassay of human calcitonin: clinical measurement, relation to serum calcium and studies in patients with medullary cancer. *N. Engl. J. Med.*, **283**, 890–5.
201 Jackson, C.E., Tashjian, A.H. Jr and Miller, H.H. (1973) Detection of medullary cancer by calcitonin assay in families. *Ann. Intern. Med.*, **78**, 845–52.
202 Wells, S.A., Dilley, W.G., Farndon, J.A. *et al.* (1985) Early diagnosis and treatement of medullary thyroid carcinoma. *Arch. Intern. Med.*, **145**, 1248–52.
203 Boothby, W.M. (1919) The value of the basal metabolic rate in the treatment of diseases of the thyroid. *Med. Clin. North Amer.*, **3**, 603–18.

CHAPTER FOUR

Clinical examination

4.1 INTRODUCTION

Diagnosis of thyroid disease starts with the interview and clinical examination. The primary physician is usually in the position of determining whether thyroid dysfunction is the cause of the patient's complaints, and the endocrinologist of confirming the diagnosis and recommending therapy. Not infrequently, unsuspected thyroid disease is found on clinical examination. The clinician should try and answer the following questions. Firstly, is the patient euthyroid, hyperthyroid, or hypothyroid? Secondly, is the thyroid enlarged (goitre) and, if so, is it symmetric, diffuse or nodular? Thirdly, is there a solitary nodule? The reader might well remark that tests of thyroid function are better to answer the first question, and imaging studies the last two questions. Although thyroid dysfunction is common, lack of dysfunction is much commoner, and it would not be cost effective, or good medicine, to order tests without good reason. Therefore, the clinician plays an important role, by recognizing an abnormality, indicating to the patient that the probable cause of symptoms has been found and ordering appropriate tests to confirm, or exclude, this with as high a degree of reliability as possible. Most thyroid diseases are treatable and curable, and in appropriate settings the nature of treatment can be introduced at this time.

4.2 GENERAL

Moderate and severe cases of hyperthyroidism and hypothyroidism can be diagnosed instantaneously in most patients. The appearance of a hyperthyroid patient with Graves' disease is characteristic (Figure 4.1). The patient is tense, nervous, restless and fidgety, the eyes are staring and often bulging, and the skin is hot and sweaty. Almost immediately after introduction to and shaking hands with the patient, the clinician knows what is wrong. Elaborate questionaires and investigations are not necessary. Similarly, at the other end of the spectrum the sluggish, sleepy, tolerant patient sitting quietly in the waiting room with a puffy, yellow face and cold, dry skin is not a diagnostic dilemma (Figure 4.2). The patients who are difficult to diagnose are those who have mild dysfunction, and whose symptoms and signs are subtle and often restricted to a single organ or system. In them, it is necessary to conduct a systematic review of symptoms and a methodical clinical examination. Some clinical investigators have used objective rating scales as a aid to making the diagnosis and for following the response to therapy. Several of these are discussed below.

4.3 EXAMINATION OF THE THYROID

In most cases of hyperthyroidism and many with hypothyroidism, the thyroid is enlarged. Exceptions are equally important.

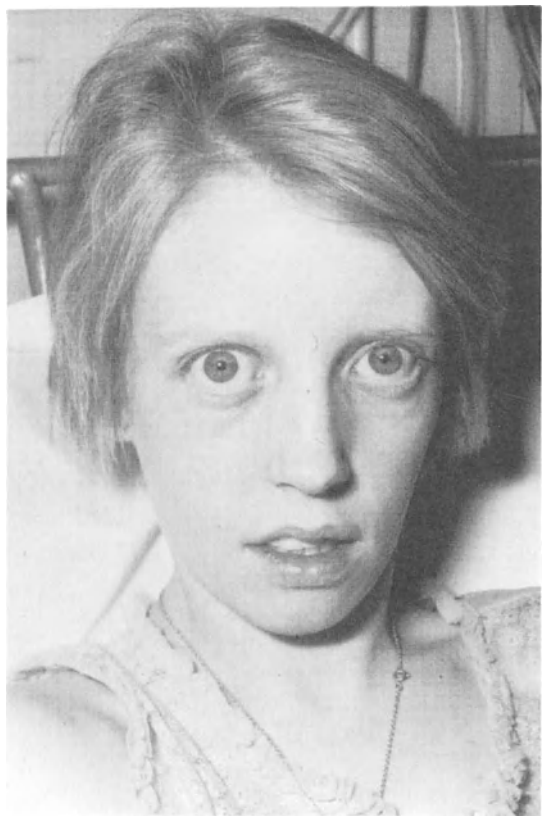


Figure 4.1 Young woman with severe Graves' hyperthyroidism. She looks startled and had upper and lower lid retraction and proptosis. She is thin and had lost about 20 pounds in spite of an excellent appetite and high caloric intake.

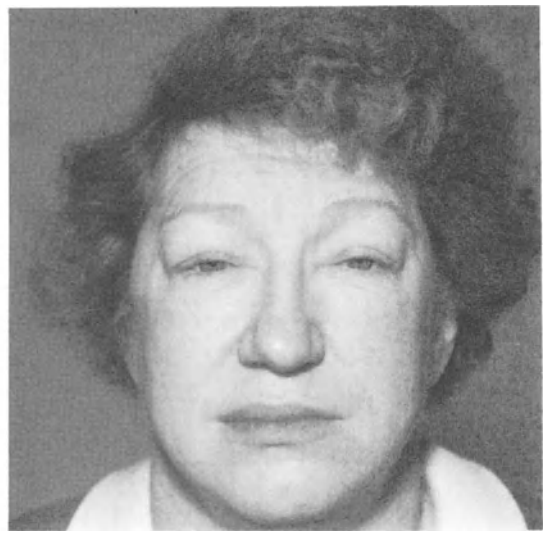


Figure 4.2 Classic appearance of severe hypothyroidism. The patient looks tired and lethargic, and there is puffiness of the face, in particular around the eyes.

For example, if a patient is clearly hyperthyroid but the thyroid cannot be felt, this suggests, a cause such as silent thyroiditis, or factitious hyperthyroidism (Chapter 5). To examine the thyroid, the entire neck must be accessible with clothes removed, the chin elevated and sufficient light available. The neck is inspected for a thyroidectomy scar, colour changes, swellings and asymmetry. Sometimes, prior operations are forgotten and the scar may be the answer for forgetfulness, which is common in hypothyroidism. The skin overlying inflammatory conditions, such as subacute thyroiditis and thyroid abscess, is often red and warm. The skin can be red and telangiectasia can be present when high doses of external radiation have been given. However, doses less than 2000 rad do not leave this sign. Goitre is the commonest cause of a midline swelling. An asymmetric goitre, or a single nodule, can cause deviation of the trachea to the opposite side. For inspection, the examiner and patient should be seated opposite each other with good light falling on to the patient's neck. The neck should be extended slightly. Because the thyroid is enveloped in the pretracheal fascia it moves with swallowing. The patient is asked to take a sip of water and hold it in the mouth until the cup and patient's hands are out of the way. On swallowing, the thyroid if enlarged is seen as a fullness which moves up and down under the skin. There is debate whether a normal thyroid is visible. In some thin people, especially women,

it is, but the finding is subtle and is often restricted to seeing the isthmus in front of the trachea. In men, a normal thyroid is seldom visible. It is not critical if such a subtle finding is missed. The important mistakes are when a large goitre is overlooked and thyroid dysfunction not considered as a result. An alternative method of inspection is to have the patient lie supine with a pillow under the neck to cause full extension, in which case the spine pushes the thyroid anteriorly. This can help to visualize small nodules.

Palpation of the thyroid is the most important part of its examination. I prefer to examine the gland from behind the patient who is seated. The examiner's thumbs are placed in the midline of the back of the neck on each side of the spine. The pulps of the first, second and third fingers of each hand are placed just to the side of the midline. I feel for the thyroid cartilage, then the suprasternal notch to determine the area of interest. About midway between these, the isthmus lies in front of the trachea. It is usually easier to feel the inferior border of the isthmus by gentle rotatory or up and down movement of the fingers, which should move the skin and subcutaneous tissue over the deeper structures. It is important not to press too firmly, or to poke directly into the trachea, since this is sensitive and usually causes coughing and makes further examination more difficult. Having the patient swallow helps to define the isthmus as it slides beneath the examining fingers. When the inferior border of the isthmus is located it is followed laterally, first to one side, then to the other to the inferomedial aspect of the lobes. Both hands are moved to one side. For examinion of the left lobe, the fingers of the examiner's left hand gently pull the sternocleidomastoid muscle back, thus exposing the thyroid. Having located the inferior border of the lobes, the examiner should try and follow the margin round the entire lobe. In goitres, this can be easy. In many normal people no tissue, or at best a slight sensation of fullness, is all that can be felt. The same sequence is conducted on the opposite lobe. The examiner defines the size, consistency, shape of the lobes, determines if there is a nodule, or nodules and if there is tenderness. In the case of a diffusely enlarged thyroid, the examiner should determine the size of the gland, its consistency, whether it is nodular and if there is fixation deeply or superficially. The normal thyroid is approximately 20 g and, as stated, is often not visible or palpable. Therefore, if the normal gland cannot be felt and is assumed to be 20 g, it could be argued that the size of enlarged glands can only be estimated. Nevertheless, with constant practice, best obtained by working with an experienced endocrinologist, a degree of accuracy can be obtained. Studies comparing the estimated weight of the thyroid by clinical examination compared with the true weight at operation shows a tendency to overestimate small glands and underestimate large ones. It will be seen in Chapter 5 that this estimation is used to determine how much radioiodine to prescribe for treatment of hyperthyroidism. In Graves' disease, the thyroid is diffusely enlarged and can range from 20 g to more than 100 g, and it is usually soft to rubbery in consistency. It is fixed neither deeply nor superficially. The thyroid in lymphocytic thyroiditis (Hashimoto's thyroiditis), is also diffusely enlarged, it is easy to palpate the margin of the gland and the feel is rubbery to firm. In some cases, the gland has a granular or bosselated feel. These findings are not different from those of simple goitre, and the final diagnosis depends on the clinical findings plus laboratory results. If the gland is fixed deeply, the most likely cause is carcinoma. Riedel's thyroiditis, which is not malignant and is extremely rare, invades surrounding tissues. Hashimoto's thyroiditis, which is common clinically, very rarely extends outside the gland.

Percussion has a minor role in cases of goitre in which the inferior margin cannot be felt. Substernal extension can be recognized by dullness to percussion over the manubrium and upper sternum. Radiographic studies, or ^{123}I scintigram, are more accurate.

Using the diaphragm of a stethoscope, the clinician should listen for a systolic bruit which is most characteristic of Graves' hyperthyroidism.

When a nodule is palpated, it should be characterized by its size, shape, consistency, fixation, tenderness and whether there is associated lymph node enlargement. Of these, the size can be determined with some objectivity. Callipers can be used to measure length and breadth. Some clinicians find that drawing the shape and size of the nodule on a piece of paper laid over the nodule valuable as a record which can be compared with subsequent measurements. None of these is absolute, but they help to determine if a lesion is enlarging or not. No clinician, irrespective of his or her experience and skill, can determine the pathology of a nodule. However, some nodules are more suspicious of being cancerous and others of being cystic, and a clinical impression can aid the determination of which investigations, if any, are advised. As stated in Chapters 3 and 7, the most definite test of a nodule is fine-needle aspiration (FNA). Thyroid nodules can usually be differentiated from enlarged nodes, branchial cleft cysts, carotid body tumours and thyroglossal cysts based on their location and movement on swallowing. Lymph nodes, branchial cleft cysts and carotid body tumours are more lateral. Cysts transilluminate. None of these move with swallowing. Thyroglossal cysts lie above the isthmus and move upward with protrusion of the tongue and sometimes with swallowing. Occasionally, a prominent, or asymmetric, tracheal ring is misinterpreted as a hard thyroid nodule. The ring can usually be followed laterally around its circumference, thus excluding the possibility of a thyroid nodule. I usually auscultate large nodules before aspirating them to ensure there is no bruit which would prompt an alternative approach.

An alternative method of palpating the thyroid is from the front. The pulp of the thumbs are used in the same rotatory and up and down action as described. I find this less satisfactory as I have less fine touch sense in my thumbs than fingers. Nevertheless, some clinicians prefer this. It can be coupled with inspection from the front.

4.4 DIAGNOSTIC INDICES

The clinical symptoms and signs of hyperthyroidism and hypothyroidism are presented in Chapters 5 and 6. Some clinicians have developed indices by giving a numeric score to certain features which, when added together, indicate whether there is thyroid dysfunction or not. The benefits of these indices are that they are not operator dependent, they ensure the clinical features are looked for and they allow repeat results to be compared. The experienced clinicians does not require such an aid, and frequently the patient is the best judge of response to treatment, and judicious use of FT_4 and TSH measurements defines the progress objectively.

Crooks *et al.* [1] developed a diagnostic index which had two functions, firstly to establish that a patient was hyperthyroid, and secondly to graph the response to treatment [2]. They used features of hyperthyroidism which are expected to change with therapy of the disease. Their index was verified mathematically. It is shown in Table 4.1.

Klein *et al.* [3] described an alternative scale for assessing the response of the patient to therapy. They state that Crooks *et al.* 'did not apply the evaluation to treated patients'; however, they did. The items used in the system of Klein *et al.* are shown in Table

Table 4.1 Thyrotoxicosis therapy index developed by Crooks *et al.* [1, 2]

Symptom	*Score*	*Sign*	*Score*
Dyspnoea on effort	+1	Hyperkinetic movement	+4
Palpitations	+2	Fine finger tremor	+1
Tiredness	+2	Hands: hot	+2
		moist	+1
Preference for cold	+5		
Nervousness	+2	Resting pulse >85/min	+3
Appetite increased	+1		
Weight decreased	+4		

1 point deducted for each 4 pounds weight gain.
0–5 considered normal.

Table 4.2 Hyperthyroid symptom scale developed by Klein *et al.* [3]

Symptom or sign
1 Nervousness
2 Sweating
3 Heat tolerance
4 Hyperactivity
5 Tremor
6 Weakness
7 Hyperdynamic precordium
8 Diarrhoea
9 Appetite
10 Incapacitation

Each of the 10 characteristics is graded on a scale of 0–4. For example, incapacition is scored 0 = None, 1 = 10% reduction, 2 = 30% reduction, 3 = 60% reduction, and 4 = 90% reduction in daily function. The maximum score for all 10 items is 40 points. Patients with proven hyperthyroidism had scores greater then 20, and when they were euthyroid the scores were less than 10. The article should be consulted for details of each characteristic.

Table 4.3 Diagnostic index for premyxoedema of Ikram *et al.* [4]

Factor	*If present*	*If absent*
1 Thyroid antibodies + to +++	+50	−50
2 Thyroid antibodies (trace)	+25	−50
3 Cholesterol greater than 300 mg/dl	+50	−20
4 TSH greater than 4.2	+60	−20
5 Reduced thyroid reserve*	+40	−60
6 Past ^{131}I therapy	+40	0
7 Thyroidectomy	+30	0
8 Follow-up of goitre	+20	0
9 Fall in cholesterol on LT_4	+20	−40
10 Ankle jerk half relaxation time 360–480 msec	+20	0
11 Pernicious anaemia and Addison's disease	+10	0
12 Coronary artery disease	+10	0
13 Strokes	+5	0
14 Blood relative with thyroid disease (each one)	+10	0
15 Blood relative with pernicious anaemia	+5	0
16 Family history of coronary disease (each one)	+5	0
17 Fall in cholesterol with clofibrate	+5	−20
18 Corneal arcus	+5	0
19 Vitiligo	+5	0
20 Ankle reflex <360 msec on LT_4	+10	−10

Sum of scores more than 100 diagnostic.
Sum of scores 80–100 equivocal.
Sum of scores less than 80 negative.
*See original article for explanation of scoring of this item. Based on radioiodide uptake before and after TSH injection which is not now advised as a test.

Table 4.4 Symptoms and signs of hyperthyroidism

General
Insomnia
Weight loss
Youthfulness
Increased drug tolerance
Increased vitamin requirement
Accelerated growth
Hyperkinesis
Fatigue
Heat intolerance

Brain
Nervousness
Psychosis
Labile mood
Irritability

Cardiorespiratory
Hypertension
Heart failure
Arrhythmias
Dyspnoea
Palpitations
Tachycardia

Gastrointestinal
Thirst
Hyperdefecation
Diarrhoea
Increased appetite
Hunger
Weight loss

Lymphatic–blood
Lymphocytosis
Splenomegaly

Muscular
Weakness
Tremor

Genitourinary
Oligomenorrhoea

Skeletal
Osteoporosis
Increased rate of closure
Bone pain
Clubbing*
Periosteal new bone*

Endocrine
Goitre*

Special senses
Stare
Lacrimation*
Diplopia*
Periorbital oedema*
Proptosis*
Corneal ulcer*

Skin
Hair loss
Onycholysis
Heat
Sweating
Fineness
Pretibial thickening*

*Not induced by administration of excess thyroxine or triiodothyronine. Tabulation developed by the late Joseph P. Kriss.

Table 4.5 Symptoms and signs of hypothyroidism

General
Weight gain
Cold intolerance
Lassitude
Growth retardation
Hypersomnia
Decreased drug tolerance
Aged appearance
Decreased activity

Brain
Depression
Psychosis
Cerebellar signs
Poor memory
Poor concentration
Agitation
Lower intelligence (infant)

Cardiorespiratory
Hoarseness
Bradycardia
Dizziness
Hypotension
Hypertension
Pericardial effusion

Gastrointestinal
Decreased appetite
Large tongue
Constipation
Hypoglycaemia

Muscular
Cramps
Stiffness

Genitourinary
Menorrhagia
Infertility
Decreased libido
Abortion

Skeleton
Short stature
Epiphyseal closure delay
Delayed dentition
Stippled epiphysis (child)

Endocrine
Reduced secretion of other glands

Special senses
Deafness
Numbness
Stuffy nose

Skin
Cold
Dry
Puffy
Hair loss
Brittle nails
Raynaud's disease
Yellow colour

Tabulation developed by the late Joseph P. Kriss.

4.2. This is somewhat more subjective but, nonetheless, ensures that 10 important symptoms and signs are recorded at each visit.

Ikram *et al.* [4] devised a diagnostic index for 'premyxoedema' which they thought would be valuable in screening large numbers of patients, determining if additional tests were advisable and preventing misdiagnosis based on the result of a single test. Their index includes family history, clinical findings, as well as tests and, in these regards, differs from the two presented above. This is more of *aide-mémoire* and is shown in Table 4.3. Clinicians may find these short lists helpful, or may develop their own diagnostic lists. More comprehensive lists of symptoms and signs are provided in Tables 4.4 and 4.5.

Patients with thyroid dysfunction are anxious, depressed, weepy, and irritable due to the thyroid disease *per se*, and not just as a response to the illness. Their personal and family situations have often been greatly dis-

rupted. These patients need gentle, sympathetic care. The dramatic responses to treatment of both hyperthyroidism and hypothyroidism which usually accompany return of function to normal are rare in medicine. The vast majority of patients are abundantly satisfied with the final outcome. Because thyroid dysfunction is common and, in most cases, treatable, clinicians should be vigilant and try not to overlook their diagnosis.

KEY FACTS

- Diagnosis of thyroid disease starts with the history and physical examination.
- Abnormalities of thyroid structure and function are common and the clinician should have a low threshold for considering these.
- Thyroid dysfunction often involves one system more than others and the clinician again must consider the thyroid as a potential cause.
- A thyroid nodule should be evaluated for size, consistency, mobility, site, presence of other nodules or enlarged cervical lymph nodes.
- Diagnostic indices for hyperthyroidism and hypothyroidism can be useful *aide mémoires* which ensure the clinician rules in or out these diagnoses.
- Experienced endocrinologists probably do not benefit from these indices.
- The importance of listening to the patient cannot be overemphasized.

REFERENCES

1 Crooks, J., Murray, I.P.C. and Wayne, E.J. (1959) Statistical methods applied to the clinical diagnosis of thyrotoxicosis. *Quart. J. Med.*, **28**, 211–34.

2 Crooks, J., Wayne, E.J. and Robb, R.A. (1960) A clinical method of assessing the results of therapy in thyrotoxicosis. *Lancet*, **1**, 397–401.

3 Klein, I., Trzepacz, P.T., Roberts, M. *et al.* (1988) Symptom rating scale for assessing hyperthyroidism. *Arch. Intern. Med.*, **148**, 387–90.

4 Ikram, H., Banim, S. and Fowler, P.B.S. (1973) Diagnostic index for premyxoedema. *Lancet*, **2**, 1405–8.

CHAPTER FIVE

Hyperthyroidism

5.1 INTRODUCTION

This chapter deals with a variety of clinical conditions in which there is excessive effects of thyroid hormones on the tissues. Hyperthyroidism is the general term, although some workers restrict this to conditions where the thyroid, *per se*, is overactive. I use hyperthyroidism to imply that there is too much thyroid hormone in the circulation, irrespective of its source. A second term, **thyrotoxicosis,** literally means 'toxic' because of too much thyroid hormone. However, many patients with high serum thyroid levels are not toxic. Nevertheless, in this chapter the two terms are used interchangeably. Most frequently, there are high levels of total hormones and, most often, both T_4 and T_3 are above normal. On occasion, total hormone values are normal and only the free hormones are high. In a minority of patients, only one hormone is abnormal, usually T_3.

Table 5.1 lists the causes of hyperthyroidism. The causes have been divided into three categories. Firstly, the common clinical syndromes with increased uptake of iodine in the thyroid. In North America and Europe, Graves' disease or diffuse toxic goitre is the commonest syndrome. Toxic nodular goitre is less common in North America, where the diet is replete with iodine, but is an important cause in central Europe.

Secondly, somewhat paradoxically there are several conditions in which the uptake of radioiodine is low. In some of these, this results from high levels of circulating hormones suppressing TSH and, in turn, trapping by the thyroid (factitious, iatrogenic and iodine induced). In others, the thyroid is damaged and releases stored hormones, but the basic pathology make the gland in-

Table 5.1 Causes of hyperthyroidism

Common with increased trapping of iodine by the thyroid	
1	Graves' disease: toxic diffuse goitre toxic goitre with functioning nodules (Marine Lenhart syndrome)
2	Single toxic nodule
3	Toxic multinodular goitre
All associated with reduced uptake of iodine in the thyroid	
4	Iatrogenic hyperthyroidism
5	Factitious hyperthyroidism
6	Hamburger hyperthyroidism
7	Silent thyroiditis
8	Postpartum thyroiditis
9	Subacute thyroiditis
10	Cancer invading thyroid
11	Iodine induced (Jod Basedow phenomenon)
12	Struma ovarii
13	Metastatic functioning thyroid cancer
Uncommon: uptake of iodine in the thyroid is variable	
14	Pituitary hyperthyroidism
15	Non-pituitary tumour secreting excess TSH
16	Inappropriate TSH secretion
17	Hyperthyroidism from trophoblastic tumours

capable of trapping iodine (thyroiditides, and invasive pathologies).

Thirdly, there are several unrelated conditions which are not common and not associated with low radioiodine uptake. Most of these are caused by excess TSH or TSH-like material, which is inappropriate under the circumstances.

Each entity is discussed separately. Since most of the clinical features, complications and treatments are similar, they are not repeated but discussed under the first heading of Graves' disease. There are clinical features which are peculiar to Graves' disease, infiltrative ophthalmopathy, dermopathy and acropachy. These are discussed separately after clinical features. Whenever there are differences in other entities, they are presented in the appropriate section. Because of differences in clinical features and management at the extremes of age, there are short sections concerned with hyperthyroidism in children and the elderly towards the end of the chapter.

Hyperthyroidism complicating pregnancy also merits separate discussion. The most severe form of thyrotoxicosis, thyroid storm or thyroid crisis, can be precipitated in patients with hyperthyroidism of any cause and this topic is given a separate section at the end of the chapter.

5.2 GRAVES' DISEASE OR DIFFUSE TOXIC GOITRE

5.2.1 INTRODUCTION

This section deals specifically with Graves' disease [1]. The use of eponyms is becoming less common and it is true that Parry [2] who described this syndrome in 1825 did so before Graves in 1835. In addition, in several European countries Basedow [3] is credited by the eponym. Nevertheless, because of common usage in the English literature, I use the terms Graves' disease and diffuse toxic goitre synonymously. For easy access, the original publications and short historical vignettes are collected in Major's text [4]. A recent article and a book about Robert Graves provide excellent accounts of him as a physician, educator and person [5*a*,*b*]. The symptoms and signs of hyperthyroidism, which are common to all causes, are discussed in this section, and then characteristics found only in Graves' disease are discussed. Extrathyroidal manifestations can occur before the patient is hyperthyroid (indeed the patient might never become hyperthyroid) or after the hyperthyroidism has been treated sucessfully. When there is ophthalmopathy and the patient is euthyroid, the term euthyroid Graves' ophthalmopathy is used. In general, therapy is directed at the clinical problem. If the patient is hyperthyroid, the hyperthyroidism is treated and, likewise, if there is only ophthalmopathy that alone is treated.

The aetiology of Graves' disease is understood and, although at the time of writing it does not influence treatment, this is discussed in moderate detail. The clinical aspects are presented by system and because complications of thyrotoxicosis are simply extremes of these, they are included. The laboratory diagnosis is simple and the tests used were described in Chapter 4. Therapy applies to all causes of hyperthyroidism with increased trapping of iodine in the thyroid.

5.2.2 AETIOLOGY

There is compelling evidence that Graves' disease is caused by an antibody against the TSH receptor of the follicular cell. The antibody is capable of stimulating the function of the cell. It is designated thyroid receptor antibody or TRAb [6]. This abnormal stimulator was discovered in 1956. Adams and Purves [7] were evaluating a biological assay for TSH, which they had developed in guinea pigs. The animals were injected with radioiodine, which was trapped by the

thyroid and then they were given L thyroxine to prevent release of the radioiodine from the gland. Serum containing TSH when injected into the guinea pig caused a brisk release of radioiodine into the circulation which peaked at about 2 hours. Serum from a patient with Graves' disease caused a delayed discharge of endogenous radioiodine. The factor in the serum was called long acting thyroid stimulator (LATS) because of its delayed course of action. It was shown to be an immunoglobulin of lgG class and therefore, it differed from TSH in structure and action [8]. McKenzie substituted mouse for guinea pig in the biological assay, thus simplifying the logistics and reducing cost [9]. Two excellent reviews from 1968 are provided for readers interested in early developments [10, 11]. It was only possible to demonstrate the presence of LATS in the serum of 20–40% of patients with classic Graves' disease, and if concentrates of gamma globulin were tested the sensitivity rose to approximately 70% with 7% false positives. Kriss *et al.* [8] showed that thyroid tissue neutralized LATS and Adams and Kennedy [12] discovered that LATS negative serum could neutralize LATS. Presumably a material similar to LATS was present in the serum which attached to the same site as LATS. This new material was called **LATS protector** [LATS–P]. However, as stated, serum containing LATS–P did not cause release of endogenous radioiodine using the mouse model. Adams [13] credits Doniach with the answer to the conundrum, namely LATS–P is a human specific antibody which does not function in the mouse model. LATS–P was subsequently shown to function as expected as a thyroid stimulator when infused into human volunteers [14].

The biological assay for LATS was unwieldy and lacking in sensitivity, and was replaced by *in vitro* assays. These fell into two major categories: assays which used inhibition of binding of radiolabelled TSH to its receptor on thyroid membranes, or those that demonstrated an increase in function of thyroid tissue [15]. The former showed one of the functions of the abnormal stimulator, namely, its ability to attach to the TSH receptor and prevent TSH binding, but could not demonstrate function and was called **TSH-binding inhibiting activity** or **TSH-binding inhibiting immunoglobulin** [TBIA or TBII]. The latter type of assay which showed function, such as increasing cyclic AMP in human thyroid slices, was called thyroid stimulating antibody or immunoglobulin (TSAb, or TSI). This somewhat confusing list of abbreviations is actually abbreviated for simplicity! A more complete tabulation is found in a review by McKenzie [16], but the terms have been unified by the Nomenclature Committee of the American Thyroid Association to thyroid receptor antibody, TRAb. The method used for the determination should then be appended for complete definition of the assay.

Different assays produce somewhat different results on the same samples, but 85–95% of patients with active Graves' disease test positive, and tests in those with dermopathy or ophthalmopathy are almost invariably positive [17]. The test is positive in up to 5% of controls. Sensitivity ranges from 85–95%, and specificity is approximately 95%.

Is measurement of TRAb important in the diagnosis of Graves' disease? I would argue not. If the patient is hyperthyroid with a diffuse goitre and ophthalmic features, it is not relevant whether TRAb can be measured or not. In addition, finding TRAb in the serum of a normal person would not lead to antithyroid treatment. The test has been used to try and predict if a patient taking antithyroid medications has gone into remission, the inference being if TRAb values become unmeasurable, remission has occurred. Unfortunately, the data is not clear cut, with some investigators finding this reliable [18] and others not [19]. Rees-Smith [20] has suggested that the test might not be of value in iodine-deficient regions, because the

availability of iodine may be the factor which determines whether hyperthyroidism recurs, not TRAb. Its main use is in patients with Graves' disease who are pregnant. High titres are predictive of neonatal Graves' disease [21]. This is discussed below under hyperthyroidism in pregnancy.

This begs the question of how the antibody comes to be present in the circulation? There is a genetic predisposition, and some families have several affected members. The risk in Caucasians is greatest in those who have tissue type HLA–DR3. Nonetheless, not all people with this tissue type develop Graves' disease – not even a minority do. Patients with Graves' disease can have other tissue types. Volpe [22] has promoted the theory that the disease) is due to a deficiency in suppressor T cells. This allows the production of TRAb by B cells which would not occur if these cells were suppressed. This theory is consistent with the belief that emotional stress, such as an accident or bereavement, triggers Graves' disease. It has been shown that such stress can affect the immune sytem [24]. Some investigators believe that stress does not cause hyperthyroidism, but think the patient is already mildly hyperthyroid at the time of the stressful situation and, therefore, does not handle the situation well and comes to medical attention. A study comparing the type and severity of stresses in patients with Graves' disease with those in patients attending an orthopaedic clinic showed no difference [25]!

Alternatively, the antigen, that is the TSH receptor, could be altered so that a normal immune system responds by mounting an antibody response. One precipitating factor could be viral. The finding of Graves' disease in patients with Hodgkin's disease who have had external radiation over the thyroid, points to the possibility that the radiation acts by altering thyroid membrane antigens [26].

Graves' disease is an autoimmune disease in which the hyperthyroidism is due to an antibody against the TSH receptor, which is capable of stimulating follicular cells to make and secrete thyroid hormones. The thyroid is not under normal control and pituitary TSH is suppressed by high levels of thyroid hormones. What precipitates the disease is not fully understood.

5.2.3 CLINICAL FEATURES AND COMPLICATIONS

The clinical features of hyperthyroidism are presented systemically. This is not meant to imply that all systems are involved in each patient. The spectrum of involvement varies greatly, depending on the severity of the disease, its duration, the age of the patient and the presence of coexisting disease, as well as individual factors such as race, gender and personality which are difficult to characterize. Any differences due to the cause of hyperthyroidism are discussed in appropriate sections, but those to be described next can occur in all of them.

Hyperthyroidism in the young, the elderly and the pregnant have differences, and these are discussed separately at the end of the chapter, although in each case, Graves' disease is the most likely cause and the most likely condition to produce management problems.

Table 5.2 shows the percentage of patients who had some of the common symptoms and signs. Women are about 4–8 times more likely to have Graves' disease. Graves' disease occurs at any age, but the highest incidence is from 40–60 years.

Nervousness and irritability are abundantly obvious to close relatives and colleagues, and usually to the patient. Restlessness interferes with concentration, and performance at work or school deteriorates. Minor personal slights cause inappropriate emotional outbursts and weeping. Insomnia is very common and the patient describes thoughts rushing through the mind while

Table 5.2 Symptoms and signs of Graves' hyperthyroidism

	% involved			
Symptom/sign [ref]	*[50]*	*[51]*	*[52]*	*Control*
Nervousness	99	54	59	21
Weight loss	85	79	52	2
Heat intolerance	89	67	73	41
Palpitations	89	–	75	26
Fatigue	88	71	80	31
Dyspnoea	75	–	81	40
Polyphagia	65	13	32	2
Tachycardia	100	88	68	19
Goitre	100	67	87	11
Tremor	97	41	66	26

she lies awake; the problem is aggravated by heat intolerance and palpitations. Fatigue follows. Nervousness can become extreme to the point of delirium, at which time the patient by definition has thyroid storm (see below). I have seen patients who were admitted for psychiatric care due solely to hyperthyroidism. The difficulty of excluding the diagnosis of hyperthyroidism in acute psychiatric patients is described in Chapters 3 and 12. There are reports of hyperthyroidism causing people to commit criminal offences, but whether it is the only factor is hard to defend [28, 29]. A fine tremor of the fingers is very common, and this can be demonstrated by having the patient hold the hands outstretched with the fingers apart. It is usually not necessary to place a sheet of paper on top of the outstretched fingers, but this accentuates the sign. The quality of writing deteriorates and can cause embarassment in banks, etc., and cups and saucers are rattled and objects dropped. Tremor can be seen in the tongue when it is extended. In more severe cases, the entire body shakes and the complaint may be of internal rather than finger tremor. Other causes of tremor which should be considered include familial, alcohol and drug abuse, excess caffeine, nervousness and phaeochromocytoma. These can usually be excluded by history and examination.

Reflexes are unusually brisk. Signs of upper motor neurone lesion are rare, but have been reported and have improved with beta-blockers and correction of hyperthyroidism [29].

Thyrotoxic periodic paralysis is a rare complication of hyperthyroidism, whose pathogenesis is not fully understood. Almost all patients have been Oriental [30], although it has been seen in Caucasian [31], Chicano and Philipino [32]. It is seen predoninantly in men, and familial cases have been reported. McFadzean and Yeung [33] found this in 23 of 178 hyperthyroid men in Hong Kong, but only in 2 of 1188 women. The onset is most commonly between 30 and 50 years, which probably corresponds to the onset of hyperthyroidism. The usual underlying cause of hyperthyroidism is Graves' disease, but it is hyperthyroidism *per se*, not the cause of the hyperthyroidism, which is at fault. It has been precipitated by excess oral thyroxine [34] and in toxic multinodular goitre [35]. It disappears when the patient is euthyroid and recurs if there is a relapse. The paralysis is commonest at night and starts with weakness of the legs. Muscles of the trunk and bulbar area can be affected [36]. A preceding high carbohydrate meal (often with alcohol) is frequently obtained by history. This plus the finding of low serum K^+ [33, 37] point to insulin playing a role in the pathogenesis. Feely [38] found a marked rise in red cell K^+. Muscle fibres examined by electron microscopy show dilatation of the endoplastic reticulum with vacuolar changes. Sudden onset of periodic paralysis in an adult man should point to a diagnosis of hyperthyroidism. Familial (non-thyroidal) periodic paralysis always presents in childhood. Those patients I have seen have all been flagrantly thyrotoxic. During an attack if K^+ is low, it can be replaced cautiously, but the goal is rapid cure of hyperthroidism. Beta blockers are valuable in providing partial protection while awaiting definitive treatment [39].

Proximal muscle weakness is present in about 50% of hyperthyroid patients [40]. It can limit the patient in simple tasks, such as rising from the sitting position and walking up stairs. Objective evidence of muscle weakness was found in 81.5% of patients by Ramsay [40], and the range from six articles quoted by this investigator was 55–81.5%. The strength is regained when hyperthyroidism is cured. However, muscle bulk is not recovered in full for some time after that. Myasthenia gravis is found in association with autoimmune thyroid diseases more frequently than by chance [41]. Therefore, unusual myopathic features, such as ptosis or muscle weakness brought on rapidly by exercise, should be investigated with this in mind.

Tachycardia is almost a universal finding. The cardiac output is high, pulse pressure increased and heart beat forceful. The patient is aware of the heart thumping, especially after exercise or while lying on the left side in bed. Ability to exercise decreases and is often attributed to being out of shape. Palpitations can occur as a result of sinus tachycardia, ectopic beats, supraventricular tachycardia and atrial fibrillation. Heart block has been described in severe cases [42–45]. Ventricular fibrillation is a very rare complication [46]. However, in a short period before I wrote the first draft of this section, I saw two middle-aged women, one with ventricular fibrillation, the other with heart block from hyperthyroidism. Myocardial infarction from spasm of the coronary arteries appears to be a real phenomenon in hyperthyroidism [46–48]. In elderly patients with new onset heart failure or arrhythmias, it is advisable to measure FT_4 and TSH. Cobler *et al.* [49] found thyrotoxicosis to be the cause of atrial fibrillation in 31% of elderly institutionalized women, and 11% of elderly men. Atrial fibrillation was present at the time of diagnosis in 10% of hyperthyroid patients studied by Williams [50] and Mornex and Orgiazzi [51], and 19% by Wayne [52]. This range or higher is still found in current practice [53]. Atrial fibrillation can cause emboli, both to the systemic and pulmonary circulations [54, 55]. Staffurth *et al.* [56] recorded 26 episodes of systemic embolization in 262 patients with thyrotoxicosis and atrial fibrillation. Seventeen emboli were to the brain. Twelve occurred when the patients were hyperthyroid, 11 euthyroid and 3 occurred coincidentally with reversion to sinus rhythm. The authors recommend anticoagulants in any patient who has had an embolus and in young patients until sinus rhythm has occurred, either spontaneously or by electrical conversion.

In all patients with cardiac complications, the hyperthyroidism should be treated as expeditiously as possible, usually with antithyroid drugs, then definitively with radioiodine. Atrial fibrillation frequently reverts spontaneously when the patient is euthyroid [57], but if not can be electrically converted after it is clear the patient is no longer hyperthyroid. Cardiomyopathy, which is due to severe hyperthyroidism, is rare in practice. This so-called thyrotoxic heart disease causes congestive failure and usually recovers when the patient is made euthyroid. It is serious and can cause death in patients of all age groups [58, 59]. Management of cardiac complications should be shared with a cardiologist.

Hunger and increased appetite are very common. In spite of the increased appetite often coupled with thirst for cold drinks (usually high in calorie content), the patient's weight remains stable or loss occurs. In the early phase of the illness, before unpleasant symptoms occur, weight loss is accepted happily and weight gain is often a concern of successful treatment. Rosenthall *et al.* [60] described seven hyperthyroid patients aged 35 to 66 with severe and prologed vomiting which was controlled by antithyroid medications. This symptom can be a sign of impending crisis, and should alert the clinician of the need for early

prescription of treatment. Whether this is due to activation of the 'chemoreceptor trigger zone', or to gastric stasis, is unclear. Parkin *et al.* [61] found gastric stasis attributable to hypomagnesaemia, and this biochemical finding has been reported in some patients with apathetic hypothyroidism. Serum magnesium is not measured routinely, but in hyperthyroidism with a complication it should be, and corrected if low. Hyperdefecation is common and severe diarrhoea is encountered less frequently. Malabsorption with more than 7 g fat in the stool in 24 hours is found in about 25% of patients, and this improves when the patient is euthyroid [62]. Severe, watery diarrhoea is less common, but should be thought of as a rare presenting sign of hyperthyroidism. Abnormalities in liver enzymes can be found in moderate to severely hyperthyroid patients, but morphological changes in the liver on biopsy are mild [63, 64]. Finding high results on routine chemical panel should not lead to liver biopsy.

Haematologically there are few changes of significance in most patients. However, because of the association of Graves' disease with other autoimmune conditions, pernicious anaemia and thrombocytopenia are found more commonly. Herbert [65] in a review of three publications found that 3.1% of patients with Graves' disease had pernicious anaemia, and from 10 papers that 1.9% of patients with pernicious anaemia had Graves' disease. There are many reports and anecdotal statements concerning the association of easy bruisability and Graves' disease. Low platelet counts and true idiopathic thrombocytopenic purpura are well documented [66–68]. It is important to exclude antithyroid medications as the cause of thrombocytopenia, since treatment differs from the idiopathic variety. In active Graves' disease, the total polymorphonuclear count can be low [69], the total lymphocyte count can be high and the suppressor T lymphocyte count reduced [70]. The spleen is enlarged in about 30% of patients, but is seldom palpable, and there are reports of thymic enlargement [71]. Lymph node enlargement, especically the left subtrapezoid nodes during the hyperthyroid phase, are thought to reflect drainage of thyroid antigens to these nodes [72]. Iron deficiency anaemia is almost always due to blood loss; the source should be found and treatment directed at that and iron replacement.

Hypercalcaemia has been reported in almost one-quarter of hyperthyroid patients [73], and in any series the mean value is statistically higher than in controls. The cause is thought to be due to thyroid hormone causing increased osteoclastic activity, so that bone calcium is lost and hypercalcaemia and hypercalciuria result. The question arises, is the hypercalcaemia due to thyrotoxicosis alone, or is there coexisting hyperparathyroidism? In the former, serum phosphate tends to be high, in the latter low. Because serum phosphate is dependent on diet and renal function, this measurement alone can be misleading. Until recently, there was disparate information concerning parathormone values in hyperthyroidism. High, normal and low results were reported. It appears the discrepancies were due to differences in assays. Using the midregion specific assay, Mallette *et al.* [74, 75] found low values, appropriate for hypercalcaemia being due to thyrotoxicosis. Alkaline phosphatase levels are frequently high and can take up to 1 year to return to normal after successful treatment of hyperthyroidism [76]. There are cases of hyperparathyroidism coexisting with thyrotoxicosis [77], and to add another related factor, hyperparathyroidism has been documented to occur more commonly in patients who have had neck irradiation [78, 79], including radioiodine ^{131}I therapy [80]. The bone density can be reduced as determined by single or dual photon densitometry, and severe osteopenia and fractures can result [81]. Similar findings occur in patients overtreated with exogenous thyr-

oid hormone [82–84]. Treatment of hyperthyroidism can slow and reverse these findings, thus restoration of physiological levels of FT_4 and TSH is warranted.

With fee exceptions, moderate and severe hyperthyroidism cause a drop in libido. Infertility has been reported in men [85]. One report of gynecomastia in 83% of men [85] is considerably higher than my experience, but reminds clinicians that it can occur. Sex hormone binding globulin values are increased. However, this should not be measured routinely, as it returns to normal with restoration of euthyroidism. In women, oligomenorrhoea is common. The periods are short and light and secondary amenorrhoea can occur.

The skin is moist, warm and soft. Facial wrinkles are lost, only to be regained when treatment is successful. Onycholysis, separation of the nail from the nail bed, is overlooked unless the nails are examined carefully. These are called Plummer's nails. The hair is soft and fine and does not take a permanent wave. Vitiligo has been reported in 6–7% of patients with Graves' disease [87, 88], but it is also found with the same frequency in Hashimoto's disease and primary hypothyroidism.

For continuity, clinical and therapeutic aspects of the severest form of thyrotoxicosis, thyroid crisis or storm are presented together at the end of the chapter.

5.2.4 SPECIFIC MANIFESTATIONS OF GRAVES' DISEASE

(a) Infiltrative ophthalmopathy; Graves' ophthalmopathy; malignant exophthalmos; dysthyroid ophthalmopathy

Introduction and aetiology

The ophthalmopathy of Graves' disease is not seen in the other conditions which cause hyperthyroidism, but it is seen occasionally in patients with Hashimoto's thyroiditis or primary hypothyroidism [89]. It is puzzling why the contents of the orbit are involved in autoimmune thyroid disease. Originally, the main lesion was thought to be an increase in fat in the orbit [90], but results from autopsies [91], surgery and non-invasive imaging including ultrasound [92, 93], CT [94] and NMRI have shown that the major change is an increase in the bulk of orbital muscles, sometimes to a dramatic degree. Why the muscles are involved is becoming apparent from laboratory studies. Thyroglobulin, antithyroglobulin and complexes of thyroglobulin/antithyroglobulin have been shown to attach preferentially to membranes made from eye muscles [95]. Monoclonal antibodies made *in vitro* against orbital antigen have been shown to react with thyroid membranes and the converse has also been demonstrated [96]. Thus autoantibodies made against thyroid antigens could attach to orbital antigens, either muscle membrane or to fibrous tissue between muscle fibres. Antibody-antigen complexes are known stimuli for immune cells, such as lymphocytes and macrophages, and in the acute inflammatory stage of the ophthalmopathy, the orbital muscles are infiltrated with these cells and there is oedema and inflammation. As the muscles become infiltrated and inflamed, they swell within the fixed space of the boney orbit and the globe is compressed from the back and pushed anteriorly. The enlarged muscles do not relax well. The alteration in anatomy causes obstruction to venous and lymph drainage and further oedema and swelling occurs.

The ophthalmopathy is usually bilateral, although there is often a disparity in severity between the eyes. Sometimes the ophthalmopathy is unilateral. This makes the immunological explanation given above difficult to accept. However, if the autoantibodies arrive at the orbit by a route different from the blood stream, asymmetry would be possible. Kriss [97] demonstrated that radiolabelled colloidal material and thyro-

globulin when injected into the thyroid left via the lympahtics and travelled fairly rapidly to the preauricular nodes, which are close to the back of the orbit. Similar material injected into eye muscles at operation migrated to the same nodes. Thus continuity from thyroid to orbit was demonstrated via the lymphatics. The concentration of thyroglobulin and antithyroid antibodies are high in the local lymphatics. In addition, the flow from the thyroid is quite asymmetric. This experiment shows how thyroid antigen, antithyroid antibody, complexes of both and possibly lymphocytes from the thyroid could gain asymmetric access to the orbit.

Clinical aspects

The American Thyroid Association published a mnemonic, NOSPECS, to help classify and compare patient with infiltrative ophthalmopathy [98]. This is shown in Table 5.3. Donaldson *et al.* [99] modified this by adding a numeric score to the objective SPECS. Although no classification is ideal, this one allows comparison between patients and provides an objective way of determining natural history and response to therapy. It does not give appropriate weight to problems such as loss of vision, since soft tissue signs are scored the same as double vision and visual loss. Figure 5.1 shows a range of abnormalities in patients with infiltrative ophthalmopathy.

The onset can be gradual or explosive. It can occur while the patient is hyperthyroid, euthyroid, or hypothyroid. Gorman [100] found that the distribution of onset was from 18 months before, to 18 months after, the onset of hyperthyroidism. His data suggest that hyperthyroidism and ophthalmopathy are simply manifestations of one disease and treatment of one does not cause the other. This relationship is confirmed by an almost identical series of Marcocci *et al.* [101]. The role of therapy as a cause or precipitating factor of ophthalmopathy has been, and still is, a cause for debate. Some authors have blamed ^{131}I. We and others have noted a striking relationship between onset of progressive ophthalmopathy and radioiodine therapy for hyperthyroidism, and found this in 97 of 311 patients whose eyes were sufficiently bad to require radiation therapy (see below) [102, 103]. This could be due to patient selection and due to the fact that most hyperthyroid patients are treated with ^{131}I. In contrast, Gwinup *et al.* [104] found patients treated with antithyroid drugs did worse from the ophthalmic point of view. A recent study showed no difference in incidence of ophthalmopathy after radioiodine compared to antithyroid drugs or thyroidectomy in Graves' patients. In that study, approximately 1 out of 20 patients who had no prior ophthalmopathy developed eye disease and 1 out of 5 who already had eye signs got worse [105]. About 3–5% of all patients with Graves' disease got severe ophthalmopathy. However, if diagnostic tests, such as ultrasound or CT, of the orbits are obtained in all patients with Graves' hyperthyroidism, degrees of ophthalmopathy are seen in almost all of them [92, 93]. Men with Graves' disease are proportionately more likely to get eye disease, 29% of Gorman's and our series were men [100, 102], compared to the 10–15% incidence of men with Graves' hyperthyroidism. Young patients are rarely found to have progressive infiltrative ophthalmopathy, although they have lid retraction and proptosis. Recent data strongly associates smoking and ophthalmopathy.

The patient complains of a gritty or sandy feeling in the eyes, tearing is noted, and there is usually intolerance to bright lights and sunlight. The lids are retracted, more often the upper lids, but quite often upper and lower lids. Upper lid retraction is an important clue in differentiating Graves' ophthalmopathy from other causes of proptosis where the lid is usually pushed forward with the globe, and not retracted (a differential diagnosis is given in Table 5.4).

Table 5.3 Classfication of ophthalmopathy of Graves' disease

Class	*Mnemonic*	*Severity Score* 1	2	3
0	No signs or symptoms			
1	Only signs			
2	Soft tissue	Minimal	Moderate	Severe
3	Proptosis	>20–23	>23–27	>27
4	Extraocular muscle	Infrequent diplopia	Frequent diplopia	Constant diplopia
5	Cornea	Slight stippling	Marked stippling	Ulceration
6	Sight loss	20/25–20/40	20/45–20/100	<20/100

Ophthalmic index = sum of scores of five categories SPECS.

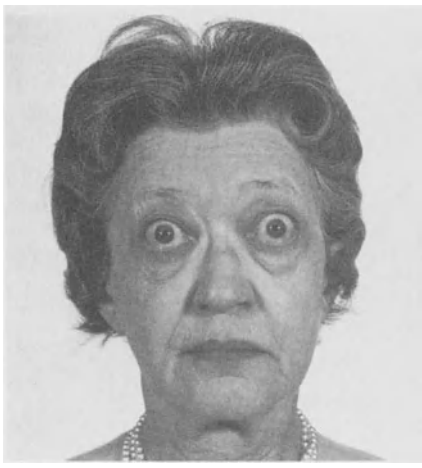
Table 5.4 Causes of proptosis

Unilateral – Graves' ophthalmopathy
Orbital pseudotumour
Abscess
Lymphoma
Tumour: benign
malignant primary
metastatic
Cysts: congenital
parasitic
Orbital varix
Haemorrhage

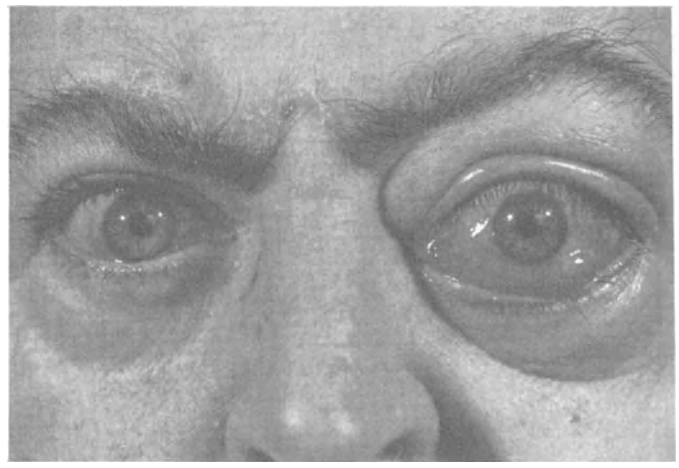
Bilateral – Graves' ophthalmopathy
Orbital pseudotumour
Carotid–cavernous fistula

The lids become puffy and the red, swollen tearing eyes are a source of embarrassment to the patient. As the eyes become more proptotic, the appearance is altered and comparison with photographs help to determine the degree of abnormality and its rate of progression. More severe involvement of the muscles causes double vision. This is not due to a defect in the cranial nerves which control the muscles, but the muscles themselves. The problem is one of failure to relax; thus the antagonist, not agonist, muscle is at fault. From CT imaging, it is recognized that the muscles which are most often the largest are the medial and inferior recti, and as would be expected the double vision is most prominent when the patient looks upward and outward. The muscle defect can progress to the point where no movement of the globe is possible (frozen orbit). However, downward and inward gaze is usually preserved except in the most severe cases.

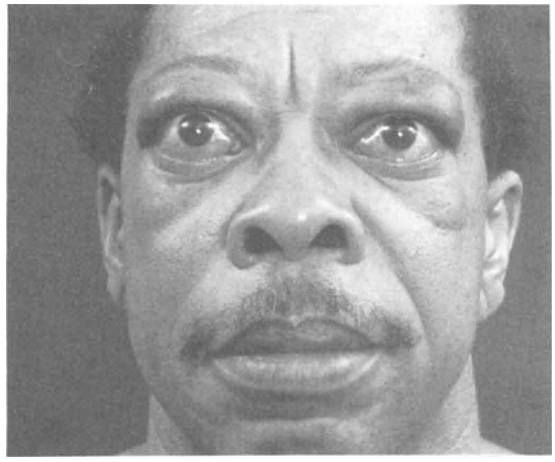
Severe proptosis plus retraction of the lids can leave the cornea exposed and abrasions can occur. This is very serious since untreated ulceration can become infected, result in panophthalmitis, and progress to the point where the globe has to be removed. The patient should consult an ophthalmologist, and corneal staining should be done to determine whether there are small ulcers. The bulky recti muscles come to a confluence at the back of the orbit where they surround the optic nerve. As the muscles



(a)

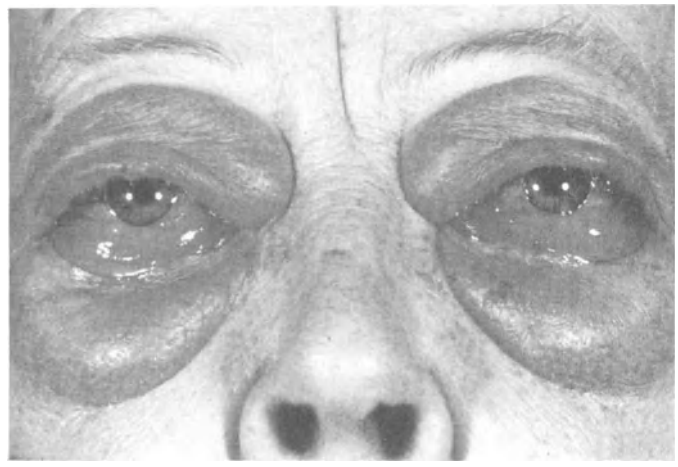


(b)



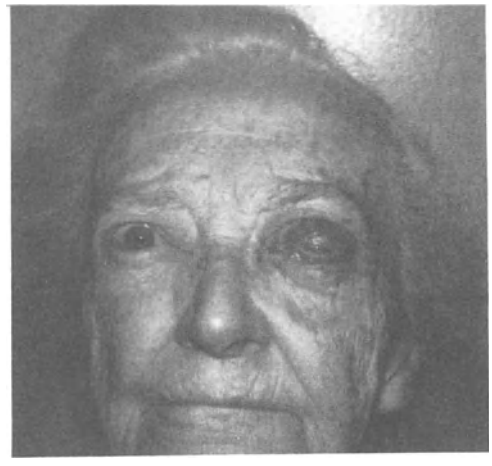
(c)

Figure 5.1 Appearance of patients with various gradations of Graves' ophthalmopathy.
(a) Proptosis and upper and lower lid retraction plus mild infraorbital oedema.
(b) Proptosis with lid retraction, both features are worse on the left; there is also marked periorbital oedema and chemosis.
(c) Proptosis, lid retraction, and supraorbital oedema with restriction of upward gaze in the right eye.
(d) Extremely severe inflammatory opthalmopathy with bilateral periorbital oedema, chemosis and scleral injection.
(e) Mild inflammatory signs in a patient who is attempting to look up and to the right. The right globe is being restricted from moving.
(f) Panophthalmitis of the left eye which resulted from corneal abrasion, ulceration and infection. The patient had moderate ophthalmopathy and could not close the lids of the left eye, resulting in the catastrophic sequence. The eye had to be enucleated.



(d)

(e)



(f)

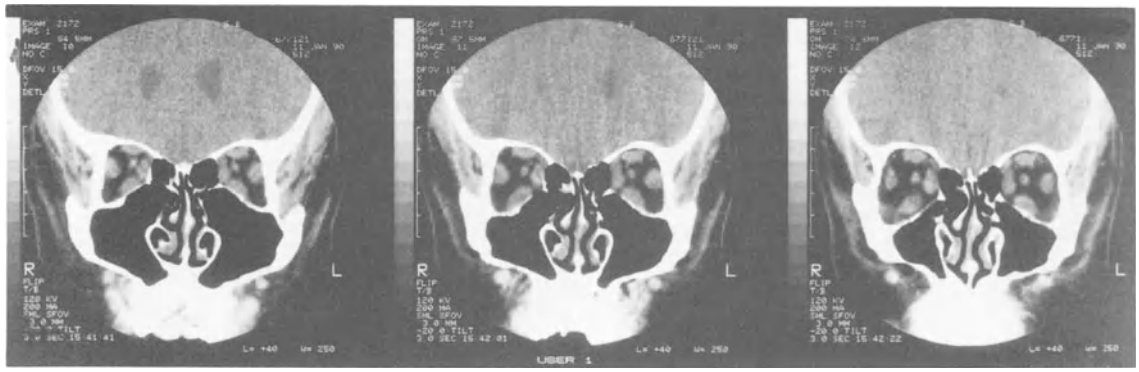


Figure 5.2 CT appearance of the orbit in Graves' ophthalmopathy showing greatly enlarged extraocular muscles on serial coronal cuts. The most posterior image is in the left panel, and it demonstrates how the optic nerve (central) is at risk of compression by the enlarged recti muscles as they converge.

enlarge, they compress the nerve and a compression neuropathy results. The disc can be normal, congested or pale. Early evidence of a problem is loss of colour vision, which is usually only detected by specific testing. Sight loss can be due to optic nerve or corneal problems, and both are medical emergencies.

Diagnosis

When the patient has bilateral proptosis and a history of Graves' hyperthyroidism, the diagnosis is easy. More than 90% of bilateral proptosis is due to this cause, so even with no history of hyperthyroidism the clinician is usually correct. Measurement of proptosis with an exophthalmometer is valuable for determining the severity of the proptosis and for following its progression, or response to therapy. There are racial and sex differences in exophthalmometry measurements. De Juan *et al.* [106] found the range in normal white men and women to be 16.0 +/− 2.30 and 14.7 +/− 1.92, and the corresponding values in African/American men and women 17.9 +/− 2.86 and 17.1 +/− 2.71. Orientals have smaller measurements, but I have not seen published results. Different instruments give different measurements in the same patient, therefore the same instrument should be used for sequential measurements. Different observers using the same instrument can record disparate measurements, and careful setting of the base and alignment of the instrument, firm pressure on the canthus and avoidance of parallax are important. Trainees should practice at all possible times and compare their measurements with those of an experienced ophthalmologist or thyroidologist. Early symptoms of grittiness and tearing without hyperthyroidism are often misdiagnosed as allergies. Fifty per cent of unilateral proptosis are due to infiltrative ophthalmopathy (Table 5.4), and knowledge of current or past Graves' hyperthyroidism clinches the diagnosis. In unilateral cases where there are no additional clinical features of Graves' disease, it is important to exclude an orbital space-occupying lesion such as a tumour, (benign or malignant, primary or metastatic), pseudotumour, lymphoma and inflammatory pathologies. The best way is by orbital CT (or NMR) using a current generation machine with a computer program capable of providing sagittal and coronal cuts of the orbits. The appearance of infiltrative ophthalmopathy is characteristic (Figure 5.2), and the most frequent differential,

orbital pseudotumour, can usually be recognized. It is not necessary to use radiographic contrast to diagnose Graves' ophthalmopathy. However, it often is in the case of a pseudotumour.

Intraocular pressure is high when measured in an eye looking upwards [107]. This is due to the enlarged muscles pressing on the globe. This is not specific and should not be used diagnostically, and it should not be accepted as glaucoma unless the pressure is also high with the gaze downward.

When there is no history of Graves' disease, diagnosis is helped by finding high levels of antithyroid antibodies. A suppressed TSH or blunted rise in TSH in response to TRH point to subclinical hyperthyroidism, but some patients are euthyroid by all criteria, and are said to have euthyroid Graves' disease.

Treatment

Mild ophthalmopathy requires only simple supportive measures and visits to determine there is no progression. Intolerance to bright lights is helped by tinted glasses, and flaps on the legs of spectacles help to prevent gusts of wind blowing in from the side causing irritation. Dryness is treated with demulcent eye drops, such as 4% methylcellulose, and the patient might have to insert a drop every 2–3 hours. If it appears the lids do not appose at night, they can be taped shut, or goggles, such as used by swimmers (racing goggles) can be worn to protect the eyes at the expense of glamour. Sleeping with the head of the bed elevated reduces the degree of puffiness in the morning, but not all patients tolerate this. I have been unimpressed of the value of diuretics in helping the local oedema. Slight diplopia is helped by spectacles with prism lenses, and a trial with temporary 'stick on prisms' helps to determine whether the expense of permanent prisms is justified. If the ophthalmopathy is fluctuating, I advise against spending a lot of money on new prescriptions for spectacles, since changes will occur with certainty.

To treat severe forms, called in older textbooks 'malignant exophthalmos', the approaches attempt to reduce the inflammation and swelling of the muscles, or to make more space for them. The former is by glucocorticosteroids (steroids for short), external radiotherapy, or chemotherapy, the latter by surgery.

Steroids are the most widely used treatment and doses of 40–80 mg prednisone daily by mouth can improve soft-tissue swelling and restore visual loss [108]. Prummel *et al.* [109] showed that steroids were superior to cyclosporin in a controlled study in which 18 patients were randomly selected to be treated either with prednisone or cyclosporin. Eleven out of 18 responded to prednisone (60 mg for 2 weeks, 40 mg for 2 weeks, 30 mg for 4 weeks, 20 mg for 4 weeks, and then tapering over the next 2 months). Only 4 out of 18 who received cyclosporin (7.5 mg per g daily for 3 months) got better. This amount of prednisone inevitably causes side-effects. In the above study, 17 out of 18 had moderate or severe complications. Therefore, the dose of steroid has to be reduced to reduce complications at a rate which might not be commensurate with clinical improvement. In many patients, there is a critical dose of prednisone below which the signs recur, and this dose is only found by trial and error. If that dose is small, e.g. 10–15 mg daily, the patient often accepts the compromise between tolerable side-effects and benefit to the eyes. However, if the critical dose is too high and if it is recalled the patients with ophthalmopathy are on average age of about 50 years, weight gain, bone loss, diabetes, hypertension, etc. may not be accepted with equanimity. For these reasons, many patients have to stop steroids and consider an alternative treatment.

We have preferred supravoltage radiotherapy. It is critical that the technique of

Table 5.5 Patients treated with orbital radiotherapy [103]

Number of patients	311
Men/women	98/213
Mean age (years)	53
Mean length of symptoms (months)	12
Number previously hyperthyroid	244
Number concurrently hyperthyroid	52
Number worse after radioiodine	97
Number worse after surgery	10
Number taking steroids	98
Number with prior decompression	10

Table 5.6 Results of radiation therapy for Graves' ophthalmopathy, 311 patients

	Percentage			
Sign	*Worse*	*Same*	*Improved*	*Resolved*
Soft tissue	2	19	22	58
Proptosis	6	42	19	32
Eye muscle	1	38	29	32
Cornea	4	20	4	73
Sight loss	4	34	16	45

Adapted from Kriss *et al.* [103].

delivery follows that advocated by Donaldson *et al.* [99] to ensure that the cornea and lens are not included in the radiation port. We have used 2000 rad (20 Gy) delivered over 10 days. Some have used smaller doses with success. This form of treatment was introduced by Jones in 1955, but the equipment was not suited for this [110]. The rationale is that the lymphocytes in the orbital muscles, thought to be causal, are radiosensitive. Therefore killing these cells should cure the problem. Why do new cells not enter the muscles and perpetuate the condition? In brief why this therapy works is not known. Details of 311 patients treated at Stanford are shown in Table 5.5. Of 311 patients treated, 80% had improvement in soft-tissue signs, 51% in proptosis, 61% in diplopia, 77% of corneal problems and 61% of visual loss [103]. Prednisone was being taken by 98 patients (29%) when they were referred for orbital radiotherapy, and 74 (76%) were able to discontinue it after radiation (Table 5.6). A slight flare in soft-tissue signs is seen in some patients between the 4th and 8th day of radiation; this is temporary and usually is predictive of a good response. There has been no occurrence of radiation cataracts, or other radiation-induced complication in this series. However, other therapist have described problems which were due to deviations from the protocol. After orbital radiation, 51 patients had eye muscle surgery, 28 lid surgery and 12 decompression. The analysis of the results of radiation therapy described above were concluded whenever surgery or any other treatment was prescribed, so that the effects of radiation alone could be determined.

Surgery creates more space by removing one or more of the walls of the orbit. This is called **orbital decompression**. The most commonly used approach involves removal of the inferior-medial walls – the Ogura technique [111, 112]. The operative approach is through a Caldwell-Luc incision, which is used commonly to drain the maxillary sinus. The operator continues through the sinus and removes the bony structures leaving the orbital periosteum as a 'hammock' for the orbital contents to lie on. The eye muscles then sit more inferiorly, and the globe moves back on average 3–6 mm. In addition, removal of the lateral wall achieves a 5–8 mm reduction in proptosis. A lateral–inferior approach is gaining in popularity, produces 3–6 mm reduction in proptosis, but does leave a scar [113]. Correction of the problem by rebuilding the bony structures around the globe has been described [114, 115]. None of these operations deals with the cause of the ophthalmopathy. Double vision can be worsened, or occur for the first time after decompression and a second muscle-balancing procedure is often required. I have

not used this often in patients with progressive inflammatory ophthalmopathy, but have recommended it in patients with severe proptosis. If there is progression of disease after surgical decompression, I recommend external radiation.

Other approaches for progressive infiltrative ophthalmopathy include immunosuppressive drugs such as cyclosporin as described above and cyclophosphamide. Their use is limited to small trials and side-effects are such that routine use is not recommended [116]. Plasmapheresis to remove pathogenic immunoglobulins has been moderately successful in small numbers of patients [117]. Total ablation of thyroid [118], to remove all antigen, has not been beneficial in several trials and is not recommended, although the patient should be made euthyroid.

There is no good trial to determine the best way of treating the patient who is hyperthyroid and has severe ophthalmopathy. The argument has already been made that treatment of hyperthyroidism does not influence the ophthalmopathy, yet in some cases acceleration of signs weeks after ^{131}I makes it appear there is a relation. Three possible approaches are as follows. The first is to treat the eyes with orbital radiation and simultaneously treat the hyperthyroidism with radioiodine. The second is to prescribe steroids for the ophthalmopathy and treat the hyperthyroidism with ^{131}I. When hyperthyroidism has been controlled, if the ophthalmopathy persists it can be treated by external radiation or decompression, my preference being the former. Alternatively, the ophthalmopathy can be treated with radiation and the hyperthyroidism with antithyroid drugs. When the ophthalmopathy has been stable for several months, the hyperthyroidism is treated definitively with radioiodine. At this time, there are insufficient patients treated to provide guidance as to the best sequence.

The treatments described are for progressive ophthalmopathy. The patient can present, or be left after these therapies, with problems such as lid retraction, diplopia and redundant tissues caused by periorbital oedema that can be treated by appropriate surgical procedures. Lid retraction can be corrected by recession of upper and lower lid retractors. Tarsorrhaphy brings the lids into apposition at the expense of altering their natural contour. Diplopia not corrected by prisms is managed by surgery on the ocular rotatory muscles. Because of the various presentations and problems, our patients are generally seen by thyroidologists, radiation therapists and ophthalmologists prior to management decisions.

Excellent reviews by Kriss [119] and Jacobson and Gorman [120] with somewhat contrasting advice, illustrate that this condition is not straightforward to manage, and patients should probably be referred to centres where there is a team experienced in all aspects of its management. A recent report shows a very stastistically significant relationship of Graves' ophthalmopathy with cigarette smoking and patients should be counselled to stop [121].

For completeness it is necessary to mention the condition of orbital pseudotumour. This disease is not related to Graves' ophthalmopathy, indeed, it may be several diseases and the cause, or causes, are unknown. It can involve one or both orbits, and it produces a clinical picture similar to Graves' ophthalmopathy (Figure 5.3). There is proptosis, periorbital oedema and diplopia, but no evidence of thyroid autoimmunity, no history of hyperthyroidism and, usually, no lid retraction. It is diagnosed by clinical suspicion and CT scan (Figure 5.4). We have found it responds well to radiation therapy, but the diagnosis should be confirmed by biopsy before this treatment is given because orbital lymphoma can give a similar CT finding. An analysis of treatment of 20 cases of pseudotumour showed complete resolution of ophthalmopathy in 15

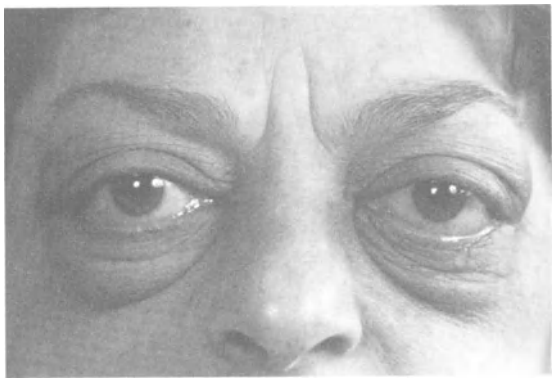


Figure 5.3 Appearance of a patient with biopsy-proven bilateral orbital pseudotumour. Clinically, there is bilateral proptosis and periorbital oedema, and this is difficult to differentiate from Graves' ophthalmopathy. One helpful clinical feature is lack of upper lid retraction.

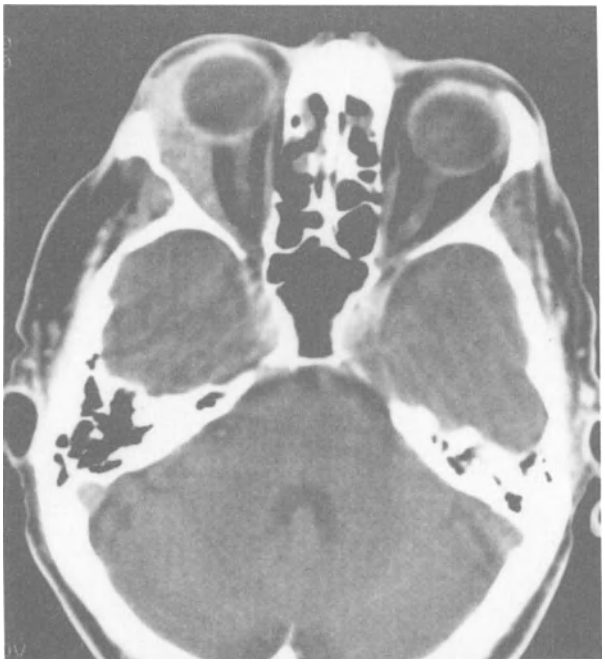


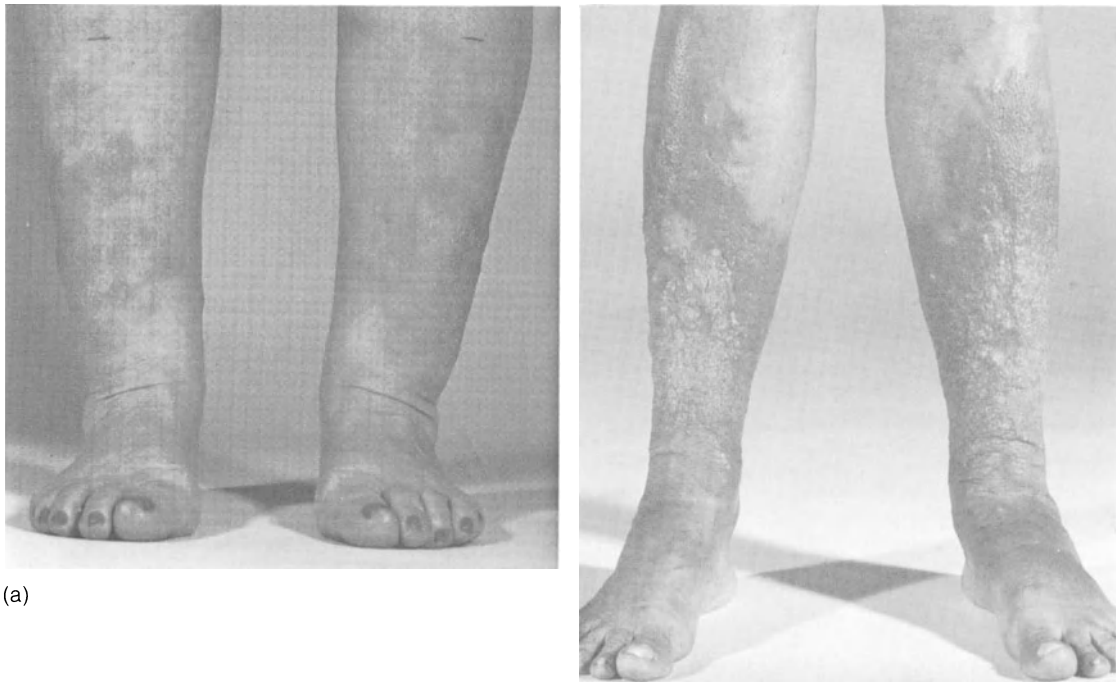
Figure 5.4 CT appearance in orbital pseudotumour of the left orbit. This is not the same patient as Figure 5.3. The abnormality is mostly between the muscle bundles in this case in the lateral aspect of the orbit, although the inflammatory infiltrate can involve the muscles as well.

cases [122]. During the same period, 12 patients with lymphomatous or atypical lymphoid infiltrate of the orbit were treated. Eight of the 12 had no systemic evidence of lymphoma.

(b) Dermopathy (pretibial myxoedema)

Dermopathy is a perplexing aspect of Graves' disease. It occurs in 1–4% of patients and is almost exclusively found in the pretibial regions. The term 'dermopathy' is preferred to pretibial myxoedema, which implies an association with hypothyroidism. The lesion varies in severity from slight discoloration of the skin to elephantiasis. Most commonly it appears as a round, or oval lesion 2–4 cm in diameter, which has a pink to brown colour (Figure 5.5a). More than one lesion can be present and they can become confluent (Figure 5.5b). They are often asymptomatic and are frequently not recognized by the patient to be associated with the thyroid condition. They are not related to thyroid status and can occur during hyperthyroidism, euthyroidism or hypothyroidism. Anecdotally, some cases occur in close temporal relation to therapy of hyperthyroidism with radioiodine. Dermopathy coexists with ophthalmopathy and usually TRAb titres in the serum are high. However, the TRAb does not cause the dermopathy [123]. Experimental work suggests that there is a compound in the serum which stimulates fibroblasts to produce excess hyaluronic acid [124]. It also appears that fibroblasts from the pretibial area are different from others in their response. Pretibial myxoedema is rich in mucopolysaccharides, in particular hyaluronic acid [125].

As mentioned, the lesions are usually asymptomatic, but more extensive lesions can itch and produce a feeling of heaviness and discomfort. The major problem is that they are unsightly and force women to wear trousers instead of skirts. When the lesions are large, symptomatic or unsightly, the best treatment is topical fluorinated corticosteroid



(a)

(b)

Figure 5.5 (*a*) Typical appearance of dermopathy, 'pretibial myxoedema'. The lesion is circumscribed, usually on the shin, and slightly raised with browny discoloration. (*b*) Extensive confluent dermopathy.

cream applied at night and covered with an occlusive dressing, such as Seran wrap [126]. Severe cases require high potency preparations which should be used sparingly due to concern about absorption into the systemic circulation. Systemic steroids are not helpful and cause side-effects. Injection of steroids into the lesion can leave 'healed' pits [123]. Surgery should not be done, since ugly scarring results. This also applies to biopsy, which is seldom necessary to establish the diagnosis if the patient has Graves' disease with ophthalmopathy.

(c) Acropachy

Thyroid acropachy consists of clubbing of the distal phalanges of the fingers and toes, plus osteoarthopathy of the phalanges with swelling and puffiness of the overlying soft tissues. It is rare, occurring in less than 1% of patients with Graves' disease [127]. When present, the patient almost invariably has both infiltrative ophthalmopathy and dermopathy. These relationships strongly suggest that this is an autoimmune condition. However, there are no data concerning the pathogenesis. Acropachy is more likely to occur after treatment of hyperthyroidism, and it severity is not influenced by thyroid status [128–132]. The first report in English was in a 22-year-old man in whom acropachy and dermopathy arose 8 months after partial thyroidectomy for Graves' hyperthyroidism [130]. Acropachy can be asymptomatic, but in cases where there is marked soft-tissue involvement the fingers can be stiff

and painful. Men are affected more often than women. In his review of the literature in 1960, Gimlette [129] found 12 men and 7 women with this manifestation. However, 5 out of his 6 personal cases were women. Because of the associated conditions of Graves' disease and the frequent history of treatment of hyperthyroidism, the diagnosis is seldom difficult. Other forms of arthropathy, such as rheumatoid arthritis and osteoarthritis, are excluded by history and examination. Other causes of finger clubbing and osteoarthropathy including pulmonary conditions, such as cancer and bronchiectasis, cirrhosis and malabsorptive symptoms are usually diagnosed by history. Familial clubbing is usually recognized as such and antedates all thyroid problems. Acropachy has been misdiagnosed as acromegaly, and it should be recalled that Graves' disease can coexist with acromegaly. On occasion, the diagnosis is made by radiograph or bone scintigraphy. In the former there is periosteal reaction in the phalanges and sometimes in the metacarpals and metatarsals and even the distal long bones of the limbs. Gimlette [129] states the radiographic findings are different from other forms of osteoarthropathy, with a bubbly periosteal reaction. Scintigraphic findings show linear uptake in cortical bone producing a tram-line appearance [133, 134]. The scintigraphic findings are not pathognomonic; they exclude arthritides and acromegaly, but are the same as pulmonary osteoarthropathy. No single treatment has been uniformly successful. The patient described by Parker *et al.* [133] was significantly improved by topical glucocorticosteroids under occlusive dressings.

5.2.5 ASSOCIATED AUTOIMMUNE DISEASES

Graves' disease is an organ-specific autoimmune disease and it is associated with other autoimmune disorders, both organ specific and generalized, more frequently than by chance. Vitiligo, myasthenia [135] and pernicious anaemia have been mentioned above. There are a number of reports of Addisonian adrenal insufficiency with Graves' disease [136]. This is important because hyperthyroidism is not tolerated well in this situation, and any suspicion of adrenal insufficiency should prompt a synthetic ACTH stimulation test and, if abnormal, replacement therapy with hydrocortisone. Rheumatoid arthritis is 6 to 10 times more common than in controls [137].

5.2.6 LABORATORY DIAGNOSIS

The first step in laboratory diagnosis is to suspect the patient is hyperthyroid. In moderately severe cases this is not problematic, and if there is a diffuse goitre and proptosis, the diagnosis is Graves' disease. However, as has been discussed, the diagnosis can on occasion be difficult because one organ is involved alone, or to an inappropriate degree. Testing should be directed to proving there are high levels of circulating hormones; I find FT_4 the most sensitive single test, with FT_4I an alternative. This is coupled with TSH to demonstrate that the pituitary is suppressed by the high T_4 and T_3. For primary work-up, it is usually not necessary to measure T_3. However, I leave this to the individual practitioner. I ask the laboratory to hold the serum and if FT_4 and TSH do not correspond, e.g. normal FT_4 and low TSH, I request T_3 without recalling the patient. True T_3 toxicosis is not common, therefore it is not cost effective to measure T_3 in every patient. I recommend measuring radioiodine ^{123}I uptake to ensure that the thyroid is actively trapping. It is not necessary to obtain a scintigram if the thyroid is diffusely enlarged on palpation.

In classic cases of Graves' disease, I have not found measurement of TRAb or other antibodies to be particularly helpful. TRAb is not always present in the circulation, and if absent in a patient with all the features of

Graves' disease, does this change the diagnosis or treatment? I think not. One exception to this is the pregnant woman with Graves' disease, where high levels of maternal TRAb can cause neonatal Graves' disease, but even in this situation the association is not inevitable and the endocrinologist and obstetrician should be alert to this problem irrespective of TRAb levels. This is discussed below. Does knowledge of the levels of antithyroglobulin and antimicrosomal antibodies alter management? I do not believe so.

Laboratory diagnosis is therefore simple and inexpensive.

5.2.7 TREATMENT OF HYPERTHYROIDISM

It is generally accepted that hyperthyroid patients should be treated unless the symptoms and signs are very mild and the patient can be monitored closely to ensure the disease is not progressing. There is evidence that mild hyperthyroidism, perhaps even subclinical biochemical hyperthyroidism, produces long-term complications including osteoporosis [138]. Untreated hyperthyroidism can progress to thyroid storm and cause death.

In a review of the outcome of hyperthyroidism (largely Graves' disease) prior to modern therapies, Wilson [139] found that approximately 33% of patients died, 33% spontaneously got better and 33% remained chronically unwell. It is difficult to relate these numbers to present practice, because we are now able to diagnose hyperthyroidism at a very early stage and we recognize many transient causes, plus our general supportive care is superior. Nevertheless, two important facts are seen: some untreated patients die and others recover without therapy.

There are three broad forms of treatment: medications, radioactive iodine and operation. They are not exclusive of one another; for example, medications are used to make a patient well prior to surgery. They might also be used for a short time while awaiting the response to radioiodine. If a patient relapses after thyroidectomy, radioiodine becomes the therapy of choice. It is apparent that none of the treatments tackle the basic pathophysiological problem of reducing or eliminating TRAb. Antithyroid medications might have a minor immunosuppressive role as will be discussed below, but all work by reducing the level of circulating thyroid hormones, either by interfering with their formation or removing their source.

5.2.8 ANTITHYROID MEDICATIONS

Antithyroid drugs are used primarily to treat Graves' hyperthyroidism. Medications which are valuable in treatment of hyperthyroidism can be categorized into five groups. (1) Those that interfere with synthesis of thyroid hormones at the cellular level, including propylthiouracil, methimazole and carbimazole. Ions such as perchlorate and thiocyanate compete for the iodine trapping mechanism, but serious toxicity greatly reduces their role. (2) Those which interfere with the release of formed hormones. Inorganic iodine works largely this way. Lithium has a similar effect but, in practice, this action is more of a problem when lithium is used to treat psychosis, than a benefit in treating hyperthyroidism. (3) Those that interfere with the conversion of T_4 to T_3 in peripheral tissues. Propylthiouracil has a minor effect but, in practice, this is of questionable importance. Iodinated contrast agents, such as Ipodate, act in this fashion. Propranolol causes a minor reduction in T_4 deiodination to T_3. (4) Those drugs which interfere with the action of thyroid hormones on peripheral tissues. The beta-blocking drugs act this way. (5) Those that have an immunosuppressive role. These include methimazole and propylthiouracil. However, there is considerable debate as to

Table 5.7 Drugs used to treat hyperthyroidism: review of their actions and their clinical role

Category (see text)	*Action*	*Relative importance of action*	*Medication*	*Use*
1	*Blocking iodination of tyrosine (reduced coupling)*	++++	*Propylthiouracil*	*Primary*
			Methimazole	*"*
			Carbimazole	*"*
	Compete with iodine for trapping	++++	*Potassium perchlorate*	*Not advised*
			Sodium thiocyanate	*"*
2	*Block release of formed hormones*	++++	*Iodine*	*Adjuvant*
		++	*Lithium*	*Not advised*
3	*Reduce conversion of T_4 to T_3*	+	*Propylthiouracil*	*Primary*
			Propranolol	*Adjuvant*
4	*Interfere with action of T_4, T_3*	++++	*Propranolol*	*Adjuvant*
			Atenolol	
5	*Immunosuppressive*	+	*Propylthiouracil*	*Primary*
			Methimazole	*"*
			Carbimazole	*"*

how much of their action derives from this. The weight of evidence points to reduction in formation of thyroid hormone being significantly more important. True immunosuppressive drugs are too toxic for routine use in hyperthyroidism. Table 5.7 shows the drugs used, and their main actions and roles.

The drugs from group 1 are the most frequently used in practice. Their structures are shown in Figure 5.6. They reduce iodination of tyrosine, but there is disagreement how this occurs. When the ratio of antithyroid drug to iodine is high, the drug interferes with the peroxidase enzyme. When the ratio of drug to iodine is low, the drug is oxidized and less iodine is organified [140]. The coupling of iodotyrosines is also reduced. In part this is due to inhibition of the peroxidase enzyme, which also catalyses this step. However, interaction of the drug directly with thyroglobulin altering the tertiary structure cannot be excluded.

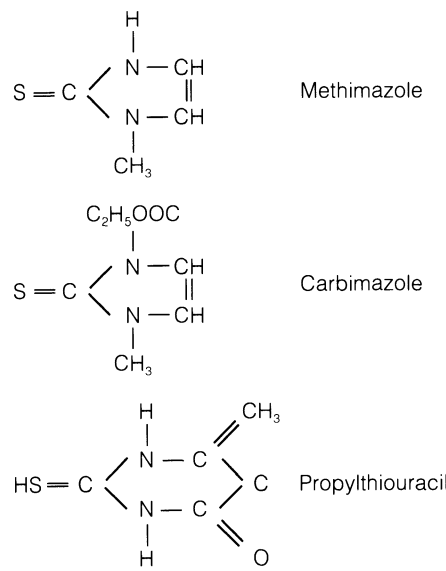


Figure 5.6 Structure of three most commonly used antithyroid drugs (thioureylenes): methimazole, carbimazole and propylthiouracil.

Each of these medications is absorbed rapidly after oral administration. Propylthiouracil has a short half-life in the plasma, of the order of 1–2 hours, and 80% is excreted in the urine in 24 hours. Methimazole has a half-life of 6–8 hours [141, 142], is somewhere between 10–100 times as potent as propylthiouracil and is not protein bound. The protein binding of propylthiouracil is

advantageous when treating pregnant or lactating women, since smaller amounts of medication cross the placenta or enter the milk. Lazarus *et al.* [142] showed that 10 mg methimazole or carbimazole produced 90% inhibition of organification after 8 hours in 8 out of 11 hyperthyroid patients. Carbimazole is converted to methimazole *in vivo*, and it is likely that methimazole is the active metabolite. One hundred mg propylthiouracil caused inhibition of about 60% after the same length of time. Methimazole or carbimazole can be given once daily [143–145], whereas propylthiouracil has to be taken 2 to 4 times each day [146]. There is national and individual preference concerning which drug is used. In the USA, propylthiouracil is favoured, in the UK, carbimazole, and in mainland European countries, methimazole. Cooper [143] has presented a case for methimazole based on convenience of once a day ingestion, cost and minor reduction in serious complications.

The medications are prescribed in larger doses at the start to 'load' the system. The actual amount will depend on the severity of hyperthyroidism, the need for urgent control and the weight of the patient. For propylthiouracil, 100–200 mg 3 times daily and for the methimazole and carbimazole 30–60 mg once a day are usual ranges. As the patient's condition improves, the dose is titrated and a maintenance dose for propylthiouracil ranging from 50 mg twice daily to as much as 100 mg 3 times a day is prescribed. For methimazole or carbimazole, a single dose of 10–20 mg is usually adequate. Several studies have shown that on average it takes about 8 weeks for patients to become euthyroid [147, 148]. Some patients require larger doses. However, Cooper [149] demonstrated that resistance was more likely to be due to non-compliance. He studied nine patients whose hyperthyroidism was poorly controlled by daily doses of 800 mg or more of propylthiouracil. Six of the nine, including a patient I treated, had undetectable propylthiouracil in the serum shortly after they said they took the medication. In an additional two patients, the data pointed to non-compliance but was not unequivocal. The aim should be to maintain the lowest dose of medication that keeps the patient euthyroid. There is considerable debate about how long treatment should be continued and about the expected response rate. These two are somewhat related.

A proportion of patients with Graves' disease have a spontaneous remission. In fact, some go on to become hypothyroid [150]. Clinical features which have been recognized to predict remission with modest reliability are a short history of hyperthyroidism, a small goitre, disappearance of a goitre on treatment and no family history of hyperthyroidism. Remission rates range from 13–80% [151]. It is not obvious that all patients studied had Graves' disease and inclusion of patients with thyroiditides would bias the remission rate favourably. Alexander *et al.* [152] were the first to demonstrate that modest doses of inorganic iodine could increase the relapse rate, and this was confirmed by a retrospective analysis of published results by Wartofsky [153] and an evaluation of patients treated by that author. There was an inverse relationship of remission rate versus iodine intake. Since iodine intake in the diet increased in the USA from 1950 to 1970, the remission rate using medications fell. In 1973, Wartofsky [153] reported a remission rate of 14%, and in 1987 investigators including Wartofsky found the remission rate to be 50.7%, which was attributed to a fall in dietary iodine [151]. In my experience, the remission rate in the USA is considerable less than 50%, and further studies are awaited with interest. It would seem fair to state the remission rate lies somewhere between 20–50%. If this is the case, how long should antithyroid medication be prescribed before it is stopped to determine whether remission has occurred? Standard therapy has been for 12–18 months, and the

remission rates quoted above relate to such reports. Greer *et al.* [154] advocated a shorter course. They treated patients until they became euthyroid and stopped the drug. Thirty-eight per cent went into lasting remission after an average of 4.5 months of treatment. This is no different from the result expected from a longer course and might be somewhat better. Burr *et al.* [155] could not reproduce these results, and 22 of 25 patients (88%) treated on a similar protocol relapsed within 4 weeks of stopping medication.

The proportion of patients with lasting remission increases with the length of treatment [156]. I have found that some patients prefer antithyroid medications to the alternatives, and provided they are euthyroid clinically and biochemically and the dose of medication is modest, e.g. 200 mg propylthiouracil or 20 mg methimazole, I continue that treatment until remission occurs, or indefinitely if it does not. These drugs all have similar toxicity. About 5% of patients experience minor side-effects, such as skin rashes, arthralgias, gastrointestinal upset, and some patients develop a strange disagreeable aftertaste. About 0.5–1% have a major complication, the most common being agranulocytosis (leukocyte count less than 0.25×10^9/l), which has been reported in 0.1–0.5% [157, 158]. It appears to be immunologically mediated. Other major complications are hepatitis and vasculitis. Cooper *et al.* [159] state the risk of agranulocytosis is less with small doses of methimazole, such as 25–30 mg daily. They found no relation to the dose of propylthiouracil. The risk is greater in patients over 40 years of age [149]. A recent multinational study showed that antithyroid drugs were associated with a relative risk of agranulocytosis of 102 (that is patients were 102 times more likely to get agranulocytosis) [160]. This seems a considerable risk. However, when calculated differently, these drugs only produce 6.3 cases per 10^6/week. The complication occurs rapidly and usually within the first 3 months of therapy. Routine white cell counts at clinic visits are of no value in predicting the problem. It should be recalled that a modest leukopenia is found in Graves' disease and the antithyroid medications cause a leukopenia of $3–4 \times 10^9$/l in about 10% of patients, which does not progress to agranulocytosis. Patients should be told to stop the medication and report symptoms such as sore throat, fever, or infection to their physicians. A 'stat' white cell count and differential establishes the diagnosis. The patient should be hospitalized, and if necessary antibiotics given to treat apparent infections. A rise in white cell count is to be anticipated over the course of several days, but deaths have occurred. Aplastic anaemia is very rare, although the international study mentioned previously, found the relative risk to be 9.2. They found four cases in their investigation. This contrasts with the well-known risk of aplastic anaemia from potassium perchlorate, which is not used in the USA to treat hyperthyroidism.

Hepatitis is associated with propylthiouracil, but apparently not with other antithyroid drugs [161]. This occurs within 6 months of starting therapy. Hanson [162] reported two cases and reviewed the literature and found only one case occurring after 6 months; the remaining seven were on propylthiouracil from 2 weeks to 5 months. Seven of the eight patients were less than 30 years of age and were women. However, these data most probably reflect the age and gender of patients treated with these drugs. Propylthiouracil should be stopped and tests done to ensure there is not an alternative cause, such as viral or alcoholic hepatitis. Paradoxically, propylthiouracil has been used in treatment of alcoholic hepatitis [163]. Vasculitis, or a lupus-like syndrome, is very rare and appears to be more common with propylthiouracil than the other drugs. Based on the data, there is a recommendation to use methimazole with an initial loading of 30 mg, which can be taken once daily. In patients with large goitres and severe hyperthyroidism, this dose might not be enough,

and as the dose increases, so does the risk of complications.

Beta-blocking drugs are very valuable in the treatment of hyperthyroidism [164], but in most cases play an adjuvant role. I prefer propranolol and the dose varies from 20 mg 3 times a day to 60 mg 4 times a day, most patients responding well to 40 mg 3 or 4 times each day. Several of the symptoms and signs of hyperthyroidism, such as tachycardia and tremor, are similar to those of overstimulation of the sympathetic nervous system; the levels of catecholamines in the circulation are normal, but there is evidence of an increase in their receptors. Beta-blockers act at this site. Propranolol alone has a minor effect in reducing the conversion of T_4 to T_3. One study showed no difference clinically between propranolol, oxprenolol, atenolol and acebutolol, but only propranolol caused a fall in T_3 [165]. Each clinician should gain experience with the use of one preparation. These drugs do not make the patient euthyroid. The pulse rate is slowed, tremor and sweating reduced and general well-being improved. However, objective evidence of thyrotoxicosis persists clinically and biochemically. A thyroid storm has occurred in a patient who appeared appropriately treated with propranolol [166]. Rubenfeld *et al.* [167] showed that propranolol is metabolized faster in hyperthyroidism, and the serum levels can be lower than anticipated.

Iodine has paradoxical effects on the thyroid. In a subsequent section in this chapter, its role in producing hyperthyroidism is discussed. However, in Graves' hyperthyroidism, pharmacological doses, such as 5 drops of SSKI, containing 180 mg of iodine, rapidly reduce the release of preformed thyroid hormones. Iodine has an adjuvant role rather than an independent one. Iodide should not be used in the treatment of toxic nodular goitre. The usual preparations are SSKI and Lugol's iodine.

Lithium has been shown to produce goitre and hypothyroidism in euthyroid patients taking the drug for its anti-psychotic properties [167–170]. It has been investigated in the treatment of hyperthyroidism. In a randomized trial comparing lithium carbonate with methimazole, the former showed no advantage and 73% of patients had side-effects attributable to the drug [171]. Lithium in combination with carbimazole produced a larger fall in thyroid hormones than carbimazole alone [172]. A third study showed that smaller doses of radioiodine could be used because the ^{131}I was retained longer in the thyroid [173]. Any role that lithium has in the treatment of hyperthyroidism is minor, and would be based on unusual clinical requirements.

5.2.9 RADIOACTIVE IODINE THERAPY

(a) Introduction

The radionuclide of iodine which is now used universally is ^{131}I. In the past, trials of ^{130}I and ^{125}I were conducted, but these radionuclides showed no advantage over ^{131}I. This section deals specifically with radioiodine in the treatment of Graves' hyperthyroidism. In Chapter 13, I have tried to bring together the effects of various types and doses of radiation on the thyroid, and have attempted not to repeat data here. The thyroid cannot differentiate radioiodine from inorganic, non-radioactive ^{127}I. Therefore, when radioiodine is introduced into the plasma it is trapped in the same proportion as inorganic iodine. Most of the iodine is rapidly organified and stored in the colloid in thyroglobulin. Iodine-131 emits beta particles which are locally destructive over several hundred micrometres; it also emits high-energy gamma rays, which can be detected externally and which contribute approximately 10% of the radiation dose to the gland. In Graves' hyperthyroidism, the distribution of iodine is fairly homogeneous; therefore the cells are irradiated uniformly, with the exception of the most peripheral rim of the gland, which is not radiated from all sides. The diameter of follicles in Graves'

hyperthyroidism is less than the path-length of the beta particles, and the length of the follicular cells considerably less. As a result, the radioiodine is expected to cause equal damage across the length of the cells, but because the nucleus is the most radiosensitive part, it bears the brunt of the damage. Radioiodine causes a proportion of the follicular cells to die, and so they do not function. This is the rationale for the treatment. The proportion of cells killed depends on the amount of radiation concentrated in the thyroid and this is discussed below.

(b) History

The first patient was treated with radioiodine in January 1941, the radionuclide was ^{130}I (half-life 12.5 hours). In 1942, two groups of investigators published their preliminary results [174, 175]. Because the patients were also treated with inorganic iodine after the radioiodine, it was not possible to determine which was responsible for clinical improvement. Chapman [176] treated the first patients with radioiodine alone in May 1943, and in 1946 reported on 22 patients treated with 14–54 mCi of ^{130}I [177]. Iodine-131 was introduced in 1946 [176], and there are many articles indicating its efficacy and safety. A representative segment of the literature is discussed below. Greig *et al.* [178] suggested that ^{125}I, because of its low energy Auger and conversion electrons, might control hyperthyroidism without producing hypothyroidism. The clinical results using this radionuclide are presented briefly.

(c) Results of radioiodine therapy and methods of calculating the dose

The goal of radioiodine treatment is to render all patients euthyroid with a single therapy dose within a reasonable period of time. This goal cannot be achieved. The clinician and patient have to accept that a rapid one-dose cure causes hypothyroidism; alternatively, any attempt to prevent hypothyroidism inevitably causes delay in treatment of hyperthyroidism and frequently the need to retreat. At this juncture I admit my preference for the former. In early reviews approximately 10% of patients treated with ^{131}I became hypothyroid. In some patients, the hypothyroidism did not occur for many years after treatment [179]. In 1961, Beling and Einhorn [180] demonstrated a rise in hypothyroidism with increasing passage of time after treatment, and this finding has been reproduced in many subsequent publications [180–184]. Nofal *et al.* [183] and Blahd and Hays [185] found that 70% of patients were hypothyroid 10 years after therapy, and there was no evidence of a plateau at this time. It is not clear why early investigators did not recognize the incidence of postradioiodine hypothyroidism. It seems likely that insensitive tests might have contributed. Clearly, if hypothyroidism was considered a problem, the method of reducing the incidence was to reduce the amount of radioiodine prescribed. The 'conventional' dose was in the range of 150–160 μCi/g of thyroid, and trials of 50% of this dose were undertaken. Even with the low doses, hypothyroidism occurred and the incidence continued to rise with time [147, 186–191]. In addition, the proportion of patients remaining hyperthyroid for long periods of time increased, and these patients required antithyroid medication for months or longer to keep them well, and many required second or third treatments with radioiodine. Therefore, the logistics of taking medications and the potential risks were added plus a larger total radiation burden than that of a single dose.

The methods of 'calculating' the dose of radioiodine are discussed and results of several publications presented. I accept that some posttreatment hypothyroidism is a *sine qua non*, and because this is simple to diagnose and treat, it is not considered a complication of treatment. The radiation dose to the thyroid depends on the amount of ^{131}I prescribed, its percentage uptake in the thyr-

oid, the average life (effective half-life × 1.44) and the size of the thyroid. The outcome depends on the result of these, plus some individual sensitivity factor, or factors which cannot be defined, or measured.

There are many methods of determining how much ^{131}I is to be prescribed. (1) The simplest, but not necessarily the best, is to give all patients the same dose irrespective of the size of the gland or its uptake of radioiodine. The routine amount varies from 2.5 mCi (92.5 MBq), 10 mCi (370 MBq) [192] to 15 mCi (555 MBq) [193]. (2) Some physicians prescribe a specific amount per gram of thyroid; this takes into consideration the size of the thyroid but not its uptake. (3) Most clinicians, including myself, prescribe a given amount of ^{131}I per gram of thyroid corrected for uptake. (4) This approach has been expanded to prescribe increasing amounts per gram as the size of the thyroid increase [194]. (5) Other investigators plan to deliver a specific number of rads to the thyroid and to do this they have to know thyroid size, uptake and effective half-life of ^{131}I in the gland.

Let us look at the results. In the first situation, where a fixed dose is prescribed, Lowe *et al.* [191] reported an incidence of 19% hypothyroidism after single doses of 2.5 mCi (92.5 MBq). Ten mCi (370 MBq) produced hypothyroidism in 50% of patients at 3 months and 69% at 1 year [192]. In spite of this, 19% of the total group required retreatment for persistent thyrotoxicosis. With 15 mCi [555 MBq], 64% were hypothyroid after 1 year, and 5.5% remained hyperthyroid [193]. Scott *et al.* [195] treated 75 patients with 16.2 mCi (600 MBq], and 31 became euthyroid and 44 hypothyroid, and all were cured of hyperthyroidism by 3 months. Empiric doses of radioiodine work. If the wish is to ablate a hyperthyroid gland with a high degree of certainty, for example, in a patient with cardiac complications, a single dose of 15–16 mCi (555–600 MBq) seldom fails. The simplicity and lack of measurement are considered as disadvantages. There is no way of knowing how much ^{131}I is retained in the thyroid, or of calculating the radiation dose. Nevertheless, it works!

Using the second approach, the dose is calculated from the weight of the thyroid multiplied by a predetermined dose of $^{131}I/g$. Dunn and Chapman [182] used this approach and gave 165 μCi/g which they thought delivered 120 μCi/g retained in the thyroid. If the uptake was 73%, that would be true, but the retained amount could range from 50 μCi to 160 μCi depending on thyroidal trapping. After 10 years follow-up, 50% were hypothyroid.

Thirdly, when the dose is determined from the size of the thyroid and percentage uptake of iodine, the formula is:

$$\text{Dose in } \mu\text{Ci} = \frac{\textit{Weight of gland (g)} \times \textit{Desired } \mu\text{Ci/g} \times 100}{\textit{Uptake}}$$

Using this approach, Cunnien *et al.* [196] also found an increase in hypothyroidism with time, and more hypothyroidism in recent years. They evaluated the results of radioiodine treatment at several time periods from 1952 to 1977. Although the policy of prescribing approximately 160 μCi/g was upheld, the incidence of hypothyroidism increased through the study and the need to retreat decreased. In 1952, 3% became hypothyroid in 3 months, and 40% by 1 year. In 1977, 36% and 91% were hypothyroid after the same intervals. The only difference was the clinicians' estimate of gland size, and because this is on the numerator of the equation above, it increases the total dose prescribed. The implication is that clinicians desire a rapid one-dose cure with the knowledge that hypothyroidism would occur, and they report a gland size which results in prescription of a dose expected to answer the desire. Another study done by myself and the late Dr W.R. Greig [147] evaluated 160 μCi/g in 38 patients versus 80

μCi/g in 36 patients. The two groups of patients were well matched for age, size of thyroid and 24-hour uptake. Each patient received a single therapeutic dose and to ensure they remained euthyroid, they received carbimazole and L thyroxine for 10 months. On review 20 months after therapy, 21% of the standard group were hypothyroid and 37% had relapsed, in contrast to 8% and 47% respectively in the low-dose group. Rapoport *et al.* [189] used this method, but planned to have a retained dose of 50 μCi/g. Antithyroid drugs were needed in most patients, and when they were stopped at 1 year, 54% of the patients were hyperthyroid and 7% permanently hypothyroid.

Therefore, if this formula is used, no single dose per g will result in euthyroidism. Small retained doses leave a significant proportion of patients hyperthyroid; large doses produce hypothyroidism.

The fourth method of altering the dose per g based on the gland size was introduced by Goolden and Fraser [188] and reintroduced by Roudebush *et al.* [194]. The rationale was that hypothyroidism appeared more often in patients with small thyroids, and retreatment was more common in those with large glands. Goolden and Fraser [188] prescribed 60 μCi/g retained in the thyroid for glands smaller than 40 g and 80 μCi/g, and 100 μCi/g for glands of 40–49 g and 50–59 g respectively. At 1 year, 38.5% were still hyperthyroid and only 8% hypothyroid. No longer follow-up is available. In the study of Roudebush *et al.* [194], the therapeutic schedule was to have a retained dose of 40 μCi/g in glands of 20 g, or less, up to 100 μCi/g in glands greater than 100 g. After follow-up of 1 year, 9.7% were hypothyroid and 24.2% hyperthyroid. The results appeared promising. However, at the end of 11 years, 76% were hypothyroid [197]. The authors conclude there is 'no way to modify therapy with ^{131}I alone to produce early control of thyrotoxicosis and a low incidence of hypothyroidism'.

Finally, the most complicated approach is to determine that a specific radiation dose is required, e.g. 7000 rad (70 Gy). One μCi of ^{131}I in 1 g tissue for 1 hour gives 0.433 rad. It is possible to work back and with knowledge of the gland size, uptake and average life (effective half-life × 1.44) to determine the dose required. The measurement of effective half-life is time consuming and some authorities simply assume a value, in the range of 4–6 days. If this value is assumed, both the effective half-life and gland size are estimates and it therefore does not seem rational to take time for elaborate measurements which are inherently flawed. In addition, what is the best dose, 6000, 7000, 10 000 rad (60, 70 100 Gy), or more?

Smith and Wilson [198] compared 7000 rad with 3500 rad. One year after treatment with the former dose, 8% were hypothyroid and 44% hyperthyroid and, with the latter, 4% were hypothyroid and 65% hyperthyroid. A small group of 26 patients were given 14 000 rad, but when the incidence of hypothyroidism at 6 months was found to be 19%, it was felt unjustified to continue that part of the experiment! Holm *et al.* [199] 'aimed at 6000 rad per treatment' in patients with Graves' disease and noted as others have, an increase in hypothyroidism with time [200]. It is of interest that patients treated from 1970–5 had an average 10.4% annual incidence rate for hypothyroidism for the first 7 years, in contrast to 4% in 1951–5, and approximately 5% from 1956–65. This trend is similar to that described by Cunnien *et al.* [196] which has been discussed. In the present report, there was no easy explanation, although the introduction of TSH measurements seemed to coincide with the increased incidence of hypothyroidism. Patients who responded to one dose had a lower incidence of hypothyroidism. In this study 56% were cured by one dose, 28% required two doses, 10% three and 6% more than three treatments. Therefore, the attempt to prevent hypothyroidism by prescribing a small dose first, resulted in retreatment and a higher long-term incidence

of hypothyroidism. Originally, Staffurth [201] designed 'to give between 7000–10 000 rads'. Of 298 patients treated, 60 (20%) required a second dose, and 22 (7%) three or more treatments. After a follow-up of 17 years, 78% were hypothyroid, or 4.6% per year. Thereafter, he prescribed from 3500–5000 rad (35–50 Gy), and the patients were treated with carbimazole for up to 1 year. In the second group, 55% were hypothyroid at 15 years, at an average rate of 3.6% annually (62.2% predicted at 17 years, which was the follow-up in the first group), and 11% required a repeat dose. He concludes that unless ablation is required for medical reasons, the patient 'should only be given a small dose of radioiodine so that the onset of hypothyroidism is delayed as long as possible. Alternatively, a low dose of antithyroid drug can be continued indefinitely in this group'. The data shows that even when efforts are made to calculate with some precision the radiation dose to the thyroid, euthyroidism is an untenable goal.

In summary, irrespective of the method used to determine what therapy dose is prescribed, there is a trade-off. Higher doses cure hyperthyroidism with greater regularity, but cause more hypothyroidism; lower doses cause less hypothyroidism but fail to cure hyperthyroidism. Patients are referred for treatment of hyperthyroidism and, usually, there has been lengthy discussion between patient and physician about the relative merits of the three forms of therapy, and the decision made that radioiodine is the simplest, safest and least expensive. It is my opinion that it does not make sense to delay restoration of euthyroidism for an extended period, simply to reduce by a small degree, the incidence of post-treatment hypothyroidism. The preceding data shows that hypothyroidism can be caused by the smallest therapeutic doses, and the incidence continues to rise irrespective of the dose. By delaying recovery from hyperthyroidism, the clinician puts the patient at risk of complications and, in many cases, antithyroid drugs have to be prescribed for many months, or longer. Recall the decision had been made to treat with radioiodine in preference to medications. A second radioiodine therapy is required more often, and that increases the risk of hypothyroidism. It is accepted that every clinician working in this field routinely ablates the thyroid to produce hypothyroidism when thyrotoxicosis is causing complications such as cardiac arrhythmias. Therefore, hypothyroidism *per se* is not looked on as a major complication. Hypothyroidism is easy to diagnose, especially if the physician knows it is about to occur. In this setting, muscle cramps are characteristic and measurement of FT_4 and TSH clinch the diagnosis. Treatment of hypothyroidism is not difficult. However, residual functioning thyroid which is insufficient to maintain euthyroidism is often non-suppressible, and the replacement dose of L thyroxine can be less than that required to treat primary hypothyroidism. The dose has to be titrated in each patient, and this may require two or three visits over 3–6 months to establish the optimum dose clinically and biochemically. Therefore, why not treat the complaint which brought the patient to a doctor originally, accept that hypothyroidism will occur, take steps to ensure this is understood by the patient and to ensure follow-up and appropriate testing and treatment when necessary? I have generally used 160 Ci/g, corrected for uptake to treat patients with Graves' hyperthyroidism.

(d) Complications of radioiodine-131

Because this radionuclide is used widely to treat Graves' disease in patients of all ages, clinicians should be acquainted with potential and real problems. Knowledge of lack of certain complications, such as induction of cancer of the thyroid and other organs, is very important for discussion with patients. The complications are presented in the time course that they can occur, but because of considerable variation of several (there is considerable overlap), they are listed in Table 5.8.

Table 5.8 Complications and risks – real and theoretical – from radioiodine

Radiation thyroiditis
Thyroid crisis
Vocal cord paralysis
Hypoparathyroidism
Hyperparathyroidism
Ophthalmopathy
Thyroid cancer
Leukaemia
Infertility
Genetic problems

It is not uncommon for a mild exacerbation of thyrotoxicosis to occur several days after ^{131}I. This is due to the release of preformed hormone from disrupted follicles. Frank thyroid storm is not common, but is well documented [202, 203]. McDermott *et al.* [204] documented 16 reports from the literature. This serious complication has been reported as early as 1 day and as late as 20 days from the time of treatment. There are undoubtedly others unpublished cases. The patients were usually older than 40 years (14 of the 16), and had severe thyrotosicosis, frequently with cardiac complications. Thyroid storm has also been found in patients with toxic nodular goitres who receive radioiodine therapy. It is therefore my policy to pretreat older patients (usually those older than 50 years), and those who are truly thyrotoxic, with antithyroid medications for 2–3 months as a preliminary step to ^{131}I treatment. This allows the patient to be rendered euthyroid, it depletes the thyroid of stored hormone, and it allows continued frank discussion about ^{131}I treatment when the patient is euthyroid. Propylthiouracil is stopped for 3 or 4 days, and methimazole for 4 to 7 days before measuring uptake and prescribing therapy. I cannot recall any patient spontaneously improving permanently with this short course of antithyroid medication. Repeat radioiodine uptake after this course of medication is frequently higher than the original measurement because the gland is depleted of iodine, therefore a larger percentage of treatment is trapped. As a result I repeat the uptake meaurement immediately prior to radioiodine therapy so that dose calculations can be made. Several investigators have shown that methimazole is somewhat radioprotective [205], therefore the dose of ^{131}I prescribed should not be reduced. One report compares the results of ^{131}I therapy in patients simultaneously taking antithyroid drugs compared with controls who were not on medications at the time of radioiodine treatment [206]. Thirteen patients were in the trial group; one became hypothyroid (8%), three needed retreatment and the mean dose was 15.8 mCi (585 MBq). The normal group received a mean of 9.2 mCi (340 MBq); 36% became hypothyroid, and 29% were retreated. The numbers of patients are too small to draw conclusions, although hypothyroidism was reduced in the study group in spite of prescription of a larger dose. This is due to rapid loss of ^{131}I from the thyroid, rather than radioprotection from the antithyroid drugs.

It is important to recognize that in several large series there has not been a single case of thyroid storm [207, 208]. It should be rare, especially if precautions taken. Treatment is described under thyroid storm.

Radiation thyroiditis is very rare with the doses used to treat Graves' disease. There is pain over the thyroid, which radiates to the jaw or ears, and the gland is tender to palpation [199]. The overlying skin can appear red. This complication is treated with analgesics and, if symptoms are very severe, a short course of steroids. Sialitis from therapeutic radioiodine therapy of Graves' disease is rare [210, 211]; it usually involves the parotid because it has the highest saliva to serum concentration of iodine. This is transient and subsides without treatment. The problem is more frequent in patients with thyroid cancer who are treated with ^{131}I, be-

cause the doses are an order of magnitude greater. In 1968 Silver [212] commented that ^{131}I caused no detectable injury to the recurrent laryngeal nerves. There are now two cases where the temporal relationship of hoarseness, vocal cord paralysis, and therapeutic radioiodine strongly implicates ^{131}I [213, 214]. I still have difficulty accepting that the radiation dose to the recurrent laryngeal nerve would be sufficient to damage the nerve. Pressure entrapment from swelling of the thyroid is probable. The first patient received 7.3 mCi (272 MBq) and had a 24 hour uptake of 93% [213]. She became hoarse after 1 week and that symptom had not improved after 1 year. Robson [214] reported the first case in the UK in 1981, where about 3000 patients receive this treatment annually. The patient became hoarse the day after 6 mCi radioiodine (222 MBq) and recovered after 15 months. It is notable that this complication has not been reported with larger cancerocidal doses of ^{131}I.

Hypocalcaemia and hypoparathyroidism have been reported very infrequently after ^{131}I. It is also unlikey that the radiation from adjacent thyroid would be sufficient to cause this, unless the parathyroids are all intrathyroidal. Alternatively, hypocalcaemia might be due to rapid correction of calcium deficiency which is characteristic of hyperthyroidism, or release of calcitonin by the radioiodine. The delay from radioiodine treatment to diagnosis of hypocalcaemia ranges from 5 days [215] to 2 years [216], and the doses ranged from 4 mCi (148 MBq) to 30 mCi (921 MBq) [217]. Those cases arising longer than 1 month from therapy are probably due to some other cause. In contrast, there is an increase in hyperparathyroidism after radioiodine, and it is not clear whether this is the result of the increased relation of hyperparathyroidism with Graves' disease *per se*, or whether it is caused by radiation to the parathyroids [80]. Whatever the aetiology, the problem is uncommon clinically.

There is temporal evidence of worsening of infiltrative ophthalmopathy in about 5% of patients (20% of those who already have ophthalmopathy at the time of radioiodine therapy) after radioiodine, but this is probably part of the natural history of the disease. The corollary, that about 33% of patients referred to us with severe progressive ophthalmopathy had radioiodine within 1 year seems paradoxical, but is consistent with Gorman's theory that ophthalmopathy occurs in a normal distribution from 18 months before to 18 months after the onset of hyperthyroidism. Gwinup *et al.* [104] showed that ophthalmopathy was more likely to occur in patients treated with antithyroid drugs.

All of the above are rare and unlikely to be found in routine clinical practice. The major risks as far as the patient is concerned are: will this treatment cause leukaemia or cancer, will it make me infertile, and will it effect my offspring?

All radiation is potentially carcinogenic [218]. There is evidence from several sources, including survivors of atomic fallout, spondylitic patients treated with spinal radiation, cancer patients treated with radiation and infants exposed to radiation *in utero*, that the incidence of leukaemia is increased by radiation. There is no increase in patients treated with ^{131}I. The relationship was investigated by the Cooperative Follow-up Study [219]. Seventeen patients out of 18379 treated with radioiodine developed leukaemia, the total review was 119000 patient years. Of the 10731 patients treated by operation, 16 subsequently were found to have leukaemia. There was no evidence to support the thesis that radioiodine caused leukaemia. There are other reviews [220] and single case reports, but their authors conclude there is no added risk [221, 222]. Chromosomal abnormalities are found in circulating lymphocytes after standard doses of ^{131}I, as well as larger doses used to treat thyroid cancer [223–226]. Similar abnormalities are

seen in the lymphocytes of patients treated with ^{125}I [227]. It is thought that cells with visible chromosomal abnormalities are sterile and although they are viable and even functional, they cannot divide and hence cannot become malignant. Concern about leukaemia is not a reason to advise against ^{131}I treatment.

There is no evidence of an increased incidence of thyroid cancer in patients who have received radioiodine therapy. This topic is discussed and referenced in full in Chapter 13 [228–232]. Cancers in other organs are no more common in patients treated with ^{131}I [233, 234].

The radiation doses from ^{131}I in the treatment of Graves' disease does not reduce fertility in either sex. Hyperthyroidism *per se* often reduces libido and, in addition, it is generally accepted that fertility in hyperthyroid women is reduced. When someone is hyperthyroid, unprotected intercourse might seem safe, but patients should be advised that one of the first signs of improvement after any form of therapy is unexpected pregnancy, and appropriated steps taken to avoid this.

Over more than 40 years of use of ^{131}I, there has been a progressive move to treat younger patients, including those who plan to have children.

This caused concern that the gonadal dose would increase the risk of genetic malformation in the offspring. The ovaries receive less than 3 rad per 10 mCi (370 MBq) [235, 236], and this theoretically could add 20 to 30 cases of genetic malformation per 1 000 000 births per rad. This has to be contrasted to the risk without radiation, which is reported to be 10.65%, i.e. 106 500 abnormalities per 1 000 000. There is no evidence that the number or type of abnormality in children whose parents received ^{131}I differ from babies born to age- and sex-matched controls [237, 238].

In summary, problems occurring days to weeks after ^{131}I treatment of Graves' hyperthyroidism are encountered very infrequently. Of these, thyroid storm has to be recognized early and treated urgently, as outlined at the end of the chapter. The theoretical long-term risks of an increase in cancer and genetic malformations to offspring have not been documented.

(e) Therapeutic uses of other radionuclides of iodine

The first radionuclide of iodine used to treat hyperthyroid patients was ^{130}I. Its half-life is too short. A small number of patients were treated with ^{133}I. The radionuclide which has been used most often after ^{131}I was ^{125}I. This was introduced in an effort to prevent post-treatment hypothyroidism, yet control hyperthyroidism. Greig *et al.* [178] drew attention to the microscopic dosimetry of ^{125}I, which preferentially radiates the apex of the follicular cell, the site of hormone synthesis. The nucleus receives less than 10% of the radiation [239]. I with Greig treated 355 hyperthyroid patients with this radionuclide [240]. After follow-up of an average of 49 months, 63.4% were euthyroid, 33.5% hypothyroid and the remainder hyperthyroid. No dose per gram of thyroid produced euthyroidism in all patients, and both hypothyroidism and persistent hyperthyroidism were found. In general, small doses left the patient hyperthyroid, and large doses caused hypothyroidism. Several other groups of investigators published similar results [241–243]. One considerable disadvantage of ^{125}I is its long half-life, which can cause an environmental hazard. Because it does not provide a conclusive advantage over ^{131}I, I do not recommend its use.

(f) Precautions and logistics of radioiodine treatment

Patients treated with radioiodine are a source of radiation, and precautions are necessary when they are discharged after treatment. In the USA, no specific restrictions are required if the activity at discharge

is 8 mCi or less, or the exposure is 1.8 mR/h at 1 m [244]. In spite of that, all patients should be advised to sleep in a separate bed for 2 nights. Their urine is radioactive and should not be kept for tests. Suitable arrangements of travel home have to be made in advance, preferably the patient can drive home alone. Children should not accompany hyperthyroid relatives to the hospital at the time of therapy. Before therapy, a negative pregnancy test should be documented in women of childbearing age. Even using serum beta HCG, false negative results are possible in the first week after conception. Stoffer and Hamburger [245] in a survery of members of the American Thyroid Association found that 237 pregnant women had been treated with radioiodine during the first trimester. Of 182 allowed to proceed to term, there were 2 spontaneous abortions, 2 stillbirths and 1 child with biliary atresia. Based on these results, they do not advise therapeutic abortion. Inadvertent treatment after 12 weeks puts the infant's thyroid at risk, and the investigators found 6 cases of neonatal hypothyroidism. This should not happen.

Women must stop breastfeeding. Radioiodine-131, because of its relatively long half-life, its concentration in the mammary glands and secretion in milk, coupled with the small size of the thyroid in the newborn and its higher uptake, can be potentially hazardous for weeks [246]. Reference 246 is an excellent review of published data of radiation hazard to babies from various radiopharmaceuticals secreted in milk. Derived results indicate that the babies' thyroid would receive 27 rad/μCi ^{131}I in breast milk (5.7 Gy/MBq). The maximal permissible dose is 150 *mrad (0.0005 Gy)*! It is not wise to attempt to restart breastfeeding. Breastfeeding should be interrupted for 2–3 days after the mother receives a tracer dose of 20 μCi ^{123}I (0.74 MBq). After treatment the mother should be restricted from contact with her children, and if they can be looked after by a relative or friend for 3 or 4 days, that is preferable. Patients should be informed of the effect of distance, time and shielding in reducing radiation to others. Radiation falls by the square of the distance and directly with time. Walls provide some degree of shielding, those in granite houses more than those made from woodframe and plasterboard.

5.2.10 SURGICAL TREATMENT OF GRAVES' DISEASE

(a) History

Surgical treatment was the earliest treatment for Graves' disease. Thyroid surgery as a standard therapy was introduced by Kocher who, by 1889, had done 350 operations with a mortality of 2.4%. The history has been reviewed by Halsted [247] and Mansberger [248]. The operation was reserved for seriously ill patients and, at times, involved removal of thyroid tissue in stages, as many as seven operations being done to achieve the end result. Other procedures were ligation of the arterial supply, but the clinical studies of Mayo [249, 250] and Lahey [251] indicated a better outcome with subtotal thyroidectomy. Even 70 years ago, there was debate about how much thyroid tissue should be left. The introduction of inorganic iodine as a preoperative treatment [252] made a dramatic change in the selection of patients for operation, and on the safety of the procedure and reduction in the incidence of postoperative thyroid storm. Iodine given for 7–10 days reduced the degree of hyperthyroidism and made the thyroid less vascular. It was soon recognized that the hyperthyroid gland escaped from the inhibitory effect of iodine after that time. Until the early 1940s, surgery was the only definitive treatment. It remains an effective and valuable therapy. However, because of the safety and simplicity of radioiodine, plus the availability of antithyroid medications, it is used less frequently. Periodically, there is

Table 5.9 Results of surgical treatment of Graves' hyperthyroidism with special reference to the increase in hypothyroidism in most recent reports

Reference	*Year*	*% hypothyroid*	*% hyperthyroid*
254	1964	5	8
255	1966	10.6	5.8
256	1968	6.5	11.4
260	1970	25	7
271	1972	49	NA
263	1982	55	0

an advocate for resurgence of this treatment [253].

(b) Results and complications of surgery

Before looking at the selection of patients for surgery and the logistics of rendering the patient euthyroid for operation, let us review the results and potential problems of operation. The ideal goal of the operation is to remove enough thyroid to cure the hyperthyroidism, and leave sufficient to prevent hypothyroidism. This cannot be achieved in all patients. Table 5.9 shows the incidence of these in several series. Up to 1970, there was, on average, approximately 10% recurrence and 10% hypothroidism [254–256]. The final outcome was usually defined by clinical evaluation, or by tests which are now recognized to be crude and of modest diagnostic value. In these reports, hypothyroidism was most likely to result in patients with high levels of circulating antithyroid antibodies [257, 258], or with significant lymphoid tissue in the resected gland [259]. The incidence of hypothyroidism increases with time. After 1970, many reports showed a higher frequency of hypothyroidism, 25% [257], 36% [260, 261], 49% [262] and 55% [263]. Concidentally, with the increase in hypothyroidism there were less recurrences, e.g. Lee *et al.* [263] had none. This was due to a change in philosophy of the surgeons, who planned to do near total thyroidectomy. Bradley *et al.* [264] reviewed the literature of those reports where this was the aim, and in combined results in 1296 patients calculated the recurrence rate to be 3.4%, and postoperative hypothyroidism was found in 52.6%. This trend is reversed in a recent publication from France where only 14.5% became hypothyroid, most within 1 year of operation, whereas 18% relapsed, some as long as 6 years after surgery [265]. This is retrogressive because those patients who relapse have to be treated with radioiodine, since there is considerable selection of patients for operation, often as a result of the alternative treatments being positively excluded, e.g. severe reaction to antithyroid drugs plus an obsessive fear of radioiodine. Therefore, when there is a recurrence of hyperthyroidism, this is of considerable import. The risk of repeat operation is significant and recurrence is best treated with radioiodine [266]. In contrast, hypothyroidism is easy to diagnose and easy to treat, and should not be judged as postoperative morbidity. When hypothyroidism occurs, it is unlikely that the patient will relapse and surgery has been successful. Some surgeons allow the patient to become hypothyroid and do not introduce L thyroxine immediately, because some patients will achieve euthyroidism by high TSH levels stimulating the remnant to function normally. Because there is an incidence of late hypothyroidism, it has been my policy to start replacement therapy whenever there is a rise in TSH, and to continue it for life. The patients are told preoperatively that this is the probable outcome

There are important complications of thyroid operations. Provided patients are properly prepared for surgery, mortality is very low but increases with age. Wound infection, atelectasis, pneumonia and pulmonary embolus can occur as with any major operation [267]. Many patients are fully ambulant within a few hours, and provided there are no problems can be discharged from hospital between 24–48 hours after the procedure. As

many as 30% notice a change in voice post-operatively [268]; in some this is due to intubation and in others to transient damage to the recurrent laryngeal nerves but, fortunately, permanent damage is uncommon. Riddell [269] by meticulous identification of the nerves plus electrical stimulation to test their integrity, reduced the risk to 1.7% in 1700 patients. A 1–2% incidence of this complication is anticipated. The long-term result is a change in the pitch of voice, an inability to sing, and difficulty in projecting the voice when lecturing or shouting. Hyperventilation in an effort to continue talking can cause dizziness. It is wise to wait at least a year before considering any treatment to the cord, because compensatory changes occur which bring the cords closer together, with an acceptable result. If the improvement with time is insufficient, the paralysed cord can be augmented with an injection of silicone. Fortunately, bilateral recurrent laryngeal nerve damage is very rare. In this situation, the voice can appear remarkably normal; the problem is one of breathing and surgical correction by arytenoidectomy or tracheostomy inevitably causes a deterioration in the voice. The patient is happy to accept this if it allows her to breathe.

Hypocalcaemia from damage to the parathyroid glands complicates about 2% of operations [270]. This is largely due to damage to the parathyroids or their vascular supply at the time of surgery. An alternative cause of hypocalcaemia is rapid reversal of the negative calcium balance of hyperthyroidism [271]. This is temporary but requires treatment with vitamin D and calcium. Because of the possibility that hypoparathyroidism is temporary, efforts should be made to lower the doses of medications and try to discontinue them provided the patient has no symptoms and remains normocalcaemic. This should only be done when close communication between patient and physician is possible. A rapidly developing wound haematoma is an important complication which can require re-exploration to find the bleeding site. In emergent situations where there is dyspnoea or dysphonia, it is necessary to open the wound urgently. Nurses and physicians responsible for the patient should be educated about this potential problem, and any change in breathing or voice should prompt urgent consultation by the surgical team. Because the scar is in a visible position, keloid formation is an unfortunate occurrence. The neck and upper chest are more common areas for this to happen, and it is more common in African and African–American patients. Lesser degrees of problem with the scar are often a source of unhappiness, especially in younger women who have this area uncovered. Local injection of fluorinated glucocorticosteroids are of considerable help, or in exceptional situations surgical removal of the unsightly tissue should be considered. With time, the colour of the wound alters, and unsightly pink areas become less noticeable and of no concern to many patients.

Patients referred for operation should be informed about potential complications and their management and have time to discuss these.

(c) Selection of patients for operation

Which patients should have surgery to treat Graves' disease? It is easier to start with those who should not. The elderly and those with cardiac complications are not candidates for operation. There is still concern among some patients and physicians that radioiodine causes long-term complications and genetic defects in offspring, and in some these concerns provide an insurmountable barrier to radioiodine. If such a patient is allergic to antithyroid medications, the best approach is operation. Thyroid cancer can coexist with Graves' hyperthyroidism (Chapter 13), and if there is a nodule in a diffusely enlarged gland, it should be subjected to FNA; if the cytology is anything but benign, an operation deals with both conditions.

Many articles state that large glands should be treated operatively. However, this is not a *sine qua non*, because these glands frequently melt away after ^{131}I treatment. Surgery has been advocated in children because there has been concern about treating children with ^{131}I, but there is solid data which points to radioiodine as the primary treatment of choice. I refer very few patients for operation with Graves' hyperthyroidism. In each patient, there has been a constellation of factors which culminated in this decision. One young woman became hyperthyroid postpartum with classic Graves' disease. She dearly wished to breastfeed but was very thyrotoxic. After prolonged discussion with her and her husband, it was agreed to start propylthiouracil and continue breastfeeding [272]. The debate about breastfeeding and antithyroid drugs is expanded below in the section on hyperthyroidism in pregnancy. She wished to become pregnant again and to breastfeed the expected second baby. Although propylthiouracil was accepted during breastfeeding, she felt the risk to the unborn child from propylthiouracil during pregnancy was greater. I advised stopping breastfeeding, treating with ^{131}I and planning the second pregnancy about 1 year after that. The patient refused to stop breastfeeding, opted for operation and breastfed while recovering in hospital. The operation cured her hyperthyroidism, and removed any concerns of antithyroid drugs and ^{131}I on her subsequent children. She quickly became pregnant with twins, but tragically one was stillborn. Because of her concern about radioiodine before and medications during pregnancy, it is likely she would have blamed either of these for the baby's demise.

(d) Preparation for surgery

Because the surgery is elective, and because the greatest risk is of crisis in an uncontrolled hyperthyroid patient, it is very important to render the patient euthyroid prior to operation. This has traditionally been done using standard antithyroid drugs, and 7–10 days before the operation inorganic iodine is added to the regime to reduce the vascularity of the gland. By this approach, it can take 8–12 weeks to render the patients euthyroid. The medications should be stopped postoperatively. As an alternative, several groups have shown that beta-blockers made the patient well enough for surgery in a few days. Usually propranolol has been prescribed in a dose of 40 mg 4 times a day [263, 273, 274]. In spite of the data, I find little to support this recommendation. Toft *et al.* [274] admitted the patients to hospital 4 days preoperatively and titrated the propranolol to the optimal level as judged by pulse less than 90/min, and the medication was continued for 7 days postoperatively. Four days in hospital would add substantially to the cost and would not be acceptable in the USA. There is abundant evidence that beta-blockers do not make the patient euthyroid. The biochemical abnormalities persist, and there are well-documented cases of thyroid storm occurring in patients treated only with propranolol [275]. In addition, why should there be such a need to operate quickly? The surgery is not urgent. A more acceptable regime is to combine beta-blockers with inorganic iodine [276]. Iodine should not be used in patients with toxic nodular goitre because hyperthyroidism can be worsened [277], or in patients who are severely hyperthyroid [278].

In summary, surgery as treatment of Graves' hyperthyroidism has a small but important place. The goal of the surgeon should be to remove as much thyroid as possible, yet preserve the functions of the parathyroids and recurrent laryngeal nerves. Permanent euthyroidism or, more likely, hypothyroidism are to be expected, and the incidence of recurrence should be less than

5%. Patients should be euthyroid before the procedure.

5.2.11 WHICH THERAPY?

The clinician and patient are in the enviable position of having three well-tried therapeutic methods for Graves' disease. There is no other disease where the options are so varied and successful. In some clinical situations, the choice is clear cut, e.g. in a relapse after thyroidectomy, ^{131}I is advised; in a thyroid storm, antithyroid drugs. How does the clinician advise the patient about the optimum approach in the individual. A frank discussion of the logistics of each method, the expected results and potential risks is the first step. For primary therapy, the role of surgery has lessened, and the choice comes down to medications or ^{131}I. Radioiodine in an adequate dose cures hyperthyroidism in all patients, but causes hypothyroidism. In some series, almost all patients are hypothyroid by 1 year. If this possibility is recognized and the patient is willing to take L thyroxine for life, this is the simplest approach. There has been doubt expressed about prescribing ^{131}I to children, adolescents and young patients who plan to have children. No increased risk has been demonstrated, and the approach ensures that mothers are not taking antithyroid medications during pregnancy and puerperium, or when whey are breastfeeding. Therefore an argument can be made for using this treatment in patients of all age groups, the only exceptions being if the patient is pregnant, or breastfeeding. I usually advise a short course of antithyroid drugs prior to radioiodine if the patient is very thyrotoxic or over 50–55 years.

Medications can be used in exactly the same settings, but the patient should recognize the chance of long-term remission is less than 50% (the results vary considerably, most reporting from 20–50%), and that therapy is generally prescribed for 12–18 months. Relapse can be treated with a second course of medication, but at this point ^{131}I is preferred. I have treated several patients who had repeated courses of antithyroid drugs (prescribed by other physicians), with short remissions. They were cured by 1 dose of ^{131}I and, to a person, each regretted not having proceeded with ^{131}I from the start. It has been calculated that primary treatment with radioiodine is the least costly. The number of follow-up visits is less. A significant proportion of patients treated with drugs eventually have the combined costs of that treatment and subsequent definitive therapy with ^{131}I. Therefore, ^{131}I has a definitive role in most patients with Graves' hyperthyroidism. During pregnancy, hyperthyroidism should be treated with propylthiouracil, and this drug appears to be safe for breastfeeding. Antithyroid drugs have an important role in rendering patients euthyroid for surgery and, as mentioned, in some cases before radioiodine. Surgery is advised when there is a suspicious nodule in addition to Graves' disease, and in specific situations, such as reaction to antithyroid medication, coupled with fear of radioiodine. Table 5.10 lists possible

Table 5.10 Bias to specific therapy of Graves' disease in various clinical situations

Patient group	*Antithyroid drugs*	*Radioiodine*	*Surgery*
Neonatal	++++	–	–
Juvenile	+	+++	+
Young woman, not pregnant	+	+++	+
Young woman, pregnant	++++	–	+
Man	+	++++	+
Elderly	+	++++	–
Coexistent cold nodule	–	–	++++

treatments for Graves' hyperthyroidism in several clinical categories.

5.3 FUNCTIONING AUTONOMOUS THYROID NODULE, SINGLE AND MULTIPLE

5.3.1 INTRODUCTION

Functioning autonomous thyroid nodules are also called hot nodules because of their appearance on radiouclide scan. The nodule is not under normal physiological control of the pituitary, and concentrates more radioiodine than the surrounding normal thyroid. Patients with hot nodules can be euthyroid, although a proportion of them are hyperthyroid due to the nodule secreting excessive amounts of thyroid hormones, in particular T_3. Plummer [279] was the first to differentiate hyperthyroidism due to diffusely hyperfunctioning goitre, namely Graves' disease, from hyperthyroidism due to nodular goitre. He did not differentiate single toxic nodule from toxic multinodular goitre. This section deals first with the single nodule. However, the distinction is not clear cut, since additional impalpable nodules can be detected by scintigraphy, by the surgeon at operation, or by the pathologist. Hamburger [280] has argued that Goetsch [281, 282] rather than Plummer should be remembered by the eponym for this disorder. Goetsch [281, 282] demonstrated that the follicular cells in toxic adenoma (his term) contained abundant mitochondria, suggesting that the cells were indeed hyperfunctioning. The best early clinical description of the condition is that of Boothby [283]. Nevertheless, Plummer's name will not be dislodged easily because of prolonged usage.

5.3.2 AETIOLOGY

In the vast majority of cases, the cause of nodular formation is not known. There are sparse reports of hot nodules occurring after external neck irradiation [284, 285], suggesting, but not proving, that radiation was causal. Growth factors including insulin, somatomedins and even oestrogen (in view of the remarkable proportion of women with this disease), have been suggested as possible factors. None has been proven to be the aetiological factor.

5.3.3 PATHOLOGY

The lesions are usually adenomas and, on occasion, adenomatous hyperplasia. The tumour is usually encapsulated. The follicles are similar in appearance and can be termed microfollicular, fetal, embryonal, or simple. There is no capsular or vascular invasion. There are few mitoses. It is not possible from review of the histology to predict if the nodule causes hyperthyroidism or not.

5.3.4 CLINICAL FEATURES

Patients with hot nodules usually seek medical care because of the nodule *per se*. This applies whether they are euthyroid or hyperthyroid. Those who are hyperthyroid have the appropriate symptoms and signs, but they are usually less marked than in patients with Graves' disease. Those features which are specific for Graves' disease, such as infiltrative ophthalmopathy, dermopathy and acropachy, are not found in patients with toxic hot nodules. Because the onset of hyperthyroidism is subtle, the patient can have mild symptoms which go unrecognized for years. Not infrequently, they have had a non-toxic nodule for years prior to that. Autonomous nodules are more likely to cause toxicity in older patients, and because of the prevalence of cardiac problems in this age group, heart complications due to hyperthyroidism, such as atrial fibrillation or cardiac failure, are not infrequent findings. The remarkable trend for hot nodules to occur in women is shown in Table 5.11,

Table 5.11 Gender of patients with hot nodules (from seven publications)

	Women	*Men*	*Total*	*Reference*
	31	4	35	286
	33	2	35	287
	50	4	54	288
	21	2	23	289
T	53	9	62	290
NT	302	20	322	290
T	234	29	263	291
NT	252	22	274	291
	21	7	28	292
	997 (91%)	99 (9%)	1096	

T = Toxic.
NT = Non-toxic.

which also highlights that the gender bias is greater for non-toxic nodules.

In almost every series, the average age of patients with toxic hot nodules is greater than that in euthyroid patients. Toxicity is also more common in patients with large nodules [286, 288, 289]. The implication is that hot nodules in young patients are likely to be small and, as the patient and the nodule age, the latter grows and, at some point, secretes excessive amounts of thyroid hormones. Most patients who are euthyroid at presentation remain euthyroid. Burman *et al.* [288] studied 48 patients for an average of 2 years (4–136 months) and none developed hyperthyroidism. Two of the nodules underwent degeneration, which is well recognized as one of the expected outcomes [293]. Degeneration has been described after injection of TSH used prior to reimaging suppressed normal thyroid [294, 295]. This test is not recommended therapeutically, and it is seldom necessary diagnostically. In another series, 14 of 159 patients with non-toxic hot nodules became hyperthyroid after a follow-up of 1–6 years, but the risk of hyperthyroidism was 1 in 5 in those whose nodules were 3 cm in diameter or larger [290]. Table 5.12 gives an overview of statistics from seven studies of the proportion of patients who are hyperthyroid at presentation and on follow-up.

Very rarely, hyperthyroidism is transient and due to the release of stored hormore as a result of haemorrhagic infarction [299]. Autonomous nodules are rare in children [285, 300], and any such nodule in a child must raise a higher concern of its being malignant [301].

5.3.5 DIAGNOSIS

The evaluation of thyroid nodules has evolved recently. Many authorities recommend fine-needle aspiration first. This is discussed in full in Chapter 7. This contrasts with earlier approaches which started with radionuclide scintigraphy. Although the clinical features discussed above are important, it can be seen that *a priori* most patients with autonomous nodules cannot be differentiated from those with non-functioning nodules unless hyperthyroidism is present. Only 5–20% of nodules are hot on scan, therefore, it is economically sounder to biopsy all nodules with the intention of obtaining a pathological diagnosis to stratify the 80–95% which are cold on scan into low or high risk of malignancy. Hot nodules are rarely malignant (*vide infra*). However, on cytological examination, they frequently show a microfollicular pattern, which means that a low-grade follicular cancer cannot be excluded. The clinician has a dilemma: in unselected patients with solitary nodules, if a radionuclide scan is ordered first, the most likely finding will be a cold nodule. If biopsy is done first, a 'benign' hot nodule might be diagnosed cytologically as a suspicious lesion. It would appear acceptable to obtain a scan first to find those with hot nodules, and then biopsy the cold ones. Alternatively, if a biopsy is done first, a radionuclide scan would be obtained if the cytology shows a

Table 5.12 Hyperthyroidism and hot nodules

No. of patients	*Hyperthyroid at presentation*	*Hyperthyroid on follow-up*	*Follow-up years*	*Reference*
35	18	4	NA	286
54	2	0	0.3–13	288
349	62	14	1–6	290
34	19	NA	NA	292
29	2	1	2–8	296
22	1	0	2–7	297
58	0	6	1–12	298
581	104 (18.5%)	25/457 (5.5%)		

microfollicular pattern. Thus surgery would be avoided in a euthyroid patient with an autonomous nodule.

If the patient is hyperthyroid and has a nodule, the most probable diagnoses are solitary toxic hot nodule, Graves' disease plus a solitary cold nodule or hemiagenesis of the gland. The last is very rare and it should be possible to discriminate between the first two on clinical grounds. A radionuclide scan will make the distinction. In the first, there is a 'hot' nodule with suppression of surrounding tissue (Figure 5.7), in the second there is a diffusely enlarged hyperactive gland with a cold nodule (Figure 5.8). A cold nodule in this setting will require full work up independent of the hyperthyroidism.

Iodine–123 is recommended for thyroid scintigraphy. Historically, ^{131}I was used, but it gives an unacceptable radiation dose to the thyroid (Chapter 3). Most, but not all, nodules which are 'hot' on a ^{123}I scan are 'hot' when scanned with ^{99m}Tc (pertechnetate). Conversely, most, but not all, cold nodules on a ^{123}I scan are cold with ^{99m}Tc. Since there are many reports of disparate findings [302–304], and since the definition and knowledge of the natural history of hot nodules are based on radioiodine scanning, why not use ^{123}I? It has been suggested that a ^{99m}Tc scintigram should be obtained first and if the nodule is hot to proceed to a ^{123}I scan. Why not use ^{123}I first? When a scan is obtained it is extremely important to ensure that the palpable nodule corresponds precisely to the hot nodule.

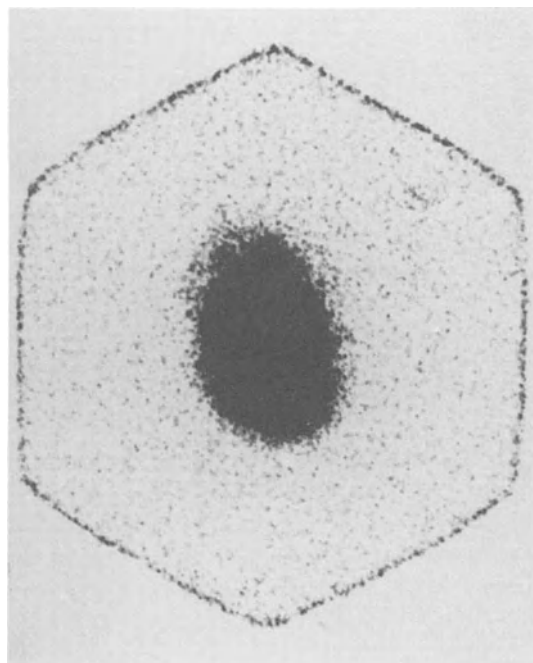


Figure 5.7 Thyroid scintigram showing intense focal uptake in the thyroid nodule with suppression of remainder of the gland. This is typical of a toxic hot nodule.

The remainder of the gland can be suppressed to varying degrees, because the

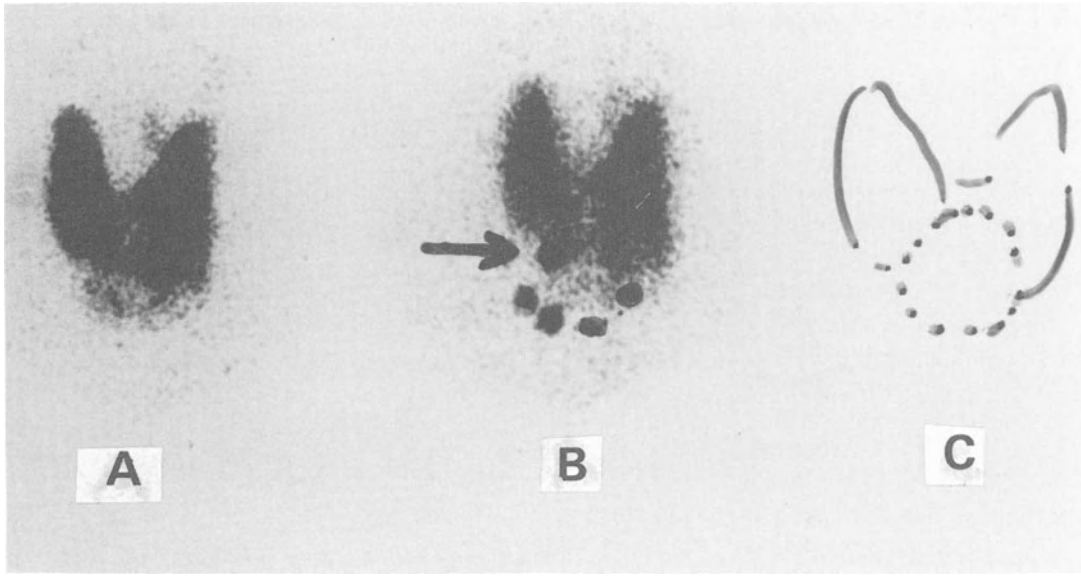


Figure 5.8 Thyroid scintigram in a 44-year-old woman with classical Graves' hyperthyroidism. However, on palpation of her thyroid, in addition to diffuse enlargement a firm nodule was felt beneath the isthmus. This nodule is cold on scan. Pathology showed the cold nodule was benign adenomatous hyperplasia. A: Scan alone. B: Scan with markers around nodule. C: Schematic of findings.

nodule by its autonomous production of hormones suppresses the pituitary secretion of TSH. The degree of suppression depends not only on the level of thyroid hormones, but the scintigraphic technique. With older equipment (a rectilinear scanner), the suppression tended to be exaggerated, and in cases where no thyroid was seen in the contralateral lobe, that tissue could be imaged albeit faintly using a gamma camera. In patients where only the hot nodule is seen and hemiagenesis cannot be excluded (Figure 5.9), the functioning tissue should be shielded with a lead strip and imaging continued. Suppressed thyroid will be imaged if the procedure is continued for a sufficiently long time. The missing lobe in hemiagenesis can never be imaged. Alternatively, ultrasound can be employed to demonstrate the presence of atrophic thyroid. It is almost never necessary to do a TSH stimulation test to visualize the suppressed tissue. Also, it is almost never necessary to do a T_3 suppression test to prove the nodule is autonomous for reasons explained below.

To define the thyroid status of the patient FT_4, T_3 and TSH should be obtained. A proportion of patients with hot nodules have true T_3 toxicosis, and in early studies when T_3 measurements became available, 40% of hyperthyroid patients with hyperfunctioning nodules had normal T_4 and FT_4I [290, 305, 306]. A borderline high T_3 with suppressed TSH can explain mild or atypical hyperthyroid symptoms. There is no recent study comparing FT_4 with T_3 in this setting.

A spectrum of results can be found. All three tests might be normal, in which case the patient has a non-toxic autonomous nodule. FT_4 and T_3 might both be high and TSH low; the patient, therefore, has a toxic hot nodule. These two extremes are easy to understand and to treat. It is more difficult when thyroid hormone levels are normal,

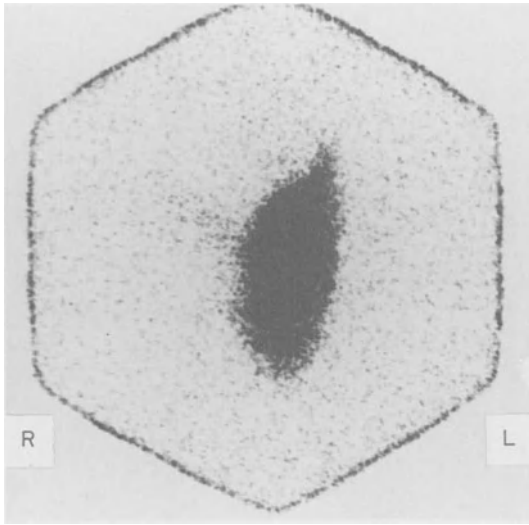


Figure 5.9 ^{123}I scintigram in a 23-year-old man with mild hyperthyroidism and a palpable left lobe of the thyroid. The scan does not look like a hot nodule but either an ultrasound, or a TSH stimulation test, would be necessary to prove there is no thyroid on the right side and that the diagnosis is hemiagenesis with hyperthyroidism. The final diagnosis was Graves' disease with hemiagenesis of the thyroid.

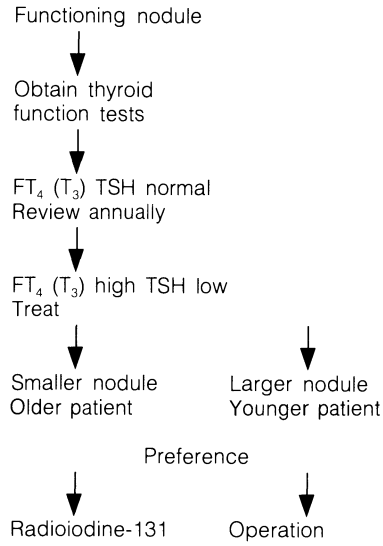


Figure 5.10 Algorithm for diagnostic work-up of a patient with a functioning thyroid nodule.

but TSH suppressed. The clinician has to consider the clinical features, the degree of suppression of the normal thyroid on the scan, the size of the nodule and the degree of normality of the blood tests. Figure 5.10 provides an algorithm for the management of patients with autonomous nodules.

5.3.6 ARE HOT NODULES EVER MALIGNANT?

Means [307] reports 'we have never found a hot nodule which has shown histologic evidence of malignancy'. Similarly, Miller and Hamburger [308] state no proved case of a hot cancer which could be confused with a benign lesion has yet been reported. Table 5.13 shows the incidence of cancer in hot nodules from several surgical series.

Table 5.13 Number of cancers found in surgically treated hot nodules

Number of cancers	*Number of hot nodules*	*Reference*
0	10	309
0	40	291
0	40	310
3	200	311
0	27	296
2	5	312

Rare cancers have been found in hot nodules; Livadas *et al.* [311] reported three cases, but there was an explanation for each one, e.g. the cancer was in a small cold spot within the hot nodule, or there were several nodules one of which was cancerous. Becker *et al.* [313] described two cases which were small and lying within the hot nodule. Of the three cases reported by Nagai *et al.* [285], one was in a child and one in a man who had received external radiation to the neck. Both of these situations must be accepted as high risk for malignancy. The

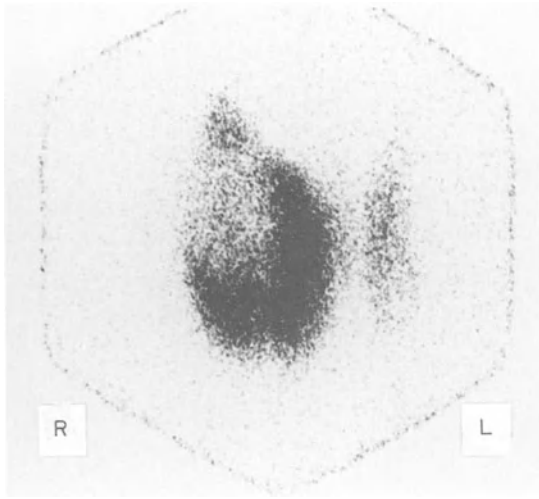


Figure 5.11 Hot nodule in the right lobe of the thyroid with a cold area in the upper outer aspect: owl's eye sign. This is almost always due to cystic degeneration of the nodule. The left lobe is somewhat suppressed. Radioiodine uptake at 24 hours is 60%.

third cancer was in a cold spot within the hot nodule, which is troublesome because this appearance is usually attributed to cystic degeneration (Figure 5.11). Sandler *et al.* [314] added a single case and provided an extensive review of the literature.

Although several well-documented cases have been recognized, the data stress the infrequency of thyroid cancer appearing as a hot nodule with the following provisos:

1. The radionuclide used is ^{123}I **not** ^{99m}Tc.
2. Two nodules are present, one hot on scan and benign, the other cold and malignant. This emphasizes the importance of marking palpable nodules on the scan and correlating the scintigraphic and clinical findings.
3. An occult cancer is found in adjacent thyroid tissue. This would have the same significance as an occult cancer found after thyroid surgery for any other disease. It should not be construed as a cancerous hot nodule.

5.3.7 TREATMENT OF AUTONOMOUS THYROID NODULES

The majority of patients with autonomous thyroid nodules are euthyroid clinically and biochemically. It is generally agreed that these patients do not require therapy, but reassurance that the nodule is benign and that the condition will remain stable. Some have argued that surgical removal of nodules at this stage removes any chance of hyperthyroidism in the future. They support their argument by citing a very low complication rate and a very low incidence of postsurgical hypothyroidism. However, it is my opinion that unless there are features which would predict a problem, such as rising thyroid function tests, a large nodule (greater than 3 cm) or a nodule that is growing, observation at 6–12 month intervals is appropriate treatment. Attention should then be paid to any clinical or biochemical evidence of hyperthyroidism.

Hyperthyroidism when it occurs is almost always permanent. There are anecdotal reports of nodules and toxicity disappearing due to degeneration. Nevertheless, definitive therapy with surgery or radioiodine will be necessary in almost all hyperthyroid patients. Antithyroid drugs are not recommended because spontaneous cure is so rare and because the nodule can continue to grow. A short course of antithyroid drugs might be used preoperatively.

Surgery, usually lobectomy, has the benefit of controlling hyperthyroidism rapidly; the nodule is removed, and any lingering doubt the patient has about malignancy excluded. Prior to surgery, the patient should be made euthyroid, either with antithyroid drugs or, if the symptoms are mild, with beta-blockers. Eyre-Brooke and Talbot [315] operated on 60 patients without complication, and only 6.6% became hypothyroid postoperatively. Similar statistics have been reported by Bransom *et al.* [287] who found that only 5 of 35 became hypothyroid.

Table 5.14 Amount of radioiodine-131 required to deliver 30 000 rad (300 Gy) to the centre of a hot nodule assuming 30% uptake and an effective half-life of 5 days. Selectively extracted from Gorman and Robertson [317]

Nodule diameter (cm)	*Dose (mCi)*	*(MBq)*
2	5.6	207
3	18.3	677
4	42.0	1554
5	80.0	2960

Table 5.15 Comparison of different doses of ^{131}I used by three groups of investigators to treat hyperthyroid hot nodules

Diameter of nodule	*Volume (cc)*	*Reference*		
		319	*320*	*317*
2	4.2	2.2	2.5	5.6
3	14.2	7.6	8.5	18.3
4	33.5	17.9	20.0	42.0
5	65.0	34.7	40.0	80.0

Doses in mCi; to convert to MBq multiply by 3.7.

Radioiodine-131 has also been used with success. This avoids surgery but does not work as fast and is not universally effective. Frequently, the nodule persists after treatment. The speed of recovery, overall effectiveness, and ultimate size of the nodule depend on the amount of ^{131}I prescribed. It is generally accepted that the amount of radiation required to treat a hot nodule is greater than that for Graves' disease [316]. Gorman and Robertson [317] provide detailed dosimetry calculations for the amount of ^{131}I necessary to deliver 30 000 rad (300 Gy) to the centre of hot nodules of various sizes. They stress that the volume increases considerably as the diameter increases ($4/3\ \pi r^3$). Table 5.14, which extracts data from their article, shows the doses they recommend, assuming an uptake of 30% at 24 hours, and an effective half-life of 5 days. Their doses are quite large. In contrast, Ratcliffe *et al.* [318] recommend a fixed dose of 15 mCi (555 MBq). Forty-one of their 48 patients were euthyroid at 6 months, and none became hypothyroid. Unfortunately, they do not provide information about the size or activity of the hyperactive nodules, so it is impossible to calculate μCi/g. Ross *et al.* [319] found an average dose of 10.3 mCi (385 MBq; 160 μCi/g of nodule) produced euthyroidism in 41 of 45 patients in 6 months. Three patients remained hyperthyroid and 3 had a late recurrence; none became hypothyroid. Weiner [320] delivered 200 μCi/g of nodule which is similar to the dose recommended by Hamburger and Hamburger [321] to treat toxic multinodular goitre. Using this dose, 75 of 88 patients became euthyroid, 1 hypothyroid and 12 remained hyperthyroid. Five of these 12 required small doses of antithyroid drugs. It can be seen from Table 5.15 that Wiener [320] prescribes approximately one-half of the dose that Gorman and Robertson [317] advise for nodules of any size. Ross *et al.* [319] prescribe about 20% less than Wiener [320]. Who is correct? It is legitimate to prescribe 160 μCi/g of nodule corrected for uptake in patients with mild to moderate hyperthyroidism. Larger doses, such as 200–250 μCi/g, are advised for patients with more severe hyperthyroidism and in older patients where rapid control is desirable.

There is concern that the suppressed tissue is subjected to a significant radiation dose from ^{131}I concentrated in the hot nodule. This is addressed well by Gorman and Robertson [317]. The concerns about this are (1) the radiation might cause cancer in adjacent thyroid, and (2) it might cause hypothyroidism. There is only one report of thyroid cancer occurring after ^{131}I treatment of a hot nodule [322], so that risk appears hypothetical. Likewise, the long-term results of ^{131}I therapy discussed above show a very low incidence of hypothroidism. In this context, it is important to discuss the results of

Goldstein and Hart (289), who found 8 of 22 (32%) became hypothyroid 4–64 months after ^{131}I. This high percentage has been explained by the fact that their patients were euthyroid prior to treatment, therefore normal thyroid was not suppressed and trapped sufficient ^{131}I to cause hypothyroidism. This should be kept in mind if patients are pretreated with antithyroid drugs. It has also influenced some physicians to give T_3 for several days prior to radioiodine to suppress normal thyroid maximally. This approach can cause worsening of hyperthyroidism by adding fuel to the fire, and is seldom necessary.

In summary, either surgery or radioiodine will cure toxic hot nodules. When is one prescribed in preference to the other? In younger patients, surgery is the more obvious choice, likewise when the nodule is large. However, increasing age and increasing nodule size are related, so the clinician can be faced with a conflict, such as an elderly patient with a very large nodule. Radioiodine would be better for the former, surgery for the latter. The author's preference is to advise surgery for patients 45 years or younger, or for those with nodules 4 cm in diameter, or larger. Each patient should have the benefit of a detailed discussion of both therapies including risks, benefits, expected outcomes, logistics and even costs. Only then can the optimum decision be reached individually. A patient might be so concerned about radiation or about surgery that referral for the alternative is better.

5.3.8 PROGNOSIS

Most patients with autonomous nodules are euthyroid and remain so. The risk of cancer in a hot nodule is extremely small. Because a small proportion of patients will become hyperthyroid, follow-up is important. Inorganic iodine can increase the risk of developing hyperthyroidism, which can be serious [298, 323]. Therefore, patients should be warned about radiocontrast studies and about medications that contain large quantities of iodine. A proportion of nodules will get smaller and rarely might disappear as a result of cystic degeneration. Hyperthyroidism should be treated by surgery or radioiodine. Posttreatment hypothyroidism is rare, so thyroid replacement is usually not necessary. Some argue it will prevent formation of another nodule, but there is not a lot of data to support that. Follow-up should be arranged after therapy to ensure that the patient is euthyroid. In surgical cases, visits at 6 weeks and 1 year should suffice. After radioiodine, more frequent visits might be required because of the expected slower response. Occasionally, an antithyroid medication is required for a few weeks or months while awaiting recovery.

5.4 TOXIC MULTINODULAR GOITRE

Toxic multinodular goitre is very similar to single toxic nodule in all aspects except that more than one nodule is autonomous. The condition is a more common cause of hyperthyroidism in regions of low iodine intake, than in the USA. The patients are somewhat older than those with Graves' disease. Diagnosis is based on clinical examination, a low TSH and high FT_4 and/or T_3. Scintigraphy with ^{123}I shows two or more areas of increased uptake, which correspond to palpable nodules (Figure 5.12). Treatment depends on the degree of enlargement of the thyroid, local symptoms and the age and general health of the patient. Surgery has the merit of removing the goitre in addition to controlling hyperthyroidism. Jensen *et al.* [324] report 16% hypothyroidism 1 year after operation. In view of the greater age of patients plus more associated conditions, there has been a trend to operate less and to treat with ^{131}I. Uptake is lower in multinodular goitre than Graves' disease, and it is agreed the former is more radioresistant; therefore, the dose required for a successful outcome is

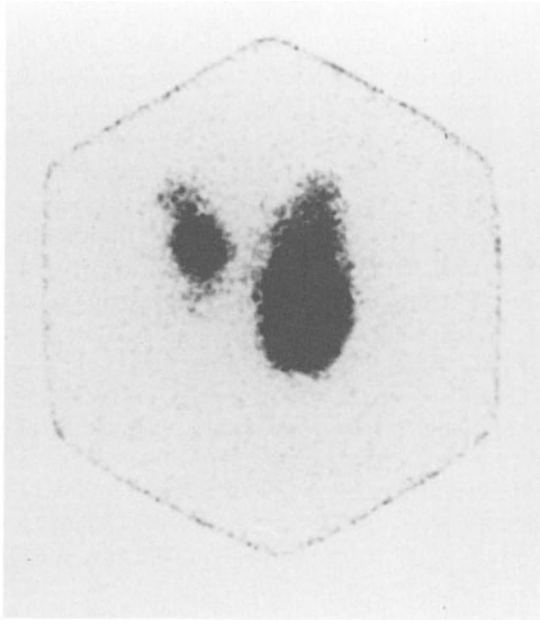


Figure 5.12 Thirty-seven-year-old woman who is hyperthyroid clinically and biochemically. She has a palpable left-sided thyroid nodule. Scan with 200 μCi ^{123}I shows a large hot nodule in the left lobe, plus a small, impalpable hot nodule in the right lobe. The remainder of the thyroid is almost completely suppressed. A scan 5 years earlier in a different institute was almost identical, but at that time she was euthyroid. The current diagnosis is toxic nodular goitre.

substantial. Jensen *et al.* [324] found the same frequency of hypothyroidism, 16% 1 year after ^{131}I, as with surgery. Twenty-four per cent required a second treatment because of persistent hyperthyroidism. The average first treatment was 37 mCi (1370 MBq), the range of doses was from 6.3–150 mCi (233–1550 MBq), and so it is difficult to interpret the outcome.

Hamburger and Hamburger [321] prescribed 200 μCi/g corrected for uptake. Initial doses ranged from 25–200 mCi (925–7400 MBq). These are similar to those used to treat thyroid cancer, and the precautions outlined in Chapter 8 have to be followed. In this investigation, 78% were cured by one dose.

Radioiodine is a safe, effective treatment for toxic multinodular goitre, and can replace surgery for many patients. In general, antithyroid drugs are not recommended as the primary therapy because spontaneous remission is not expected. Older patients forget to take their pills. Charkes [325] has used the eponym Marine Lenhart syndrome for the rare condition of Graves' disease with functioning nodules. He states this is important to differentiate from toxic nodular goitre, because the response to radioiodine was poor. His mean dose was 8.6 mCi (318 MBq), which would not be enough to treat most multinodular goitres, and it is likely that euthyroidism would be obtained if 200 μCi/g is prescribed. As discussed above, when there is concern about a 'cold' nodule in the thyroid coexisting with Graves' disease, it should be biopsied and, if the pathology is not unequivocally benign, surgery is advised.

5.5 HYPERTHYROIDISM WITH LOW UPTAKE OF RADIOIODINE

The next ten conditions are taken together because they have in common the symptoms and sign of hyperthyroidism: high levels of circulating hormones, suppressed TSH and low uptake of radioiodine. The first three are closely related since they all involve the intake of too much thyroid hormone. The second three are thyroiditides. Silent and postpartum thyroiditis are so similar that any distinction is academic. Cancer invading the thyroid has many clinical features in common with subacute thyroiditis. Iodine-induced hyperthyroidism has gained more importance because iodine contrast is used with increasing frequency, and iodine-containing medications, such as amiodarone are prescribed in large quantities. Finally, in the event of nuclear accidents, iodine is prescribed to interfere with the trapping of ^{131}I in the thyroids of normal persons. The very rare but fascinating struma ovarii, when it causes hyperthyroidism, can suppress the

normal thyroid's ability to trap iodine. Finally, a small number of follicular cancers produce enough thyroid hormone to cause hyperthyroidism.

5.6 IATROGENIC HYPERTHYROIDISM

Prescription of excessive amounts of thyroid hormone is much more common than factitious hyperthyroidism, and it is usually easier to diagnose and treat. The thyroid medication is usually taken for well-founded medical reasons, but the dose is simply too much. It is interesting to note that the normal replacement dose has decreased over the last 10–15 years, as the testing of thyroid function and our knowledge of thyroid physiology has become more sophisticated. In the early 1970s many patients took 300 μg of L thyroxine, yet now the average dose ranges from 100–200 μg depending on the weight of the patient. With the introduction of FT_4 measurements, many patients were found to have levels above normal, and using newer TSH assays even more were found to have suppressed values. When L thyroxine is for replacement and not for TSH suppression, as in patients with thyroid cancer, it is more correct to keep the TSH in the normal range [326, 327]. Some patients admit frankly that they feel better on a slightly supraphysiological dose, they can eat more without weight gain, they have more energy and achieve more. Nevertheless, they are probably balancing these subjective benefits against long-term objective problems, such as osteoporosis and possibly cardiac and hepatic toxicity [87, 328–330]. The diagnosis is usually a laboratory one since the degree of hyperthyroidism is marginal. The treatment is to titrate the dose of L thyroxine such that FT_4 and TSH are physiological.

5.7 FACTITIOUS THYROTOXICOSIS

Surreptitious ingestion of excessive amounts of thyroid hormone is a rare cause of thyrotoxicosis. Gorman *et al.* [331] and Rose *et al.* [332] each described three patients, and Harvey [333] diagnosed four cases in the surprisingly short time of 4 months. The patients do not volunteer that they are taking the medication and actually deny it vehemently, even when the evidence in favour of the diagnosis is incontrovertible. The diagnosis should be considered in a patient who is clinically and biochemically hyperthyroid, but who has no goitre, no infiltrative eye signs, and low radioiodine uptake. The other low-uptake conditions are alternative diagnoses. In iatrogenic thyrotoxicosis there is no attempt to conceal that thyroid medication is taken. The pain and malaise of subacute thyroiditis makes this easy to exclude. 'Hamburger' thyrotoxicosis should not occur because of regulations against thyroid being included in ground meat. The most difficult differential is silent thyroiditis. In factitious thyrotoxicosis, because the thyroid is suppressed, there should be low or absent levels of thyroglobulin [334] unless there is a coexiting thyroid disorder. Thyroglobulin is high in the hyperthyroid phase of silent thyroiditis, because the gland has been disrupted. If this does not clinch the diagnosis, radioiodine uptake can be repeated after exogenous TSH. There is a rise in factitious thyrotoxicosis, because the gland is normal, and usually there is no rise in silent thyroiditis. In cases which are still not resolved, a whole-body ^{123}I scan should be done to ensure that there is not an ectopic source of hormone production.

Almost all patients are women and there is often a history of a psychiatric problem, which is usually labelled as hysterical. Although self-medication is difficult to prove, there is often a source for thyroid hormone, e.g. from a relative, or the patient is in the health care profession. If the patient can be hospitalized and guaranteed to have no access to thyroid hormone, the high blood values fall with the anticipated half-life of about 1 week for thyroxine. Should the patient be more sophisticated and take

triiodothyronine, FT_4 and T_4 are low and this can cause further diagnostic confusion. I consulted on a 67-year-old woman with classic apathetic hyperthyroidism caused by her surreptitious ingestion of 400 μg L thyroxine daily, which she obtained by filling an old prescription. The diagnosis was made by finding a high FT_4 which fell by 50% in a week in hospital. The hospitalization was for suspected malignancy because of chronic diarrhoea and weight loss. She had no palpable thyroid, low ^{123}I uptake, negative whole body ^{123}I scan, negative antithyroid antibodies and undetectable thyroglobulin. The medical student reached the diagnosis by phoning the only pharmacy in the patient's home town! A previous physician had prescribed thyroxine more than a decade before for uncertain reasons. Even with all this data, the patient denied taking the medicine. Treatment requires the assistance of a psychiatrist.

5.8 HAMBURGER THYROTOXICOSIS

Two very well-documented studies showed unequivocally that localized outbreaks of thyrotoxicosis were due to ingestion of thyroid in ground beef [335, 336]. Both occurred in the mid-west of America, one in Nebraska [335] and the other at the junction of Minnesota, South Dakota and Iowa [336]. The patients had fairly abrupt onset of nervousness, sleeplessness, weight loss, increased heart rate, shortness of breath, etc. and in general did not have enlarged thyroids. They were biochemically hyperthyroid, and when radioiodine uptakes were measured they were low. Hedberg *et al.* [336] found the median 24 hour value to be 2%, and 23 of 25 results were less than 10%. The similarity to silent thyroiditis is remarkable, especially since silent thyroiditis appears to be more common in this area, although outbreaks are not found. In addition, the endemic syndrome could not be differentiated from iodine-induced hyperthyroidism on the basis of this data. In Nebraska, 49 patients in a small community had the condition in a 3-month period and, in retrospect, they were found to buy more beef in one supermarket than control patients. There were 129 patients in the other outbreak which lasted several months longer. Investigation of beef from the incriminated source showed a high iodine and thyroid hormone (both T_4 and T_3) content. A quarter-pound hamburger contained 1300 μg T_4 and 76 μg T_3. The condition was cured by stopping eating meat containing thyroid, and symptoms seldom persisted longer than 8 weeks. Volunteers who ate this meat got rapid increases in serum hormone levels. The thyroid was included in neck muscle trimmings, and now this is prohibited by US Department of Agriculture regulations. Not even the pharmaceutical companies want animal thyroid any more, because almost all patients who take thyroid use L thyroxine.

5.9 SILENT THYROIDITIS

In this condition, there is transient thyrotoxicosis caused by release of stored hormones from the thyroid. The hyperthyroid episode is short, lasting weeks or months, but it is followed by hypothyroidism which can be prolonged. The serum levels of thyroid hormones are high, TSH is suppressed and radioiodine uptake low. Hyperthyroid symptoms are treated by beta-blockers and hypothyroid symptoms with L thyroxine. This syndrome is described in full in Chapter 9.

5.10 POSTPARTUM THYROIDITIS

This syndrome has a time course similar to silent thyroiditis. Since it occurs within 6 months of delivery, it is called postpartum thyroiditis. Postpartum thyroiditis is common, affecting approximately 5% of women after delivery and, unfortunately, the symptoms and signs are easily attributed to postpartum blues or depression. The hyperthyr-

oid phase is treated with beta-blockers and the hypothyroid phase with L thyroxine. This is discussed in full in Chapter 9.

5.11 SUBACUTE THYROIDITIS

Subacute, granulomatous or De Quervain's thyroiditis is thought to be a viral inflammation of the thyroid. In addition to a time course similar to silent thyroiditis, there is pain and tenderness in the thyroid and systemic features, such as fever, malaise and laboratory evidence of inflammation with a rapid sedimentation rate. A detailed description with references is to be found in Chapter 9.

5.12 HYPERTHYROIDISM DUE TO CANCER INVADING THYROID

A very small number of patients have presented with a syndrome of hyperthyroidism and pain in the thyroid, which was due to metastatic cancer invading the gland. The topic of metastases to the thyroid is dealt with in Chapter 8. The association of hyperthyroidism and metastasis is so rare that the clinician would not be faulted at the onset for diagnosing and treating subacute thyroiditis. Additional symptoms of malaise, weight loss, plus an elevated sedimentation rate are all consistent with thyroiditis. The cancers which have caused this are lymphoma [337], pancreas [338], breast [339], lung [340], vagina [341] and adenocarcinoma of an unknown source [342]. The cause is due to the cancer disrupting follicles and releasing stored hormones into the circulation.

If a patient with a known primary cancer presents with thyroiditis and hyperthyroidism, this diagnosis should be excluded by fine-needle aspiration. However, most patients with metastases to the thyroid are euthyroid, and most cases of subacute thyroiditis are not due to metastases. The thyroid is firm to hard, diffusely enlarged and it can be painful. Thyroid blood tests are elevated and TSH suppressed. Radioiodine uptake is usually low. Once the diagnosis is established, hyperthyroidism is treated with beta-blockers and coincidental treatment of the cancer. In the case of lymphoma, a reasonable prognosis is expected with appropriate radiation therapy and chemotherapy. The fact that the other types of cancers have spread to the thyroid is a gloomy prognostic factor. Therapy for the thyroid lesion should be tempered with the knowledge that the long-term prognosis is poor. Because of the pathogenesis of the condition, antithyroid medications and radioiodine do not help and the condition of the patient usually excludes thyroidectomy.

For completeness, there is one report of anaplastic cancer of the thyroid causing hyperthyroidism, most probably by the same mechanism [343]. Since anaplastic cancers do not function, the cancer cannot have been producing the hormone (see 5.15).

5.13 IODINE-INDUCED HYPERTHYROIDISM (JOD BASEDOW PHENOMENON)

Iodine in large doses can cause the syndrome of iodism, with increased salivation, an unpleasant taste in the mouth, a painful salivary gland, tearing, running nose and acne. Iodine can cause fever (pyrexia) of unknown origin [344]. These disappear over a few days after the iodine is stopped. Hypersensitivity angiitis and polyarteritis nodosa-like syndromes are thought to be due to an iodide-protein complex which acts as an antigen [345]. Rarely, iodine causes an allergic reaction which is more common in patients with hypocomplementaemia [346]. These are not described further. About 100 μg of iodine is adequate for normal thyroid function. There are intrinsic mechanisms within the follicular cell which modulate function, so that rapid alterations in iodine availability are not associated with changes in thyroid fuction [347]. Whenever there is a

reduction in available iodine, compensatory mechanisms attempt to re-establish homeostasis by increasing iodine trapping and secreting proportionately more T_3. An increase in plasma inorganic iodine results in a reduction in trapping. A single dose of 100 mg of iodine suppresses 24 hour uptake to less than 1.5% [348]. In addition, organification is decreased (Wolff–Chaikoff effect) and the thyroid produces a normal amount of hormone. In certain circumstances, such as pre-existing Hashimoto's thyroiditis [349], Graves' disease treated by operation or ^{131}I, excess iodine causes hypothyroidism [350]. In contrast, in some patients excess iodine does cause thyrotoxicosis. Many of the patients who become hyperthyroid have euthyroid nodular goitres, either multinodular or uninodular. As a corollary, most of the reports of community outbreaks of iodine-induced hyperthyroidism come from countries or regions that are deficient, or marginally deficient, in iodine. Vagenakis *et al.* [351], however, described iodine-induced hyperthyroidism in iodine-replete individuals in Boston.

The first record of iodine causing thyrotoxicosis dates from 1820. Wilson [352] published a brief early history of the discovery of iodine and its use in treating goitre. The description of what is clearly hyperthyroidism antedates the classic papers of Graves and Basedow, who are remembered eponymously. The term Jod Basedow (iodine-induced Basedow) is not precise, since the patients usually have nodular, not diffuse, goitres and there is no evidence that autoimmunity is causal. Stewart and Vidor [353] documented an increase in thyrotoxicosis in Tasmania, from approximately 20–25 cases a year to 80–100 cases. The original increase could be related to iodine-containing disinfectants used in the dairy industry, which increased the iodine content of milk. This increase in dietary iodine was perpetuated by iodine added to flour. *Pari passu* with the rise in number of thyrotoxic patients, there was a fall in radioiodine uptake and thyroid size in the population. When there is an increase in hyperthyroidism in a community, the cause is likely to be dietary, but alternative sources should be kept in mind. Table 5.16 lists several of the important sources. More extensive lists are found in reviews by Fradkin and Wolff [354], and Martino *et al.* [355].

Table 5.16 Sources of iodine as cause of Jod Basedow phenomenon

Iodine	Potassium iodide Lugol's solution Saturated solution Ki
Radiographic contrast	Ipanoic acid Ipodate Metrizamide Diatrozide
Medications	Amiodarone Expectorants Iodochlorhydroxyquinolone Vitamin with iodine (kelp) Food colouring
Topical	Betadine Tincture of iodine

One of the commonest situations to get a high dose of iodine is as a patient in hospital. Radiographic contrast agents contain from 30–50% iodine and since they are administered in significant volumes (50–150 ml), many grams of iodine are prescribed. This complication is more common in areas where daily iodine intake is low, such as Germany and Tuscany [355]. In the USA iodine-induced hyperthyroidism is not common, but cases are documented [356–358]. Hyperthyroidism has been precipitated by topical iodine applied to an open wound [359, 360].

Because the hyperthyroidism occurs weeks after the prescription of iodine, the association can be overlooked. The relationship is better recognized in iodine-lacking regions, and in those areas caution

should be used when iodine or contrast is given to a patient with a nodular goitre [356, 361]. It has been suggested in iodine-deficient areas that the patients with nodular goitres should be studied to determine if there is autonomous thyroid function and, if so, careful follow-up is advised. Iodine has been reported to cause a painful thyroiditis [362].

A variety of medications, such as expectorants, vitamin pills, kelp and antidiarrhoeal preparations, contain iodine. In the past several years, the drug that has caused the most concern in this respect is amiodarone. Amiodarone is widely used as an antiarrhythmic agent, and it contains two atoms of iodine per molecule, or 37.2% iodine by weight. The drug is prescribed in a dose range of 200–600 mg (sometimes even higher), and the iodine is released slowly with a half-life of weeks. The thyroids of patients ingesting amiodarone have been shown to have high iodine levels as measured by fluorescent scanning. The radioiodine uptake measurements are reduced. There appears to be a paradoxical effect on the thyroid. In some regions, amiodarone causes hyperthyroidism and in other regions hypothyroidism. To add more confusion, the drug interferes with 5′ monodeiodination of thyroid hormones, so T_4 can be high yet the patient normal (euthyroid hyperthyroxinaemia) [363]. Inhibition of this enzyme also causes rT_3 to be high [364]. It can also alter pituitary release of TSH and slightly raised values do not necessarily imply hypothyroidism. Therefore, care is necessary when interpreting test results in patients and in publications. The excess iodine is more likely to produce hyperthyroidism in iodine-deficient areas, where patients have more multinodular goitres with autonomous function [365, 367]. Livadas *et al.* [366] showed that small increases of inorganic iodine (100 μg daily for the first week, increasing to 200 μg in the second week, and 400 μg/day in the third week) caused a rise in both T_4 and T_3. In iodine-replete areas, the excess iodine is more likely to cause hypothyroidism. This difference was demonstrated in two populations given amiodarone. In Worcester, Massachusetts, USA, an iodine-sufficient city, 22% became hypothyroid and 2% hyperthyroid, whereas in West Tuscany, Italy, a region of low iodine intake, 10% became hyperthyroid and 5% hypothyroid [367].

Gammage and Franklyn [368], in a review, state that the incidence of overt hyperthyroidism and hypothyroidism are each 2%. In a study of 128 patients in Australia, 7% were hyperthyroid, 33.6% euthroid but with hyperthyroxinaemia, and 7% had a high TSH [369]. Therefore, 47% could be judged to have a thyroid problem. To prove that hyperthyroidism is present, there has to be careful evaluation of the clinical features, and the best tests are T_3, FT_3 and TSH [369]. In a study from Israel, 20 of 97 patients became thyrotoxic and 16 hypothyroid [370]. Martino *et al.* [365] found the radioiodine uptake values to be higher than in iodine-induced hyperthyroidism from other causes. Amiodarone-induced hyperthyroidism in patients with heart disease and arrhythmias is serious, since the cardiac problems can be worsened by hyperthyroidism caused by the drug used for their treatment. Weight loss, weakness and breathlessness can be due to cardiac disease, and tremor and myopathy has been caused by amiodarone without hyperthyroidsm, therefore clinical diagnosis is not straightforward. The presence of a nodular goitre helps to establish the diagnosis, but is not found in all cases. The condition is more common in men but, in part, this is due to the gender of patients being treated with amiodarone. Rarely, amiodarone causes a painful thyroiditis [371].

Treatment of amiodarone-induced hyperthyroidism is not easy. Theoretically, the condition should improve after the drug is stopped. However, because of its long half-life, improvement is not to be anticipated for

weeks, and hyperthyroidism has occurred after the drug has been discontinued. Because patients with malignant arrhythmias die suddenly, and the response to amiodarone is so satisfactory, there is reluctance to stop it. There is no role for radioiodine because the uptake in the thyroid is too low. Thyroidectomy is not usually a viable approach in patients with cardiac disease. Most agree that the response to standard antithyroid medications is disappointing. Martino *et al.* [355] found that a combination of methimazole and potassium perchlorate provided rapid improvement. Newnham *et al.* [369] could not substantiate this with propylthiouracil and potassium perchlorate. Because potassium perchlorate can cause aplastic anaemia, it is hard to promote its use, and therapy should include stopping amiodarone and prescribing a standard antithyroid drug in moderately high doses, such as methimazole 60 mg daily, or propylthiouracil 200 mg 3 times a day. Prednisone has been successful in limited numbers of patients, but has not been used in a controlled trial [372].

5.14 STRUMA OVARII

Struma ovarii is a rare ovarian tumour. In two large reviews, it accounted for a fraction of 1% of the lesions [373, 374]. The basic tumour is a teratoma or dermoid, and for the designation of struma ovarii, thyroid tissue must make up more than 50% of the tumour. The tumours are unilateral in 90% of patients, and they are usually benign. In one series, 20 of 25 were benign [375]. In a review of the world's literature, Pardo-Mindan and Vasquez [376] could find only 17 cases which had metastasized. The thyroid tissue seldom causes hyperthyroidism. The ovarian lesion can be asymptomatic and found on gynaecological examination, it can cause ascites, very rarely hyperthyroidism, and even less frequently the presentation is due to metastases [377]. One of the problems of attributing hyperthyroidism to struma ovarii is that the cervical thyroid has been enlarged in several of the reports [375, 378], and sophisticated imaging techniques were not available. The coexistence of a cervical goitre and ovarian struma is consistent with Graves' disease where TRAb stimulates all thyroid tissue. However, it is generally accepted that struma ovarii causing hyperthyroidism functions autonomously and suppresses the normal thyroid. Therefore, this is one of the situations where the patient is hyperthyroid and radioiodine uptake in the cervical thyroid low. Cause and effect can be assumed when there is hyperthyroidism, low uptake in the neck and increased uptake over an ovary, having made sure that the counts are not from the bladder [379] and the hyperthyroidism is cured by removing the ovary.

The correct treatment is surgical removal of the ovary, and because the patient is hyperthyroid, correction of thyroid status should precede operation. Preparatory treatment depends on the severity of thyrotoxicosis and the age of patient, but usually includes standard antithyroid medications plus, in severe cases, beta-blockers. Radioiodine is less advisable. One somewhat difficult problem is to determine when a struma ovarii is malignant. The usual criteria of tissue invasion cannot be applied, because in teratomas multiple tissues interdigitate. For this reason, it is better to have the entire lesion for pathological interpretation. In addition, the effect of radiation on the other elements of the teratoma are not known. The topic of malignant struma ovarii is discussed in Chapter 8.

5.15 METASTATIC FUNCTIONING THYROID CANCER

Hyperthyroidism in patients with metastatic thyroid cancer is almost always found when there is a large volume of follicular cancer autonomously secreting excess thyroid hor-

mones. Although it is included with hyperthyroidism with low uptake in the neck, the low uptake is due to surgical removal of the primary cancer. In most patients, there is extensive metastatic cancer so there is no diagnostic surprise. There are reports of large primary cancers causing hyperthyroidism, in which case there is uptake by the thyroid.

Federman [380] described three patients and reviewed an additional 10 from the literature. Ten of the 13 were women. Thyroid surgery was usually done years before the hyperthyroid phase, and occasionally the pathology was interpreted as benign follicular adenoma [380, 381]. Almost all patients have bulky disease in the lungs [382], bones [380], liver [383], or a combination of these sites [384, 385]. In contrasts, Pont *et al.* [386] published a report in a 52-year-old woman with T_3 toxicosis due to an enormous primary follicular cancer, and drew attention to four similar reports in the literature. I have treated an 11-year-old girl who had biochemical T_3 hyperthyroidism due to a functioning carcinoma that was confined to the thyroid. She was referred for operation because she had a large, hot nodule which was assumed to be benign.

Because widespread metastases are usually present and the primary lesion is available for pathological review in most cases, it is not difficult to make the diagnosis. It should be pointed out that the majority of patients with metastatic follicuar cancer are euthyroid, but in patients with significant spread it is wise to measure FT_4, T_3 and TSH to define thyroid status.

Since the metastases are functioning, there is the potential for radioiodine therapy. Provided thyroid surgery has been completed, exogenous thyroid is stopped and whole-body scintigraphy with 2 mCi ^{131}I obtained. Measurement of uptake in lesions and, where possible, determination of their volume, allow calculations of what dose of radiation can be delivered. Iodine contrast should not be used for radiographic studies. In cases where the thyroid has not been removed, this must be done first, but because the patient is hyperthyroid, it is necessary to prescribe antithyroid medications for a few weeks to achieve euthyroidism. Inorganic iodine should not be part of the preoperative preparation, since this can delay, or jeopardize, radioiodine therapy. When there is some normal thyroid *in situ*, e.g. a lobe, plus distant metastases, the therapeutic approach requires careful evaluation of the distribution of radioiodine on whole-body scintigram, including the remnant. This determines if sufficient radioiodine can be trapped in the thyroid and metastases to proceed with ^{131}I ablation, or whether a repeat operation on the thyroid is advised. Although it can be possible to control hyperthyroidism and reduce the size of metastases with radioiodine, it is seldom possible to ablate this amount of bulky disease. As discussed in Chapter 8, one of the bad prognostic factors is distant lesions, especially in the skeleton, liver and brain. Prior to ^{131}I therapy, the clinician must determine whether the release of stored hormone by radioiodine distruction of follicles would compromise the patient's health. There is a report of thyroid storm resulting after a therapeutic dose of 100 mCi ^{131}I in a 79-year-old man with follicular cancer, who was already hyperthyroid prior to therapy [387]. Pretreatment with large doses of propylthiouracil for several weeks will render the patient euthyroid and deplete stores of thyroid hormone, and might even increase the proportion of ^{131}I trapped by the cancer. Fortunately, this cause of hyperthyroidism is so rare it is unlikely to be seen by most endocrinologists.

5.16 HYPERTHYROIDISM DUE TO A HIGH TSH OR TSH-LIKE MATERIAL

Table 5.17 gives a list of causes of this form of hyperthyroidism. There are other potential

Table 5.17 Hyperthyroidism due to a high TSH or TSH-like factor

1 Pituitary tumour secreting TSH
2 Non-pituitary cancer secreting TSH
3 Resistance to thyroid hormones:
(*a*) selective in pituitary
(*b*) generalized
4 TSH-like factor (HCG) from trophoblastic tumours

causes but since they are hypothetical I have not included them. Interested readers are referred to the excellent reviews by Weintraub *et al.* [388] and Brenner-Gati and Gershengorn [389].

5.17 PITUITARY HYPERTHYROIDISM

Under normal conditions, the thyroid is under control of the pituitary through TSH. Hyperthyroidism can result from overproduction and secretion of TSH. However, in contrast to Cushing's disease where the adrenal cortical hyperfuction is usually due to increased production of ACTH by the pituitary, hyperfunction of the thyroid is seldom due to pituitary disease. Tolis *et al.* in 1978 [390] found 18 case reports in the literature and added one, and, in 1983. Smallridge and Smith [391] collected 33 cases, (16 men and 17 women). The age range was 17–58 years. Tolis *et al.* [390] defined four criteria necessary to establish this diagnosis and I have added a fifth (number 1 below) and modified their third.

1. The patient should be hyperthyroid clinically.
2. There should be supraphysiological serum levels of TSH plus high levels of thyroid hormones.
3. There should be a pituitary tumour which produces an excess of alpha subunits of TSH, and does not respond to T_3 suppression, or TRH stimulation.
4. Thyrotrophes should be identified in the pituitary tumour.
5. Treatment of the pituitary tumour should cure the hyperthyroidism.

Many of the reports fail to fulfil one or more of these criteria, often for technical reasons, such as the unavailability of a TSH assay or immunostaining techniques at the time the patient was studied. It is of interest that in the past, before there were assays for TSH and LATS, that the primary abnormal lesion in hyperthyroidism was thought to be the pituitary. This is discussed in the section on the aetiology of Graves' disease (above). Factors which point to this diagnosis are hyperthyroidism, plus visual field defect, disturbance in other pituitary functions, and raised intracranial pressure. The most difficult differential diagnosis is inappropriate elevation of TSH, which is described below. Pituitary tumors causing hyperthyroidism secrete an excess of alpha units to total TSH (molar ratio), whereas the ratio is less than one when there is not a tumour [393]. The presence of any of the extrathyroidal symptoms and signs described above should prompt measurement of TSH if that has not already been obtained. If the value is high, a CT or NMRI image of the pituitary should be obtained. Almost all cases reported to date have had tumours of 1 cm or greater. Thyroid antibodies, including TRAb, are not present [393]. Somewhat unexpectedly, exophthalmos has been present in some patients with this syndrome. This has not been adequately explained except by direct invasion of the tumour into the orbit [394], although coexisting Graves' disease could explain two of the cases.

Treatment should be directed at the pituitary tumour. Because the patient is hyperthyroid, the symptoms should be controlled first with antithyroid medication. Smallridge and Smith [391] found that surgery plus external radiation was most likely to be successful, curing 8 of 9, compared to 8 of 16, by surgery alone and 1 of 4 by radiation alone.

5.18 NON-PITUITARY CANCER SECRETING TSH

There are no *bona fide* reports of hyperthyroidism due to ectopic production of TSH by a cancer. This contrasts with the syndromes of ectopic ADH and ACTH.

5.19 HYPERTHYROIDISM WITH INAPPROPRIATE TSH SECRETION

This syndrome results from tissue resistance to thyroid hormones. It can be divided into those patients who have selective resistance in the pituitary, and those who have generalized resistance.

In the first group, the coexistence of hyperthyroidism and high TSH points to the diagnosis of a pituitary tumour, which is the main differential diagnosis. However, there is no clinical or radiological evidence of a pituitary lesion and there are several other differences. The TSH rises in response to TRH, and it can be suppressed by T_3, although the dose necessary is usually supraphysiological. The ratio of alpha subunits to TSH is less than 1. The syndrome is rare but perhaps is overlooked, since Spanheimer *et al.* [395] recognized three cases at a time when there were only eight reports in the literature. Until recently, physicians did not measure TSH to diagnose hyperthyroidism, and often the first indication of the syndrome was after therapy when both thyroid hormones and TSH were measured. Subtotal thyroidectomy and antithyroid medication are almost invariably followed by relapse. After radioiodine ablation of the thyroid, the usual replacement dose of L thyroxine is found to be ineffective. The lesion is thought to be either a defect in the conversion of T_4 to T_3 in the thyrotrophe, or resistance to thyroid hormones at that level. The fact that TSH can be suppressed by T_3 points to the former mechanism.

Provided the patient is clinically hyperthyroid and biochemical tests confirm a high TSH, a TRH test, CT of the pituitary and assay of alpha subunit and total TSH should be obtained [396]. If there is no evidence of a pituitary lesion, therapy should be an ablative dose of radioiodine. Treatment of subsequent hypothyroidism is best done with T_3, but it may be necessary to reach a compromise with a slightly elevated TSH because the remainder of the body can be mildly thyrotoxic, even when TSH is above normal.

The other syndrome in which there is total resistance to thyroid hormones was first described by Refetoff *et al.* [397, 398]. The patient presents with a goitre, high thyroid hormone levels and a high TSH. It is extremely important to determine clinically if the patient is hyperthyroid. In this syndrome, because all tissues are resistant, the patient can live in symbiosis with the high blood levels. There is no doubt that some euthyroid patients have been treated for hyperthyroidism, often starting with medications, then surgery and finally radioiodine. The clinicians were treating the high test results, not the patients. If the patient is euthyroid, no treatment is necessary [399]. Because the condition is transmitted as an autosomal dominant, it is wise to screen close relatives to document the biochemical findings and warn against inappropriate therapy. The TSH can be suppressed by T_3, but prolonged treatment can cause hyperthyroidism. If there is hyperthyroidism, the best treatment is radioiodine. There is no reason why a patient with this disorder cannot get Graves' disease, but this will be a rare finding.

5.20 HYPERTHYROIDISM FROM TROPHOBLASTIC TUMOURS

Another rare cause of hyperthyroidism is trophoblastic tumour, either a benign mole, or malignant choriocarcinoma. In Western countries, about 1 in 2000 pregnancies is complicated by a mole, whereas choriocarcinoma is 30 times less common. Oriental

women are affected about 10 times as often.

The first report of hyperactivity of the thyroid in a patient with a mole, which was cured by removal of the mole, was by Tisne *et al.* in 1955 [400]. Only one of their three patients was clinically hyperthyroid, but all had elevated radioiodine uptakes. Odell *et al.* [401] found high thyroid function tests in 7 of 93 patients with trophoblastic tumours. Hershman and Higgins [402] treated two patients with severe hyperthyroidism, and Higgins *et al.* [403] demonstrated a spectrum of thyroid function from normal to significanctly hyperthyroid. Frequently, the degree of biochemical abnormality was disproportionately greater than the clinical features of hyperthyroidism.

Hyperthyroid patients have diffuse goitre with a bruit, but there is no infiltrative ophthalmopathy, dermopathy, or acropachy. New onset of hyperthyroidism in a pregnant woman is likely to be Graves' disease, but if there is any uncertainty, abdominal ultrasound, plus measurement of chorionic gonadotropin, should be done. Symptoms such as tachycardia and looseness of the bowels can be wrongly attributed to the tumour [404], and in a patient with a known trophoblastic tumour, thyroid function should be measured with FT_4 and TSH. As discussed in Chapter 3, total hormone values are high in normal pregnancy and can be confusing. In hyperthyroidism in pregnancy, FT_4 is high, total hormones are outside the expected range for pregnancy and TSH is suppressed. There is a reduced rise in TSH in response to intravenous TRH, but this test is seldom necessary. Radioiodine uptake is high and TRAb is absent. Therefore, the cause of hyperthyroidism is neither TSH nor TRAb. The weight of evidence indicates that HCG secreted by the tumour is the thyroid stimulator [405], although this is not entirely settled [406]. HCG displaces TSH from its receptor and increases cyclic AMP, albeit with 1/1000 the potency of TSH. However, because the level of HCG is so high, it is capable of producing hyperactivity of the thyroid. Hershman [405] states that hyperthyroidism is usually associated with levels of HCG greater than 300 U/ml. Removal of the tumour, usually by curettage, results in fall of HCG and reversal of hyperthyroidism, and this should be the goal of treatment. In patients who are severely hyperthyroid, the symptoms and signs should be controlled with propylthiouracil, beta-blockers, and in very ill patients with the addition of oral or intravenous iodine before the mole is removed. When the cause is metastatic choriocarcinoma, the treatment is anticancer chemotherapy with actinomycin D under the supervision of an oncologist.

Hyperthyroidism has been described in men with teratoma of the testis secreting large amounts of HCG [407, 408]. This is rare. Stromberg *et al.* [409] described four men with hyperthyroidism who previously had been treated for malignant teratoma of the testis and were clinically and biochemically free of cancer. Clearly, the hyperthyroidism in these four patients was not due to HCG. This report draws attention to the fact that common causes of hyperthyroidism occur commonly.

5.21 HYPERTHYROIDISM IN THE YOUNG, THE OLD AND PREGNANT

Because of differences in presentation, diagnostic difficulties and differences of opinion about treatment each of these deserves individual attention.

5.22 HYPERTHYROIDISM IN CHILDREN

By far the most common cause of hyperthyroidism in children is Graves' disease. The symptoms and signs are similar to those in adults, with several exceptions. Between 10–20% of patients gain weight and a detailed

history of their calorie intake, which is enormous, points to the cause. Although ophthalmic signs are very common, they almost never progress to the severe infiltrative state and seldom require treatment, such as surgical decompression or orbital radiation. Behavioural problems are very common and the child can be disruptive at home and in school, class-work deteriorates, writing is sloppy and grades fall. Rapid permanent reversal of these problems argues for a treatment which does just that, namely radioiodine. The bone age is advanced, but in about 80% of cases the child is thin and even cachectic. There is a majority of girls, 72% [410], 75% [411], 84% [412, 413] in four sizeable reviews. Goitre is absent in about 5% of patients, therefore its absence does not exclude the diagnosis.

A child who develops a tremor, loses weight, or has a new onset of behavioural problems should be tested for hyperthyroidism, although there are alternative causes, such as substance abuse, dieting, anorexia nervosa, emotional problems and family disharmony. The testing is simple: FT_4 and TSH and ^{123}I uptake. If these establish the diagnosis of Graves' disease, the clinician is faced with the difficult decision of advising the patient and family about optimal therapy. Several groups of investigators have advocated radioiodine in this age group. However, I was slow to reach the same conclusion, but now believe it is correct. About 20 years ago from the time of writing, when I was fairly junior, I was asked to treat a hyperthyroid teenager with radioiodine. The boy had not been well controlled with antithyroid medications, and had relapsed after thyroidectomy. At that time in the UK, it was very rare for patients less than 40 years to be treated with ^{131}I. The youth responded well to a single dose which had been designed to make him hypothyroid, and several years of unsuccessful medical and surgical management were brought to a rapid conclusion. Freitas *et al.* [413] entitle their article 'Iodine-131: optimal therapy for hyperthyroidism in children and adolescents?' They treated 51 children and 92% became hypothyroid. There were no subsequent thyroid cancers, and babies mothered and fathered showed no differences compared to those expected. A series of publications from the Cleveland clinic from 1965 to 1988 [410, 414, 415] have addressed this issue. Long-term review of 208 children continued to show ^{131}I to be effective and safe. The aim was to deliver 100–200, μCi/g (3.7–7.4 MBq/g), this is a wide range and does not provide readers with a definitive policy. There were 217 offspring of whom four had congenital defects, two with clubfoot, one with tracheo-oesophageal fistula and one with patent ductus which closed spontaneously. Hamburger [411] treated 191 children with radioiodine. Many of these had failed to be controlled with antithyroid medications, or had relapsed after the antithyroid drugs were stopped. Eighty-five per cent responded to one radioiodine therapy. Originally, he prescribed 200 μCi to be retained per g (7.4 MBq) and the average patient receives about 10 mCi (370 MBq) the aim being to produce hypothyroidism. Twenty-six women have subsequently borne children and three men have fathered children, the total number of pregnancies was 53, of which 49 children were healthy. There was one spontaneous abortion, one induced abortion, one hydrocephalic and one hyperactive child.

Nevertheless, many patients and their parents have concerns about radioactive iodine and it is critical that the clinician should provide a comprehensive review of all the options as well as a specific recommendation, thus allowing the family to have input in the decision, and not be left stuck between the three options. At first sight antithyroid medications would appear to provide this least aggressive therapy. There are several major drawbacks. First, children are notoriously bad at taking medications regularly. In this regard, methimazole has the great

advantage of being prescribed once a day. The proportion of patients who fail to come under control for this or other reasons, is high. Hamburger [411] could not produce control in 99 of 182 patients. Secondly, the incidence of side-effects is higher in children. Hamburger [411] noted 17%, and Barnes and Blizzard [412] 14% of children had side-effects of which 43% were major. Buckingham *et al.* [416] also reported 14%, and Hayles and Zimmerman [417] in a review of six publications determined the incidence to be 24%. Thirdly, the long-term remission rate is not high and, as stated by McArthur [418], in most patients the disease is unrelenting in its progress. Therefore, for one reason or another, patients treated at first by medications end up having definitive therapy later. If medications are preferred, methimazole is started with a dose of 0.5–0.7 mg/kg/day; propylthiouracil 10 times as much. The latter has to be given 2–4 times daily. The dose is reduced proportionally with clinical improvement. In most children, the therapy has to be continued for years, and often when the patient is old enough to leave the paediatric clinic, definitive therapy is instituted.

Surgery in children has more complications and there are more recurrences. Five of 11 who were followed by Hamburger [411] relapsed. It is generally accepted that after recurrence, radioiodine is the optimal therapy. If it is accepted as optimal at that juncture, and the evidence shows it is effective and safe, why wait until the child and family have been through months or years of unsuccessful therapies before proceeding with radioiodine? I hope the argument in favour of one-dose radioiodine in this age group is compelling.

5.23 HYPERTHYROIDISM IN THE ELDERLY

The clinical presentation of hyperthyroidism in the elderly can be quite different from that described above. The syndrome of apathetic hyperthyoidism is common, although not restricted to older patients [419]. The original articles describing this syndrome are valuable reading [420, 421]. The causes of hyperthyroidism include all those listed above. However, several reports stress the increased incidence of toxic nodular goitre, which can account for more than 50% of cases. In contrast Tibaldi *et al.* [422] diagnosed toxic nodular goitre in only 4 (3 multinodular) of 25 very elderly patients. One series infers the proportion of hyperthyroid patients who are elderly is increasing [423].

Table 5.18 Some symptoms and signs of hyperthyroidism in elderly patients compared with younger patients

	Elderly	*Very old*[b]	*Young*[a]
Number	65	25	45
Age	50–78	75–95	20–29
Palpitations	60%	36%	100%
Goitre	58%	32%	98%
Tremor	71%	8%	96%
Eye signs	28%	12%	71%

[a] Extracted from Kawabe *et al.* [427].
[b] Extracted from Tibaldi *et al.* [422].

Several comprehensive papers deal with this topic [422, 424–427]. Table 5.18 shows differences in the incidence of clinical features in control patients, elderly and very elderly hyperthyroid. The older the patient, the less frequent the classic features. The absence of a goitre and the rarity of ophthalmopathy in those with Graves' disease is notable. The diagnosis should be considered in an old patient with weight loss, gastrointestinal symptoms and chronic ill health. A patient with these is likely to be labelled as having an occult malignancy and subjected to tests designed to find the primary cancer. In those with cardiac failure and/or arrhythmias, numerically the most likely cause is primary ischaemic or hypertensive heart disease. Only when investigations show a high cardiac output is hyperthyroidism suspected.

Diagnostic tests should include FT_4 and TSH. Uptake and scintigraphy with ^{123}I can be valuable to determine if the thyroid traps avidly and appears more active than the impression from clinical examination. In the elderly, especially if there are coexisting medical problems, T_3 values are lower than 'normal'. Therefore, borderline high values in the range 150–220 ng/dl (2.4–3.4 nmol/l) can be evidence of hyperthyroidism. In two series, T_3 values were above normal in only 50% [422] and 66% of patients [428]. My preference is to rely on the first two measurements. Forfar *et al.* [57] have advocated the use of the TRH test to prove hyperthyroidism as a cause of cardiac arrhythmias. These results also have to be interpreted with caution, because elderly euthyroid men often have a flat response. In addition, suppressed basal TSH predicts a flat response, therefore TRH testing is usually superfluous. The high prevalence of thyroid dysfuntion in the elderly is discussed in Chapter 4, and tests should be ordered with minimal clinical suspicion, because thyroid diseases, whether hyper-, or hypothyroidism, are among the few curable pathologies in this age group.

Treatment would generally be ^{131}I, but at this age pretreatment with antithyroid medications until the patient is euthyroid is prudent. An alternative is the careful use of beta-blockers before and after radioiodine therapy, plus inorganic iodine for several weeks after ^{131}I therapy. Unless there is a major clinical problem, such as asphyxiation from a large nodular goitre, surgery should be avoided.

5.24 HYPERTHYROIDISM IN PREGNANCY AND IN THE NEONATE

Hyperthyroidism is said to complicate 0.2% of pregnancies [429]. In the USA, hyperthyroidism during pregnancy is caused by Graves' disease in 95% of cases. This is important because the fetus is potentially at risk for neonatal Graves' disease, and it will be exposed to antithyroid medications given to the mother. This discussion is limited to Graves' disease, but if the clinical features are atypical an alternative cause should be sought.

The diagnosis of hyperthyroidism in pregnancy is not straightforward, because some features of normal pregnancy are those of hyperthyroidism [430–432]. In normal pregnancy, there is a rise in pulse rate, which is bounding, a feeling of heat, plus sweating. In countries where iodine intake is marginal, goitre in pregnancy is common. In fact, one of the first pregnancy tests 2000 years ago was a thread round the neck of women slaves. Breakage of the thread by an expanding goitre signalled successful conception. There is no data on the sensitivity or specificity of the test! There is increased clearance of iodine by the kidney during pregnancy, a fall in plasma inorganic iodine, and if the latter falls sufficiently, the thyroid under TSH stimulation undergoes hypertrophic and hyperplastic changes in an effort to trap more iodine and produce physiological amounts of thyroid hormone. In a study in Scotland, 80% of pregnant women had goitres, and plasma inorganic iodine fell from 0.2 μg/dl in controls to 0.09, μg/dl prior to delivery [433]. In the USA iodine levels in the blood are four times as great and a goitre is not a normal finding [434]. A goitre was palpated in 6% of 300 adolescent girls who were pregnant compared with 5% in 600 controls [435]. Half of the goitres were due to autoimmune disease or subacute thyroiditis. Levy *et al.* [436] did 'blind' palpation of the thyroids of 49 pregnant women and 49 controls and found no increase in goitre in the former. Therefore, the finding of goitre should be a stimulus to find the cause and consider the possibility of Graves' disease. If the resting pulse is consistently above 90/min and if there is loss of weight, thyroid function should be tested. Total thyroid hormone levels in pregnancy can be difficult to interpret. This is because the high oestrogen

levels cause a rise in thyroid binding globulin, and this in turn increases total T_4 and T_3 to maintain free hormones in the physiological ranges. FT_4 falls slightly throughout pregnancy, but the values do not drop into the hypothyroid range. TSH values are also 'normal', therefore measurement of these give a precise indication of thyroid status. Total T_4 values range from 7–15 μg/dl (90–193 nmol/l) and T_3 from 100–250 ng/dl (1.54–3.84 nmol/l). If these tests are used, they should be interpreted along with T_3RU or thyroid binding globulin measurement as discussed in Chapter 3. When the clinical syndrome is of hyperthyroidism but not Graves' disease, it can be important to determine if the thyroid can trap iodine or not. Low uptake causes, such as silent thyroiditis, should not be treated with antithyroid drugs, an important fact in pregnancy. It is justifiable to obtain an uptake measurement with a tracer dose of 10 μCi ^{123}I. This would give a 10 week fetus about 0.3 mrad (0.00003 Gy) in comparison with about 150 mrad from background throughout the pregnancy [437]. Trophoblastic tumour as a cause of hyperthyroidism in pregnancy should also be considered. In cases of Graves' hyperthyroidism, measurement of maternal TRAb might be of value in anticipating neonatal Graves' disease [438]. Moderate or severe hyperthyroidism is likely to cause infertility. Hyperthyroidism in pregnancy, therefore, can be considered in two settings. Firstly, the patient who is mildly hyperthyroid prior to becoming pregnant but in whom the diagnosis is first made during pregnancy. Secondly, the diagnosis had already been established and antithyroid medications prescribed. Because of concern about taking pharmacological agents during pregnancy or breastfeeding, there is an argument for treating Graves' disease in women of childbearing age with ^{131}I before they conceive. However, in the situation where hyperthyroidism complicates pregnancy, treatment is advised because hyperthyroidism increases the risk of spontaneous abortion and malformations [439]. Pregnancy is a time of immunological quiescence. The maternal immune system accepts a foreign graft (50% foreign) without rejecting it. This tolerance also applies to immunological diseases including Graves' disease. There is a tendency for levels of TRAb to fall and the disease to remit as the pregnancy proceeds. As a result, treatment can be tapered and stopped in some patients. In one series this occurred in 39% of patients [440]. In every case, primary treatment is with antithyroid drugs.

Prophylthiouracil is preferred because of the association of aplasia cutis with methimazole. Propylthiouracil is given 3 times a day in a dose range of 50–150 mg 8-hourly depending on the severity of symptoms and signs. The dose is titrated to achieve clinical and biochemical euthyroidism. It is important to cure hyperthyroidism, but equally important to avoid hypothyroidism. This requires clinic visits with testing at intervals of 4–6 weeks. If TSH rises, the dose should be reduced and, as stated above, it may be possible to stop treatment in the last month. Relapse after delivery should be anticipated. The complications of treatment are no different in pregnancy, but there is the additional concern that the baby could be adversely affected. There is no evidence of propylthiouracil causing malformations. Nevertheless, the dose should be kept to the smallest required for maternal well-being. There is also concern that the baby will be born hypothyroid and goitrous, and have permanent reduction in higher intellectual functions. No difference in children who were exposed to antithyroid drugs compared to control siblings were found up to age 10.5 years in one study [441]. In a second investigation, T_4 values were lower but the findings returned to normal quickly [442]. However, in this study, T_4 was prescribed along with propylthiouracil. The reason for the combination is to maintain euthyroidism in mother and baby if the dose of propyl-

thiouracil is too great. There is a considerable flaw to this protocol. Propylthiouracil crosses the placenta, whereas T_4 does not. Combined therapy protects the mother from hypothyroidism, but could well put the fetus at greater risk. I do not recommend combined treatment, but advise careful titration of propylthiouracil alone. In cases where the symptoms are pronounced, beta-blockers, such as propranolol, 20–40 mg 2–4 times a day, or atenolol 50–100 mg daily, are appropriate. As the hyperthyroidism comes under control the dose of beta-blocker is reduced and, if possible, stopped. A review of beta-blockers in pregnancy shows them to be safe [443]. Iodine should, if possible, be avoided. There are reports of it producing a goitre in the fetus of such a dimension as to obstruct labour and cause death [444]. A brief course in preparation for surgery is discussed below.

Surgical treatment of Graves' disease in pregnancy is acceptable, but now rarely done. A general anaesthetic is not without risk to the fetus and if the thyrotoxicosis is controlled with an acceptable dose of propylthiouracil (300 mg/day), medical management should be continued. If the thyrotoxicosis requires larger doses for control, or if there are complications from the drugs, surgery is advised. The operation has had best results when done in the middle trimester, but when necessary can be done at any time. In one series of 33 patients, 26 were operated on in the middle trimester, 2 in the first and 5 in the last. All but one patient were delivered at term [445]. There are no recent sizeable series. The patient should be euthyoid prior to operation using antithyroid drugs and a brief course of iodine. If euthyroid, why operate? When there is a complication from propylthiouracil, preparation is with propranolol and iodine, the latter being used for only a few days. Eclampsia and delivery are potential causes of thyroid storm in patients with poorly controlled hyperthyroidism [446]. Thyroid storm is discussed in the next section. Therapy includes aggressive management of hyperthyroidism. Plasma exchange has been used to lower the levels of thyroid hormones rapidly [447].

Assuming that hyperthyroidism has been controlled successfully with propylthiouracil, which has been stopped by the end of the eighth month and delivery of a healthy child results, the mother will probably wish to breastfeed. She progresses well for a few weeks, then hyperthyroidism recurs. In this setting it is usually a recurrence of Graves' disease, but postpartum thyroiditis also occurs at this time. Absence of goitre is more common in the latter, and the differentiation is important since treatments differ. Iodine-123 uptake differentiates these, but breastfeeding has to be stopped for 2 days. Recurrent Graves' hyperthyroidism is treated with propylthiouracil. Statements in most standard texbooks that this is a contraindication to breastfeeding should be reassessed. Almost all authors refer to a paper by Williams *et al.* [448] from 1944 as reason to advise against breastfeeding. That paper deals with thiouracil. In contrast, propylthiouracil is protein bound in the serum and little is excreted in milk [449]. There would appear to be negligible risk of hypothyroidism in the baby, and the tiny doses would be unlikely to cause complications. Cooper [157] quotes the treatment of four breastfeeding mothers and I have experience with three [272]. The women specifically ask if this can be done, and a full account of the historical facts and current knowledge are discussed. I have tested thyroid function in the babies using a small volume of blood from a heel stick. The results have all been normal.

Immunoglobulins in the mother cross the placenta into the fetus and provide passive immunity for the first few weeks of life. Maternal autoantibodies also cross the placenta and can cause disease in the newborn. Neonatal Graves' disease is the best example of an autoimmune disorder. The

baby is born hyperthyroid with goitre and the disease remits in the same length of time that the maternal TRAb is cleared from the child's circulation. There are similar numbers of boys and girls with neonatal Graves' disease. The condition is rare and only about 1 mother out of 70 with Graves' disease will have a hyperthyroid baby. The first report was in 1910, and a comprehensive review in 1978 [450] documented only 82 cases. The mother usually has Graves' hyperthyroidism. However some have been hyperthyroid and are actually hypothyroid and taking replacement L thyroxine. Maternal infiltrative ophthalmopathy and dermopathy increase the risk, but this is because they are consistently associated with higher titres of TRAb. Current or past Graves' disease should alert clinicians to this possibility, and sometimes the diagnosis can be suspected before delivery when the baby is small for dates, and the fetal heart rate is persistently above 160/min. At birth, the child can be hyperthyroid, but antithyroid drugs given to the mother up to the time of delivery can protect the baby for hours to days; therefore, delayed hyperthyroidism should be sought in this setting. Passage of antithyroid drugs from the mother to the fetus has been used to treat suspected intrauterine Graves' disease [451, 452]. This has to be done with close co-operation of the endocrinologist, obstetrician and paediatrician.

The thyrotoxic infant is of low birth weight, irritable, hungry, has tachycardia, diarrhoea and sweats. Goitre is almost always present and mild eye signs are common. The diagnosis is a clinical one, which is confirmed by measurement of FT_4 and TSH. Thyroid hormones levels are high for several days after delivery; in our experience FT_4 values in healthy newborns were 4.24 ± 0.23 ng/dl [453] (95 ± 5 pmol/l). Rapid, intense uptake of an intravenous tracer dose of 30 μCi ^{99m}Tc is a quick and helpful test [451]. High levels of TRAb which disappear with a half-life of 1–2 weeks clinches the diagnosis, but therapy should not await receipt of test results.

Treatment is with propylthiouracil 5 mg/kg in divided doses each day, plus 1 drop of Lugol's iodine daily. Propranolol in a dose of 2–4 mg/day can be added if there is persistent tachycardia in spite of the first two medications. Neonatal Graves' disease is serious. Fortunately, it is transient in the large majority of cases. Hyperthyroidism in babies has been associated with craniosynostosis and raised intracranial pressure [454, 455]. The increased risk of malformations has been discussed, Momotani *et al.* [439] in a study comparing hyperthyroid women who received no treatment with those who did, found the following results. Hyperthyroidism alone was associated with 6% of malformations, hyperthyroidism not adequately controlled with methimazole with 1.7%, euthyroid Graves' with 0.3% and euthyroid due to methimazole 0%. Note the antithyroid drug was methimazole.

5.25 THYROID CRISIS (STORM)

Thyroid crisis is an extremely serious complication of hyperthyroidism, which carries a significant mortality especially when the diagnosis is delayed and treatment not introduced with expediency [456–458]. It is the severe end of the spectrum of hyperthyroidism, and usually occurs in patients who have been hyperthyroid for some time. There are several common precipitating causes including surgical operations, infections and medical problems. Sometimes, the hyperthyroidism has been recognized and treated, but the patient discontinues antithyroid medications. As an index of the severity of the pre-existing hyperthyroidism, Mazzaferri and Skillman [459] found weight loss of 20–50 pounds in 13 out of 22 patients. Pneumonia was the most common associated factor, occurring in 9 out of 22 patients. Thyroidectomy was causal in 5. However, as

was discussed above, surgery for hyperthyroidism should only be undertaken when the patient is euthyroid. Roizen and Becker [460] reported three cases due to infection, three to vascular incidents, three to drug reactions, three to stopping antithyroid medications and one each to thyroidectomy and radioiodine. The possibility that radioiodine can cause thyroid storm should be considered in older hyperthyroid patients, those who are severely hyperthyroid and those with large nodular glands [58]. In these situations, pretreatment with antithyroid drugs is recommended. Diabetic coma is a well-recognized precipitant [461, 462]. The complications and stresses of pregnancy as precipitants are discussed above.

In most large series, the age and gender of patients is not different from those recorded without storm [459], although some investigators find a slight bias to an older age. The diagnosis is a clinical one. The criteria include very severe thyrotoxicosis, central nervous system abnormalities with confusion, delirium and coma, pyrexia and extreme tachycardia (130–200/min). The emergency of the condition is emphasized and the patient should be hospitalized [463]. Routine thyroid function tests do not determine whether a patient has thyroid crisis. T_4 and T_3 values are not different in those with thyroid crisis compared with hyperthyroid patients who do not have the problem. Brooks and Waldstein [464] demonstrated that FT_4 and the dializable fraction were higher in six patients with crisis, but there was overlap with results from 15 patients with uncomplicated hyperthyroidism. The diagnosis and treatment should not await test results. Once it is recognized that the patient has storm, treatment should be started. One possible exception to this policy is the use of a thyroid flow study with intravenous ^{99m}Tc. In severe hyperthyroidism, there is almost instantaneous visualization of the thyroid after the injection [465]. This is only warranted when the diagnosis is in doubt. These patients are very ill and consideration should be given for their placement in an intensive care unit.

Treatment is aimed at rapid control of thyrotoxicosis, the precipitating cause (if definable), and general supportive measures. Thyrotoxicosis is treated with large doses of propylthiouracil, such as 300 mg every 4–6 hours. Propylthiouracil is theoretically superior to methimazole, because it not only interferes with synthesis in the thyroid, but also interferes with peripheral conversion of T_4 to T_3. The equivalent dose of methimazole is 20–30 mg every 4 hours. Whichever drug is used is administered orally, and in severely ill patients administration by nasogastric tube is often necessary. Iodine is given to prevent the release of preformed hormones, and this can be given orally or by infusion of 1 g sodium iodide every 12 hours. The radiographic contrast agent ipodate (Oragrafin) has been shown to have a dramatic affect clinically and biochemically in severe hyperthyroidism [466]. Its action is multifactorial: the iodine content prevents release of thyroidal hormones, it has a marked effect in decreasing the conversion of T_4 to T_3, and it decreases the percent of FT_4 in plasma. The dose is 1–3 g orally daily. A beta-blocking drug is prescibed; I prefer propranolol. The range of dose is from 20–60 mg every 6 hours; the effect of a starting dose of 40 mg can be observed and subsequent doses titrated as necessary. Deaths have occurred in spite of propranolol [166, 275] and Hellman *et al.* [467] stress the need for serum levels above 50 ng/ml, and found that a total daily dose of 160 mg is sometimes insufficient. The response of the pulse rate is of prime importance, but biochemical monitoring can add information. Traditionally, corticosteroids have been prescribed, but their role is not well defined, although they do reduce conversion of T_4 to T_3. This is already the case with the specific drugs discussed above and, unless there is reason to believe there is lack of hydrocortisone (co-

existing Addison's disease), it need not be prescribed.

Treatment of precipitating illness includes appropriate antibiotics for pneumonia, etc. Supportive care is extremely important. Intravenous fluids, electrolytes and calories are necessary for several days. Hyperthermia requires cooling blankets and acetaminophen can be used. Salicylates should not be given. Cardiac failure is treated with oxygen, diuretics, digoxin and appropriate monitoring, which can include a Swan–Ganz catheter. Very rarely, if these measures are unsuccessful, plasma exchange can be considered [468].

The dose of antithyroid medications are titrated as the patient's condition improves and iodine is stopped. A decision has to be made about definitive long-term management, which in this setting is most probably ^{131}I, which can be prescribed 4–6 weeks later, by which time inorganic iodine no longer lowers trapping.

KEY FACTS

- Hyperthyroidism implies overactivity of the thyroid and thyrotoxicosis (the response of the body to too much thyroid hormone).
- In practice, the terms hyperthyroidism and thyrotoxicosis are used interchangeably.
- There are many syndromes causing hyperthyroidism, the commonest is **Graves' disease**.
- Graves' disease is an organ-specific, autoimmune disease in which there is production of antibodies to the TSH receptor, called thyroid receptor antibody (TRAb)
- TRAb acts like TSH and stimulates all steps of thyroid hormone production and secretion. However, it has a longer time course.
- In Graves' disease, thyrotoxicosis is common; a small proportion of patients have an ophthalmopathy, a smaller proportion dermopathy and a very small proportion acropachy.
- Hyperthyroidism is diagnosed by high FT_4, low TSH and high RAIU.
- Treatment can be with antithyroid drugs, surgery or radioiodine ^{131}I.
- Medical therapy has the benefit of effectiveness and fairly rapid onset. It has the problems of uncertainty of long-term remission and side-effects including skin rashes, agranulocytosis and hepatitis.
- Surgical therapy is used less often – it is effective but more costly and invasive.
- ^{131}I is effective, but cure is delayed for 2–4 months and hypothyroidism is to be expected.
- Ophthalmopathy occurs in 5% of patients and can cause Soft-tissue swelling, Proptosis, Extraocular muscle involvement, Corneal involvement and Sight loss (SPECS).
- Ophthalmopathy when severe and progressive is treated by steroids or surgical decompression of the orbit, or by external radiotherapy.
- Dermopathy is treated by local steroid cream.
- **Functioning single and multiple nodules** – single functioning nodule usually does not cause hyperthyroidism.
- A small proportion of patients are hyperthyroid and T_3 can be the only hormone elevated.
- Diagnosed by high T_3 (FT_4), low TSH; a palpable nodule that concentrates excess ^{123}I.
- Scintigraphy with ^{123}I and ^{99m}Tc can give different results (^{123}I is preferred).
- Women are more likely to have functioning nodules (>10/1).
- Hot nodules are almost always benign.
- Treatment is surgical removal or ^{131}I ablation.
- In general, surgery is preferred in younger patients and those with bigger nodules.

- **Toxic multinodular goitre** is more common in women.
- A diagnosis made clinically and confirmed by high FT_4, low TSH, and scintigraphy showing multiple functioning nodules.
- Therapy is by surgery or ^{131}I.
- There are several conditions where the patient is thyrotoxic, but there is low uptake of radioiodine.
- **Iatrogenic hyperthyroidism** is easy to diagnose from the patient's history, high FT_4, low TSH and low RAIU.
- **Factitious hyperthyroidism** is difficult to diagnose because the patient conceals the important information.
- Factitious hyperthyroidism is characterized by high FT_4, low TSH, low RAIU and low thyroglobulin.
- **Hamburger thyrotoxicosis** due to thyroid in ground meat is difficult to diagnose clinically.
- In hamburger thyrotoxicosis there is high FT_4, low TSH, low RAIU and low thyroglobulin.
- Usually there is a regional cluster of cases.
- **Silent thyroiditis** is discussed fully in Chapter 9.
- In silent thyroiditis, there is high FT_4, low TSH, low RAIU but high thyroglobulin and often high levels of antibodies.
- The thyrotoxicosis is of short duration and is usually followed by a return to normal.
- **Postpartum thyroiditis** is similar to silent thyroiditis, but occurs 2–6 months after delivery.
- **Subacute thyroiditis** is discussed fully in Chapter 9.
- In subacute thyroiditis, there is transient thyrotoxicosis, plus pain in the neck, plus systemic illness.
- There is elevated FT_4, low TSH, low RAIU and high ESR.
- **Hyperthyroidism due to cancer invading thyroid** is rare and clinically not difficult to diagnose.
- FT_4 is high, TSH low and a biopsy of the mass shows pathology.
- **Iodine-induced hyperthyroidism (Jod Basedow phenomenon)** usually arises in a patient with a non-toxic nodular goitre.
- Most often the source of iodine is medicinal, such as amiodarone or radiographic contrast.
- **Struma ovarii** causing hyperthyroidism is very rare and is difficult to diagnose.
- In struma ovarii, there is high FT_4, low TSH, low RAIU over the thyroid, but high uptake over the ovarian lesion.
- Great care is necessary to ensure that radioiodine in the bladder is not interpreted as struma ovarii.
- **Metastatic functioning thyroid cancer** is usually obvious from the patient's history and clinical examination.
- There are several syndromes where hyperthyroidism is caused by excess TSH or TSH-like material.
- **Pituitary tumour secreting TSH** can be misinterpreted as Graves' disease.
- In pituitary hyperthyroidism, the key diagnostic factor is measurable TSH in a hyperthyroid patient who has high FT_4.
- In general, TSH is not stimulated by TRH or suppressed by T_3, and the ratio of alpha TSH/TSH is more than 1.
- There is usually evidence of a pituitary tumour on NMRI.
- **Non-pituitary cancer secreting TSH** is theoretically possible, but not well documented.
- **Hyperthyroidism with inappropriate TSH secretion** is difficult to differentiate from pituitary tumour secreting TSH.
- In general, TSH is stimulated by TRH, is suppressed by T_3, and the ratio of alpha TSH/TSH is less than 1.
- There is no evidence of a pituitary tumour.
- **Hyperthyroidism from trophoblastic**

tumours are rare but more common in oriental women.

- The hyperthyroidism is due to very high levels of HCG, which mimic TSH.
- **Hyperthyroidism during pregnancy** is more likely to be due to Graves' disease, but in atypical cases trophoblastic tumour should be considered since the pregnancy has to be terminated, and in choriocarcinoma chemotherapy is necessary.
- **Hyperthyroidism in children** is usually due to Graves' disease.
- The diagnosis in children is frequently delayed and symptoms attributed to hyperactivity, behavioural problems, etc.
- Diagnosis is made by high FT_4, low TSH and high RAIU.
- Therapy is as in adults, with ^{131}I providing a quick, permanent cure.
- **Hyperthyroidism in the elderly** can present differently, with apathy being common.
- Diagnosis is made by high FT_4, low TSH and high RAIU.
- Treatment is usually with ^{131}I but pretreatment with antithyroid drugs is usually advised.
- **Hyperthyroidism in pregnancy** is usually due to Graves' disease.
- Clinical diagnosis can be difficult since in normal pregnancy the pulse is rapid, the skin is warm, etc.
- Diagnosis is made by high FT_4 and low TSH. It is usually not advisable to do RAIU although the risk to the fetus is extremely low.
- TRAb should be measured, and if it is high, neonatal Graves' disease anticipated.
- Therapy when pregnant is with propylthiouracil; maternal hypothyroidism should be avoided.
- Frequent biochemical monitoring is necessary.
- Often the therapy can be stopped by 7–9th month, but relapse is often found weeks after delivery.
- It is safe to breastfeed when taking propylthiouracil.
- Neonatal Graves' disease is very rare, and usually occurs when mother has high levels of TRAb.
- **Thyroid storm** is a clinical diagnosis of severe thyrotoxicosis with delirium or coma.
- It has a high mortality rate.
- Precipitating causes include infection, surgery, diabetes and radioiodine therapy.
- Therapy includes high doses of antithyroid drugs plus beta-blockers and inorganic iodine.
- Monitoring in an intensive care unit is advised.
- Potential causes must be looked for and treated.

REFERENCES

1 Graves, R.J. (1835) *London Med. Surg. J.*, **7** (2), 516.

2 Parry, C.H. (1825) Collections from the unpublished papers of the late Caleb Hillier Parry, Vol 2, pp. 11–128.

3 Von Basedow, C.A. (1840) Exophthalmos durch hypertrophie des zellgewebes in der augenhohle. *Wochenschrift Gesammte Heilkunde*, **6**, 197.

4 Major, R.H. (1945) *Classic Descriptions of Disease: With Biographical Sketches of the Authors*, 3rd edn, Charles C Thomas, Springfield.

5 *a* Taylor, S. (1986) Graves of Graves' disease, 1796–1853. *J. Roy. Coll. Phys.*, **20**, 298–300.

5 *b* Taylor, S. (1989) *Robert Graves: The Golden Years of Irish Medicine*, The Royal Society of Medicine, London.

6 Committee on Nomenclature of the American Thyroid Association (1987) Revised nomenclature for test of thyroid hormones and thyroid-related proteins in the serum. *J. Clin. Endocrinol. Metab.*, **64**, 1089–94.

7 Adams, D.D. and Purves, H.D. (1956) Abnormal responses in the assay of thyrotrophin. *Proc. Univ. Otago Med. Sch.*, **34**, 11–12.

8 Kriss, J.P., Pleshakov, V. and Chien, J.R. (1964) Isolation and identification of the long-acting thyroid stimulator and its relation to hyperthyroidism and circumscribed pretibial

myxedema. *J. Clin. Endocrinol. Metab.*, **24**, 1005–28.
9 McKenzie, J.M. (1958) Delayed thyroid response to serum from thyrotoxic patients. *Endocrinol*, **62**, 865–8.
10 Kriss, J.P. (1968) The long-acting thyroid stimulator. *Calif. Med.*, **109**, 202–13.
11 Ochi, Y. and DeGroot, L.J. (1968) Long acting thyroid stimulator of Graves's disease. *N. Engl. J. Med.*, **278**, 718–21.
12 Adams, D.D. and Kennedy, T.H. (1967) The occurrence in thyrotoxicosis of a gamma globulin which protects LATS from neutralisation by an extract of thyroid gland. *J. Clin. Endocrinol. Metab.*, **27**, 173–7.
13 Adams, D.D. (1988) Long-acting thyroid stimulator: how receptor autoimmunity was discovered. *Autoimmunity*, **1**, 3–9.
14 Adams, D.D., Fastier, F.N., Howie, J.B. *et al.* (1974) Stimulation of the human thyroid by infusions of plasma containing LATS protector. *J. Clin. Endocrinol. Metab.*, **39**, 826–32.
15 Zakarija, M., McKenzie, J.M. and Banovac, K. (1980) Clinical significance of thyroid-stimulating antibody in Graves' disease. *Ann. Intern. Med.*, **93**, 28–32.
16 McKenzie, J.M. (1980) Thyroid-stimulating antibody (TSAb) in Graves' disease. *Thyroid Today*, (ed. J.H. Oppenheimer) **2** (5), 1–5.
17 Morris, J.C. III. Hay, I.D., Nelson, R.E. *et al.* (1988) Clinical utility of thyrotropin-receptor antibody assays: comparison of radioreceptor and bioassay methods. *Mayo Clin. Proc.*, **63**, 707–17.
18 Wilson, R., McKillop, J.H., Pearson, D.W.M. *et al.* (1985) Relapse of Graves' disease after medical therapy: predictive value of thyroidal technetium–99m uptake and serum thyroid stimulating hormone receptor antibody levels. *J. Nucl. Med.*, **26**, 1024–8.
19 Madec, A.M., Laurent, M.C., Lorcy, Y. *et al.* (1984) Thyroid-stimulating antibodies: an aid to the strategy of treatment of Graves' disease? *Clin. Endocrinol.*, **21**; 247–55.
20 Rees-Smith, B. (1988) Autoantibodies to the thyrotropin receptor. *Endocrine Rev.*, **9**, 106–21.
21 Munro, D.S., Dirmikis, S.M., Humphries, H. *et al.* (1978) The role of thyroid-stimulating immunoglobulins of Graves' disease in neonatal thyrotoxicosis. *Br. J. Obstet. Gyn.*, **85**, 837–43.
22 Volpé, R. (1981) Auto-immunity in the endocrine system. *Monograph Endocrinol.*, **20**, 19–111.
23 Strakosch, C.R., Wenzel, B.E., Row, V.V. *et al.* (1982) Immunology of autoimmune thyroid disease. *N. Engl. J. Med.*, **307**; 1499–504.
24 Bartrop, R.W., Lockhurst, E., Lazarus, L. *et al.* (1977) Depressed lymphocyte function after bereavement. *Lancet*, **1**, 834–6.
25 Wilson, G.M. (1967) *The Treatment of Thyrotoxicosis*, Symposium Thyroid Disease and Calcium Metabolism, Royal College of Physicians, Edinburgh, pp. 51–76.
26 Wasnich, R.D., Grumet, F.C., Payne, R.O. *et al.* (1973) Graves' ophthalmopathy following external neck irradiation for nonthyroidal neoplastic disease. *J. Clin. Endocrinol. Metab.*, **37**, 703–13.
27 Davis, P.J., Rappeport, J.R., Lutz, J.H. *et al.* (1971) Three thyrotoxic criminals. *Ann. Intern. Med.*, **74**, 734–5.
28 Rockey, P.H. and Griep, R.J. (1980) Behavioral dysfunction in hyperthyroidism: improvement with treatment. *Arch. Intern. Med.*, **149**, 1194–7.
29 Rothberg, M.P., Shebert, R.T., Levey, G.S. *et al.* (1974) Propranolol and hyperthyroidism: reversal of upper motor signs. *JAMA*, **230**, 1017.
30 Okinaka, S., Shizume, K., Iino. S. *et al.* (1957) The association of periodic paralysis and hyperthyroidism in Japan. *J. Clin. Endocrinol. Metab.*, **17**, 1454–9.
31 Dyde, J.A. (1965) Hyperthyroidism complicated by periodic paralysis. *Postgrad. Med. J.*, **41**, 286–7.
32 Barnard, J.D., Larson, M.A., Norris, F.H. Jr (1972) Thyrotoxic periodic paralysis in Californians of Mexican and Filipino ancestry. *Calif. Med.*, **116**, 70–4.
32 *a* Leung, A.K.C. (1985) Familial 'hashitoxic' periodic paralysis. *J. Roy. Soc. Med.*, **78**, 638–40.
32 *b* Sum, C.F., Fok, A.C.K., Tan, K.T. *et al.* (1988) Human leucocyte antigen in a Chinese family with thyrotoxic periodic paralysis in Singapore. *Br. Med. J.*, **297**, 594–5.
33 McFadzean, A.J.S. and Yeung, R. (1967) Periodic paralysis complicating thyrotoxicosis in Chinese. *Br. Med. J.*, **1**, 451–5.
34 Ober, K.P. and Hennessey, J.F. (1981) Jod Basedow and thyrotoxic periodic paralysis. *Arch, Intern. Med.*, **141**, 1225–7.
35 Layzer, R.B. and Goldfield, E. (1974) Periodic paralysis caused by abuse of thyroid hormone. *Neurol.*, **24**, 949–52.
36 Edelman, J. and Stewart-Wynne, E.G. (1981) Respirarory and bulbar paralysis with relapsing hyperthyroidism. *Br. Med. J.*, **283**, 275–6.
37 Guthrie, G.P. Jr, Curtis, J.J. and Beilman,

K.M. (1978) Hypophosphatemia in thyrotoxic periodic paralysis. *Arch. Intern. Med.*, **138**, 1284–5.
38 Feely, J. (1981) Potassium shift in thyrotoxic periodic paralysis. *Postgrad. Med. J.*, **57**, 238–9.
39 Yeung, R.T.T. and Tse, T.F. (1974) Thyrotoxic periodic paralysis: effect of propranol. *Am. J. Med.*, **57**, 584–90.
40 Ramsay, I. (1966) Muscle dysfunction in hyperthyroidism. *Lancet*, **3**, 931–5.
41 Drachman, D.B. (1962) Myasthenia gravis and the thyroid gland. *N. Engl. J. Med.*, **266**, 330–3.
42 Muggia, A.L., Stjernholm, M. and Houle, T. (1970) Complete heart block with thyrotoxic myocarditis; report of a case. *N. Engl. J. Med.*, **283**, 1099–100.
43 Campus, S., Rappelli, A., Malavasi, A. *et al.* (1975) Heart block and hyperthyroidism: report of two cases. *Arch. Intern. Med.*, **135**, 1091–5.
44 Stern, M.P., Jacobs, R.L., and Duncan, G.W. (1970) Complete heart block complicating hyperthyroidism. *JAMA*, **212**, 2117–19.
45 Eraker, S.A., Wickamasekaran, R. and Goldman, S. (1978) Complete heart block with hyperthyroidism. *JAMA*, **239**, 1644–6.
46 Wei, J.Y., Genecin, A., Greene, H.L. *et al.* (1979) Coronary spasm with ventricular fibrillation during thyrotoxicosis: response to attaining euthyroid state. *Am. J. Cardiol.*, **43**, 335–9.
47 Featherstone, H.J. and Stewart, D.K. (1983) Angina in thyrotoxicosis: thyroid-related coronary artery spasm. *Arch. Intern. Med.*, **143**, 554–5.
48 Kotler, M.N., Michaelides, K.M., Bouchard, R.J. *et al.* (1973) Myocardial infarction associated with thyrotoxicosis. *Arch. Intern. Med.*, **132**, 723–8.
49 Cobler, J.L., Williams, M.E. and Greenland, P. (1984) Thyrotoxicosis in institutionalised elderly patients with atrial fibrillation. *Arch. Intern. Med.*, **144**, 1758–60.
50 Williams, R.H. (1946) Thiouracil treatment in thyrotoxicosis. *J. Clin. Endocrinol. Metab.*, **41**, 354–61.
51 Mornex, R. and Orgiazzi, J.J. (1980) Hyperthyroidism, in *The Thyroid Gland*, (ed. M. De Visscher), Raven Press, New York, pp. 279–63.
52 Wayne, E.J. (1954) The diagnosis of thyrotoxicosis. *Br. Med. J.*, **1**, 411–19.
53 Bar-Sela, S., Ehrenfeld, M. and Eliakim, M. (1981) Arterial embolism in thyrotoxicosis with atrial fibrillation. *Arch. Intern. Med.*, **141**, 1191–2.
54 Hausmann, W. (1974) Thyrotoxic cardiomyopathy complicated by systemic and pulmonary embolism. *Proc. Roy. Soc. Med.*, **68**, 327.
55 Giddings, H.B. and Surks, M.I. (1978) Cerebral embolization in atrial fibrillation complicating hyperthyroidism. *JAMA*, **240**, 2567–8.
56 Staffurth, J., Gibberd, M., Tang Fui, S.N. (1977) Arterial embolism in thyrotoxicosis with atrial fibrillation. *Br. Med. J.*, **2**, 688–90.
57 Forfar, J.C., Miller, H.C. and Toft, A.D. (1979) Occult thyrotoxicosis: a correctable cause of idiopathic atrial fibrillation. *Am. J. Cardiol.*, **44**, 9–12.
58 Parker, J.L.W. and Lawson, D.H. (1973) Death from thyrotoxicosis. *Lancet*, **2**, 894–5.
59 Magner, J.A., Clark, W. and Allenby, P. (1988) Congestive heart failure and death in a young woman with thyrotoxicosis. *West J. Med.*, **149**, 86–91.
60 Rosenthal, F.D., Jones, C. and Lewis, S.I. (1977) Thyrotoxic vomiting. *Br. Med. J.*, **2**, 209–11.
61 Parkin, A.J., Nisbet, A.P. and Bishop, N. (1981) Vomiting due to gastric stasis as the presenting feature in thyrotoxicosis. *Postgrad. Med. J*, **57**, 405.
62 Miller, L.J., Gorman, C.A. and Go, V.L.W. (1978) Thyroid-gut interrelationships. *Gastroenterology*, **75**, 901–11.
63 Ashkar, F.S., Miller, R., Smoak, W.M. *et al.* (1971) Liver disease in hyperthyroidism. *South Med. J.*, **64**, 462–5.
64 Marks, P. and Ashraf, H. (1978) Apathetic hyperthyroidism with hypomagnesaemia and raised alkaline phosphatase concentration. *Br. Med. J.*, **1**, 821–2.
65 Herbert, V. (1986) The blood, in *Werner's The Thyroid*, 5th edn, (eds S.H. Ingbar and L.E. Braverman), J.B. Lippincott Company, Philadelphia, pp. 878–84.
66 Dunlap, D.B., McFarland, K.F. and Lutcher, C.L. (1974) Graves' disease and idiopathic thrombocytopenic purpura. *Am. J. Med. Sci.*, **268**, 107–11.
67 Grish, L.S. and Meyerson, R.M. (1957) Thyrotoxicosis associated with thrombocytopenia and hypersplenism. *Am. J. Clin. Pathol.*, **27**, 328–31.
68 Hymes, K., Blum, M., Lackner, H. *et al.* (1981) Easy bruising, thrombocytopenia, and elevated platelet immunoglobulin G in Graves' disease and Hashimoto's thyroiditis. *Ann. Intern. Med.*, **94**, 27–30.

69 Irvine, W.J., Wu, F.C.W., Urbaniac, S.J. *et al.* (1977) Peripheral blood leukocytes in thyrotoxicosis (Graves') disease as studied by conventional light microscopy. *Clin. Exp. Immunology*, **27**, 216–21.
70 Wall, J.R., Gray, B. and Greenswood, D.M. (1977) Total and activated peripheral blood T-lymphocytes in patients with Graves' disease. *Acta Endocrinol.*, **85**, 753–9.
71 Van Herle, A.J. and Chopra, I.J. (1971) Thymic hyperplasia in Graves' disease. *J. Clin. Endocrinol. Metab.*, **32**, 140–6.
72 Mahaux, J.E., Chamla-Soumenkoff, J., Delcourt, R. *et al.* (1971) Painful enlargement of left subtrapezoid lymph nodes in Graves' disease. *Br. Med. J.*, **1**, 384.
73 Baxter, J.D. and Bondy, P.K. (1966) Hypercalcemia of thyrotoxicosis. *Ann. Intern. Med.*, **65**, 429–42.
74 Mallette, L.E. and Tuma, S.N. (1984) A new radioimmunoassay for the midregion of canine parathyroid hormone. *Mineral Electrol. Metabol.*, **10**, 43–7.
75 Mallette, L.E., Rubenfeld, S. and Silverman, V. (1985) A controlled study of the effects of thyrotoxicosis and propranolol treatment on mineral metabolism and parathyroid hormone immunoreactivity. *Metabolism*, **34**, 999–1006.
76 Cooper, D.S., Kaplan, M.M., Ridgway, E.C. *et al.* (1979) Alkaline phosphatase isoenzyme patterns in hyperthyroidism. *Ann. Intern. Med.*, **90**, 164–8.
77 Arem, R., Lim-Abrahan, M.A. and Mallette, L.E. (1986) Concomitant Graves' disease and primary hyperthyroidism: influence of hyperthyroidism on serum calcium and parathyroid hormone. *Am. J. Med.*, **80**, 693–8.
78 Christensson, T. (1977) Hyperparathyroidism and radiation therapy. *Ann. Intern. Med.*, **89**, 216–17.
79 Rao, S.D., Frame, B., Miller, M.J. *et al.* (1980) Hyperparathyroidism following head and neck irradiation. *Arch. Intern. Med.*, **140**, 205–7.
80 Rosen, I.B., Palmer, J.A., Rowen, J. *et al.* (1984) Induction of hyperparathyroidism by radioactive iodine. *Am. J. Surg.*, **148**, 441–5.
81 Fraser, S.A., Smith, D.A., Anderson, J.B. *et al.* (1975) Osteoporosis and fractures following thyrotoxicosis. *Lancet*, **1**, 981–3.
82 Fallon, M.D., Perry, H.M. III, Bergfeld, M. *et al.* (1983) Exogenous hyperthyroidism with osteoporosis. *Arch. Intern. Med.*, **143**, 442–4.
83 Ross, D.S., Neer, R.M., Ridgway, E.C. *et al.* (1987) Subclinical hyperthyroidism and reduced bone density as a possible result of prolonged suppression of the pituitary thyroid axis with L-thyroxine. *Am. J. Med.*, **82**, 1167–70.
84 Auwerx, J. and Bouillon, R. (1986) Mineral and bone metabolism in thyroid disease: a review. *Quart. J. Med.*, **232**, 737–52.
85 Clyde, H.R., Walsh, P.C. and English, R.W. (1976) Elevated plasma testosterone and gonadotropin levels in infertile males with hyperthyroidism. *Fertil. Steril.*, **27**, 662–6.
86 Becker, K.L., Winnacker, J.L., Matthews, M.J. *et al.* (1968) Gynecomastia and hyperthyroidism. An endocrine and histologic investigation. *J. Clin. Endocrinol Metab.*, **28**, 277–85.
87 Morgans, M.E. (1964) Hyperthyroidism, in *The Thyroid Gland*, Vol 2, (eds R.V. Pitt-Rivers and W.R. Trotter), Butterworth, London, p. 159.
88 Ochi, Y. and DeGroot, L.J. (1969) Vitiligo in Graves' disease. *Ann. Intern. Med.*, **71**, 935–40.
89 Wyse, E.P., McConahey, W.M., Woolner, L.B. *et al.* (1968) Ophthalmopathy without hyperthyroidism in patients with histologic Hashimoto's thyroiditis. *J. Clin. Endocrinol. Metab.*, **28**, 1623–9.
90 Rundle, F.F. and Pochin, E.E. (1944) The orbital tissues in thyrotoxicosis: a quantitative analysis relating to exophthalmos. *Clin. Sci.*, **5**, 51–74.
91 Hufnagel, T.J., Hickey, W.F., Cobbs, W.H. *et al.* (1984) Immunohistochemical and ultrastructural studies on the exenterated orbital tissues of a patient with Graves' disease. *Ophthalmology*, **91**, 1411–19.
92 Werner, S.C., Coleman, D.J. and Franzen, L.A. (1974) Ultrasonographic evidence of a consistent orbital involvement in Graves' disease. *N. Engl. J. Med.*, **290**, 1447–50.
93 Forrester, J.V., Sutherland, G.R. and McDougall, I.R. (1977) Dysthroid ophthalmopathy orbital evaluation with B-scan ultrasonography. *J. Clin. Endocrinol. Metab.*, **45**, 1353–6.
94 Enzmann, D.R., Donaldson, S.S. and Kriss, J.P. (1979) Appearance of Graves' disease on orbital computed tomography. *J. Comput. Assist. Tomogr.*, **3**, 815–19.
95 Konishi, J., Hermann, M.M. and Kriss, J.P. (1974) Binding of thyroglobulin and thyroglobulin-antithyroglobulin immune complex to extraocular muscle membranes. *Endocrinol.*, **95**, 434–6.
96 Tao, T.W., Cheng, P., Pham, H. *et al.* (1986) Monoclonal antithyroglobulin antibodies

derived from immunisation of mice with human eye muscle and thyroid membranes. *J. Clin. Endocrinol. Metab.*, **63**, 577–82.
97 Kriss, J.P. (1970) Radioiosotope thyroidolymphography in patients with Graves' disease. *J. Clin. Endocrinol. Metab.*, **31**, 315–24.
98 Werner, S.C. (1969) Classification of the eye changes of Graves' disease. *J. Clin. Endocrinol. Metabol.*, **29**, 982–4.
99 Donaldson, S.S., Bagshaw, M.A. and Kriss, J.P. (1973) Supervoltage orbital radiotherapy for Graves' ophthalmopathy. *J. Clin. Endocrinol. Metab.*, **37**, 276–85.
100 Gorman, C.A. (1983) Temporal relationship between onset of Graves' ophthalmopathy and diagnosis of thyrotoxicosis. *Mayo Clin. Proc.*, **58**, 515–19.
101 Marcocci, C., Bartalena, L., Bogazzi, F. *et al.* (1989) Studies on the occurrence of ophthalmopathy in Graves' disease. *Acta Endocrinol.*, **120**, 473–8.
102 Kriss, J.P., McDougall, I.R., Donaldson, S.S. (1987) Non-thyroidal complications of Graves' disease: perspective on pathogenesis and treatment, in *Thyroid Autoimmunity*, (eds A. Pinchera, S.H. Ingbar, J.M. McKenzie and G.F. Fenzi), Plenum Publishing Corporation, New York and London, pp. 263–9.
103 Kriss, J.P., Petersen, I.A., Donaldson, S.S. *et al.* (1989) Supervoltage orbital radiotherapy for progressive Graves' ophthalmopathy: results of a twenty year experience. *Acta Endocrinol.*, **121** (suppl. 2), 154–9.
104 Gwinup, G., Elias, A.N. and Ascher, A.S. (1982) Effect on exophthalmos of various treatment methods of Graves' disease. *JAMA*, **247**, 2135–8.
105 Sridama, V. and De Groot, L.J. (1989) Treatment of Graves' disease and the course of ophthalmopathy. *Am. J. Med.*, **87**, 70–3.
106 De Juan, E., Hurley, D.B. and Sapira, J.D. (1980) Racial differences in normal values of proptosis. *Arch. Intern. Med.*, **140**, 1230–1.
107 Gamblin, G.T., Harper, D.G., Galentine, P. *et al.* (1983) Prevalence of increased intraocular pressure in Graves' disease – evidence of frequent subclinical ophthalmopathy. *N. Engl. J. Med.*, **308**, 420–4.
108 Werner, S.C. (1966) Prednisone in emergency treatment of malignat exophthalmos. *Lancet*, **1**, 1004–7.
109 Prummel, M.F., Mouritis, M.P.H., Berghout, A. *et al.* (1989) Prednisone and cyclosporine in the treatment of severe Graves' ophthalmopathy. *N. Engl. J. Med.*, **321**, 1353–9.
110 Jones, A. (1951) Orbital X-ray therapy of progressive exophthalmos. *Br. J. Radiol.*, **29**, 637–46.
111 Ogura, J.H., Wessler, S. and Avioli, L.V. (1971) Surgical approach to the ophthalmopathy of Graves' disease. *JAMA*, **216**, 1627–31.
112 Ogura, J.H. and Lucente, F.E. (1974) Surgical results of orbital decompression for malignant exophthalmos. *Laryngoscope*, **84**, 637–44.
113 McCord, C.D. Jr (1981) Orbital decompression for Graves' disease: exposure through lateral canthal and inferior fornix incision. *Ophthalmology*, **88**, 533–41.
114 Wolfe, S.A. (1977) A rationale for the surgical treatment of exophthalmos and exorbitism. *J. Maxillo-facial Surg.*, **5**, 249–57.
115 Wolfe, S.A. (1978) Modified three-wall orbital expansion to correct persistent exophthalmos or exorbitism. *Plastic and Reconstruct. Surg.*, **64**, 448–55.
116 Utech, C., Cordes, M., Pfannensteil, P. *et al.* (1987) Immunosuppressive treatment of Graves' ophthalmopathy with cyclosporin A and ciamexon, in *Thyroid Autoimmunity*, (eds A. Pinchera, S.H. Ingbar, J.M. McKenzie and G.F. Fenzi), Plenum Press, New York and London, pp. 541–4.
117 Dandona, P., Marshall, N.J., Bidey, S.P. *et al.* (1979) Successful treatment of exophthalmos and pretibial myxoedema with plasmpheresis. *Br. Med. J.*, **1**, 374–6.
118 Catz, B. and Perzik, S.L. (1969) Total thyroidectomy in the management of thyrotoxic and euthyroid Graves' disease. *Am. J. Surg.*, **118**, 434–9.
119 Kriss, J.P. (1980) Pathogenesis and treatment of Graves' ophthalmopathy. *Thyroid Today* **7** (2), 1–7.
120 Jacobson, D.H. and Gorman, C.A. (1984) Endocrine ophthalmopathy: current ideas concerning etiology, pathogenesis, and treatment. *Endocrin. Rev.*, **5**, 200–20.
121 Shine, B., Edwards, O.M. and Weetman, A.P. (1989) Graves' ophthalmopathy and smoking. *Acta Endocrinol.*, **121** (suppl. 2), 182–4.
122 Austin-Seymour, M.M., Donaldson, S.S., Egbert, P.R. *et al.* (1985) Radiotherapy of lymphoid diseases of the orbit. *Int. J. Radiat. Oncol. Biol. Phys.*, **11**, 371–9.
123 Kriss, J.P. (1987) Pathogenesis and treatment of pretibial myxedema. *Endocrinol. Metab. Clin. N. Am.*, **16**, 409–15.
124 Cheung, H.S., Nicoloff, J.T., Kamiel, M.B. *et al.* (1978) Stimulation of fibroblast biosynthe-

tic activity by serum of patients with pretibial myxedema. *J. Invest. Dermatol.*, **71**, 12–17.
125 Sissons, J.C. (1968) Hyaluronic acid in localised myxedema. *J. Clin. Endocrinol. Metab.*, **28**, 433–41.
126 Kriss, J.P., Pleshakov, V., Rosenblum, A. *et al.* (1967) Therapy with occlusive dressings of pretibial myxedema with fluocinolone acetonide. *J. Clin. Endocrinol. Metab.*, **27**, 595–604.
127 Freedberg, I.M. and Vogel, L.N. (1986) The skin, in *Werner's The Thyroid*, 5th edn, (eds S.H. Ingbar and L.E. Braverman), The Lippincott Company, Philadelphia, pp. 811–16.
128 Goette, D.K. (1980) Thyroid acropachy. *Arch. Dermatol.*, **116**, 205–6.
129 Gimlette, T.M.D. (1960) Thyroid acropachy. *Lancet*, **1**, 22–4.
130 Thomas, H.M. Jr (1933) Acropachy: secondary subperiosteal new bone formation. *Arch. Intern. Med.*, **51**, 571–87.
131 Nixon, D. and Samols, E. (1970) Acral changes associated with thyroid diseases. *JAMA*, **212**, 1175–81.
132 Diamond, M.T. (1959) The syndrome of exophthalmos, hypertrophic osteoarthropathy and localized myxedema: A review of the literature and report of a case. *Ann. Intern. Med.*, **50**, 206–19.
133 Parker, L.N., Wu, S-Y., Lai, M.K. *et al.* (1982) The early diagnosis of atypical thyroid acropachy. *Arch. Intern. Med.*, **142**, 1749–51.
134 Siegel., R., Thrall, J. and Sisson, J. (1976) ^{99m}Tc-pyrophosphate scan and radiographic correlation in thyroid acropachy: case report. *J. Nucl. Med.*, **17**, 791–3.
135 Engel, A.G. (1984) Myasthenia and myasthenic syndromes. *Ann. Neurol.*, **16**, 519–34.
136 Naqui, J. (1967) Co-existence of Addison's disease and thyrotoxicosis. *Postgrad. Med. J.*, **43**, 129.
137 Goldring, S.R. and Krane, S.M. (1986) The skeletal system, in *Werner's The Thyroid*, 5th edn, (eds S.H. Ingbar and L.E. Braverman) The Lippincott Company, Philadelphia, pp. 930–48.
138 Ross, D.S. (1988) Subclinical hyperthyroidism: possible danger of overzealous thyroxine replacement therapy. *Mayo Clin. Proc.*, **63**, 1223–9.
139 Wilson, G.M. (1967) *The treatment of thyrotoxicosis*, Symposium Thyroid Disease and Calcium Metabolism, Royal College of Physicians, Publication 33, Edinburgh, pp. 51–76.
140 Taurog, A. (1976) The mechanism of action of the thioureylene antithyroid drugs. *Endocrinol.*, **98**, 1031–46.
141 Marchant, B., Lees, J.F.H. and Alexander, W.D. (1978) Antithyroid drugs. *Pharmacol. Ther. B.*, **3**, 305–48.
142 Lazarus, J.H., Marchant, B., Alexander, W.D. *et al.* (1975) ^{35}S-antithyroid drug concentration and organic binding of iodine in the human thyroid. *Clin. Endocrinol.*, **4**, 609–15.
143 Cooper, D.S. (1986) Which antithyroid drug? *Am. J. Med.*, **80**, 1165–8.
144 Bouma, D.J. and Kammer, H. (1980) Single daily dose methimazole treatment of hyperthyroidism. *West J. Med.*, **132**, 13–15.
145 MacFarlane, I.A., Davies, D., Longson, D. *et al.* (1983) Single daily dose short term carbimazole therapy for hyperthyroid Graves' disease. *Clin. Endocrinol.*, **18**, 557–61.
146 Gwinup, G. (1978) Prospective randomized comparison of propylthiouracil. *JAMA*, **239**, 2457–9.
147 McDougall, I.R. and Greig, W.R. (1972) Combined carbimazole-^{131}I therapy for thyrotoxicosis. *Scot. Med. J.*, **17**, 57–61.
148 Crooks, J. and Wayne, E.J. (1960) A comparison of potassium perchlorate, methylthiouracil and carbimazole in the treatment of thyrotoxicosis. *Lancet*, **1**, 401–4.
149 Cooper, D.S. (1985) Propylthiouracil levels in hyperthyroid patients unresponsive to large doses: evidence of poor patient compliance. *Ann. Intern. Med.*, **102**, 328–31.
150 Wood, L.C., Peterson, M. and Ingbar, S.H. (1972) Delayed hypothyroidism following antithyroid therapy in Graves' disease *Clin. Res.*, **20**, 625.
151 Solomon, B.L., Evaul, J.E., Burman, K.D. *et al.* (1987) Remission rates with antithyroid drug therapy: continuing influence of iodine intake? *Ann. Intern. Med.*, **102**, 510–12.
152 Alexander, W.D., Harden, R. McG., Koutras, D.A. *et al.* (1965) Influence of iodine intake after treatment with antithyroid drugs. *Lancet*, **2**, 866–8.
153 Wartofsky, L. (1973) Low remission after therapy for Graves' disease: possible relation of dietary iodine with antithyroid drugs. *JAMA*, **226**, 1083–8.
154 Greer, M.A., Kammer, H. and Bouma, D.J. (1977) Short-term antithyroid drug therapy for the thyrotoxicosis of Graves' disease. *N. Engl. J. Med.*, **297**, 173–6.
155 Burr, W.A., Fitzgerald, M.G. and Hoffenberg, R. (1979) Relapse after short-term antithyroid therapy of Graves' disease. *N. Engl. J. Med.*, **300**, 200.
156 Slingerland, D.W. and Burrows, B.A. (1979)

Long-term antithyroid treatment in hyperthyroidism. *JAMA*, **242**, 2408–10.
157 Cooper, D.S. (1984) Antithyroid drugs. *N. Engl. J. Med.*, **311**, 1353–62.
158 Rosove, M.H. (1977) Agranulocytosis and antithyroid drugs. *West J. Med.*, **126**, 339–43.
159 Cooper, D.S., Goldminz, D., Levin, A.A. *et al.* (1983) Agranulocytosis associated with antithyroid drugs: effects of patient age and drug dose. *Ann. Intern. Med.*, **98**, 26–9.
160 International agranulocytosis and aplastic anaemia study (1980) Risk of agranulocytosis and aplastic anaemia in relation to use of antithyroid drugs. *Br. Med. J.*, **297**, 262–5.
161 Weiss, M., Hassin, D. and Bank, H. (1980) Propylthiouracil-induced hepatic damage. *Arch. Intern. Med.*, **140**, 1184–5.
162 Hanson, J.S. (1984) Propylthiouracil and hepatitis: two cases and a review of the literature. *Arch. Intern. Med.*, **144**, 994–6.
163 Orrego, H., Blake, J.E., Blendis, L.M. *et al.* (1987) Long-term treatment of alcoholic liver disease with propylthiouracil. *N. Engl. J. Med.*, **317**, 1421–7.
164 Mazzaferri, E.L., Reynolds, J.C., Young, R.L. *et al.* (1976) Propranolol as primary therapy for thyrotoxicosis. Results of a long-term prospective trial. *Arch. Intern. Med.*, **136**, 50–6.
165 Jones, M.K., Birthwell, J., Owens, D.R. *et al.* (1981) Beta-adrenergic blocking drugs and thyroid hormones in hyperthyroid subjects. *Postgrad. Med. J.*, **57**, 207–9.
166 Eriksson, M., Rubenfeld, S., Garber, A.J. *et al.* (1977) Propranolol does not prevent thyroid storm. *N. Engl. J. Med.*, **296**, 263–4.
167 Rubenfeld, S., Silverman, V.E., Welch, K.M.A. *et al.* (1979) Variable plasma propranolol levels in thyrotoxicosis. *N. Engl. J. Med.*, **300**, 353–4.
168 Burrow, G.N., Burke, W.R., and Himmelhoch, J.M. (1971) Effect of lithium on thyroid function. *J. Clin. Endocrinol. Metab.*, **32**, 647–52.
169 James, R.J. and Darken, R.A. (1976) Lithium carbonate and hypothyroidism. *Med. J. Aust.*, **1**, 266–7.
170 Spaulding, S.W., Burrow, G.N., Bermudez, F. *et al.* (1972) The inhibitory effect of lithium on thyroid hormone release in both euthyroid and thyrotoxic patients. *J. Clin. Endocrinol. Metab.*, **35**, 905–11.
171 Kristensen, O., Andersen, H.H. and Pallisgaard, G. (1976) Lithium carbonate in the treatment of thyrotoxicosis: a controlled trial. *Lancet*, **1**, 603–5.
172 Turner, J.C. and Brownlie, B.E.W. (1976) Lithium and thyrotoxicosis. *Lancet*, **2**, 904.
173 Turner, J.G., Brownlie, B.E.W., Rogers, T.G.H. (1976) Lithium as an adjuvant to radioiodine therapy for thyrotoxicosis. *Lancet*, **1**, 614–15.
174 Hertz, S. and Roberts, A. (1942) Application of radioactive iodine in the therapy of Graves' disease. *J. Clin, Invest.*, **26**, 624.
175 Hamilton, J.G. and Lawrence, J.H. (1942) Recent clinical developments in the therapeutic application of radiophosphorus and radioiodine. *J. Clin. Invest.*, **26**, 624.
176 Chapman, E.M. (1983), History of the discovery and early use of radioactive iodine. *JAMA*, **250**, 2042–4.
177 Chapman, E.M. and Evans, R.D. (1946) The treatment of hyperthyroidism with radioactive iodine. *JAMA*, **131**, 86–91.
178 Greig, W.R., Smith, J.F.B., Gillespie, F.C. *et al.* (1969) Iodine-125 for thyrotoxicosis. *Lancet*, **1**, 755–7.
179 Chapman, E.M. and Maloof, F. (1955) The use of radioactive iodine in the diagnosis and treatment of hyperthyroidism: ten years' experience. *Medicine*, **34**, 261–321.
180 Beling, U. and Einhorn, J. (1961) Incidence of hypothyroidism and recurrences following ^{131}I treatment of hyperthyroidism. *Acta Radiologica*, **56**, 275–88.
181 Green, M. and Wilson, G.M. (1964) Thyrotoxicosis treated by surgery or ^{131}I: with special reference to the development of hypothyroidism. *Br. Med. J.*, **1**, 1005–10.
182 Dunn, J.T. and Chapman, E.M. (1964) Rising incidence of hypothyroidism after radioactive iodine. *N. Engl. J. Med.*, **271**, 1037–42.
183 Nofal. M.M., Beierwaltes, W.H. and Patno, M.E. (1966) Treatment of hyperthyroidism with sodium iodide ^{131}I. *JAMA*, **197**, 605–10.
184 Bronsky, D., Kiamko, R.T. and Waldstein, S.S. (1968) Post-therapeutic myxedema. *Arch. Intern. Med.*, **121**, 113–17.
185 Blahd, W.H. and Hays, M.T. (1972) Graves' disease in the male. *Arch. Intern. Med.*, **129**, 33–40.
186 Teczan, U.P., Frelick, R.N. and Mecklenburg, R.C. (1967) Low dose therapy for hyperthyroidism. *Del. Med. J.*, **39**, 142–6.
187 Zellman, H.E., Matiz, H., Bartels, E.C. *et al.* (1968) Radioactive iodine in hyperthyroidism *Lahey Clin. Foun. Bull.*, **17**, 137–43.
188 Goolden, A.N.C. and Fraser, T.R. (1969)

Treatment of thyrotoxicosis with low doses of radioactive iodine. *Br. Med. J.*, **3**, 442–3.

189 Rapoport, B., Caplan, R. and DeGroot, L.J. (1973) Low-dose sodium iodide I–131 therapy in Graves' disease. *JAMA*, **224**, 1610–13.

190 Cevallos, J.L., Hagen, G.A., Maloof, F. *et al.* (1974) Low-dosage ^{131}I therapy of thyrotoxicosis (diffuse goiters). *N. Engl. J. Med.*, **290**, 141–3.

191 Lowe, D.C., Montgomery, D.A.D., Hadden, D.R. *et al.* (1971) *Hyperthyroidism treated with propranolol and a 2.5 millicurie dose of radioactive iodine*, Paper 18, Fourth European Thyroid Association Meeting, Berne, Switzerland.

192 Von Hofe, S.E., Dorfman, S.G., Carretta, R.F. *et al.* (1978) The increasing incidence of hypothyroidism within one year after radioiodine therapy for toxic diffuse goiter. *J. Nucl. Med.*, **19**, 180–4.

193 Kendall-Taylor, P., Keir, M.J. and Ross, W.M. (1984) Ablative radioiodine therapy for hyperthyroidism: long term follow up study. *Br. Med. J.*, **289**, 361–3.

194 Roudebush, C.P., Hoye, K.E. and DeGroot, L.J. (1977) Compensated low-dose ^{131}I therapy of Graves' disease. *Ann. Intern. Med.*, **87**, 441–3.

195 Scott, G.R., Forfar, J.C. and Toft, A.D. (1984) Graves' disease and atrial fibrillation: the case for even higher doses of therapeutic iodine-131. *Br. Med. J.*, **289**, 399–400.

196 Cunnien, A.J., Hay, I.D., Gorman, C.A. *et al.* (1982) Radio-iodine induced hypothyroidism in Graves' disease: factors associated with the increasing incidence. *J. Nucl. Med.*, **23**, 978–83.

197 Sridama, V., McCormick, M., Kaplan, E.L. *et al.* (1984) Long-term follow-up of compensated low-dose ^{131}I therapy for Graves' disease. *N. Engl. J. Med.*, **311**, 426–32.

198 Smith, R.N. and Wilson, G.M. (1967) Clinical trial of different doses of ^{131}I in the treatment of thyrotoxicosis. *Br. Med. J.*, **1**, 129–32.

199 Holm, L-E., Lundell, G., Israelsson, A. *et al.* (1982) Incidence of hypothyroidism occurring long after iodine–131 therapy for hyperthyroidism. *J. Nucl. Med.*, **23**, 103–7.

200 Holm, L-E. (1982) Changing annual incidence of hypothyroidism after iodine–131 therapy for hyperthyroidism. 1951–75. *J. Nucl. Med.*, **23**, 108–12.

201 Staffurth, J.S. (1987) Hypothyroidism following radioiodine treatment of thyrotoxicosis. *J. Roy. Coll. Phys.*, **21**, 55–7.

202 Shafer, R.B. and Nuttall, F.Q. (1971) Thyroid crisis induced by radioactive iodine. *J. Nucl. Med.*, **12**, 262–4.

203 Hayek, A. (1978) Thyroid storm following radioiodine for thyrotoxicosis. *J. Pediatrics*, **93**, 978–80.

204 McDermott, M.T., Kidd, G.S., Dodson, L.E. Jr. *et al.* (1983) Radioiodine-induced thyroid storm: case report and literature review. *Am. J. Med.*, **75**, 353–9.

205 Crooks, J., Buchanan, W.W., Wayne, E.J. *et al.* (1960) Effect of pretreatment with methylthiouracil on results of ^{131}I therapy. *Br. Med. J.*, **1**, 151–4.

206 Steinbach, J.J., Donoghue, G.D., Goldman, J.K. (1979) Simultaneous treatment of toxic diffuse goiter with I–131 and antithyroid drugs: a prospective study. *J. Nucl. Med.*, **20**, 1263–7.

207 Cassidy, C.E. and Astwood, E.B. (1959) Evaluation of radioactive iodine (^{131}I) as a treatment for thyrotoxicosis. *N. Engl. J. Med.*, **261**, 53–8.

208 Sheeler, L.B. and Skillern, P.G. (1984) Radioiodine-induced thyroid storm, a point of controversy (letter). *Am. J. Med.*, **76**, A69.

209 Volpe, R., Schatz, D.L., Scott, A. *et al.* (1960) Radioactive iodine in the treatment of hyperthyroidism. *Can. Med. Ass. J.*, **83**, 1407–13.

210 Goolden, A.W., Mallard, J.R. and Farran, H.E.A. (1957) Radiation sialitis following radioiodine therapy. *Br. J. Radiol.*, **30**, 210–12.

211 Rigler, R.G. and Scanlon, P.W. (1955) Radiation parotitis from radioactive iodine therapy. *Mayo Clin. Proc.*, **30**, 149–53.

212 Silver, S. (1968) Treatment of hyperthyroidism with ^{131}I, in *Radioactive Nuclides in Medicine and Biology*, vol 2, 3rd edn, Lea and Febiger, Philadelphia, pp. 144–94.

213 Snyder, S. (1978) Vocal cord paralysis after radioidine therapy. *J. Nucl. Med.*, **19**, 975–6.

214 Robson, A.M. (1981) Vocal-cord paralysis after treatment of thyrotoxicosis with radioidine. *Br. J. Radiol.*, **54**, 632.

215 Freeman, M., Giuliani, M., Schwartz, E. *et al.* (1969) Acute thyroiditis, thyroid crisis, and hypocalcemia following radioactive iodine therapy. *N.Y. State J. Med.*, **69**, 2036–41.

216 Gilbert-Dreyfus, Zara, M., Gali, P. (1958) Cateracte tétanique après IRA-thérapie. *Semaine Hop. Paris*, **34**, 1301–4.

217 Townsend, J. (1962) Hypoparathyroidism following radioactive iodine therapy for intractable angina pectoris. *Ann. Intern. Med.*, **55**, 662–3.

218 Committee on the Biological Effects of Ionizing Radiation (1980) *The Effects on Populations of Exposure to Low Levels of Ionizing Radiation*, National Academy of Sciences, Washington DC.

219 Saenger, E.L., Thoma, G.E. and Tomkins, E.A. (1968) Incidence of leukemia following treatment of hyperthyroidism: preliminary report of the Cooperative Thyrotoxicosis Follow-up Study, *JAMA*, **205**, 147–54.

220 Pochin, E.E. (1960) Leukaemia following radioactive treatment of thyrotoxicosis. *Br. Med. J.*, **2**, 1545–50.

221 Werner, S.C., Gittleshon, A.M. and Brill, A.B. (1961) Leukemia following radioiodine therapy of hyperthyroidism. *JAMA*, **177**, 646–9.

222 McCormack, K.R. and Sheline, G.E. (1963) Leukemia after radioiodine therapy for hyperthyroidism. *Calif. Med.*, **98**, 267–8.

223 Boyd, E., Buchanan, W.W. and Lennox, B. (1966) Damage to chromosomes by therapeutic doses of radioiodine. *Lancet*, **1**, 977–8.

224 MacIntyre, M.N. and Dobyns, B.M. (1962) Anomalies in chromosomes of the circulating leukocytes in man following large doses of radioactive iodine. *J. Clin. Endocrinol. Metab.*, **22**, 1171–81.

225 Nofal, N.M. and Beierwaltes, W.H. (1964) Persistent chromosomal aberrations following radioiodine therapy. *J. Nucl. Med.*, **5**, 840–50.

226 Cantolino, S.J., Schmickel, R.D., Ball, M. *et al.* (1966) Persistent chromosomal aberrations following radioiodine therapy for thyrotoxicosis. *N. Engl. J. Med.*, **275**, 739–45.

227 Boyd, E., Ferguson-Smith, M.A., McDougall, I.R. *et al.* (1974) Chromosome breakage in human peripheral lymphocytes after radioactive iodine ^{125}I therapy. *Radiation Res.*, **57**, 482–7.

228 Dobyns, B.M., Sheline, G.E., Workman, J.B. *et al.* (1974) Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the Cooperative Thyrotoxicosis Therapy Follow-up Study. *J. Clin. Endocrinol. Metab.*, **38**, 976–98.

229 Holm, L-E., Dahlqvist, I., Israelsson, A. *et al.* (1980) Malignant thyroid tumors after iodine-131 therapy. A retrospective cohort study. *N. Engl. J. Med.*, **303**, 188–91.

230 Holm, L-E. (1984) Malignant disease following iodine-131 therapy in Sweden, in *Radiation Carcinogenesis: Epidemiology and Biological Significance*, (eds J.D. Boice Jr and J.F. Fraument Jr) Raven Press, New York, pp. 263–71.

231 McDougall, I.R., Nelsen, T.S. and Kempson, R.L. (1981) Papillary carcinoma of the thyroid seven years after I–131 therapy for Graves' disease. *Clin. Nucl. Med.*, **6**, 368–71.

232 Tomlison, C., Knowles, K.W. and McDougall, I.R. (1991) Papillary cancer in a patient treated with radioiodine for Graves' hyperthyroidism: case report and a review of the risk. *Clin. Nuc. Med.*, in press.

233 Hoffman, D.A., McConahey, W.M., Diamond, E.L. *et al.* (1982) Mortality in women treated for hyperthyroidism. *Am. J. Epidemiol.*, **115**, 243–54.

234 Hoffman, D.A. (1984) Late effects of I–131 therapy in the United States, in *Radiation Carcinogenesis; Epidemiology and Biological Significance*, (eds J.D. Boice Jr and J.F. Fraument Jr), Raven Press, New York, pp. 273–80.

235 Robertson, J.S. and Gorman, C.A. (1976) Gonadal radiation dose and its genetic significance in radioiodine therapy of hyperthyroidism. *J. Nucl. Med.*, **17**, 826–35.

236 Henneman, G., Krenning, E.P. and Sankaranarayanan, K. (1986) Place of radioactive iodine in the treatment of thyrotoxicosis. *Lancet*, **1**, 1369–72.

237 Chapman, E.M. (1971) Treatment of hyperthyroidism with radioactive iodine, in *Nuclear Medicine*, 2nd edn, (ed. W.H. Blahd), McGraw-Hill Book Company, New York, pp. 711–34.

238 Safa, A.M., Schumaker, O.P. and Rodriguez-Antunez, A. (1975) Long-term follow-up results in children and adolescents treated with radioactive iodine (^{131}I) for hyperthyroidism. *N. Engl. J. Med.*, **292**, 167–71.

239 Gillespie, F.C., Orr, J.S. and Greig, W.R. (1970) Microscopic dose distribution from ^{125}I in the toxic thyroid gland and its relation to therapy. *Br. J. Radiol.*, **43**, 40–7.

240 McDougall, I.R. and Greig, W.R. (1976) ^{125}I therapy in Graves' disease: long-term results in 355 patients. *Ann. Intern. Med.*, **85**, 720–3.

241 Lewitus, Z., Lubin, E., Rechnic, J. *et al.* (1971) Treatment of thyrotoxicosis with ^{125}I and ^{131}I. *Sem. Nucl. Med.*, **1**, 411–21.

242 Weidinger, P., Johnson, P.M. and Werner, S.C. (1974) Five years' experience with iodine-125 therapy of thyrotoxic Graves' disease. *Lancet*, **2**, 74–7.

243 Siemsen, J.K., Wallack, M.S., Martin, R.B. *et al.* (1974) Early results of ^{125}I therapy of thyrotoxic Graves' disease. *J. Nucl. Med.*, **15**, 257–60.

244 NRCP Report No. 37 (1970) *Precautions in the*

Management of Patients who have Received Therapeutic Amounts of Radionuclides, October 1, and second reprinting 15 March 1978.

245 Stoffer, S.S., Hamburger, J.I. (1976) Inadvertent ^{131}I therapy for hyperthyroidism in the first trimester of pregnancy. *J. Nucl. Med.*, **17**, 146–9.

246 Mountford, P.J. and Coakley, A.J. (1989) A review of the secretion of radioactivity in human breast milk: data. quantitative analysis and recommendations. *Nucl. Med. Comm.*, **10**, 15–27.

247 Halstead, S. (1920) The operative story of goiter; the author's operation, *Johns Hopkins. Hosp. Rep.*, **19**, 71–257.

248 Mansberger, A.R. (1988) One hundred years of surgical management of hyperthyroidism. *Ann. Surg.*, **207**, 724–9.

249 Mayo, C.H. (1905) Goiter: with preliminary report of one hundred and eighty-two operations on the thyroid. *Trans South Surg. Gyn. Assoc.*, **18**, 145–66.

250 Mayo. C.H. (1908) A consideration of the mortality in one thousand operations for goiter. *Trans South Surg. Gyn. Assoc.*, **21**, 275–87.

251 Lahey, F.H. (1931) How much tissue should be removed in toxic goiter? *Trans South Surg. Assoc.*, **44**, 258–70.

252 Plummer, H.S. (1923) Results of administering iodine to patients having exophthalmic goiter. *JAMA*, **80**, 1955.

253 Reeve, T.S. (1988) Surgical treatment for thyrotoxicosis. *Br. J. Surg.*, **75**, 833–4.

254 Green, M. and Wilson, G.M. (1964) Thyrotoxicosis treated by surgery or iodine-131 with special reference to the development of hypothyroidism. *Br. Med. J.*, **1**, 1005–10.

255 Bowers, R.F. (1966) Surgical treatment of hyperthyroidism: follow up of 103 cases. *Am. Surgeon*, **32**, 89–95.

256 McNeil, A.D. and Thomson, J.A. (1968) Long-term follow up of surgically treated thyrotoxic patients. *Br. Med. J.*, **3**, 643–6.

257 Buchanan, W.W., Koutras, D.A., Crooks, J. *et al.* (1962) The clinical significance of the complement fixation test in thyrotoxicosis. *J. Endocrinol.*, **24**, 115–25.

258 Irvine, W.J., MacGregor, A.G. and Stuart, A.E. (1962) The prognostic significance of thyroid antibodies in the management of thyrotoxicosis. *Lancet.*, **2**, 843–7.

259 Greene, R. (1950) The significance of lymphadenoid changes in the thyroid gland. *J. Endocrinol.*, **7**, 1–6.

260 Olsen, W.R., Nishiyama, R.H., Graber, L.W. *et al.* (1970) Thyroidectomy for hyperthyroidism. *Arch. Surg.*, **101**, 175–80.

261 Hedley, A.J., Flemming, C.J., Chester, M.I. *et al.* (1970) Surgical treatment of thyrotoxicosis. *Br. Med. J.*, **1**, 519–23,

262 Hedley, A.J., Ross, I.P., Beck, J.S. *et al.* (1971) Recurrent thyrotoxicosis after subtotal thyroidectomy. *Br. Med. J.*, **4**, 258–61.

263 Lee, T.C., Coffey, R.J., Currier, B.M. *et al.* (1982) Propranolol and thyroidectomy in the treatment of thyrotoxicosis. *Ann. Surg.*, **195**, 766–72.

264 Bradley, E.L. III, Di Girolamo, M. and Tarcan, Y. (1980) Modified subtotal thyroidectomy in the management of Graves' disease. *Surgery*, **87**, 623–9.

265 Ozoux, J.P., de Calan, L., Portier, G. *et al.* (1988) Surgical treatment of Graves' disease. *Am. J. Surg.*, **156**, 177–81.

266 McLarty, D.G., Alexander, W.D., Harden, R. McG. *et al.* (1969) Results of treatment of thyrotoxicosis after post-operative relapse. *Br. Med. J.*, **3**, 200–3.

267 Gould, E.A., Hirsch, E., Brecher, I. *et al.* (1965) Complications arising in the course of thyroidectomy. *Arch. Surg.*, **90**, 81–5.

268 Painter, N.S. (1960) The results of surgery in the treatment of toxic goitre: a review of 172 cases. *Br. J. Surg.*, **48**, 291–6.

269 Riddell, V. (1965) The selection of patients for thyroidectomy. *Br. J. Surg.*, **52**, 721–7.

270 Wade, J.H.S. (1965) Three major complications of thyroidectomy. *Br. J. Surg.*, **52**, 727–31.

271 Michie, W., Pegg, C.A.S. and Bewsher, P.D. (1972) Prediction of hypothyroidism after partial thyroidectomy for thyrotoxicosis. *Br. Med. J.*, **1**, 13–17.

272 McDougall, I.R. and Bayer, M.F. (1986) Should a woman taking propylthiouracil breast feed? *Clin. Nucl. Med.*, **11**, 249–50.

273 Michie, W., Hammer-Hodges, D.W., Pegg, C.A.S. *et al.* (1974) Beta-blockade and partial thyroidectomy for thyrotoxicosis. *Lancet*, **1**, 1009–11.

274 Toft, A.D., Irvine, W.J., Sinclair, I. *et al.* (1978) Thyroid function after surgical treatment of thyrotoxicosis: a report of 100 cases treated with propranolol before operation. *N. Engl. J. Med.*, **298**, 643–7.

275 Jamison, M. and Done, H.J. (1979) Postop thyrotoxic crisis in a patient prepared for thyroidectomy with propranolol. *Br. J. Clin. Pract.*, **33**, 82–3.

276 Feek, C.M., Sawers, J.S., Irvine, W.J. *et al.* (1980) Combination of potassium iodide and

propranolol in preparation of patients with Graves' disease for thyroid surgery. *N. Engl. J. Med.*, **302**, 883–5.
277 Unger, J., Couturier, E., Durez, M. *et al.* (1981) Failure to reach euthyroidism with potassium iodide and propranolol in preparation of a patient with Graves' disease for surgery, (letter). *J. Endocrinol Invest.*, **4**, 367.
278 Feek, C.M. and Toft, A.D. (1981) Response to previous reference. *J. Endocrinol. Invest.*, **4**, 367–8.
279 Plummer, H.S. (1913) The clinical and pathological relationships of hyperplastic and non hyperplastic goiter. *JAMA*, **61**, 650–1.
280 Hamburger, J.I. (1987) The autonomously functioning thyroid nodule: Goetsch's disease. *Endocrine Reviews*, **8**, 439–47.
281 Goetsch, E. (1916) Functional significance of mitochondria in toxic thyroid adenomata: preliminary report. *Johns Hopkins Hosp. Rep.*, **27**, 129–33.
282 Goetsch, E. (1918) Newer methods in the diagnosis of thyroid disorders: pathological and clinical. *N.Y. State J. Med.*, **18**, 259–67.
283 Boothby, W. (1921) Adenoma of the thyroid with hyperthyroidism (thyrotoxic adenoma). *Endocrinology*, **5**, 1–20.
284 Scott, R.S., Brownlie, B.E.W. and Bremner, J.M. (1978) Toxic autonomous thyroid nodule following neck irradiation. *Aust. N.Z.J. Med.*, **8**, 521–2.
285 Nagai, G.R., Pitts, W.C., Basso, L. *et al.* (1987) Scintigraphic hot nodules and thyroid cancer. *Clin. Nucl. Med.*, **12**, 123–7.
286 Blum, M., Shenkman, L. and Hollander, C.S. (1975) The autonomous nodule of the thyroid: correlation of patient age, nodule size and functional status. *Am. J. Med. Sci.*, **269**, 43–50.
287 Bransom, C.J., Talbot, C.H., Henry, L. *et al.* (1979) Solitary toxic adenoma of the thyroid. *Br. J. Surg.*, **66**, 590–5.
288 Burman, K.D., Earll, J.M., Johnson, M.C. *et al.* (1974) Clinical observations on the solitary autonomous thyroid nodule. *Arch. Intern. Med.*, **134**, 915–19.
289 Goldstein, R. and Hart, I.R. (1983) Follow-up of solitary autonomous thyroid nodules treated with ^{131}I. *N. Engl. J. Med.*, **309**, 1473–76.
290 Hamburger, J.I. (1980) Evolution of toxicity in solitary non toxic autonomously functioning nodules. *J. Clin. Endocrinol. Metab.*, **50**, 1089–93.
291 Psarras, A., Papadopoulos, S.H., Livadas, D. *et al.* (1972) The single thyroid nodule. *Br. J. Surg.*, **59**, 545–8,
292 Ramsay, I., Marsden, P., Richardson, P.J. *et al.* (1972) Thyroid 'hot' nodules. *Postgrad. Med, J.*, **48**, 577–83.
293 Blum, M. and Nocero, M.A. (1974) Spontaneous resolution of a euthyroid autonomous nodule of the thyroid. *Am. J. Med. Sci.*, **264**, 49–54.
294 Soin, J.S., Beal, W. and Burdine, J.A. (1974) Disappearance of autonomous thyroid nodule under TSH stimulation. *J. Nucl. Med.*, **15**, 1209–11.
295 Kammer, H. and Loveless, M.D. (1978) Disappearance of a hyperfunctioning thyroid nodule following TSH stimulation. *J. Nucl. Med.*, **19**, 1149–50.
296 McCormack, K.R. and Sheline, G.E. (1967) Long-term studies of solitary autonomous thyroid nodules. *J. Nucl. Med.*, **8**, 701–8.
297 Silverstein, G.E., Burke, G. and Cogan, R. (1967) The natural history of the autonomously hyperfunctioning thyroid nodule. *Ann. Intern. Med.*, **67**, 539–48.
298 Wiener, J.D. and De Vries, A.A.A. (1979) On the natural history of Plummer's disease. *Clin. Nucl. Med.*, **4**, 181–90.
299 Hamburger, J.I. and Taylor, C.I. (1979) Transient thyrotoxicosis associated with acute hemorrhagic infarction of autonomously functioning thyroid nodule. *Ann. Intern, Med.*, **91**, 406–9.
300 Abe, K., Konno, M., Sato, T. *et al.* (1980) Hyperfunctioning thyroid nodules in children. *Am. J. Dis. Child*, **134**, 961–3.
301 Popma, B.H., Cloutier, M.D. and Hayles, A.B. (1973) Thyroid nodule producing T_3 toxicosis in a child. *Mayo Clin. Proc.*, **48**, 273–5.
302 Shambaugh, G.E., Quinn, J.L., Oyasu, R. *et al.* (1974) Disparate thyroid imaging. Combined studies with pertechnetate Tc-99m and radioactive iodine. *JAMA*, **228**, 866–9.
303 Barth, J.D., Bakker, W.H. and Henneman, G. (1978) Discrepancies between iodine and technetium thyroid scintigraphy. *JAMA*, **240**, 463–4.
304 Erjavic, M., Mavrin, T., Auersperg, M. *et al.* (1977) Comparative accumulation of ^{99m}Tc and ^{131}I in thyroid nodules: case report. *J. Nucl. Med.*, **18**, 346–7.
305 Sterling, K., Refetoff, S., Selenkow, H.A. (1970) Thyrotoxicosis due to elevated serum triiodothyronine levels. *JAMA*, **213**, 571–5.
306 Larsen, P.R. (1972) Triiodothyronine, review

of recent studies of its physiology and pathophysiology in man. *Metabol.*, **21**, 1073–92.
307 Means, J.H. (1970) *Thyroidology 1950* The Pharos Nov.
308 Miller, J.M. and Hamburger, J.I. (1965) The thyroid scintigram. 1. The hot nodule. *Radiol.*, **84**, 66–73.
309 Landgarten, S. and Spencer, R.P. (1973) A study of the natural history of 'hot' thyroid nodules. *Yale J. Biol. Med.*, **46**, 259–63.
310 Perlmutter, M. and Slater, S.L. (1956) Which nodular goiter should be removed? *N. Engl. J. Med.*, **255**, 65–71.
311 Livadas, D.P., Kotoulas, O.B., Bouropoulou, V. *et al.* (1977) The coexistence of thyroid malignancy with autonomous hot nodules of the thyroid. *Clin. Nucl. Med.*, **2**, 350–4.
312 Kendall, L.W. and Condon, R.E. (1969) Prediction of malignancy in solitary thyroid nodules. *Lancet*, **1**, 1071–3.
313 Becker, F.O., Economou, P.G. and Schwartz, T.B. (1963) The occurrence of carcinoma in 'hot' thyroid nodules. *Ann. Intern. Med.*, **58**, 877–82.
314 Sandler, M.P., Fellmeth, B., Salhany, K.E. *et al.* (1988) Thyroid carcinoma masquerading as a solitary benign hyperfunctioning nodule. *Clin. Nucl. Med.*, **13**, 410–15.
315 Eyre-Brook, I.A. and Talbot, C.H. (1982) The treatment of autonomously functioning thyroid nodules. *Br. J. Surg.*, **69**, 577–9.
316 Skillern, P.G., McCullagh, E.P. and Clamen, M. (1962) Radioiodine in diagnosis and therapy of hyperthyroidism. *Arch. Intern. Med.*, **110**, 888–97.
317 Gorman, C.A. and Robertson, J.S. (1978) Radiation dose in the selection of ^{131}I or surgical treatment for toxic thyroid adenoma. *Ann. Intern. Med.*, **89**, 85–90.
318 Ratcliffe, G.E., Cooke, S., Fogelman, I. *et al.* (1986) Radioiodine treatment of solitary functioning thyroid nodules. *Br. J. Radiol.*, **59**, 385–7.
319 Ross, D.S., Ridgway, E.C. and Daniels, G.H. (1984) Successful treatment of solitary toxic nodules with relatively low-dose iodine-131, with low prevalence of hypothyroidism. *Ann. Intern. Med.*, **101**, 488–90.
320 Wiener, J.D. (1985) Long-term follow-up after iodine-131 treatment for Plummer's disease (autonomous goiter). *Clin. Nucl. Med.*, **10**, 256–9.
321 Hamburger, J.I. and Hamburger, S.W. (1985) Diagnosis and management of large toxic multinodular nodules. *J. Nucl. Med.*, **26**, 888–92.
322 Hamburger, J.I. and Meier, D.A. (1971) Cancer following treatment of an autonomously functioning thyroid nodule with sodium iodide I–131. *Arch. Surg.*, **103**, 762–4.
323 Blum, M., Kranjac, T., Park, C.M. *et al.* (1976) Thyroid storm after cardiac angiography with iodinated contrast medium: occurrence in a patient with a previously euthyroid autonomous nodule of the thyroid. *JAMA*, **235**, 2324
324 Jensen, M.D., Gharib, H., Naessens, J.M. *et al.* (1986) Treatment of toxic multinodular goiter (Plummer's disease): surgery or radioiodine? *World J. Surg.*, **10**, 673–80.
325 Charkes, N.D. (1972) Graves' disease with functioning nodules (Marine Lenhart syndrome). *J. Nucl. Med.*, **13**, 885–92.
326 Cooper, D.S. (1988) Thyroid hormone and the skeleton: a bone of contention. *JAMA*, **259**, 3137–41.
327 Hay, I.D. (1988) Immunometric thyrotropin assays: current roles and future directions. *Mayo Clin. Proc.*, **63**, 1230–3.
328 Ross, D.S. (1988) Subclinical hyperthyroidism: possible danger of overzealous thyroxine replacement therapy. *Mayo Clin. Proc.*, **63**, 1223–9.
329 Fallon, M.D., Perry, H.M. III, Bergfeld, M. *et al.* (1983) Exogenous hyperthyroidism with osteoporosis. *Arch. Intern. Med.*, **143**, 442–4.
330 Paul, T.L., Kerrigan, J., Kelly, A.M. *et al.* (1988) Long-term L-thyroxine is associated with decreased hip bone density in premenopausal women. *JAMA*, **259**, 3137–41.
331 Gorman, C.A., Wahner, H.W. and Tauxe, W.N. (1969) Metabolic malingerers. Patients who deliberately induce or perpetuate a hypermetabolic or hypometabolic state. *Am. J. Med.*, **48**, 708–14.
332 Rose, E., Sanders, T.P., Webb, W.L. *et al.* (1969) Occult factitial thyrotoxicosis. Thyroxine kinetics and psychological evaluation in three cases. *Ann. Intern. Med.*, **71**, 309–15.
333 Harvey, R.F. (1973) Thyroxine 'addicts'. *Br. Med. J.*, **2**, 35–6.
334 Mariotti, S., Martino, E., Cupini, C. *et al.* (1982) Low serum thyroglobulin as a clue to the diagnosis of thyrotoxicosis factitia. *N. Engl. J. Med.*, **307**, 410–12.
335 Kinney, J.S., Hurwitz, E.S., Fishbein, D.B. *et al.* (1988) Community outbreak of thyrotoxicosis: epidemiology, immunogenetic charac-

teristics, and long-term outcome. *Am. J. Med.*, **84**, 10–18.
336 Hedberg, C.W., Fishbein, D.B., Janssen, R.S. *et al.* (1987) An outbreak of thyrotoxicosis caused by the consumption of bovine thyroid gland in ground beef. *N. Engl. J. Med.*, **316**, 993–8.
337 Shimaoka, K., Van Herle, A.J. and Dindogau, A. (1976) Thyrotoxicosis secondary to involvement of the thyroid gland with malignant lymphoma. *J. Clin. Endocrinol. Metab.*, **43**, 64–8.
338 Erikson, M., Ajmani, S.K. and Mallette, L.E. (1977) Hyperthyroidism from thyroid metastasis of pancreatic adenocarcinoma. *JAMA*, **238**, 1276–8.
339 Rosen, I.B., Strawbridge, H.G., Walfish, P.G. *et al.* (1978) Malignant pseudothyroiditis: a new clinical entity. *Am. J. Surg.*, **136**, 445–9.
340 Tibaldi, J.M., Shapiro, L.E. and Mahadevia, P.S. (1986) Thyroiditis mimicked by metastatic carcinoma to the thyroid. *Mayo Clin. Proc.*, **61**, 399–400.
341 Crapo, L. (1989) personal communication.
342 Watts, N.B. and Sewell, C.W. (1988) Carcinomatous involvement of thyroid presenting as subacute thyroiditis. *Am. J. Med. Sci.*, **296**, 126–8.
343 Oppenheim, A., Miller, M., Anderson, G.H. *et al.* (1983) Anaplastic thyroid cancer presenting with hyperthyroidism. *Am. J. Med.*, **75**, 702–4.
344 Kurtz, S.C. and Aber, R.C. (1982) Potassium iodide as a cause of prolonged fever. *Arch. Intern. Med.*, **142**, 1543–4.
345 Rasmussen, H. (1955) Iodide hypersensitivity in the etiology of periarteritis nodosa. *J. Allergy Clin. Immunol.*, **26**, 394–407.
346 Curd, J.G., Milgrom, H., Stevenson, D.D. *et al.* (1979) Potassium iodide sensitivity in four patients with hypocomplementemic vasculitis. *Ann. Intern. Med.*, **91**, 853–7.
347 Ingbar, S.H. (1972) Autoregulation of the thyroid: response to iodide excess and depletion. *Mayo Clin. Proc.*, **47**, 814–23.
348 Sternthal, E., Lipworth, L., Stanley, B. *et al.* (1980) Suppression of thyroid radioiodine uptake by various doses of stable iodine. *N. Engl. J. Med.*, **303**, 1083–8.
349 Braverman, L.E., Ingbar, S.H., Vagenakis, A.G. *et al.* (1971) Enhanced susceptibility to iodine myxedema in patients with Hashimoto's disease. *J. Clin. Endocrinol. Metab.*, **32**, 515–21.
350 Braverman, L.E., Woeber, K.A. and Ingbar, S.H. (1969) Induction of myxedema by iodide in patients euthyroid after radioiodine or surgical treatment of hyperthyroidism. *N. Engl. J. Med.*, **281**, 816–21.
351 Vagenakis, A.G., Wang, C., Burger, A. *et al.* (1972) Iodide-induced thyrotoxicosis in Boston. *N. Engl, J. Med.*, **287**, 523–7.
352 Wilson, G.M. (1964) Two Scottish doctors and the English bronchocele. *Scot. Med. J.*, **9**, 96–102.
353 Stewart, J.C. and Vidor, G.I. (1976) Thyrotoxicosis induced by iodine contamination of food – a common unrecognised condition. *Br. Med. J.*, **1**, 372–5.
354 Fradkin, J.E. and Wolff, J. (1983) Iodide-induced thyrotoxicosis. *Medicine*, **62**, 1–20.
355 Martino, E., Aghini-Lombardi, F., Marriotti, S. *et al.* (1987) Amiodarone: a common source of iodine-induced thyrotoxicosis. *Horm. Res.*, **26**, 158–71.
356 Blum, M., Weinberg, U., Shenkman, L. *et al.* (1974) Hyperthyroidism after iodinated contrast material. *N. Engl. J. Med.*, **291**, 24–5.
357 Fairhurst, B.J. and Naqvi, N. (1975) Hyperthyroidism after cholecystography. *Br. Med. J.*, **2**, 630.
358 Shetty, S.P., Murthy, G.G., Shreeve, W. *et al.* (1974) Hyperthyroidism after pyelography. *N. Engl. J. Med.*, **292**, 682.
359 Short, R. (1909) Jodoform and thyroidism. *Br. Med. J.*, **2**, 1469.
360 Miller, H.A., Farley, J.A. and Major, D.A. (1981) Topical iodine and hyperthyroidism. *Ann. Intern. Med.*, **95**, 121.
361 Reith, P.E. and Granner, D.K. (1985) Iodine-induced thyrotoxicosis in a woman with multinodular goiter taking levothyroxine. *Arch. Intern. Med.*, **145**, 355–6.
362 Edmunds, H.T. (1955) Acute thyroiditis from potassium iodide. *Br. Med. J.*, **1**, 354.
363 Melmed, S., Nademanee, K., Reed, A.W. *et al.* (1981) Hyperthyroxinemia with bradycardia and normal thyrotropin secretion after chronic amiodarone administration. *J. Clin. Endocrinol. Metab.*, **53**, 997–1001.
364 Nademanee, K., Singh, B.N., Hendrickson, J.A. *et al.* (1982) Pharmacokinetic significance of serum reverse T_3 levels during amiodarone treatment: a potential method for monitoring chronic drug therapy. *Circulation*, **66**, 202–11.
365 Martino, E., Aghini-Lombardi, F., Lippi, F. *et al.* (1985) Twenty-four hour radioactive iodine uptake in 35 patients with amiodarone associated thyrotoxicosis. *J. Nucl. Med.*, **26**, 1402–7.
366 Livadas, D.P., Koutras, D.A., Souvatzoglou,

A. *et al.* (1977) The toxic effects of small iodine supplements in patients with autonomous thyroid nodules. *Clin. Endocrinol.*, **7**, 121–7.

367 Martino, E., Safran, M., Aghini-Lombardi, F. *et al.* (1984) Environmental iodine intake and thyroid dysfunction during chronic amiodarone therapy. *Ann. Intern. Med.*, **101**, 28–34.

368 Gammage, M.D. and Franklyn, J.A. (1987) Amiodarone and the thyroid. *Quart. J. Med. New Series*, **62**, 83–6.

369 Newnham, H.H., Chosich, N., Topliss, D.J. *et al.* (1988) Amiodarone-induced hyperthyroidism: assessment of predictive value of biochemical testing and response to combined therapy using propylthiouracil and potassium perchlorate. *Aust. N.Z. J. Med.*, **18**, 37–44.

370 Mechlis, S., Lubin, E., Laor, J. *et al.* (1988) Amiodarone-induced thyroid gland dysfuction. *Am. J. Cardiol.*, **59**, 833–5.

371 Miaskiewicz, S.L., Amico, J.A., Follansbee, W.P. *et al.* (1987) Amiodarone-associated thyrotoxicosis masquerading as painful thyroiditis. *Ann. Intern. Med.*, **107**, 118–19.

372 Wimpfheimer, C., Staubli, M., Schadelin, J. *et al.* (1982) Prednisone in amiodarone-induced thyrotoxicosis. *Br. Med. J.*, **284**, 1835–6.

373 Woodruff, J.D., Rauh, J.T. and Markley, R.L. (1966) Ovarian struma. *Obstet. Gynecol.*, **27**, 194–202.

374 Janovski, N.A. and Paramanandhan, T.L. (1973) *Ovarian Tumors*, Vol 4, *Major Problems in Obstetrics and Gynecology*, WB Saunders Company, Philadelphia, pp. 89–90.

375 Kempers, R.D., Dockerty, M.B., Hoffman, D.L. *et al.* (1970) Struma ovarii – ascitic, hyperthyroid and asymptomatic syndromes. *Ann. Intern. Med.*, **72**, 883–93.

376 Pardo-Mindan, F.J. and Vazquez, J.J. (1983) Malignant struma ovarii. Light and electron microscopic study. *Cancer*, **51**, 337–43.

377 McDougall, I.R., Krasne, D., Hanberry, J.W. *et al.* (1989) Malignant struma ovarii presenting as paraparesis from a spinal metastasis. *J. Nucl. Med.*, **30**, 407–11.

378 Smith, F.G. (1946) Pathology and physiology of struma ovarii. *Arch. Surg.*, **53**, 603–26.

379 Brown, W.W., Shetty, K.R. and Rosenfeld, P.S. (1973) Hyperthyroidism due to struma ovarii: demonstration by radioiodine scan. *Acta Endocrinol.*, **73**, 266–72.

380 Federman, D.D. (1964) Hyperthyroidism due to functioning metastatic carcinoma of the thyroid. *Medicine*, **43**, 267–74.

381 Ober, K.P., Cowan, R.J., Sevier, R.E. *et al.* (1987) Thyrotoxicosis caused by functioning metastatic thyroid carcinoma. A rare and elusive cause of hyperthyroidism with low radioactive iodine uptake. *Clin. Nucl. Med.*, **12**, 345–8.

382 Citrin, D.L., Pederson, J., Rose, D.B. *et al.* (1978) Radiation-induced carcinoma of the thyroid with severe thyrotoxicosis. *Wisc. Med. J.*, **77**, 597–9.

383 Studer, H., Veraguth, P. and Wyss, F. (1961) Thyrotoxicosis due to a solitary hepatic metastasis of thyroid carcinoma. *J.Clin. Endocrinol. Metab.*, **21**, 1334–8.

384 Chapman, C.N., Sziklas, J.J., Spencer, R.P. *et al.* (1984) Hyperthyroidism with metastatic follicular thyroid carcinoma. *J. Nucl. Med.*, **25**, 466–8.

385 Sung, L.C. and Cavalieri, R.R. (1973) T_3 toxicosis due to metastatic thyroid carcinoma. *J. Clin. Endocrinol. Metab.*, **36**, 215–17.

386 Pont, A. Spratt, D. and Shin, J.B. (1982) T_3 toxicosis due to nonmetastatic follicular carcinoma of the thyroid. *West J. Med.*, **136**, 255–8.

387 Cerletty, J.M. and Listwan, W.J. (1979) Hyperthyroidism due to functioning metastatic thyroid carcinoma. Precipitation of thyroid storm with therapeutic radioactive iodine. *JAMA*, **242**, 269–70.

388 Weintraub, B.D., Gershengorn, M.C., Kourides, M.C. *et al.* (1981) Inappropriate secretion of thyroid-stimulating hormone. *Ann. Intern. Med.*, **95**, 339–51.

389 Brenner-Gati, L. and Gershengorn, M.C. (1985) Thyroid-stimulating hormone-induced hyperthyroidism, in *The Pituitary Gland*, (ed. H. Imura), Raven Press, New York, pp. 467–500.

390 Tolis, G., Bird, C., Bertrand, G. *et al.* (1978) Pituitary hyperthyroidism: case report and review of the literature. *Am. J. Med.*, **64**, 177–81.

391 Smallridge, R.C. and Smith, C.E. (1983) Hyperthyroidism due to thyrotropin-secreting pituitary tumors. *Arch. Intern. Med.*, **143**, 503–7.

392 Kourides, I.A., Ridgway, E.C., Weintraub, B.D. *et al.* (1977) Thyrotropin-induced hyperthyroidism: use of alpha and beta subunit levels to identify patients with pituitary tumors. *J. Clin. Endocrinol. Metab.*, **45**, 534–43.

393 Kourides, I.A., Pekonen, F. and Weintraub, B.D. (1980) Absence of thyroid-binding immunoglobulins in patients with thyrotropin-

mediated hyperthyroidism. *J.Clin. Endocrinol. Metab.*, **51**, 271–4.

394 Yovos, J.G., Falko, J.M., O'Dorisio, T.M. *et al.* (1981) Thyrotoxicosis and a thyrotropin-secreting pituitary tumor causing unilateral exophthalmos. *J. Clin. Endocrinol. Metab.*, **53**, 338–43.

395 Spanheimer, R.G., Bar, R.S. and Hayford, J.C. (1982) Hyperthyroidism caused by inappropriate thyrotropin hypersecretion: studies in patients with selective pituitary resistance to thyroid hormone. *Arch. Intern. Med.*, **142**, 1283–6.

396 Gharib, H., Carpenter, P.C., Scheithauer, B.W. *et al.* (1982) The spectrum of inappropriate pituitary thyrotropin secretion associated with hyperthyroidism. *Mayo Clin. Proc.*, **57**, 556–63.

397 Refetoff, S., DeWind, L.T. and DeGroot, L.J. (1967) Familial syndrome combining deaf-mutism, stippled epiphysis, goiter and abnormally high PBI: possible target refractoriness to thyroid hormone. *J. Clin. Endocrinol. Metab.*, **27**, 279–94.

398 Refetoff S., Salazar, A., Smith, T.J. *et al.* (1983) The consequences of inappropriate treatment because of failure to recognize the syndrome of pituitary and peripheral resistance to thyroid hormone. *Metabolism*, **32**, 822–34.

399 Hughes, I.A., Ichikawa, K., DeGroot, L.J. *et al.* (1987) Non-adenomatous inappropriate TSH hypersecretion and euthyroidism requires no treatment. *Clin. Endocrinol.*, **27**, 475–83.

400 Tisne, L. *et al.* (reference in Spanish, interested readers see Higgins, H.P. *et al.* [403]).

401 Odell. W.D., Bates, R.W., Rivlin, R.S. *et al.* (1963) Increased thyroid function without clinical hyperthyroidism in patients with choriocarcinoma. *J. Clin. Endocrinol. Metab.*, **23**, 658–64.

402 Hershman, J.M. and Higgins, H.P. (1971) Hydatidiform mole – a cause of clinical hyperthyroidism. *N. Engl. J. Med.*, **284**, 573–7.

403 Higgins H.P., Hershman, J.M., Kenimer, J.G. *et al.* (1975) The thyrotoxicosis of hydatidiform mole. *Ann. Intern. Med.*, **83**, 307–11.

404 Soutter, W.P., Norman, R. and Green-Thompson, R.W. (1981) The management of choriocarcinoma causing severe thyrotoxicosis. Two case reports. *Br. J. Obstet. Gynaecol.*, **88**, 938–43.

405 Hershman, J.M. (1981) Hyperthyroidism caused by trophoblastic tumors. *Thyroid Today*, **4** (**1**), (ed. J. Oppenheimer).

406 Rajatanavin, R., Chailurkit, L-O., Srisupandit, S. *et al.* (1988) Trophoblastic hyperthyroidism: clinical and biochemical features in five cases. *Am. J. Med.*, **85**, 237–241.

407 Steigbigel, N.H. (1964) Metastatic embryonal carcinoma of the testis asssociated with elevated plasma TSH-like activity and hyperthyroidism. *N. Engl, J. Med.*, **271**, 345–9.

408 Karp, P.J., Hershman, J.M., Richmond, S. *et al.* (1973) Thyrotoxicosis from molar thyrotropin. *Arch. Intern. Med.*, **132**, 432–6.

409 Stromberg, P., Ratcliffe, J.G., Trotter, J., *et al.* (1981) Teratoma of the testis and hyperthyroidism. *Scot. Med. J.*, **26**, 346–7.

410 Safa, A.M., Schumaker, P. and Rodriguez-Antunez, A. (1975) Long-term follow-up results in children and adolescents treated with radioiodine (^{131}I) for hyperthyroidism. *N. Engl. J. Med.*, **292**, 167–71.

411 Hamburger, J.I. (1985) Management of hyperthyroidism in children and adolescents. *J. Clin. Endocrinol. Metab.*, **60**, 1019–24.

412 Barnes, H.V. and Blizzard, R.M. (1977) Antithyroid drug therapy for toxic diffuse goiter (Graves') disease: thirty years' experience in children and adolescents. *J. Pediatr.*, **91**, 313–20.

413 Freitas, J.E., Swanson, D.P., Gross, M.D. *et al.* (1979) Iodine–131: optimal therapy for hyperthyroidism in children and adolescents. *J. Nucl. Med.*, **20**, 847–50.

414 Crile, G. Jr and Schumacher, O.P. (1965) Radioactive iodine treatment of Graves' disease: results of 32 children under 16 years of age. *Am. J. Dis. Child*, **110**, 501–4.

415 Levy, W.J., Schumacher, O.P. and Gupta, M. (1988) Treatment of childhood Graves' disease. *Clev. Clin. J. Med.*, **55**, 373–82.

416 Buckingham, B.A., Costin, G., Roe, T.F. *et al.* (1981) Hyperthyroidism in children: a reevaluation of treatment. *Am. J. Dis. Child*, **135**, 112–17.

417 Hayles, A.B. and Zimmerman, D. (1986) Graves' disease in childhood, in *The Thyroid*, 5th edn, (eds S.H. Ingbar and L.E. Braverman) Lippincott, Philadelphia, pp. 1414–23.

418 McArthur, R.G. (1978) Hyperthyroidism in childhood. *Thyroid Today*, **1** (5), (ed. J.H. Oppenheimer).

419 Marks, P. and Ashraf, H. (1978) Apathetic hyperthyroidism with hypomagnesemia and raised alkaline phosphatase concentration. *Br. Med. J.*, **1**, 821–2.

420 Lahey, F.H. (1931) Non-activated (apathetic) type of hyperthyroidism. *N. Engl. J. Med.*, **204**, 747–8.
421 Lahey, F.H. (1931) Apathetic thyroidism. *Ann. Surg.*, **93**, 1021–30.
422 Tibaldi, J.M., Barzel, U.S., Albin, J. *et al.* (1986) Thyrotoxicosis in the very old. *Am. J. Med.*, **81**, 619–22.
423 Ronnon-Jensen, V. and Kirkegaard, C. (1973) Hyperthyroidism – a disease of old age. *Br. Med. J.*, **1**, 41–3.
424 Davis, P.J. and Davis, F.B. (1974) Hyperthyroidism in patients over the age of 60 years. *Medicine*, **53**, 161–81.
425 Bartels, E.C. (1965) Hyperthyroidism in patients over 65. *Geriatrics*, **20**, 459–62.
426 Thomas, F.B., Mazzaferri, E.L. and Skillman, T.G. (1970) Apathetic thyrotoxicosis: a distinctive clinical and laboratory entity. *Ann. Intern. Med.*, **72**, 679–85.
427 Kawabe, T., Komiya, I., Endo, T. *et al.* (1979) Hyperthyroidism in the elderly. *J. Am. Geriatric. Soc.*, **27**, 152–5.
428 Caplan, R.H., Glaser, J.E., Davis, K. *et al.* (1978) Thyroid function tests in elderly hyperthyroid patients. *J. Am. Geriatric Soc.*, **26**, 116–20.
429 Burrow, G.N. (1985) The management of thyrotoxicosis in pregnancy. *N. Engl. J. Med.*, **313**, 562–5.
430 Burrow, G.N. (1978) Hyperthyroidism during pregnancy. *N. Engl. J. Med.*, **298**, 150–3.
431 Burrow, G.N. (1982) Thyroid diseases, in *Medical Complications During Pregnancy*, 2nd edn, (eds G.N. Burrow and T.F. Ferris), W. B. Saunders, London, Philadelphia, Toronto, pp. 187–214.
432 Ramsay, I. (1983) Drug treatment of thyroid and adrenal disease during pregnancy, in *Clinical Pharmacology in Obstetrics*, (ed. P. Lewis), Wright PSG, Bristol, London, Boston, pp. 232–50.
433 Aboul-Khair, S.A., Crooks, J., Turnbull, A.C. *et al.* (1964) The physiological changes in thyroid function during pregnancy. *Clin. Sci.*, **27**, 195–207.
434 Caplan, R.H. and Wickus, G. (1979) Goiter and plasma inorganic iodide concentration in pregnancy: a reassessment. *JAMA*, **242**, 352–3.
435 Long, T.J., Felice, M.E. and Hollingsworth, D.R. (1985) Goiter in pregnant teenagers. *Am. J. Obstet. Gynecol.*, **152**, 670–4.
436 Levy, R.P., Newman D.M., Rejali, L.S. *et al.* (1980) The myth of goiter in pregnancy. *Am. J. Obstet. Gynecol.*, **137**, 701–3.
437 McDougall, I.R. (1989) Maternal-fetal thyroid hormone metabolism and hyperthyroidism, in *Endocrine Disorders in Pregnancy*, (eds S.A. Brody and K. Ueland), Appleton and Lange, Norwalk Connecticut/San Mateo, California, pp. 151–64.
438 Hardisy, C.A. and Munro, D.S. (1983) Serum long acting thyroid stimulator protector in pregnancy complicated, by Graves' disease. *Br. Med. J.*, **286**, 554–5.
439 Momotani N., Ito, K., Hamada, N. *et al.* (1984) Maternal hyperthyroidism and congenital malformation in the offspring. *Clin. Endocrinol.*, **20**, 695–700.
440 Montoro, M. and Mestman, J.H. (1981) Graves' disease and pregnancy. *N. Engl. J. Med.*, **305**, 48.
441 Mujtaba, Q. and Burrow, G.N. (1975) Treatment of hyperthyroidism in pregnancy with propylthiouracil and methimazole. *Obstet. Gynecol.*, **46**, 282–6.
442 Cheron, R.G., Kaplan, M.M., Larsen, P.R. *et al.* (1981) Neonatal thyroid function after propylthiouracil therapy for maternal Graves' disease. *N. Engl. J. Med.*, **304**, 525–8.
443 Rubin, P.C. (1981) Beta-blockers in pregnancy. *N. Engl. J. Med.*, **305**, 1323–6.
444 Galina, M.P., Avnet, N.L. and Einhorn, A. (1962) Iodides during pregnancy: an apparent cause of neonatal death. *N. Engl. J. Med.*, **267**, 1124–7.
445 Howe, P. and Francis, H.H. (1962) Pregnancy and thyrotoxicosis. *Br. Med. J.*, **2**, 817–62.
446 Menon. V., McDougall, W.W. and Leatherdale, B.A. (1982) Thyrotoxic crisis following eclampsia and induction of labour. *Postgrad. Med. J.*, **58**, 286–7.
447 Derksen, R.H.W.M., van de Weil, A., Poortman, J. *et al.* (1984) Plasma-exchange in the treatment of severe thyrotoxicosis in pregnancy. *Eur. J. Obstet. Gynec. Reprod. Biol.*, **18**, 139–48.
448 Williams, R.H., Kay, G.A. and Jandorf, B.J. (1944) Thiouracil. Its absorbtion, distribution, and excretion. *J. Clin. Invest.*, **23**, 613–27.
449 Kampman, J.P., Johansen, K., Hansen, J.M. *et al.* (1980) Propylthiouracil in human milk. Revision of a dogma. *Lancet*, **1**, 736–8.
450 McKenzie, J.M. and Zakarija, M. (1978) Pathogenesis of neonatal Graves' disease. *J. Endocrinol. Invest.*, **2**, 182–9.
451 Robinson, A.C., O'Connor, M.K., Tempany, E. *et al.* (1982) Thyroid pertechnetate scan in neonatal hyperthyroidism. *Ir. J. Med. Sci.*, **151**, 22–3.

452 Cove, D.H. and Johnston, P. (1985) Fetal hyperthyroidism: experience of treatment of four siblings. *Lancet*, **1**, 430–2.
453 Wilson, D.M., Hopper, A.O., McDougall, I.R. *et al.* (1982) Serum free thyroxine values in term, premature and sick infants. *J. Pediatr.*, **101**, 113–17.
454 Robinson, D.C., Hall, R. and Munro, D.S. (1969) Graves' disease, an unusual complication: raised intracranial pressure due to premature fusion of skull sutures. *Arch. Dis. Child*, **44**, 252–7.
455 Riggs, W., Wilroy, R.S. and Etteldorf, J.N. (1971) Neonatal hyperthyroidism with accelerated skeletal maturation craniosynostosis and brachydactyly. *Radiol.*, **105**, 621–5.
456 Macklin, J.F., Canary, J.J. and Pittman, C.S. (1974) Thyroid storm and its management. *N. Engl. J. Med.*, **291**, 1396–8.
457 Newmark, S.R., Himathongkam, T. and Shane, J.M. (1974) Hyperthyroid crisis. *JAMA*, **230**, 592–3.
458 Urbanic, R.C. and Mazzaferri, E.L. (1978) Thyrotoxic crisis and myxedema coma. *Heart Lung*, **7**, 435–47.
459 Mazzaferri, E.L. and Skillman, T.G. (1969) Thyroid storm: a review of 22 episodes with special emphasis on the use of guanethidine. *Arch. Intern. Med.*, **124**, 684–90.
460 Roizen, M. and Becker, C.E. (1971) Thyroid storm. *Calif. Med.*, **115**, 5–9.
461 Troen, P., Taymor, R.C. and Goldberg, B.I. (1951) Thyroid crisis associated with diabetic coma. *N. Engl. J. Med.*, **244**, 394–8.
462 Hanscom, D.H. and Ryan, R.J. (1957) Thyroid crisis and diabetic ketoacidosis. *N. Engl. J. Med.*, **257**, 697–701.
463 Ingbar, S.H. (1975) When to hospitalize the patient with thyrotoxicosis. *Hosp. Pract.*, **Jan**, 45–53.
464 Brooks, M.H. and Waldstein, S.S. (1980) Free thyroxine concentrations in thyroid storm. *Ann. Intern. Med.*, **93**, 694–7.
465 Goldfarb, C.R., Varma, C. and Roginsky, M. (1980) Diagnosis in delirium: prompt confirmation of thyroid storm. *Clin. Nucl. Med.*, **5**, 66.
466 Wu, S-Y., Chopra, I.J., Solomon, D.H. *et al.* (1978) The effect of repeated doses of ipodate (oragrafin) in hyperthyroidism. *J. Clin. Endocrinol. Metab.*, **47**, 1358–62.
467 Hellman, R., Kelly, K.L. and Mason, W.D. (1977) Propranolol for thyroid storm (letter), *N. Engl. J. Med.*, **297**, 671–2.
468 Ashkar, F.S., Katims, R.B., Smoak, W.M. III, *et al.* (1970) Thyroid storm treatment with blood exchange and plasmapheresis. *JAMA*, **214**, 1275–9.

CHAPTER SIX

Hypothyroidism

6.1 INTRODUCTION

Hypothyroidism is present when there is insufficient action of thyroid hormones to meet the requirements of the body. The vast majority of patients suffering from hypothyroidism have disease of the thyroid: primary hypothyroidism. Lesser numbers have disease of the pituitary or hypothalamus, which are called secondary and tertiary hypothyroidism respectively. These are also called central hypothyroidism. Exceptionally rare causes of hypothyroidism (quaternary hypothyroidism) are peripheral resistance to thyroid hormone [1], and inactivation of circulating hormones by specific autoantibodies [2, 3]. The severity of hypothyroidism varies from cases which are so mild that diagnosis is based on biochemical findings, to those which are life threatening and easily diagnosed clinically [4]. Severe hypothyroidism with skin changes is called myxoedema.

6.2 AETIOLOGY

The frequency of the causes of hypothyroidism depends on the age of the patient. Table 6.1 gives an extensive list of possible causes in adults, in whom the most frequent causes are autoimmune thyroiditis, or prior treatment with radioiodine, or surgery. Most patients with autoimmune thyroiditis have had Hashimoto's thyroiditis, and a small proportion Graves' disease, but they present with hypothyroidism and they have circulating antithyroid antibodies. A goitre is often palpable, although in atrophic Hashimoto's, the thyroid is usually impalpable. The relationship between primary autoimmune hypothyroidism and Hashimoto's is also discussed in Chapter 9. Goudie *et al.* [5] showed that the pathological changes in the thyroid and the titres of thyroid antibodies correspond closely. It is thought by some authorities that hypothyroidism is the inevitable end result in autoimmune thyroiditis; although this is not entirely the case, it highlights the need for long-term supervision of these patients. Other very common causes of underactivity of the thyroid are the result of treatment of hyperthyroidism. The relationship to previous radioiodine is well established and is described in detail in Chapter 5. Briefly, 10–90% will be hypothyroid one year after therapy, the larger proportion being found when larger doses of radioiodine are prescribed. Approximately 2–4% become hypothyroid annually thereafter. It is less well known that surgical treatment of hyperthyroidism results in 50% of patients becoming hypothyroid. There is some disagreement whether there is a continual increase in the percentage who become hypothyroid postoperatively. Some contend that after the first year there is no further rise, but it is my strong belief that the progressive risk continues for life. Currently, it is more common to consult on a severely hypothyroid patient with a faint thyroidectomy scar, than one who has been treated with radioiodine, because of awareness and earlier diagnosis and treatment in the latter situation. Permanent hypothyroidism has been diagnosed in patients who

Table 6.1 Causes of hypothyroidism in adults

Primary: disease in the thyroid, TSH high, FT_4 low	
Common:	autoimmune hypothyroidism
	Hashimoto's thyroiditis
	postradioiodine
	postsurgery
	antithyroid medications
	iodine deficiency
	external radiotherapy, high dose
Uncommon:	iodine excess, amiodarone,
	subacute thyroiditis, transient
	silent thyroiditis, usually transient
	lithium
Rare:	ectopic thyroid
	lymphoma
	sarcoidosis
	primary or secondary cancers
	drugs
	para-aminosalicylate
	resorcinol
	interleukin 2
	chemical brominated hydrocarb
	dietary goitrogens
Secondary: disease in the pituitary, TSH low, FT_4 low	
Rare:	pituitary tumour (60%)
	primary
	secondary
	hypophysectomy
	external radiotherapy
	granulomatous diseases
	Sheehan's syndrome
	trauma
	infections
	defective synthesis of TSH
Tertiary: disease in the hypothalamus, TSH low FT_4 low	
Very rare:	idiopathic
	tumours
	granulomatous diseases
	external radiotherapy
Quaternary: peripheral resistance to thyroid hormones, T_4, T_3 and TSH high	
Very rare:	defect in transport
	defect in receptor
	antibodies against T_4 or T_3
	antibodies against TSH

were previously hyperthyroid and treated by drugs, either inorganic iodine [6] or standard antithyroid agents [7], again stressing the need for long-term follow-up and patient education. Twenty to thirty per cent of patients who have had high-dose radiation to the neck (about 4000 rad) become clinically hypothyroid, and as many as 60–70% have biochemical hypothyroidism with an elevated TSH, or an exaggerated rise in TSH in response to TRH. Most of the reports deal with patients who had Hodgkin's disease, or lymphoma [8–10], but the same applies to patients with other cancers provided follow-up is sufficiently long [11]. Hypothyroidism is more common in those patients with lymphoma and neck radiation who also had lymphangiography, which gives a large loading dose of iodine. In 100 patients, 16 years of age or younger, who received more than 2600 rad to the thyroid as part of their treatment of Hodgkin's disease, we found more than 70% had a raised TSH. In contrast, only 24% of those who received 2500 rad or less had an elevated TSH. All had lymphangiograms; therefore the radiation dose is more important than the iodine load [12].

A number of drugs can interfere with thyroid hormone synthesis. Antithyroid drugs obviously have this action, but this cause should be clear from the history. Other drugs which are reported to cause hypothyroidism are para-aminosalicylic acid, resorcinol and ketoconazole [13]. Recently, interleukin 2 has produced hypothyroidism, probably by inducing an autoimmune thyroiditis [14]. About 3–5% of patients with manic depressive psychosis who are treated with lithium develop goitre and hypothyroidism, and those who before treatment have circulating antibodies appear to be at most risk [15]. Up to 50% of patients taking lithium have an abnormally large TSH response to injection of TRH [16]. Food faddism for cabbage or kale can produce hypothyroidism, since these vegetables contain antithyroid compounds. However, the quantity of vegetable that has to be ingested to produce hypothyroidism is beyond most people's tolerance. Inorganic iodine in large

quantities can produce hypothyroidism, partly by inhibiting release of stored hormone and also by interfering with its organification, the Wolff-Chaikoff effect [17]. It is likely that most patients who develop this problem have an underlying autoimmune thyroiditis, or have had radioiodine therapy for Graves' disease [18]. In Hashimoto's thyroiditis there is a defect in organification that can be demonstrated by the perchlorate discharge test [19], and this defect is exaggerated by iodine loading [20], although in practice the discharge test is not necessary. Iodine-induced hypothyroidism can be precipitated by dietary or medicinal iodine, and it should be recalled that one of the worst places to get a large dose of iodine is in hospital, in particular the radiology department. The relationship of goitre and hypothyroidism due to expectorants containing iodine is clearly documented [21]. Even the application of topical iodine to a perineal fistula has caused hypothyroidism [22]. To cloud the issue of iodine-induced hypothyroidism somewhat is data suggesting that prolonged intake of more than physiological quantities of iodine can actually cause autoimmune thyroiditis. This is based on comparison of the rising prevalence of Hashimoto's thyroiditis during the last half-century, and the parallel rise in consumption of dietary iodine in the USA [23]. Nowadays, iodine deficiency is unheard of in the USA and the intake, although falling in the last several years, is still about 3–5 times that required. There are, however, many countries where iodine deficiency is a major public health problem, causing hypothyroidism and cretinism (Chapter 11). Iodine is a major constituent of amiodarone, and hypothyroidism is one of the common thyroidal complications of this drug in iodine-replete patients, Kriss *et al.* [24] described five patients who became hypothyroid and developed goitre due to cobaltous chloride, which had been prescribed to treat anaemia. Exposure to lead has been reported to cause a low serum thyroxine, but it was not associated with clinical hypothyroidism [25].

Infiltrative diseases whether benign such as sarcoidosis, or malignant such as primary or secondary cancer or lymphoma, seldom cause hypothyroidism. Patients with subacute and silent thyroiditis often go through a transient hypothyroid phase, but in the latter condition 5–10% will remain permanently hypothyroid (Chapter 9).

Anti-TSH receptor antibodies have been shown in six patients to be causal [26], as have antibodies to T_4 and T_3 [27, 28]. Resistance to thyroid hormone is discussed in Chapter 3.

Inborn errors of synthesis of thyroid hormones are exceptionally rare, and they are discussed in 'Hypothyroidism in children' (below).

When there is evidence of underactivity of more than one gland, secondary or tertiary hypothyroidism must be considered. Similarly, if there is clinical evidence of pituitary disease, malfunction of the peripheral glands should be sought. Pituitary causes include hypophysectomy, radiotherapy, infarction, especially after haemorrhagic complications of pregnancy, granulomatous diseases, and benign and malignant tumours. Pituitary tumours account for 50–60% of central hypothyroidism. The symptoms and signs of hypothyroidism are usually less prominent than in unselected patients with primary hypothyroidism. Central hypothyroidism is said to be about 1/5000 as common as primary disease.

6.3 PREVALENCE

Hypothyroidism is an important disease because it is common and treatable. In population surveys, up to 1% of adults are hypothyroid [29–31]. The condition is 5–10 times more frequent in women. The elderly are effected more often: 3% of those studied by Sawin *et al.* [32] and 2.3% in the report of Bahemuka and Hodgkinson [33]. The classic

features of hypothyroidism are found in only one-third of elderly hypothroid patients, and depression is a dominant symptom. Because of the numerical importance and the clinical differences in the elderly, a separate section is devoted to this at the end of this chapter. Hypothyroidism is much less common in the newborn, and the prevalence in almost all neonatal screening programmes is approximately 1 case in 4000. Nevertheless, because of the very serious consequences of failing to make the diagnosis, the importance is stressed. The causes of neonatal hypothyroidism include agenesis and dysgenesis of the thyroid, the latter is usually incompletely descended. Inborn errors of thyroid hormone formation are very rare, and usually present in early childhood with goitre and hypothyroidism. Neonatal screening for thyroid dysfunction is standard in Western countries and Japan, but should the adult population be screened as well? Kalenberg and Kagedal [34] argue in favour of this, because they detected hypothyroidism in 1.5%, and hyperthyroidism in 1.9%, of healthy Swedish women over 60 years.

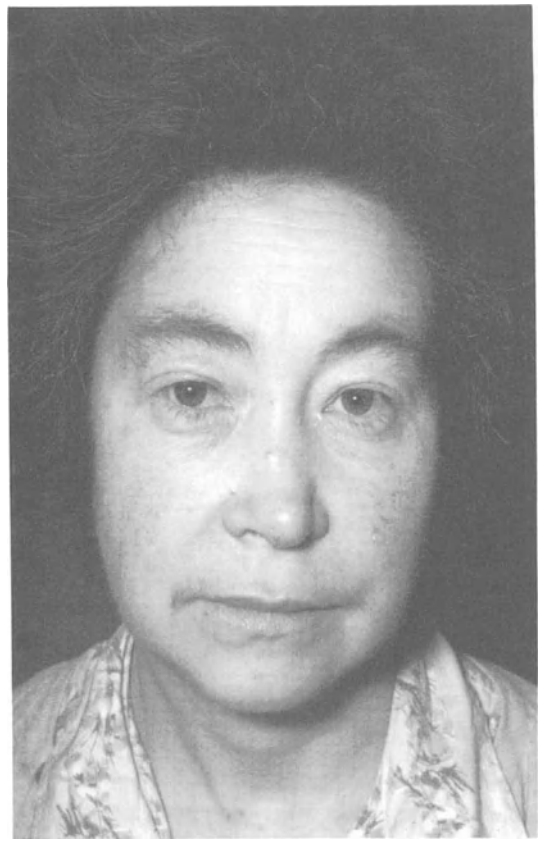


Figure 6.1 Photograph of a woman who has fairly pronounced biochemical hypothyroidism. On first inspection, she does not look particularly hypothyroid, although she does appear somewhat apathetic. Compare with Figure 4.2. Most hypothyroid patients are diagnosed before they become myxoedematous.

6.4 CLINICAL FEATURES

Among the best descriptions of severe hypothyroidism are the original ones by Curling in 1850 [35], Gull in 1875 [36] and Ord in 1878 [37]. Bloomfield [38] and Aikawa [39] have recorded succinctly the history of the description of hypothyroidism and the correlation of the diagnosis with absence, or great enlargement, of the thyroid. The patients who were described in these early papers were flagrantly myxoedematous, and a photograph of such a patient is shown in Chapter 4. In mild cases, there may be few symptoms or signs, or the features are so subtle that the diagnosis is not suspected; Figure 6.1 shows a photograph of a hypothyroid patient who might not be diagnosed by appearance. In specific clinical settings, such as after radioiodine for hyperthyroidism, the diagnosis can and should be established early, but in spontaneous cases this can be difficult.

From time to time, the clinician will encounter in hospital a grossly myxoedematous patient in whom the diagnosis has been missed. The patient is wrapped up in a heap of blankets, snoring through raucous ward

activities. All the text-book manifestation are present. This is the exception. In others, the disease causes non-specific symptoms, such as tiredness, stiffness, depression, rheumatism, constipation, etc.; alternatively, one organ is involved out of proportion to the rest of the body. The physician should be alert to the possibility of hypothyroidism as the cause of non-specific symptoms, especially in women and in the elderly, and direct the questions and physical examination accordingly. Hypothyroid patients are non-complaining and because the disease is insidious in onset, the patient, relatives and colleagues fail to recognize a difference. It is not rare to diagnose moderately severe but unsuspected hypothyroidism in relatives visiting their spouses in hospitals or in close relatives of medical colleagues, since the diagnosis is much easier for the clinician seeing the person for the first time when the features are established, than for those in frequent contact with the patient.

A common symptom is sleepiness. Many patients fall asleep immediately after dinner, and never see an entire television film (in this respect the disease can be advantageous). Sleep apnoea is common in hypothyroidism. Rajagopal *et al.* [40] studied 11 consecutive random hypothyroid patients, and demonstrated that 9 had apnoeic episodes during sleep. These were more frequent if the patient was obese. The number of apnoeic episodes was dramatically diminished after the patients were treated with thyroxine. Cold intolerance is also common, and euthyroid relatives state that the temperature in the house is maintained intolerably high. The patient wears excessive layers of clothes, or when in bed, blankets. Dryness of the skin and lacklustre hair are recognized more by female patients, who also complain of the lack of success in retaining 'permanent' curls. Sweating is greatly reduced. Non-pitting puffiness and hyperkeratosis are present in 75–90% of the patients [41]. Thinning of the hair and alopecia are less common, and have been attributed to both reduced growth as well as fragility of the internal root sheath. Nails are slow growing, brittle and ridged. Loss of hair from the outer one-third of the eyebrows is not specific for hypothyroidism.

A friend might be the first to recognize a problem by the change in the patient's voice, which is most noticeable on the telephone. Asher [42] describes the sound as 'that of a bad gramophone record of a drowsy, slightly intoxicated person with a bad cold and a plum in the mouth'. Speech is altered by enlargement of the tongue as well as oedema of the vocal cords. My otolaryngology colleagues have been the first to diagnose unsuspected hypothyroidism on direct inspection of the cords in patients who had no other features of the disorder. A mild reversible nerve deafness is found in about 25% of patients, and this can be the presenting complaint.

Breathlessness is due to weight gain, reduced cardiac output, anaemia, or pleural effusion, or any combination of these. Weight gain is very common, but it is not great, and usually is of the order of 10–20 pounds. It goes without saying that the vast majority of overweight people have no evidence of thyroid dysfunction.

Mental symptoms range from forgetfulness and depression, to the extreme of myxoedema madness [42]. Psychosis due to hypothyroidism generally occurs in long-standing cases. However, there is one report where it occurred rapidly in a young thyrotoxic woman who was made hypothyroid by too great a dose of antithyroid drugs [43]. A classic description of myxoedema psychosis appears in 'The Citadel' by A.J. Cronin [44] several years before the condition was described in the medical literature [42]. Slowness of thought and decision making are common. Occasionally, there are cerebellar signs with ataxia, nystagmus and

Table 6.2 Neurological manifestations of hypothyroidism

	Percentage of patients involved				
Sluggishness	68	–	57	40	–
Drowsiness	68	30	25	30	22
Poor memory	29	23	–	55	65
Poor hearing	31	15	9	30	53
Vertigo	8	12	16	21	12
Number studied	100	80	400	81	109
Reference	45	46	47	48	49

intention tremor, for which no other cause is found. Neuropathies are more common than generally recognized and nerve conduction studies can be abnormal in both motor and sensory nerves. The relaxation time for tendom reflexes is prolonged, usually to more than 350 ms. This was used as a test for hypothyroidism, but is too non-specific to recommend. One neuromuscular complaint that is quite characteristic is the sudden onset of muscle cramps in patients who become hypothyroid rapidly after thyroidectomy or radioiodine therapy. This is not due to hypocalcaemia, and the mechanism has not been explained. Table 6.2 shows the prevalence of common neurological symptoms in five publications. The criteria for diagnosis were not so sensitive as currently available and probably more advanced cases were included. Nevertheless, the high numbers are stressed [45–49]. Parathesiae occur in about 12% of patients. [50].

Weakness of the proximal muscles is very common, though not usually severe. Hypertrophy of the muscles is noted very rarely [50]. There are abnormalities in the muscle fibres on light and electron microscopy, and these disappear with treatment of the hypothyroidism. Halverson *et al.* [51] reported the case of a hypothyroid woman who developed severe inflammatory necrosis of muscles which resulted in renal failure from rhabdomyolysis. She was cured with thyroxine. Arthritic pains and swollen stiff joints are also common. Unlike rheumatoid arthritis, the pain is not worse in the morning. The joints involved are the knees, metacarpophalangeal and proximal interphalangeal joints. Although they are swollen and boggy, they are not inflamed or tender. Provided the underlying diagnosis is recognized, there is no need for diagnostic aspiration. When this has been done, the fluid has normal protein and white cell count and high viscosity. If attention is focused solely on the swollen joints, the true cause will be overlooked. In one series [52], the average duration of joint symptoms before the correct diagnosis was made was 11.8 years, and in a second group of 12 patients the symptoms extended for 10 years. The delay is disturbing, but the symptoms and signs disappeared with thyroid therapy, although as long as 6–12 months passed for complete resolution in those with the long-standing arthropathy. Carpal-tunnel syndrome is more common than in a matched euthyroid control group, and Bland *et al.* [53] found 5 of 49 patients with carpal-tunnel syndrome to be hypothyroid.

Bradycardia is common, and the pulse is usually regular, though severe hypothyroidism can cause malignant arrhythmias, including complete heart block [54] and ventricular fibrillation [55, 56]. Some authorities believe that these rhythm disturbances are coincidental. Pericardial effusion is characterized by a high protein content, and is usually not evident clinically; ultrasonic examination is the most sensitive method for its detection. Small asymptomatic effusions are commonly seen if this test is employed, and they disappear when the patient is euthyroid. Unless there are clinical indications, the test should not be ordered. Cardiac tamponade is very uncommon, but has been reported [57] and recently this caused a fatal outcome in a Christian Scientist [58]. It is argued whether there is an increased association of coronary artery disease in hypothyroidism [59, 60]. Both diseases are common and would be expected to coexist. In frank myx-

oedema there is more advanced coronary artery disease compared with controls [61]. Patients with subclinical hypothyroidism and autoimmune thyroiditis (diagnosed by the presence of antibodies), showed more coronary heart disease for a follow-up of 5 years than controls with negative antibodies. Therefore, preclinical and mild hypothyroidism are thought to be risk factors for premature coronary artery disease [62, 63]. The premature atherosclerosis is blamed on hyperlipoproteinaemia. However, those patients with elevated lipids are usually clinically (not subclinically) hypothyroid [64]. The debate will continue, but it is wise in a patient with premature atherosclerosis and/or hyperlipoproteinaemia to test thyroid function. Angina is not common in hypothyroidism, probably because the oxygen requirements of the tissues are lowered and the cardiac output decreased. In fact, in the 1950s and 1960s, intractable angina was treated by producing hypothyroidism medically, or by radioiodine [65]. Treatment with thyroid hormone can induce angina, and because CPK, LDH and SGOT are often above the normal range due to slow clearance, an erroneous diagnosis of myocardial infarction can be made [66]. Hypertension is found in hypothyroidism and in some it will respond to restoration of euthyroidism [67]. The term myxoedema heart was applied by Fahr [68] to the grossly dilated heart which is only found in very severe myxoedema.

Hypothyroidism can cause Raynaud's phenomenon, which usually responds to thyroxine [69], although most patients with Raynaud's are not hypothyroid.

Normochromic normocytic anaemia is a frequent finding and it improves when the patient is treated with thyroxine. The anaemia is probably due to reduced oxygen requirements. Anaemia is aggravated by blood loss, e.g. from heavy, lengthy menstrual periods. Therefore, if there is evidence of iron deficiency a source should be sought. Pernicious anaemia is found more frequently in association with autoimmune thyroid disease, and if there are any clinical or haematological features, it is important to look for vitamin B_{12} deficiency. In 116 hypothyroid patients, Tudhope and Wilson [70] found 17 with microcytic anaemia, 13 with pernicious anaemia, and 5 with normocytic anaemia. The anaemia in each patient has to be evaluated on its own merits. Macrocytic changes alone, without hypersegmented polymorphs, would favour anaemia of hypothyroidism rather than B_{12} deficiency. However, if there is any doubt, measurement of serum B_{12}: and/or a Schilling test would be appropriate. There is a clinical impression that hypothyroid patients have a bleeding tendency. However, this is seldom a clinical problem. Several case reports describe patients with a significant bleeding diathesis in whom the underlying cause is not completely defined [71]. The usual finding is similar to Von Willebrand's disease with low concentration of factor VIII and an inhibitor of coagulation [72]. Treatment with thyroxine usually corrects the problem.

Constipation, or an alteration in bowel function towards sluggishness, is characteristic. Manometric studies have shown lower intraluminal pressures in both the small intestine and colon [73]. In general, investigations are not advised because the symptoms disappear with thyroid replacement. Severe hypothyroidism can result in, or present as, an ileus [74, 75]. This is more common in the elderly and there is some evidence it is due to an autonomic neuropathy [73].

Occasionally, classic infiltrative ophthalmopathy of Graves' disease is found in hypothyroidism [76]. It is not possible to be certain if mild Graves' hyperthyroidism, or euthyroid Graves' disease, preceded the hypothyroidism. However, this is a moot point. Therapies are directed at correcting both the hypothyroidism and the eye disease, and not specifically at the underlying mechanism. The role of thyroid antibodies in the pathogenesis of the ophthalmopathy has

been discussed in Chapter 5, and it is recognized that most patients with primary hypothyroidism have circulating antibodies.

Hypothyroidism due to thyroid disease can cause galactorrhoea. This was first reported in 1956 [77], and is due to high levels of prolactin. Although galactorrhoea is uncommon in hypothyroidism, thyroid function should be tested in patients with galactorrhoea-amenorhoea syndrome, because it is so simple to diagnose and treat [78–81], and the response to thyroid replacement is gratifying.

Serum sodium is often low but, paradoxically, total body sodium is increased. It is postulated that the excess sodium is contained in myxoedematous tissues. There is inability to excrete a water load normally. This plus the hyponatraemia have led to the theory that there is inappropriate secretion of ADH [82]. Macaron and Famuyima [83] present conflicting data showing that ADH was actually correctly suppressed in a patient they studied. Whatever the mechanism, hyponatraemia is to be expected, and this plus the impaired water excretion are corrected by thyroid replacement. When thyroid therapy was introduced in the nineteenth century, its action was thought to be on the kidney because of the diuresis it produced. Hyponatraemia of hypothyroidism does not respond well to fluid deprivation, or demeclocycline.

Isolated effusions of the pleural cavity [84], peritoneal cavity [85, 86], or scrotum [87] are occasionally the presenting sign. An effusion which cannot be explained by cardiac, renal, or liver disease should raise the probability of thyroid disease. Proteinuria is seldom explained by hypothyroidism.

An increased frequency of hypothyroidism has been found in patients with Down's syndrome. Sare *et al.* [88] found this in 19 of 121 patients and Lobo *et al.* [89] in 7 of 101. The cause in virtually every patient is autoimmune thyroiditis and the response to treatment gratifying [89].

Most of the symptoms and signs of primary hypothyroidism are found in central hypothyroidism, but in the latter the severity is less marked. In central hypothyroidism, there is no goitre and there are no immunological features such as ophthalmopathy (this is rare in the primary disease as well). There may be a constellation of symptoms and signs due to deficiency of other pituitary hormones, in particular gonadotrophins, plus manifestations of a space-occupying lesion or excess hormone production from a pituitary tumour. Approximately 50–60% of cases of central hypothyroidism are due to pituitary tumours and they can cause headache and visual field defects, characteristically bitemporal hemianopia. A cautionary note is necessary: long-standing hypothyroidism can produce enlargement of the pituitary gland and its fossa [90–94]. It can also cause headache. Therefore, it is unwise to diagnose a pituitary cause of hypothyroidism simply on the basis of an enlarged pituitary fossa on CT or NMRI scan. Measurement of TSH is important, and if it is high the patient has primary hypothyroidism.

The complications of hypothyroidism are simply severe manifestations of the symptoms and signs described above.

In summary, in those patients with spontaneous hypothyroidism, the symptoms are often non-specific and insidious and include tiredness, lethargy, depression, weight gain, etc., which are ubiquitous. The signs in a well-established case are seldom missed, but in the mild case the most skilled clinician may find little of note. Because of the diverse symptoms and signs, the hypothyroid patient may be referred to a gastroenterologist, neurologist, psychiatrist, haematologist, rheumatologist, or cardiologist. These specialists frequently embark on investigations more appropriate to their usual patient population and the diagnosis of hypothyroidism is delayed. Tachman and Guthrie [72] state 'The assumption that hypothyroidism has a typical presentation is hazardous.'

6.5 ASSOCIATED DISEASES

Autoimmune thyroid diseases, including hyrothyroidism, are found more commonly in patients with other autoimmune conditions and vice versa. Tudhope [95] found that 10% of patients with primary hypothyroidism had pernicious anaemia. In contrast, 11.7% of 162 patients with pernicious anaemia were found to be hypothyroid and a further 8% had subclinical hypothyroidism [96]. This is much greater than the 2.4% found by Chanarin [97]. Krassas *et al.* [98] found thyroid antibodies in 19 of 30 patients with pernicious anaemia. The higher incidences of thyroid disease in later studies are probably due to better *in vitro* tests of thyroid dysfunction.

Primary hypothyroidism plus primary hypoadrenalism without pituitary disease is called **Schmidt's disease**. Both endocrine diseases are associated with organ-specific autoantibodies. Rarely diabetes mellitus, primary ovarian failure and hypoparathyroidism are found with primary hypothyroidism [99].

There is an increased association with autoimmune connective diseases. As an example 7 of 52 patients with progressive systemic sclerosis were diagnosed hypothyroid and 5 of the 7 had high levels of thyroid antibodies [100]. There is an increase in Sjögren's syndrome, myasthenia and rheumatoid arthritis. How *et al.* [101] reported the association with giant cell arteritis. Other references are included in Chapter 9 in the section on Hashimoto's thyroiditis.

6.6 DIAGNOSIS

There are three diagnostic steps in hypothyroidism. Firstly, proof that hypothyroidism exists. Secondly, determination of the anatomical level of the disorder. Thirdly, definition of the underlying pathology.

Even when the diagnosis of hypothyroidism is obvious clinically, it is necessary to provide laboratory documentation which will withstand critical analysis. The diagnosis of hypothyroidism is virtually synonymous with lifelong therapy with thyroid hormone. There are a few exceptions [102, 103]. Fatourechi and Gharib [104] could only find 39 cases in the literature who progressed from hypo- to hyperthyroid, and they added six additional cases. The implications of lifelong therapy with periodic clinical and laboratory evaluation are not minor.

Primary hypothyroidism is characterized by low levels of thyroxine (FT_4) and elevated TSH. This combination is found in all moderate or severe cases. In mild compensated cases, the serum thyroxine can be normal, whereas TSH is above normal. This is called **subclinical hypothyroidism, compensated, or biochemical hypothyroidism**, and is seen in patients with Hashimoto's thyroiditis, after high-dose external radiation and sometimes after treatment of Graves' disease. A low FT_4 and a normal TSH is an uncommon combination in healthy outpatients, except in those who are actually becoming hypothyroid after treatment for Graves' disease with radioiodine or surgery [105], or in the patient with central hypothyroidism. The history of prior therapy of hyperthyroidism should clinche the diagnosis, and in this situation if the tests are repeated 2–4 weeks later, the TSH is above the normal upper level and the patient is, by definition, hypothyroid. When FT_4 is low the patient is symptomatic irrespective of the TSH value, and muscle cramps at this juncture are characteristic; the sequence illustrates that FT_4 must fall before the pituitary responds [106].

I prefer to order both FT_4 and TSH, since the combination allows both sides of the pituitary thyroid axis to be evaluated. So far no mention has been made of T_3. This has been intentional. In many hypothyroid patients, T_3 is in the normal range, because high TSH causes preferential production and release of T_3. In contrast, low T_3 is found in many euthyroid sick patients who need no

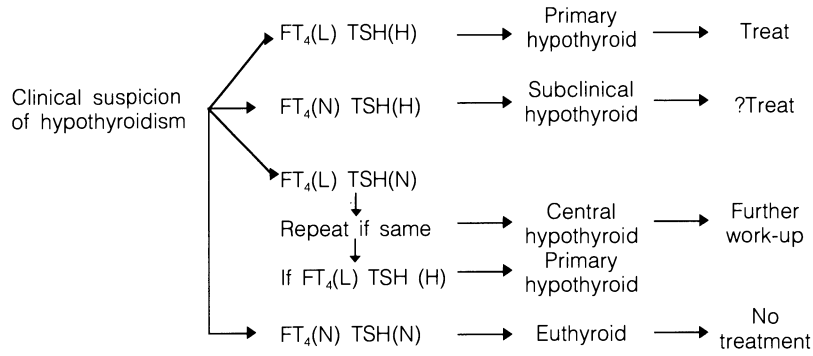


Figure 6.2 Algorithm for the management of a patient with suspected hypothyroidism.

replacement therapy (Chapter 14). In other words, measurement of T_3 to define hypothyroidism is unhelpful and can be confusing because the test has both low sensitivity and specificity.

A high TSH shows that the problem is in the thyroid. In hypothyroidism if TSH is low or normal and remains normal when retested 2–4 weeks later, this indicates central hypothyroidism. In this regard, if total T_4 measurements are used in place of FT_4, it would be important to exclude binding protein abnormalities as the cause of low T_4 values. This has been discussed in Chapter 3. When central hypothyroidism is diagnosed, the next step is to determine if the lesion is in the pituitary or hypothalamus, because disease of the former is likely to be due to a space-occupying lesion that requires specific treatment not just hormone replacement. It would appear that this differentiation is simple on the basis of response to TRH; pituitary lesions should show no rise in TSH, whereas hypothalamic lesions should, provided the pituitary is normal [107, 108]. Nevertheless, some patients with a pituitary lesion show a brisk rise in TSH after injection of TRH, and some patients with hypothalamic problems do not have the anticipated response. In spite of those limitations, most authorities support TRH testing. For final definition of the location of the pathology, the clinician has to review all clinical, biochemical and radiological data. Modern imaging techniques including state of the art CT scans or, preferably, NMRI images provide spectacular anatomical detail that assists this task. Although not common clinically, prolonged hypothyroidism can result in enlargement of the pituitary from hyperplasia and hypertrophy of the thyrotrophes, and there can be demineralization of the sella [91–93]. The point was made previously that hypothyroidism and an enlarged pituitary should not be assumed to mean pituitary hypothyroidism.

Figure 6.2 provides an algorithm for work-up of suspected hypothyroidism and its management.

In most patients with primary hypothyroidism, it is unnecessary to have a tissue diagnosis, the pathology can be determined from clinical or simple laboratory information. A patient who is hypothyroid after ^{131}I therapy needs no tests to find the cause. A middle-aged hypothyroid woman with a small, firm goitre, a family history of thyroid disease and high titres of thyroid antibodies has hypothyroidism from autoimmune thyroiditis. There are increasing numbers of reports of fine-needle biopsy in cases like the last one, and I question the need for this

unless there is a specific question to be addressed, such as a dominant nodule or sudden growth of the goitre.

There is seldom a place for obtaining ^{123}I uptake and scan. The 24-hour uptake is expected to be low, but there are other causes of low uptake including high dietary and medicinal iodine intake. In addition, the uptake can be normal due to the 'small pool pattern', where residual functioning follicular cells trap iodine avidly under TSH stimulation. These illustrate the low sensitivity and specificity of the uptake measurement in this setting. The scintigram usually provides a pictorial representation of what is palpable. Because of the universal access to precise radioimmunoassays (and IRMAs) for TSH, it is not necessary to do a TSH stimulation test to differentiate primary from central hypothyroidism. Likewise, it is not necessary to do a TRH test in primary hypothyroidism. If serum TSH is high the patient is hypothyroid, if it is normal, so is the patient. In those situations where hypothyroidism is anticipated, repeating the measurement of TSH is simpler.

Many biochemical abnormalities are found in hypothyroidism, such as high cholesterol, lipoproteins and creatine kinase, but they serve no diagnostic function. However, if a patient is found to have unexplained hypercholesterolaemia, it is prudent to ensure hypothyroidism is excluded.

Clinicians will often encounter a patient who has taken a thyroid preparation for many years, but there is no good documentation of the need for the medicine. Reasons for the medication include tiredness, depression and difficulty in losing weight. At the time the treatment was started, either no tests were done, or those which were used to establish the diagnosis are now known to be of questionable value, e.g. borderline low $PB^{127}I$. To prove the need for lifelong thyroid replacement is time-consuming and usually not accepted with equanimity by the patient. The thyroid medication has to be stopped for up to 8 weeks [109]. This is necessary to ensure that there is sufficient time for the suppressed thyroid to return to normal. The patient will often become transiently hypothyroid, and TSH will rise even if the thyroid is not required. If by 8 weeks the hypothyroidism persists, the thyroxine therapy is needed, but by this time many of the patients will have restarted the medicine and/or sought another opinion. Obviously, if the patient and tests return to normal sooner, the patient should not be taking thyroid. Stoffer *et al.* [110] found that $^{99m}TcO_4$ scintigram was valuable in this situation. If the thyroid could be visualized while the patient was taking thyroid medication there was no need for the drug and it could be stopped (temporary hypothyroid symptoms are still to be expected). In those patients where the thyroid was not imaged, treatment was recommended for life.

6.7 TREATMENT

There is no doubt that hypothyroidism, irrespective of its cause, should be treated. The first reported use of thyroid was by Murray [111], who gave glycerin extracts of sheep thyroid by subcutaneous injection. He presented a follow-up report on the first patient and estimated that she had received about 9 pints of liquid extract over 28 years [112]. Oral therapy was introduced in 1892 by McKenzie [113]. A variety of other thyroid conditions are treated with thyroid hormones. These include non-toxic goitre, Hashimoto's thyroiditis, benign thyroid nodules and thyroid cancer, although the last group are usually hypothyroid after surgical removal of the thyroid. These conditions are discussed in appropriate chapters. Obesity, depression and other non-thyroidal conditions should not be treated with thyroid hormone unless there is proven thyroid

deficiency. The main questions are which preparation, what dose, and how quickly can it be prescribed?

6.7.1 WHICH HORMONE?

Because there are two active circulating thyroid hormones, T_4 and T_3, it used to be argued that replacement therapy should contain both of these. Although it is true that the thyroid secretes both, in euthyroid people the majority of T_3 is produced from circulating T_4. Athyreotic patients treated with appropriate doses of thyroxine alone have stable and normal levels of T_4 and T_3, whereas those taking preparations containing T_3 including dessicated thyroid are less satisfactory in this respect. In 1961, MacGregor [114] asked the question, 'Why does anyone use thyroid extract?' This was based on observations on seven patients who were hypothyroid in spite of taking standard doses. He argued that variability in the preparation was the problem; this was also addressed by a short editorial in the same journal [115]. More recently, Jackson and Cobb [116] described six patients with clinical evidence of hyperthyroidism while they took dessicated thyroid, and all six had high T_3 levels, but normal T_4. The clinical and biochemical aberrations reverted to normal when the medication was changed to thyroxine. This has been described by other investigators for patients of all ages treated with whole thyroid USP [117] and thyroglobulin [118]. I have seen patients with subtle symptoms of hyperthyroidism which disappear when their treatment is switched to thyroxine, and almost routinely I recommend the change unless the patient has been on thyroid USP for years without an adverse clinical problem. The method of determining the potency of thyroid USP is based on the iodine content of the preparation. Since the distribution of iodinated proteins varies from batch to batch, and biologically inactive compounds contribute to the assay this is obviously an unsatisfactory medication.

In almost every clinical situation, L thyroxine is the preferred form of replacement. Triiodothyronine has a limited role in patients who are athyreotic after treatment for thyroid cancer and who undergo whole-body radioiodine scans to detect metastases. Triiodothyronine is said to have the advantage that it is discontinued for only 2 weeks prior to scanning, in contrast to 4–6 weeks for thyroxine. Even in this situation, I prefer to prescribe thyroxine because that is the preparation the patient takes for life, the thyroid status is smoother and changing from thyroxine to triiodothyronine periodically can be confusing for the patient. This is discussed in the Chapter 8, which deals with thyroid cancer. Larsen [119] has presented evidence that the amount of T_3 required to suppress pituitary TSH is excessive for other tissues, such as liver and kidney tissues. Therefore, most of the body is thyrotoxic at the level of T_3 which is physiological for the pituitary. The thyrotrophe responds to T_4 because it is very efficient in deiodinating T_4 to T_3 using a deiodinase enzyme that is peculiar to the pituitary and brown fat. Normally, most of intracellular T_3 in the thyrotrophe is derived from T_4, which in turn derives from serum FT_4. The usual dose of triiodothyronine is 25 μg 2 or 3 times per day.

6.7.2. HOW MUCH THYROXINE?

Not many years ago, the replacement dose of L thyroxine was on average 0.3 mg (300 μg), a dose which is now known to be excessive for most patients. The reasons for this paradox include the fact that serum T_3 could not be measured, precise measurement of TSH was not available and it was not known that T_4 was converted to T_3. Therefore, it seemed sensible to prescribe sufficient thyroxine to maintain the blood level of T_4 on the high side to compensate for the 'absent'

Table 6.3 Dose of L thyroxine in children (from Fisher and Klein [160])

Age (years)	*Dose (μg/kg/day)*
0–1	9
>1–5	6
6–10	4
11–20	3
Adult	2

T_3. It is now recognized that ingestion of T_4 alone results in normal levels of T_4 and T_3. The dose of thyroxine necessary to achieve this and to have a normal TSH is usually in the range of 100–200 μg per day [120, 121]. In adults, Stock *et al.* [121] showed the average daily dose was 165 μg; in patients over 65 years the dose was 110–120 μg per day [122]. The dose in older patients is less when expressed in μg/kg bodyweight (1.86 v. 2.06). Children require a larger dose (Table 6.3) [123]. Recently, it was recognized that the amount of thyroxine in generic and brand preparations varied [124]. To confuse matters more, the amount of thyroxine per pill in one of the named brand preparations was increasd, but the pill retained the same nominal strength and appearance. As a result, patients who had been well controlled for years became biochemically, or even clinically, hyperthyroid in spite of the fact they were taking the same preparation in apparently the same strength. This caused considerable controversy and unrest, and has been addressed in the literature [125–127]. There is recent data indicating that generic preparations have the same content as named brands [128]. L thyroxine is available in 25, 50, 75, 88, 100, 112, 125, 150, 175, 200, and 300 μg tablets (this range is not available from all manufacturers), so virtually any patient can be treated with one pill per day.

6.7.3 HOW QUICKLY?

A young healthy patient can be started on 100 μg daily and the dose increased by 50 μg increments at 2–4 week intervals. A 50 kg patient will require 100–125 μg, a 100 kg patient approximately 175–225 μg. The starting dose and increment can be selected appropriately. Since there is a transient rise in T_4 after starting treatment, it is recommended that biochemical testing is not done for about 8 weeks [129]. The speed of replacement in severely hypothyroid or elderly patients should be more cautious and 25 μg daily, or on alternate days, is suggested. Table 6.4 provides guidelines on starting, incremental and maintenance doses in various clinical settings. The most important criteria for the final maintenance dose is clinical, but with current testing it is recommended that FT_4 and TSH are in the normal range. In certain clinical situations, the goal of treatment is to suppress TSH (thyroid cancer and shrinkage of autoimmune goitre), and this can usually be achieved with FT_4 at the upper end of the normal range. Sensitive TSH measurements differentiate normal from suppressed values, so tight titration is possible. Some authorities have indicated that thyroid function tests are not valuable in determining the adequacy of replacement therapy [130], but that is not true with state of the art tests. It should be recognized that there can be small rises in T_4 and T_3 levels shortly after the medication is ingested, but I have not made it a policy to draw blood for testing at a specific time in relation to the patient taking the pill. TSH results do not fluctuate as much in relation to when thyroid is ingested.

After treatment of Graves' disease by surgery or radioiodine, any thyroid tissue left can function autonomously, therefore replacement thyroxine and endogenous thyroxine can be additive, resulting in the need for a smaller amount of oral thyroxine. The treatment has to be individualized. Over-

Table 6.4 Replacement doses of thyroxine

Patient population	*Starting dose*	*Incremental dose*	*Maintenance dose FT_4+TSH N*
Children		Dependent on age see Table 6.3	
Young adult	100 μg	50 μg	100–200 μg (approx 2 μg/kg)
Middle-aged	50 μg	50 μg	100–200 μg (approx 2 μg/kg);
Elderly	25 μg	25 μg	75–125 μg
Angina pectoris	12.5–25 μg	12.5–25 μg to tolerance	
Myxoedema coma	(*a*) 300 μg/m^2 IV	100 μg at 1 week	oral therapy on recovery
	(*b*) 200–300 μg IV	100 μg at 1 day	–
	+25 μg triiodothyronine every 12 hours until conscious		
	(*c*) 100 μg IV	100 μg daily for 7–10 days	–

treatment can produce typical features of hyperthyroidism, but this should be preventable in most cases. Recent data indicates that if TSH is chronically suppressed there is an increased incidence of osteopenia measured by dual photon-densitometry [131]. I am not aware of any increased risk of fractures in these patients, but if replacement is the reason for therapy it is better not to suppress TSH unless it is felt that the continued TSH stimulus would be undesirable as discussed above.

Thyroid hormones are not completely absorbed when given by mouth [132, 133], but it requires an unusual clinical situation, such as surgical by-pass of the gut, to make this a clinical problem [134].

One unresolved issue is whether to treat subclinical hypothyroidism (normal T_4 with slightly elevated TSH). As stated above, Hashimoto's thyroiditis, prior thyroid surgery and prior radioiodine therapy can be factors which cause this biochemical finding. It is may opinion that FT_4 is a better indicator of thyroid status than T_4 and some patients with normal T_4 have a low FT_4; therefore such a patient is truly hypothyroid. If it is accepted that a good proportion of patients with subclinical hypothyroidism will become hypothyroid in the future [29], and if it is accepted that a high TSH causes premature atherosclerosis [60–62, 135], and if it is accepted that a high TSH is a risk to a thyroid which has been irradiated, a good argument can be made to start treatment. Not all thyroidologists support these statements. It has been my policy to suppress TSH in those who have had thyroid irradiation. However, it could be argued that the treatment is only for a biochemical finding. One double-blind trial in patients with subclinical hypothyroidism showed minor benefits, both subjective and objective of thyroxine [136]. In a second study where either thyroxine 0.1 mg or a placebo was prescribed for 6 months to 20 asymptomatic women with TSH ranging from 4–15 μU/ml, there was a benefit from thyroxine in 4 patients [137]. Thus treatment is of some, but minor, value.

When treatment is for central hypothyroidism, it is essential to determine if the patient is hypoadrenal and, if so, to treat that before starting thyroxine. If this is not done, adrenal crisis can be precipitated. In other respects treatment is the same.

There was concern in the lay and medical press that breast cancer was found more frequently in women taking thyroid medication [138]. This allegation was sharply refuted by the American Thyroid Association [139] and shown to be incorrect by Shapiro *et al.* [140].

6.8 THYROID REPLACEMENT IN PATIENTS WITH ANGINA PECTORIS

The restoration of euthyroidism in a hypothyroid patient with angina pectoris can present a problem because the increase

in heart rate and metabolism often aggravates the angina even to the point of producing rest pain. The aim should be to start with a very small dose of thyroxine, and increase the dose with small increments at intervals of 3–4 weeks; the timing and size of change are dictated by the patient's symptoms. A starting dose of 12.5–25 μg and increments of the same amounts might allow return to normal thyroid function with no worsening in chest pain. Unfortunately, some patients cannot tolerate the full maintenance dose, and a compromise is reached between partial treatment and an acceptable amount of angina. Prescribing a beta-blocker along with the thyroxine can prevent angina while correcting hypothyroidism. However, when there is bradycardia, beta-blockers are contraindicated. Several groups have shown that coronary artery by-pass grafting is a valuable alternative in this predicament [141–143], and preoperative arteriography, anaesthesia and surgery are all feasible at no extra risk in hypothyroid patients. This is discussed in more detail in the next section.

6.9 ANAESTHESIA AND SURGERY IN HYPOTHYROIDISM

Endocrinologists are often asked by their surgical colleagues if it is safe to proceed with an operation in a patient who is found to be hypothyroid. Common sense, based on the pathophysiology on all the systems and publications describing patients who have done badly, dictates that surgery should be postponed until the thyroid deficiency is corrected [144, 145]. In one of these papers, only two patients were discussed; it is not certain if one of them was hypothyroid and the other was probably overtreated with thyroid extract preoperatively [144]. Review of the three cases of Kim and Hackman does not allow a diagnosis of hypothyroidism to be made at the time of surgery [145]. Some authorities recommend that thyroxine should be prescribed 48 hours before the operation [146]. Several larger studies published after the references cited above indicate that the above dogma is incorrect, and that anaesthesia and surgery are not more hazardous for hypothyroid patients. Weinberg *et al.* [147] compared the the outcome in 59 hypothyroid patients (found by tests which were not known at the time of operation) with well-matched controls of the same age and sex who were operated on for the same reasons by the same surgeons. They found no difference in outcome. Seven of the hypothyroid patients had T_4 values less than 1 μg/dl, and a further 31 had values below 3 μg/dl; therefore, moderate to severe cases were included. A prospective study in 500 patients undergoing cardiac surgery showed that 10 were hypothyroid at the time of operation and they did well [148]. The authors recommend starting thyroxine 25 μg daily postoperatively. In a third study of 49 hypothyroid patients who underwent cardiac catheterization and open heart surgery, Becker [149] concluded that these invasive procedures are safe in this setting.

In conclusion, hypothyroid patients should not be denied necessary surgery, especially emergency surgery, simply because they are hypothyroid. Careful monitoring of fluid balance is necessary to prevent hyponatraemia or overload. The doses of hypnotics and narcotics have to be reduced empirically because they are metabolized more slowly.

6.10 MYXOEDEMA COMA

Myxoedema coma is the result of long-standing untreated hypothyroidism, where the patient becomes obtunded and finally comatose. The condition is the severe end of the spectrum of hypothyroidism and is uncommon. In 1962 Sanders found only 52 cases in the literature [150], and in 1986 the number reported was said to be 200 [151]. There are undoubtably many more unreported cases and the condition merits separate

consideration, because it is a medical emergency with a very high mortality.

The patient is usually elderly, female and living alone. The condition is more common in cold climates and in cold seasons. The presentation is that of hypothermic coma, which should alert the clinician to the diagnosis. The differential includes cold exposure, often associated with alcohol and/or sedative excess, chlorpromazine overdose and overwhelming infection. The true degree of hypothermia is only measured with a low-reading thermometer, because values can be in the 70–80 degree Fahrenheit range [152]. Since myxoedema coma can be precipitated by infection, narcotics and other systemic illnesses, e.g. stroke in a hypothyroid patient, it can be impossible to establish a single diagnosis in each patient. A history from a relative or friend of the patient having treatment of thyroid dysfunction, or of taking thyroid medication, is very heldful.

When the diagnosis is suspected, it can be confirmed with a high TSH. Treatment must not await receipt of the result. The degree of elevation of TSH is less than expected due to the illness suppressing the pituitary. The author knows of no case of severe hypothyroidism due to thyroid disease in which the TSH was normal. In coma, irrespective of its cause, T_3, T_4 and even FT_4I can be low (Chapters 3 and 14). Therefore, these tests are not particularly helpful in establishing the diagnosis, but if they are normal the patient does not have myxoedema coma. A low FT_4 by a two-step technique is more reliable.

Because there is often hyponatraemia, azotaemia, hypoglycaemia, hypoxaemia and hypercapnia, appropriate investigations should be obtained as an emergency, since the results will dictate supportive management.

Treatment centres around correcting the hypothyroidism, gradual restoration of the temperature, correcting the precipitating cause and dealing with the metabolic abnormalities described above. There is debate about which hormone should be prescribed. Common sense dictates that T_3 is the hormone of choice, because of its more rapid action. Catz and Russell [153] saved 7 of 12 patients with triiodothyronine. By contrast, from the work of Holvey *et al.* [154] and subsequently Nicoloff [155], it appears that thyroxine is superior and that relatively large doses should be prescribed initially. The majority opinion supports this approach, but there are no controlled studies. Using this approach, thyroxine is given in a dose of 300 $\mu g/m^2$. The brand name, Synthroid, is available for parenteral use. No additional thyroxine is given for 1 week. Those who support the use of triiodothyronine prescribe 50 μg by nasogastric tube (parenteral triiodothyronine is not easy to obtain in the USA) as a starting dose followed by 25 μg every 12 hours.

Wartofsky [151] proposes a compromise with a loading dose of 4 μg thyroxine per kg lean body mass given intravenously along with 25 μg triiodothyronine enterally at 12 hour intervals. A second dose of 100 μg thyroxine is given 24 hours after the loading dose.

Laderson *et al.* [156] have demonstrated a rapid beneficial effect of 100 μg thyroxine by daily intravenous injection in 10 hypothyroid patients. None had myxoedema coma. There was improvement in cardiac, renal and respiratory functions. Total T_4 returned to normal quickly, and a small fall in TSH was noted by 24 hours, although even after 1 week the TSH values were not normal. The authors suggest that this approach might be as satisfactory, as supraphysiological doses and a trial in severely hypothyroid patients would appear warranted.

Hypothermia is treated best with blankets. Active warming is not advocated unless great care is taken to ensure hypotension and shock do not occur, as the peripheral vasculature dilates at a time when the heart is incapable of responding.

Infection as the precipitating cause should be sought. There may be no leukocytosis, but a left shift is an important point. Culture of blood, urine, sputum and cerebrospinal fluid are required. The CSF has a high protein content, and this alone does not indicate infection. The choice of antibiotic depends on the results of cultures and bacterial sensitivities. If infection is suspected clinically, broad-spectrum antibiotics should be prescribed while awaiting the microbiology results. Traditionally, hydrocortisone is prescribed in doses of 100–200 mg intravenously. It could be argued that the ill health plus steroids would interfere with conversion of T_4 to T_3, and thus reduce the effect of thyroxine. This does not appear to be important clinically. Some patients have combined thyroid and adrenal deficiencies and need both medications, and it is probably safer to give hydrocortisone to all patients, rather than omit it in some who will die without it.

Cardiac failure requires continuous ECG monitoring and treatment with oxygen, diuretics and digoxin. Hypoventilation may require intubation and assisted ventilation. Great caution should be exercised in the replacement of fluids, because cardiac failure is precipitated with ease. Hyponatraemia should not be treated with hypertonic saline. It should be recalled that intravenous antibiotics provide a source of volume and frequently sodium.

These patients are critically ill. They require intensive monitoring. From 1953–61 the mortality was estimated to be 80%. Even today, the mortality for patients with myxoedema coma is greater than 50% in spite of optimal care.

6.11 HYPOTHYROIDISM IN CHILDREN

Hypothyroidism at birth is called neonatal or congenital hypothyroidism; if it occurs later, the terms acquired or juvenile hypothyroidism are used. A severely hypothyroid baby at birth is called a cretin, but this name is also used to describe an infant with neurological abnormalities and severe mental deficiency due to intrauterine lack of iodine, rather than thyroid hormone deficiency. This is discussed in Chapter 11 on iodine deficiency and endemic goitre. A comprehensive list of causes of childhood hypothyroidism is given in Table 6.5 which is adapted from Hutchison [157]. Neonatal hypothyroidism (sporadic cretinism) is discussed first, then acquired hypothyroidism.

Table 6.5 Causes of hypothyroidism in children (adapted from Hutchison [157]

1. Dysgensis of thyroid
   (a) athyreosis
   (b) maldescent
   (c) maldevelopment
2. Endemic cretinism – iodine deficiency
3. Inborn enzyme defects
   (*a*) Intrathyroidal
      (i) failure of trapping
      (ii) impaired organification (+/− deafness)
      (iii) impaired coupling
      (iv) failure of deiodination
      (v) production of abnormal thyroglobulin
      (vi) unresponsiveness to TSH
      (vii) others
   (*b*) extrathyroidal
      (i) defect in action of thyroid hormones
      (ii) thyroid hormone antibodies
4. Ingestion of goitrogens
   (*a*) antenatal
   (*b*) postnatal
5. Primary thyroid diseases
6. Secondary and tertiary hypothyroidism

6.12 NEONATAL HYPOTHYROIDISM

Sporadic neonatal hypothyroidism occurs in approximately 1 out of 4000 babies. This incidence has been found in almost all screening programmes. The hypothyroidism is not due to iodine deficiency and is contrasted with endemic cretinism (Chapter 11). Undiagnosed and untreated neonatal hypothyroidism is inevitably associated with a devastating effect on intelligence. Treatment

of hypothyroidism within 6 weeks of birth has resulted in an IQ of 90 or higher in 55% of infants [158]. The 'textbook' clinical features of hypothyroidism are absent or mild, and clinicians should not expect a constipated child with noisy respirations, feeding difficulties, prolonged physiological jaundice, thick, cold, dry skin, umbilical hernia and a coarse cry. Very rarely there is muscular hypertrophy which improves with thyroxine (Kocher-Debre-Semelaight syndrome). The diagnosis is made in most cases by biochemical testing. Normal and abnormal thyroid development have been reviewed by Fisher [159] and Fisher and Klein [160].

Table 6.6 Results of screening for neonatal hypothyroidism

Number screened	*Number hypothyroid*	*Incidence*	*Reference*
(a) With thyroxine			
463 521	105	1/4414	164
475 126	109	1/4568	164
299 666	65	1/4755	164
54 714	5	1/10 900	167
265 020	45	1/5889	168
(b) With TSH			
45 000	10	1/4500	169
76 224	19	1/4012	170
30 000	9	1/3300	171
821 367	215	1/3820	168

6.12.1 AETIOLOGY

A review of developmental abnormalities in Chapter 1 is advised. The majority of cases (80–90%) are due to agenesis, ectopia, or hypoplasia of the thyroid [161]. Girls are effected twice as often [162]. Secondary hypothyroidism is much less frequent with an incidence of 1 in 50–100 000 births. Dyshormonogenesis is the cause of hypothyroidism in approximately 1 out of 30 000 births. In some cases of agenesis, there is autoimmune thyroiditis in the mother and placental transfer of antithyroid antibodies might be causal [163], although this is generally thought not to be important [164]. Transient hypothyroidism has been attributed to placental transfer of maternal immunoglobulins capable of inhibiting the binding of TSH to its receptor [165].

6.12.2 SCREENING PROGRAMMES

Three approaches exist for diagnosing neonatal hypothyroidism: measurement of T_4, TSH, or a combination of T_4 and TSH. Whichever method is used, it must be applicable to mass screening on drops of blood on filter paper. The test must be sensitive, specific, economical and rapid. There must be a reliable method of ensuring the results are relayed to the referring physician and that follow-up is undertaken. The majority of missed diagnoses have been the result of human error. Detailed discussion of the logistics and results of screening tests are presented in the monograph edited by Burrow and Dussault [166]. Table 6.6 gives an overview of the results of several screening programmes [167–171].

(a) Screening with T_4

T_4 is simpler and cheaper to assay than TSH. Most programmes accept that all babies with a T_4 less than 6 μg/dl are at risk, and should be recalled for retesting. Alternatively, patients with the lowest 5% from each assay are recalled and tests repeated. No matter which of these is used, there will be a significant number of false positives. The reason for the false positives in the former is due to low T_4 values in premature [172] and sick babies [173] and those with low levels of thyroid binding proteins. If the 5% with the lowest T_4 are considered to be at risk for hypothyroidism, and the incidence of the disease is 1/4000, to find that 1 case, 4000 babies are screened and 200 called back for repeat T_4 and TSH measurements (200 is 5% of 4000). In spite of these limitations, those programmes which employ T_4 have similar

true-positive rates as programmes which start with TSH. As an example, Mitchell *et al.* [174] screened 129 028 infants and 3800 had T_4 values less than 6 μg/dl. Of the 3800, 31 were found to have a high TSH (greater than 20 μU/ml) and 23 were found to be hypothyroid.

(b) Screening with TSH

In theory, this approach would not diagnose the very uncommon case of secondary hypothyroidism. Against this disadvantage, those euthyroid patients with low T_4 due to non-thyroidal causes would not be misdiagnosed as hypothyroid as they are in the T_4 programme. Dockeray *et al.* [170] screened 76 224 patients and found 19 hypothyroid infants, none of whom had been diagnosed clinically and only 3 were clinically hypothyroid on recall. In order to diagnose 19 patients, only 50 had to be recalled (less than 0.1%). Thirty thousand infants were screened by Sutherland *et al.* [171], who found TSH to be more sensitive and specific than T_4. There were no false negatives and the incidence of hypothyroism was 1 in 3300.

Combined T_4 and TSH and other approaches

A combination of T_4 and TSH is the best approach for diagnosing all hypothyroid neonates, but it is more complicated and expensive. Because sick neonates often have a low T_4, clinicians screening these babies frequently will be faced with low values, and it would be sensible to request TSH values as well. As an alternative, since we [175] and many other workers have shown that FT_4 is valuable in differentiating hypothyroidism from euthyroidism in sick adults who have low T_3 and T_4, we studied the role of FT_4 in sick neonates [176]. FT_4 was measured between the second and fourth day postpartum, and the results compared with those from the state screening programme, which used T_4. Sixty-six per cent of the the euthyroid sick babies had T_4 values below the 5th percentile, but none had FT_4 values below the lower limit of the adult normal range (0.8 ng/dl). Two hypothyroid babies had FT_4 values of 0.3 and 0.4 ng/dl respectively. These results appear clear cut in differentiating hypothyroid from normal, but FT_4 values in healthy babies are higher than in adults and statistically higher than in sick babies (4.24 +/− 0.23 ng/dl; [M+/−SEM] v. 3.48 +/− 0.18 ng/dl). Therefore, sick neonates had lower FT_4 values. A cut-off at 0.8 ng/dl produced no false-positive or false-negative results. This test cannot be done with a sample of blood on filter paper, and since it requires about 0.5 ml of serum, it is not suited to large screening programmes. There is a small role for FT_4 in sick babies who have a low T_4, because a normal FT_4 and TSH exclude all forms of congenital hypothyroidism.

6.13 COST BENEFIT ANALYSIS OF SCREENING FOR HYPOTHYROIDISM

The cost per individual thyroid test in a neonatal screening programme is remarkably small, but if the incidence of the condition is 1/4000, is it cost effective? Layde *et al.* [177] estimated it would cost $11 800 to identify one patient and treat for life, whereas if the baby was not diagnosed and required long-term institutional care the cost would be nine times as much. The analysis assumes the treated child achieves normal functional capacity, and there is evidence that the final IQ is closely related to the age at which treatment is started; the earlier the treatment, the higher the IQ. Forty-five per cent of the patients treated by Smith *et al.* [178] before 6 months of age attained an IQ of greater than 90, whereas only 10% achieved that when treatment was delayed beyond 6 months. The authors also found that the more severe the hypothyroidism, the lower the final IQ. Similar results were reported in 31 infants treated by Klein *et al.*

[179], who found an average IQ of 89 in 3 babies treated before 3 months, 70 in those treated between 3–7 months, and 54 in those whose treatment was delayed beyond that time. In a different study, 14 out of 19 patients treated before 3 months achieved an IQ of more than 90, compared with 14 out of 37 in whom treatment was delayed [180]. These studies were based on clinical diagnosis of hypothyroidism and, by implication, dealt with severe cases. In most of the biochemical newborn screening programmes, very few of the babies found to be h pothyroid would have been diagnosed clinically. As a result, milder cases are being treated at an earlier stage and a better prognosis may be anticipated. Neonatal hypothyroidism is three times as common as phenylketonuria, and 1–2% of long-term, institutionalized, mentally deficient patients had delayed diagnosis and treatment of hypothyroidism. Therefore, the importance of screening newborns for hypothyroidism is proven.

6.14 INBORN ERRORS OF SYNTHESIS OF THYROID HORMONES (DYSHORMONOGENESIS)

Although these deficits are rare, they are the second most common cause of congenital hypothyroidism. They are due to the absence or lack of function of one of the enzymes which produce thyroid hormones. In fully developed cases, there is hypothyroidism, low T_4, high TSH and goitre. The defects are usually transmitted as autosomal recessive.

6.14.1 DEFECT IN TRAPPING IODINE

If the baby is diagnosed hypothyroid by biochemical screening tests, then this disorder is characterized by a low radioiodine uptake by the thyroid and an associated inability of the salivary glands to trap iodine [181]. It is diagnosed by measuring thyroidal RAIU of ^{123}I and by counting ^{123}I radioactivity in weighed samples of saliva and serum. The saliva contains equal or less radioactivity, which contrasts with other intrathyroidal enzyme defects where salivary radioactivity is considerably greater than serum radioactivity. The defect can be overcome by giving pharmacological doses of iodine, but the optimal therapy is thyroxine.

6.14.2 FAILURE TO ORGANIFY IODINE

In this disorder, iodine is trapped, but it is not combined with tyrosine, hence it has two names, either a defect in **organification of iodine**, or **iodination of tyrosine**. Radioiodine uptake is rapid and increased because the high TSH stimulates the trapping mechanism. The trapped iodine is free within the follicular cell and can be discharged with perchlorate. Some of these patients also have nerve deafness, the combination is called **Pendred's syndrome**, after his description in 1896 of two women with goitre, low intellect and deaf mutism [182]. It is not clear from his description that the women had a defect in organification. Treatment is with thyroxine.

6.14.3 DEFECT IN THE COUPLING OF IODOTYROSINES

The thyroid is capable of trapping iodine and organifying it, but T_4 and T_3 are not formed. Therefore, the uptake of ^{123}I is normal or high, and perchlorate discharge negative. Whether this disorder is due to an enzyme defect or to production of an abnormal thyroglobulin which cannot provide the required tertiary structure to bring iodotyrosines into apposition for coupling, is not clear. This defect is usually diagnosed by excluding the others or by biochemical analysis of a biopsy showing that iodothyronines are absent.

6.14.4 DEFECT IN THE DEIODINATION OF IODOTYROSINES

When thyroglobulin is taken into the follicular cells by pinocytosis, it is digested by proteolytic enzymes to release iodothyronines (T_4 and T_3) and iodotyrosines (MIT and DIT). The latter are metabolically inactive, and if they are released into the circulation, the iodine they contain is lost by excretion into the urine. To preserve the iodine, there is an enzyme inside the follicular cells capable of deiodinating iodotyrosines so that the iodine can be recycled for hormone synthesis. Because the defect is also present in extrathyroidal tissues, the iodotyrosines are not metabolized and can be detected by chromatography of the urine. The defect produces hypothyroidism by iodine deficiency and it is not clear if it would be found in areas of iodine excesss.

6.14.5 DEFECT IN THE FORMATION OF THYROGLOBULIN

Thyroglobulin is a large glycoprotein (660 000 mol wt) and it has considerable potential for errors in its formation. The problem can be compared to haemoglobinopathies where a single amino acid exchange can produce devastating pathophysiological consequences. An alteration in the amino acid sequence in thyroglobulin at a hormone-forming site could result in the wrong environment for synthesis of T_4 and T_3 to proceed. The net result is reduced hormone formation, hypothyroidism, increased TSH and goitre. Diagnosis is by exclusion of the other defects.

6.14.6 TISSUE RESISTANCE TO THYROID HORMONES

Hutchison *et al.* [183] reported on a non-goitrous cretin with resistance to thyroid extract who responded satisfactorily to T_3. There are several similar reports, and there are several syndromes of resistance to thyroid hormones. Wortsman *et al.* [184] described three members of a family with high T_4, FT_4, and rT_3, plus slightly elevated T_3 and a non-suppressed TSH. There was a normal rise in TSH after intravenous TRH, and T_4 fell when T_3 was prescribed. They provide evidence for a defect in transport of thyroxine across plasma membranes. This topic is discussed in Chapter 3 on testing thyroid function, since it is more likely to be found in adults.

6.15 SCINTIGRAPHY IN NEONATAL HYPOTHYROIDISM

There is debate whether thyroid scintigraphy should be ordered in neonatal hypothyroid babies. Brooks *et al.* [161] believe it gives important anatomical information which is of prognostic significance. Agenesis and ectopia are easily diagnosed, and rapid uptake suggest an enzyme defect (trapping defect excluded). The radiation dose is very low if 5–6 MBq (approximately 150 μCi) $^{99m}TcO_4$ is used, although uptake measurements are not in the expected range with this radiopharmaceutical. ^{123}I in a dose of 5–10 μCi (200–400 kBq) is acceptable. The authors feel that the scintiphoto is very easy to explain to the parents who are then more likely to comply with recommendations.

6.16 TREATMENT

The treatment of the inborn errors of thyroid hormone synthesis is thyroxine by mouth for life. The dose is shown in Table 6.3. In those patients with apparent resistance to thyroxine, triiodothyronine can be given, and if that is not successful supraphysiological doses of thyroxine are prescribed. It should be recalled that if triiodothyronine is used to treat hypothyroidism, T_4 is very low and T_3 values considerable higher than

normal, with results of 250–300 ng/dl associated with TSH in the normal range.

6.17 ACQUIRED (JUVENILE) HYPOTHYROIDISM

The causes of juvenile hypothyroidism are similar to those of adult hypothyroidism. Autoimmune thyroiditis is more common in children than is generally recognized, and the levels of thyroid antibodies are lower than in adults. Rarely, an ectopic hypoplastic gland will be the cause, and inborn errors are encountered very rarely.

The child is quiet, well behaved and uncomplaining. Depending on the duration of the disease, there may be dry skin, constipation, delayed puberty and lethargy. Growth is almost always retarded, and a slowing in the growth curve is an important clue. Bone age lags behind chronological age. Diagnosis is made by finding a low FT_4 and a high TSH (TSH will not be high in central hypothyroidism), and if there is a mass in the region of the foramen caecum or anterior neck a ^{123}I scintigram should be obtained. The presence of thyroid antibodies in the circulation establishes the cause in most patients. Treatment is with thyroxine by mouth; the dose in children is somewhat larger on a weight basis than in adults but by puberty adult doses in the range 100–150 μg per day are usually satisfactory. The patient should be clinically and biochemically euthyroid. A word of caution is necessary. The return of thyroid status to normal is often heralded by complaints from parents and teachers that a placid, manageable child has been transformed into an unruly one. Usually this means the child is normal.

A recent report in 24 children (18 girls and 6 boys) is disquieting, because it showed these patients after treatment with thyroxine did not achieve their expected height, and they remained 2 SD below age-matched controls [185]. The most likely cause was delay in diagnosing hypothyroidism, which stresses the need for considering this diagnosis even when symptoms are non-specific.

6.18 HYPOTHYROIDISM IN THE ELDERLY

A separate discussion of hypothyroidism in the elderly is merited because there are several differences from younger adults. First, there are changes in thyroid function with increasing age. Most surveys show that T_3 values are lower in euthyroid elderly. It is not always possible to be certain that this change is not due to coexistent chronic illness (I have already recommended not measuring T_3 for suspected hypothyroidism). T_4 values are usually in the normal range, but the TSH shows a slight but progressive rise with age. If it is accepted that a high TSH means hypothyroidism, a significant proportion of elderly are hypothyroid. Robuschi *et al.* [186] found high TSH in 21% of an elderly female population in Massachusetts, and of this group one-third were hypothyroid and two-thirds subclinically hypothyroid. Brochman *et al.* [187] found TSH above 6 in 5.3% and 3.6% of elderly women and men respectively. An editorial in *JAMA* in 1952 is entitled 'Hypothyroidism, a geriatric problem'! RAIU falls in the elderly, as does the absolute iodine uptake [188]. Provided the patients studied are euthyroid, the FT_4 remains normal; therefore FT_4 and TSH are recommended for testing.

The symptoms of hypothyroidism in this age group are frequently non-specific, and are easily attributed to ageing [189]. They include tiredness, lethargy, failing memory, weakness, arthralgias, reduced mobility and depression. Hurley [189] coined the term 'masked hypothyroidism'. Because of the high incidence of hypothyroidism, testing is recommended if there is the slightest suspicion of this condition.

The replacement dose of thyroxine is less in the elderly. Davis *et al.* [190] found that

110 ± 8μg L thyroxine kept the TSH in the normal range and 139 ± 12μg suppressed the TSH. Formulae are provided by Robuschi *et al.* [186].

Dose of thyroxine
= 3.6 × lean body mass (LBM) − 30
LBM Male
= (79.5 − 0.24 × M − 0.15 × A) × M/73.2
LBM Female
= (69.8 − 0.26 × M − 0.12 × A) × M/73.2
Where M is mass in kg and A is the area in square metres.

These are somewhat complicated for everyday use, and if it is recalled that in this age group the usual range of thyroxine is somewhat less than 1 μg/lb or 2 μg/k, and that treatment should be started with a small dose such as 25 μg and increased by 25 μg increments at intervals of 2–4 weeks until 100 μg is reached. After the patient has been on that dose for 6–8 weeks, FT_4 and TSH are measured to ensure they are in the normal range. If TSH is still high, a further adjustment can be made to 112 or 125 μg depending on the degree of TSH elevation. The elderly are more likely to be taking several medications and to misinterpret instructions, or stop medication, and so it is helpful to check periodically that they are following recommendations. If TSH is found to be high, it suggests lack of compliance, or misunderstanding of the need for lifelong therapy.

KEY FACTS

- Hypothyroidism is due to insufficient thyroid hormones to meet requirements of tissues.
- Hypothyroidism is very common; the prevalence in adults is 1%.
- Hypothyroidism is 5–10 times more common in women.
- The elderly are more often hypothyroid.
- By far the three most common causes are primary hypothyroidism (autoimmune), surgical removal, and radioiodine ablation of the gland.
- Any system of the body can be involved; the more severe and more prolonged the disease, the more systemic the clinical features.
- In general, the symptoms and signs are those of reduced function.
- Diagnosis is to prove hypothyroidism is present, and to determine the anatomical level of the condition and the specific pathology.
- Usually, the cause is one of three discussed above and is obvious clinically.
- Diagnosis is confirmed by low FT_4 and high TSH.
- Treatment is with L thyroxine.
- The usual replacement dose is approximately (just less than) 1 μg/lb body weight.
- The rate of treatment depends on the severity of the disease, the age of the patient, and the presence of other conditions.
- Thyroxine should be replaced slowly in the old and infirm.
- Rarely, the pituitary or hypothalamus is at fault.
- Diagnosis confirmed by low FT_4 and low TSH.
- A TRH test is needed to determine the exact level of the lesion.
- Look for reduced function of other endocrine glands: this is very important in the case of hypoadrenalism.
- Treatment is similar to primary hypothyroidism, but other hormones may be necessary. If there is adrenal insufficiency this should be corrected first.
- Extremely severe hypothyroidism with a loss of consciousness and hypothermia is called myxoedema coma.
- The mortality from myxoedema coma is high.
- Treatment of myxoedema coma is urgent: do not wait for laboratory confirmation.

- The patient is admitted to the intensive care unit; usually a large dose of L thyroxine is given parenterally (500 μg).
- Treatment includes slow rewarming, attention to fluid and electrolyte balance and appropriate antibiotics for infection.
- Neonatal hypothyroidism should be diagnosed by blood tests shortly after birth and treatment prescribed for life.

REFERENCES

1 Refetoff, S. (1980) Resistance to thyroid hormones. *Thyroid Today*, (ed. J.H. Oppenheimer), Vol 3, Oct.

2 Karlsson, F.A., Wibell, L. and Wide, L. (1977) Hypothyroidism due to thyroid-hormone-binding antibodies. *N. Engl. J. Med.*, **296**, 1146–8.

3 Hague, R.V., Higgins, S.P. and May, P.J. (1986) Primary hypothyroidism with paradoxically elevated plasma thyroxine due to thyroxine-binding antibodies. *Postgrad. Med. J.*, **62**, 845–6.

4 Evered, D.C., Ormston, B.J., Smith, P.A. *et al.* (1973) Grades of hypothyroidism. *Br. Med. J.*, **1**, 657–62.

5 Goudie, R.B., Anderson, J.R. and Gray, K.G. (1959) Complement-fixing antithyroid antibodies in hospital patients with asymptomatic thyroid lesions. *J. Pathol. Bact.*, **77**, 389–400.

6 Wood, L.C. and Maloof, F. (1975) Thyroid failure after potassium iodide treatment of diffuse toxic goitre. *Trans, Ass, Am, Phys.*, **88**, 235–47.

7 Wood, L.C. and Ingbar, S.H. (1979) Hypothyroidism as a late sequela in patients with Graves' disease treated with antithyroid drugs. *J. Clin. Invest.*, **64**, 1429–36.

8 Smith, R.E., Adler, R.A., Clark, P. *et al.* (1981) Thyroid function after mantle irradiation in Hodgkin's disease. *JAMA*, **245**, 46–9.

9 Shalet, S.M., Rosenstock, J.D., Beardwell, C.G. *et al.* (1977) Thyroid dysfunction following external irradation to the neck for Hodgkin's disease, *Clin. Radiol.*, **28**, 511–15.

10 Slanina, J., Musshoff, K., Rahner, T. *et al.* (1977) Long-term side effects in irradiated patients with Hodgkin's disease. *Int. J. Rad. Onc. Biol. Phys.*, **2**, 1–9.

11 Shafer, R.B., Nuttal, F.Q., Pollock, F. *et al.* (1975) Thyroid function after radiation for head and neck cancer. *Arch. Intern. Med.*, **135**, 843–6.

12 Constine, L.S., Donaldson, S.S., McDougall, I.R. *et al.* (1984) Thyroid dysfunction after radiotherapy in children with Hodgkin's disease. *Cancer*, **53**, 46–51.

13 Kitching, N.H. (1986) Hypothyroidism after treatment with ketoconazole. *Br. Med. J.*, **293**, 993–4.

14 Atkins, M.S., Mier, J.W., Parkinson, D.R. *et al.* (1988) Hypothyroidism after treatment with interleukin-2 and lymphokine-activated killer cells. *N. Engl. J. Med.*, **318**, 1557–63.

15 Emerson, C.H., Dyson, W.L. and Utiger, R.D. (1973) Serum thyrotropin and thyroxine concentration in patients receiving lithium carbonate. *J. Clin. Endocrinol. Metab.*, **36**, 338–46.

16 Lazarus, J.H., John, R., Bennie, E.H. *et al.* (1981) Lithium therapy and thyroid function: a long-term study. *Psychol. Med.*, **11**, 85–92.

17 Wolff, J. (1969) Iodide goiter and the pharmacological effects of excess iodide. *Am. J. Med.*, **47**, 101–24.

18 Braverman, L.E., Woeber, K.A. and Ingbar, S.H. (1969) Induction of myxedema by iodide in patients euthyroid after radioiodine or surgical treatment of hyperthyroidism. *N. Engl. J. Med.*, **281**, 816–21.

19 Gray, H.W., Greig, W.R., Hooper, L.A. *et al.* (1972) A twenty minute perchlorate discharge test. *J. Clin. Endocrinol. Metab.*, **34**, 494–6.

20 Braverman, L.E., Ingbar, S.H., Vagenakis, A.G. *et al.* (1971) Enhanced susceptibility to iodide myxedema in patients with Hashimoto's disease. *J. Clin. Endocrinol. Metab.*, **32**, 515–21.

21 Begg, T.B. and Hall, R. (1963) Iodide goitre and hypothyroidism. *Quart. J. Med.*, **32**, 351–62.

22 Prager, E.M. and Gardner, R.E. (1979) Iatrogenic hypothyroidism from topical iodine-containing medications. *West J. Med.*, **130**, 553–5.

23 Beierwaltes, W.H. (1969) Iodine and lymphocytic thyroiditis. *Bull. All. Ind. Inst. Med. Sci.*, **3**, 145–52.

24 Kriss, J.P., Carnes, W.H. and Gross, R.T. (1955) Hypothyroidism and thyroid hyperplasia in patients treated with cobalt. *JAMA*, **157**, 117–21.

25 Robins, J.M., Cullen, M.R., Connors, B.B. *et al.* (1983) Depressed thyroid indexes associated with occupational exposure to inorganic lead. *Arch. Intern. Med.*, **143**, 220–4.

26 Endo, V.R., Konishi, J., Iida, Y. *et al.* (1983)

Primary hypothyroidism caused by TSH-receptor antibodies. *J. Nucl. Med.*, **24**, 65–6 (abstract).
27 Staeheli, V., Valloton, M.B. and Burger, A. (1975) Detection of human antithyroxine and antitriiodothyronine antibodies in different clinical conditions. *J. Clin. Endocrinol. Metab.*, **41**, 669–75.
28 Wu, S-Y. and Green, W.L. (1976) Triiodothyronine (T_3) binding immunoglobulins in a euthyroid woman: effects on measurement of T_3 (RIA) and on T_3 turnover. *J. Clin. Endocrinol. Metab.*, **42**, 642–52.
29 Tunbridge, W.M.G., Bremis, M., French, J., *et al.* (1981) Natural history of auto-immune thyrodiditis. *Br. Med. J.*, **282**, 258–62.
30 Tunbridge, W.M.G. (1982) Screening for thyroid disease in the community, *Thyroid Today*, (ed. J.H. Oppenheimer), Vol V. Sept/Oct.
31 Dos Remedios, L.V., Weber, P.M., Feldman, R. *et al.* (1980) Detecting unsuspected thyroid dysfunction by the free thyroxine index. *Arch. Intern. Med.*, **140**, 1045–9.
32 Sawin, C.T., Chopra, D., Azziz, F. *et al.* (1979) The aging thyroid. Increased prevalence of elevated serum thyrotropin levels in the elderly. *JAMA*, **242**, 247–50.
33 Bahemuka, M. and Hodgkinson, H.M. (1975) Screening for hypothyroidism in elderly inpatients. *Br. Med. J.*, **2**, 601–3.
34 Falkenberg, M. and Kagedal, B. (1985) Screening of elderly women for thyroid dysfunction. *Lancet*, **1**, 1222.
35 Curling, T.B. (1850) Two cases of absence of the thyroid body, and symmetrical swellings of the fat tissue at the side of the neck, connected with defective cerebral development. *Med. Chir. Trans.*, **33**, 303.
36 Gull, W.W. (1874) On the cretinoid state supervening in adult life in women. *Trans. Clin. Soc. Lon.*, **7**, 180–5.
37 Ord, W.M. (1878) On myxedema, a term proposed to be applied to the essential condition in the 'cretinoid' affection occasionally observed in middle-aged women. *Med. Chir. Trans.*, **61**, 57–68.
38 Bloomfield, A.L. (1958) A bibliography of internal medicine: myxedema. *Stanford Med. Bull.*, **16**, 207–17,
39 Aikawa, J.K. (1961) Myxedema. Charles C. Thomas, Springfield, Illinois.
40 Rajagopal. K.P., Abbrecht, P.H. and Derderian, S.S. (1984) Obstructive sleep apnea in hypothyroidism. *Ann. Intern, Med.*, **101**, 491–4.
41 Freedberg, I.M. (1971) Skin, in *The Thyroid*, (eds S.C. Werner and S.H. Ingbar), Harper and Row, New York, p. 722.
42 Asher, R. (1949) Myxoedema madness. *Br. Med. J.*, **2**, 555–62.
43 Herridge, C.F. and Abey-Wickram, I. (1969) Acute iatrogenic hypothyroid psychosis. *Br. Med. J.*, **3**, 154.
44 Cronin, A.J. (1937) The Citadel, Little Brown, Boston.
45 Nickel, S. and Frame, B. (1958) Neurologic manifestations of myxedema. *Neurology*, **8**, 511–17.
46 Bloomer, H.A. and Kyle, L.H. (1959) Myxedema: reevaluation of clinical diagnosis based on eighty cases. *Arch. Intern. Med.*, **104**, 234–41.
47 Watanakunakron, C., Hodges, R.E. and Evans, T.C. (1965) Myxedema. A study of 400 cases. *Arch. Intern, Med.*, **116**, 183–90.
48 Kliachko, V.R. and Prikhozhan, V.M. (1970) Neurologic disorders in primary hypothyroidism. *Problem. Endokrinol. (Mosk)*, **16**, 24–9.
49 Committee of the Society Nominated December 14, 1883 to investigate the subject of myxedema, (1988) *Trans. Clin. Soc. London*, **21**, (Suppl.).
50 Ramsay, I. (1974) *Thyroid Disease and Muscle Dysfunction*. Year Book Medical Publishers Inc. Chicago.
51 Halverson, P.B., Kozin, F., Ryan, L.M. *et al.* (1979) Rhabdomyolysis and renal failure in hypothyroidism. *Arch. Intern. Med.*, **91**, 57–8.
52 Bland, J.H. and Frymoyer, J.W. (1970) Rheumatic syndromes of myxedema. *N. Engl. J. Med.*, **282**, 1171–4.
53 Bland, J.H., Frymoyer, J.W., Newberg, A.M. *et al.* (1979) Rheumatic syndromes in endocrine disease. *Sem. Arth. Rheum.* **9**, 23–65.
54 Lee, J.K. and Lewis, J.A. (1962) Myxoedema with complete A-V block and Adams-Stoke disease abolished with thyroid medication. *Br. Heart. J.*, **24**, 253–6.
55 Macauley, M.B. and Shepherd, R.J. (1971) Syncope in myxoedema due to transient ventricular fibrillation. *Postgrad. Med. J.*, **47**, 361–7.
56 Marcuson, R.W. (1965) Ventricular fibrillation in myxoedema heart disease with spontaneous reversion. *Br. Heart J.*, **27**, 455–7.
57 Alsever, R.N. and Stjernholm, M.R. (1975) Cardiac tamponade in myxedema. *Am. J. Med. Sci.*, **269**, 117–21.
58 Kelly, J.K. and Butt, J.C. (1986) Fatal

myxedema pericarditis in a Christian Scientist. *Am. J. Clin. Pathol.*, **86**, 113–16.
59 Zondek, H. (1959) Association of myxedema heart and atherosclerotic heart disease. *JAMA*, **170**, 1920–1.
60 Bastenie, P.A. (1982) Hypothyroidism and coronary heart disease. *Acta Cardiologica*, **37**, 365–73.
61 Vanhaelst, L. and Bastenie, P.A. (1968) Heart and coronary heart disease in hypothyroidism. *Am. Heart J.*, **76**, 845–8.
62 Fowler, P.B.S. (1977) Premyxoedema: a cause of preventible coronary heart disease (editorial). *Proc. Roy. Soc. Med.*, **70**, 297–9.
63 Fowler, P.B.S. (1980) Lipid alterations in myxedema and asymptomatic thyroiditis. *Excerpta Med. Congr. Ser. No.*, **529**, 94.
64 Kutty, K.M., Bryant, D.G. and Farrid, N.R. (1978) Serum lipids in hypothyroidism: a reevaluation. *J. Clin. Endocrinol. Metab.*, **46**, 55–60.
65 Silver, S. (1968) Treatment with ^{133}I of cardiac disease in euthyroid patients, in *Radioactive Nuclides in Medicine and Biology*, Lea and Febiger, Philadelphia, p. 209.
66 Goldman J., Matz, R., Mortimer, R. *et al.* (1977) High elevations of creatine phosphokinase in hypothyroidism. *JAMA*, **238**, 325–6.
67 Castleden, C.M. and Williams, A.J. (1982) Hypothyroidism – classic symptoms plus the unexpected. *Geriatrics*, **37**, 133–8.
68 Fahr, G. (1925) Myxedema heart. *JAMA*, **84**, 345–9.
69 Shagan, B.P. and Friedman, S.A. (1986) Raynaud's phenomenon and thyroid deficiency. *Arch. Intern. Med.*, **140**, 832–3.
70 Tudhope, G.R. and Wilson, G.M. (1960) Anaemia in hypothyroidism. Incidence, pathogenesis and response to treatment. *Quart. J. Med.*, **29**, 513–17.
71 Ardeman, S., Baralessa, H. and Sale, R.F. (1981) Coagulation inhibitor in hypothyroidism. *Br. Med. J.*, **282**, 1508.
72 Tachman, M.L. and Guthrie, G.P. (1984) Hypothyroidism: diversity of presentation. *Endocrine Rev.*, **5**, 456–65.
73 Duret, R.L. and Bastenie, P.A. (1971) Intestinal disorders in hypothyroidism. Clinical and manometric study. *Am. J. Dig. Dis.*, **16**, 723–7.
74 Hohl, R.D. and Nixon, R.K. (1965) Myxedema ileus. *Arch. Intern. Med.*, **115**, 145–50.
75 Wells, I., Smith, B. and Hinton, M. (1977) Acute ileus in myxoedema. *Br. Med. J.*, **1**, 211–12.
76 Fox, R.A. and Schwartz, T.B. (1967) Infiltrative ophthalmopathy and primary hypothyroidism. *Ann. Intern. Med.*, **67**, 377–80.
77 Jackson, W.P.U. (1956) Post-thyroidectomy hypothyroidism, hypoparathyroidism, exophthalmos and galactorrhea with normal menstruation. *J. Clin. Endocrinol, Metab.*, **16**, 1245–50.
78 Edwards, C.R.W., Forsyth, I.A. and Besser, G.M. (1971) Amenorrhea, galactorrhea and primary hypothyroidism with high circulating levels of prolactin. *Br. Med. J.*, **3**, 462–4.
79 Semple, C.G., Beastall, C.H., Teasdale, G. *et al.* (1983) Hypothyroidism presenting with hyperprolactinaemia. *Br. Med. J.*, **286**, 1200–1.
80 Shasahani, M.N. and Wong, E.T. (1978) Primary hypothyroidism, amenorrhea and galactorrhea. *Arch. Intern. Med.*, **138**, 1411–13.
81 Onishi, T., Miyai, K., Aono, T. *et al.* (1977) Primary hypothyroidism and galactorrhea. *Am. J. Med.*, **63**, 373–8.
82 Pettinger, W.A., Tainer, L. and Ferris, T.F. (1965) Inappropriate secretion of antidiuretic hormone due to myxedema. *N. Engl. J. Med.*, **272**, 362–4.
83 Macaron, C. and Famuyima, O. (1978) Hyponatremia of hypothyroidism. Appropriate suppression of antidiuretic hormone levels. *Arch. Intern. Med.*, **138**, 820–2.
84 Schneirson, S.J. and Katz, M. (1958) Solitary pleural effusion due to myxedema. *JAMA*, **168**, 1003–5.
85 Paddock, F.K. (1950) Massive ascites due to myxedema. *N. Engl. J. Med.*, **242**, 822–3.
86 Levine, H.J. and Levine, S.A. (1960) Myxedema ascites: report of two cases. *Am. Heart J.*, **60**, 456–63.
87 Isaacs, A.J. and Havard, C.W.H. (1976) Myxedema and hydrocele. *Br. Med. J.*, **1**, 322.
88 Sare, Z., Ruralcaba, R.H.A. and Kelley, V.C. (1978) Prevalence of thyroid disorders in Down's syndrome. *Clin. Genet.*, **14**, 154–8.
89 Lobo, E. de. H., Kahn, M. and Tew, J. (1980) Community study of hypothyroidism in Down's syndrome. *Br. Med. J.*, **1**, 1253.
90 Cohen, K. and Felig, P. (1979) Primary hypothyroidism and the pituitary. *Arch. Intern. Med.*, **139**, 855–6.
91 Danziger, J., Wallace, S., Handel, S. *et al.* (1979) The sella turcica in end organ failure. *Radiology*, **131**, 111–15.
92 Jawadi, M.H., Ballonoff, L.B., Stears, J.E. *et al.* (1978) Primary hypothyroidism and pituitary enlargement. Radiological evidence of

pituitary regression. *Arch. Intern. Med.*, **138**, 1555–7.
93 Silver, B.J., Kyner, J.L., Dick, A.R. *et al.* (1981) Primary hypothyroidism: suprasellar pituitary enlargement and regression on computed tomographic scanning. *JAMA*, **246**, 364–5.
94 Klein, I. and Levey, G.S. (1984) Unusual manifestations of hypothyroidism. *Arch. Intern. Med.*, **144**, 123–8.
95 Tudhope, G.R. (1969) *The Thyroid and the Blood*, Heinemann Medical Books, London.
96 Carmel, R. and Spencer, C.A. (1982) Clinical and subclinical thyroid disorders associated with pernicious anemia. *Arch. Intern. Med.*, **142**, 1465–9.
97 Chanarin, I. (1969) *The Megaloblastic Anaemias*, Blackwell, London.
98 Krassas, G., McHardy-Young, S., Ramsay, I. *et al.* (1977) Thyroid function and antibody studies in pernicious anemia. *Clin. Endocrinol.*, **6**, 145–51.
99 Edmonds, M., Lamki, L., Killinger, D.W. *et al.* (1973) Autoimmune thyroiditis, adrenalitis and oophoritis. *Am. J. Med.*, **54**, 782–7.
100 Gordon, M.B., Klein, I., Dekker, A. *et al.* (1981) Thyroid disease in progressive systemic sclerosis: increased frequency of glandular fibrosis and hypothyroidism. *Ann. Intern. Med.*, **95**, 431–5.
101 How, J., Bewsher, P.D. and Walker, W. (1977) Giant-cell arteritis and hypothyroidism. *Br. Med. J.*, **2**, 99.
102 Sung, L. and McDougall, I.R. (1978) Graves' hyperthyroidism occurring spontaneously after autoimmune hypothyroidism with persistent infiltrative ophthalmopathy. *Arch. Intern. Med.*, **138**, 1009–10.
103 Constine, L.S. and McDougall, I.R. (1982) Radiation therapy for Hodgkin's disease followed by hypothyroidism and then Graves' hyperthyroidism. *Clin. Nucl. Med.*, **7**, 69–70.
104 Fatourechi, V. and Gharib, H. (1988) Hyperthyroidism following hypothyroidism. *Arch. Intern. Med.*, **148**, 976–8.
105 Henneman, G., Van Welsum, M., Bernard, B. *et al.* (1975) Serum thyrotrophin concentration: an unreliable test for detection of early hypothyroidism after thyroidectomy. *Br. Med. J.*, **4**, 129–30.
106 Toft, A.D. (1978) Predicting hypothyroidism. *Scot. Med. J.*, **23**, 263–5.
107 Pittman, J.A., Haigher, E.D., Hershman, J.M. *et al.* (1971) Hypothalamic hypothyroidism. *N. Engl. J. Med.*, **285**, 844–5.
108 Shenkman, L., Mitsuma, T., Suphavai, A. *et al.* (1972) Hypothalamic hypothyroidism. *JAMA*, **222**, 480–1.
109 Vagenakis, A.G., Braverman, L.E., Aylzi, F. *et al.* (1975) Recovery of pituitary thyrotropic function after the withdrawal of prolonged thyroid-suppression therapy. *N. Engl. J. Med.*, **293**, 681–4.
110 Stoffer, S.S., Szpunar, W.E. and Meier, D. (1983) Faster assessment of patients receiving unnecessary thyroxine treatment: concise communication. *J. Nucl. Med.*, **24**, 119–22.
111 Murray, G.R. (1891) Note on the treatment of myxoedema by hypodermic injections of an extract of the thyroid gland of a sheep. *Br. Med. J.*, **2**, 796–7.
112 Murray, G.R. (1920) Life-history of first case of myxoedema treated by thyroid extract. *Br. Med. J.*, **1**, 359–60.
113 McKenzie, H.W.G. (1892) Case of myxoedema treated with great benefit by feeding with fresh thyroid gland. *Br. Med. J.*, **2**, 440.
114 MacGregor, A.G. (1961) Why does anyone use thyroid BP? *Lancet*, **1**, 329–32.
115 Taylor, S. (1961) Thyroid extract. *Lancet*, **1**, 332–3.
116 Jackson, I.D. and Cobb, W.E. (1978) Why does anyone still use desiccated thyroid USP. *Am. J. Med.*, **64**, 284–8.
117 Penny, R. and Frasier, D. (1980) Elevated serum concentrations of triiodothyronine in hypothyroid patients. Values for patients receiving USP thyroid. *Am. J. Dis. Child*, **134**, 16–18.
118 Morillo, E. and Gardner, L.I. (1979) Hypertriiodothyroninemia in hypothyroidism treated with thyroglobulin. *Am. J. Dis. Child*, **133**, 71–2.
119 Larsen, P.R. (1982) Thyroid-pituitary interaction: feedback regulation of thyrotroph secretion by thyroid hormone. *N. Engl. J. Med.*, **306**, 23–32.
120 Evered, D., Young, E.T., Ormston, B.J. *et al.* (1973) Treatment of hypothyroidism: a reappraisal of thyroxine therapy. *Br. Med. J.* **3**, 131–5.
121 Stock, J.M., Surks, M.I. and Oppenheimer, J.H. (1974) Replacement dosage of L-thyroxine in hypothyroidism. A reevaluation. *N. Engl. J. Med.*, **290**, 529–33.
122 Rosenbaum, R.L. and Barzel, U.S. (1982) Levothyroxine replacement dose for primary hypothyroidism decreases with age. *Ann. Intern. Med.*, **96**, 53–5.
123 Rezvani, I. and Di George, A.M. (1977) Reassessment of the daily dose of oral thyroxine

for replacement therapy in hypothyroid children. *J. Pediatr.*, **90**, 291–7.
124 Stoffer, S.S. and Szpunar, W.E. (1980) Potency of brand name and generic levothyroxine products. *JAMA*, **247**, 203–5.
125 Kehoe, W.A., Dong, B.J. and Greenspan, F.S. (1984) Maintenance requirements of L-thyroxine in the treatment of hypothyroidism. *West J. Med.*, **140**, 907–9.
126 Sawin, C.T., Surks, M.I., London, M. *et al.* (1984) Oral thyroxine: variation in biological action and tablet content. *Ann. Intern. Med.*, **100**, 641–5.
127 Letters in response to reference 126. *Ann. Intern. Med.*, **101**, 140–1.
128 Curry, S.H., Gums, J.G., Williams, L.L., *et al.* (1988) Levothyroxine sodium tablets: chemical equivalence and bioequivalence. *Drug Intell. Clin. Pharm.*, **22**, 589–91.
129 Brown, M.E. and Refetoff, S. (1980) Transient elevation of serum thyroid hormone concentrations after iniation of replacement therapy in myxedema. *Ann. Intern. Med.*, **92**, 491–5.
130 Fraser, W.D., Biggart, E.M., O'Reilly, D. St. J. *et al.* (1986) Are biochemical tests of thyroid function of any value in monitoring patients receiving thyroxine replacement? *Br. Med. J.*, **293**, 808–10.
131 Ross, D.S., Neer, R.M., Ridgway, E.C. *et al.* (1987) Subclinical hyperthyroidism and reduced bone density as a possible result of prolonged suppression of the pituitary-thyroid axis with L-thyroxine. *Am. J. Med.*, **82**, 1167–70.
132 Chung, S.J. and Van Middlesworth, L. (1964) Absorption of thyroxine from the small intestine of rats. *Endocrinol.*, **74**, 694–700.
133 Read, D.G., Hays, M.T. and Hershman, J.M. (1979) Absorption of oral thyroxine in hypothyroid and normal man. *J. Clin. Endocrinol.*, **30**, 798–9.
134 Azizi, F., Belur, R. and Albano, J. (1979) Malabsorbtion of thyroid hormone after jejunoileal bypass for obesity. *Ann. Intern. Med.*, **90**, 941–2.
135 Bastenie, P.A., Vanhaelst, L. and Neve, P. (1967) Coronary artery disease in hypothyroidism. Observations in preclinical myxoedema. *Lancet*, **2**, 1221–2.
136 Cooper, D.S., Halpern, R., Wood, L.C. *et al.* (1984) L thyroxine therapy in subclinical hypothyroidism. A double blind placebo controlled trial. *Ann. Intern. Med.*, **101**, 18–24.
137 Nystrom, E., Caidahl, K., Fager, G. *et al.* (1988) A double-blind cross-over 12 month study of L thyroxine treatment of women with 'subclinical' hypothyroidism. *Clin. Endocrinol.*, **29**, 63–76.
138 Kapdi, C.C. and Wolfe, J.N. (1976) Breast cancer: relationship to thyroid supplements for hypothyroidism. *JAMA*, **236**, 1124–7.
139 Education Committee: American Thyroid Association (1977) Breast cancer and thyroid hormone therapy. *Ann. Intern. Med.*, **86**, 53.
140 Shapiro, S., Slone, D., Kaufman, D.W. *et al.* (1980) Use of thyroid supplements in relation to the risk of breast cancer. *JAMA*, **244**, 1685–7.
141 Paine, T.D., Rogers, W.J., Baxley, W.A. *et al.* (1977) Coronary artery surgery in patients with incapacitating angina pectoris and myxedema. *Am. J. Cardiol.*, **40**, 226–31.
142 Hay, I.D., Duick, D.S., Vliestra, R.E. *et al.* (1981) Thyroxine therapy in hypothyroid patients undergoing coronary revascularisation: a retrospective analysis. *Ann. Intern. Med.*, **95**, 456–7.
143 Levine, H.D. (1980) Compromise therapy in the patient with angina pectoris and hypothyroidism. A clinical assessment. *Am. J. Med.*, **69**, 411–17.
144 Abbott, T.R. (1967) Anaesthesia in untreated myxoedema: report of two cases. *Br. J. Anaesthes.*, **39**, 510–14.
145 Kim, J.M. and Hackman, L. (1977) Anesthesia for untreated hypothyroidism: report of three cases. *Anesthes. Analg.*, **56**, 299–302.
146 Murkin, J.M. (1983) Anesthesia and hypothyroidism: a review of thyroxine physiology, pharmacology, and anesthetic implications, *Anesthes, Analg.*, **61**, 371–83.
147 Weinberg, A.D., Brennan, M.D., Gorman, C.A. *et al.* (1983) Outcome of anesthesia and surgery in hypothyroid patients. *Arch. Intern. Med.*, **143**, 893–7.
148 Drucker, D.J. and Burrow, G.N. (1985) Cardiovascular surgery in the hypothyroid patient. *Arch. Intern. Med.*, **145**, 1585–7.
149 Becker, C. (1985) Hypothyroidism and atherosclerotic heart disease: Pathogenesis, medical management, and the role of coronary artery bypass surgery. *Endocrin. Rev.*, **6**, 432–40.
150 Sanders, V. (1962) Neurological manifestations of myxedema. *N. Engl. J. Med.*, **266**, 547–52.
151 Wartofsky, L. (1986) Myxedema coma, in *Werner's The Thyroid*, 5th edn, (eds S.H. Ingbar and L.E. Braverman), Lippincott, Philadelphia, pp. 1227–34.

152 Newmark, S.R., Himathongkam, T. and Shane, J.M. (1974) Myxedema coma. *JAMA*, **230**, 884–5.
153 Catz, B. and Russell, S. (1961) Myxedema shock and coma. *Arch. Intern. Med.*, **108**, 407–17.
154 Holvey, D.N., Goodner, C.J., Nicoloff, J.T. *et al.* (1964) Treatment of myxedema coma with intravenous thyroxine. *Arch. Intern. Med.*, **113**, 139–46.
155 Nicoloff, J.T. (1979) Myxedema coma, in *The Thyroid: Physiology and Treatment of Disease*, (eds J.M. Hershman and G.M. Bray), Pergamon Press, Oxford; The Lippincott Co, Philadelphia, pp. 401–9.
156 Ladenson, P.W., Goldenheim, P.D., Cooper, D.S. *et al.* (1982) Early peripheral responses to intravenous L-thyroxine in primary hypothyroidism. *Am. J. Med.*, **73**, 467–74.
157 Hutchison, J.H. (1980) *Practical Pediatric Problems*, Year Book Medical Publishers Inc, Chicago, pp. 405–21.
158 McFaul, R. and Grant, D.B. (1977) Early detection of congenital hypothyroidism. *Arch. Dis. Child*, **52**, 87–8.
159 Fisher, D.A. (1980) Perinatal thyroid development and abnormalities, in *Neonatal Thyroid Screening*, (eds G.N. Burrow and J.H. Dussault), Raven Press, New York, pp. 9–23.
160 Fisher, D.A. and Klein, A.H. (1981) Thyroid development and disorders of thyroid function in the newborn. *N. Engl. J. Med.*, **304**, 702–12.
161 Brooks, P.T., Archard, J.H., Carty, H.M.L. *et al.* (1988) Thyroid screening in congenital hypothyroidism: a review of 41 cases, *Nucl. Med. Comm.*, **9**, 613–17.
162 Fisher, D.A., Dussault, J.H., Foley, T.P. *et al.* (1979) Screening for congenital hypothyroidism: results of screening one million North American infants. *J. Pediatrics.*, **92**, 700–5.
163 Goldsmith, R.E., McAdams, A.J., Larsen, P.R. *et al.* (1973) Familial autoimmune thyroiditis: maternal-fetal relationship and the role of generalised autoimmunity. *J. Clin. Endocrinol. Metab.*, **37**, 265–75.
164 Dussault, J.H., Mitchell, M.L., LaFranchi, S. *et al.* (1980) Regional screening for congenital hypothyroidism: results of screening one million North American infants with filter spot paper T_4-TSH, in *Neonatal Thyroid Screening*, (eds G.N. Burrow and J.H. Dussault), Raven Press, New York, pp. 155–66.
165 Matsuura, N., Yamada, Y., Nohara, Y. *et al.* (1980) Familial neonatal transient hypothyroidism due to maternal TSH-binding inhibitor immunoglobulins. *N. Engl. J. Med*, **303**, 738–41.
166 Burrow, G.N. and Dussault, J.H. (1980) *Neonatal Thyroid Screening*, Raven Press, New York.
167 Irie, M. (1980) Summary of new born thyroid screening – Japanese experience, in *Neonatal Thyroid Screening*, (eds G.N. Burrow and J.H. Dussault), Raven Press, New York, pp. 139–44.
168 DeLange, F., Beckers, C., Hofer, R. *et al.* (1980) Progress report on neonatal screening for congenital hypothyroidism in Europe, in *Neonatal Thyroid Screening*, (eds G.N. Burrow and J.H. Dussault), Raven Press, New York, pp. 107–32.
169 Foley, T.P. and Murphey, W.H. (1980) Hypothyroidism at birth, during the first week of life and at approximately one month of age: comparison to primary T_4 with secondary TSH screening, in *Neonatal Thyroid Screening*, (eds G.N. Burrow and J.H. Dussault), Raven Press, New York, pp. 75–86.
170 Dockeray, S., Cahalane, S.F., Brody, M. *et al.* (1980) Screening for congenital hypothyroidism in the Republic of Ireland. *Br. Med. J.*, **281**, 1519–22.
171 Sutherland, R.M., Ratcliffe, J.G. Kennedy, R. *et al.* (1981) Neonatal screening for hypothyroidism in Scotland. Results of a pilot study. *Scott. Med. J.*, **26**, 229–34.
172 Hadeed, A.J., Assay, L.D., Klein, A.H. *et al.* (1981) Significance of transient postnatal hypothyroxinemia in premature infants with and without respiratory distress syndrome. *Pediatrics*, **68**, 494–8.
173 Cuestas, R.A., Lindall, A. and Engell, R.R. (1976) Low thyroid hormones and respiratory-distress syndrome of the newborn. *N. Engl. J. Med.*, **295**, 297–302.
174 Mitchell, M., Larsen P.R., Levey, H.L. *et al.* (1978) Screening for congenital hypothyroidism. Results in the newborn population of New England. *JAMA*, **239**, 2348–51.
175 Bayer, M.F. and McDougall, I.R. (1982) Free thyroxine by solid phase radioimmunoassay: improvement in the laboratory diagnosis of thyroid status in severely ill patients. *Clin. Chim. Acta*, **118**, 209–18.
176 Wilson, D.M., Hopper, A.O., McDougall, I.R. *et al.* (1982) Serum free thyroxine values in term, premature, and sick infants. *J. Pediatrics*, **101**, 113–17.
177 Layde, P.M., Van Allmen, S.D., Oakley,

G.P. (1979) Congenital hypothyroidism control programs: a cost benefit analysis. *JAMA*, **241**, 2290–2.

178 Smith, D.W., Blizzard, R.M. and Wilkins, L. (1957) The mental prognosis in hypothyroidism of infancy and childhood. *Pediatrics*, **19**, 1011–22.

179 Klein, A.H., Meltzer, S. and Kenny, F.M. (1972) Improved prognosis in congenital hypothyroidism treated before age of three months. *J. Pediatrics*, **5**, 912–15.

180 Raiti, S. and Newns, G.H. (1971) Cretinism: early diagnosis and its relation to mental prognosis. *Arch. Dis. Child*, **46**, 692–4.

181 Stanbury, J.B. and Chapman, E.M. (1960) Congenital hypothyroidism with goitre: absence of an iodide concentrating mechanism. *Lancet*, **1**, 1162–5.

182 Pendred, V. (1896) Deaf-mutism and goitre. *Lancet*, **2**, 532.

183 Hutchison. J.H., Arneil, G.C. and McGirr, E.M. (1957) Deficiency of an extra-thyroid enzyme in sporadic goitre. *Lancet*, **2**, 314–15.

184 Wortsman, J., Premachandra, B.N., Williams, K. *et al.* (1983) Familial resistance to thyroid hormone associated with decreased transport across the plasma membrane. *Ann. Intern. Med.*, **143**. 1145–8.

185 Rivkees, S.A., Bode, H.H. and Crawford, J.D. (1988) Long-term growth in juvenile acquired hypothyroidism. *N. Engl. J. Med.*, **318**, 599–602.

186 Robuschi, G., Safran, M., Braverman, L.E. *et al.* (1987) Hypothyroidism in the elderly. *Endocrine Rev.*, **8**, 142–53.

187 Brochman, H., Bjoro, T., Gaardner, P.I. *et al.* (1988) Prevalence of thyroid dysfunction in elderly subjects. *Acta Endocrinol.*, **117**, 7–12.

188 Editorial (1952) Hypothyroidism, a geriatric problem. *JAMA*, **149**, 664.

189 Hurley, J.R. (1983) Thyroid disease in the elderly. *Med. Clin. N. Am.*, **67**, 497–516.

190 Davis, F.B., LaMantia, R.S., Spaulding, S.W. *et al.* (1984) Estimation of a physiological replacement dose of levothyroxine in elderly patients with hypothyroidism. *Arch. Intern. Med.*, **144**, 1752–4.

CHAPTER SEVEN

Management of thyroid nodules

7.1 INTRODUCTION

A solitary thyroid nodule can be felt in 4–7% of the adult population [1–4]. At autopsy, the incidence of thyroid nodules in one series was almost 50%, but this is not the same as clinically palpable abnormalities [5]. Whenever a thyroid nodule is discovered the question arises: is it benign, or malignant? It is not easy to find a reliable figure of what percentage of thyroid nodules are malignant; the usually quoted figures of 20–30% are based on the results of surgery, and are biased in favour of high-risk cases [6–8]. Miller [9] states that 4% of non-suspicious thyroid nodules are malignant. Based on the results of fine-needle aspirate (FNA), which are discussed later, the range appears to be 5–10%. Even in this situation, there are questions of how patients were selected for FNA: was there bias towards biopsying suspicious lesions, which would produce a higher incidence? Alternatively, since most patients with benign results on FNA are not referred for operation, is it possible that some cancers are missed and the true incidence of cancer higher? In calculations made subsequently, I shall accept that 1 out of 10 clinically significant thyroid nodules is malignant.

In 1991, there will be 12 300 new cases of thyroid cancer and about 1025 deaths from thyroid cancer in the USA [10]. This contrasts with the number of persons with a thyroid nodule. If we accept that 5% of the population have nodules and there are 200 000 000 adults in the USA, there are 10 000 000 thyroid nodules. It should be understood that the number of cancers quoted above is an annual figure. Therefore, it is not correct to say the risk of a nodule being cancerous is 12 300 out of 10 000 000 cases (0.00123 or 0.123%). These numbers have also to be contrasted with the number of deaths from thyroid cancer. This has been constant for several years at approximately 1000 per year in the USA. Of the deaths about three-quarters are in patients with anaplastic or medullary cancers. Therefore, *a priori*, the risk of a thyroid nodule being malignant is approximately low (approximately 10%), and the risk of it causing death as a result of cancer is extremely small. These numbers have to be considered in relation to evaluation and treatment.

It has been argued in print that all nodules should be removed, since there is no other absolute method of ensuring we know the true pathology [12]. The counter-argument has been made, that no thyroid nodules should be removed, since few are cancerous and those cancers that cause death (anaplastic cancers) still cause death in spite of surgery [11]. This debate was contrived and somewhat artificial, but expresses the extremes of opinion. The correct approach lies somewhere in between. As many patients as possible with benign nodules should be saved from operation, and a high proportion of patients referred for surgery should be found to have cancer. We should also try to keep the number of patients who have cancer, but are not referred for operation, to a minimum. Therefore, whatever tests are

used should be both sensitive and specific.

There are situations where it is advisable to refer the patient immediately to surgery; these include any large nodule causing pressure effects or an unsightly cosmetic problem. If the patient strongly fears that the nodule is malignant and is not relieved by the results of any test, surgical excision is the treatment of choice. The patient's subsequent well-being, when he or she is told that the final pathological report shows no evidence of cancer, confirms the correctness of this decision.

In the large majority of patients, the clinician is faced with the nodule and the unanswered questions, is it benign or malignant and should one operate or not? To help answer these questions, the physician should evaluate certain aspects of the patient and nodule clinically, define thyroid status and obtain specific investigations. The consensus of opinion indicates that FNA is the single best investigation, yet frequently thyroid scintigram and sonogram are ordered by reflex. These tests, which are introduced in Chapter 3, are discussed in more detail here. Scintigraphy and sonography are discussed before FNA simply to develop an argument in favour of the last. There is also a brief review of the role of thyroid suppression.

Those tests which are sometimes of help in specific cases but not routinely, such as ^{201}TI, NMRI, fluoresent scanning, serum thyroglobulin and calcitonin, are not incorporated into the management, and their role is outlined in Chapter 3.

7.2 CAUSES OF THYROID NODULE

Benign causes of thyroid nodules include follicular adenoma, follicular adenomatous hyperplasia, colloid nodule, cysts, Hashimoto's thyroiditis, nodular Graves' disease (Marine Lenhart syndrome), acute thyroiditis, subacute granulomatous (de Quervain's) thyroiditis and hemiagenesis. Cancers include primary and metastatic lesions and lymphoma. About 70% of cancers are differentiated (Chapter 8). Some of the benign causes, such as acute and subacute thyroiditis, should not be mistaken for malignancy. Sometimes, lesions such as branchial cyst, cystic hygroma, or lymph node enlargement, are so close to the thyroid that they are thought to be thyroid nodules; usually they can be shown to lie outside the gland. Thyroid nodules, whatever their aetiology, usually move when the patient swallows, extrathyroidal masses generally do not.

7.3 CLINICAL EVALUATION OF PATIENT AND NODULE

It is not possible to use a single clinical characteristic to define the pathology of a nodule with certainty. However, there are simple factors which increase or decrease the risk of a nodule being malignant. The age of the patient, gender, family history and a history of external neck irradiation all help. The risk of a thyroid nodule being malignant in a child is relatively greater than in an adult. It is probable that some of the childhood cancers are related to radiation in infancy. The topic of radiation-induced thyroid cancer is discussed in Chapter 13. In summary, 20–30% of people who received 500–1000 rad (5–10 Gy) develop a thyroid nodule, of which 30–50% are malignant [13–21]. Certainly, a teenager with a thyroid nodule who had significant radiation to the neck in infancy must be considered to have thyroid cancer until proven otherwise. In the elderly, there is an increase in benign nodules, However, a new nodule should be worked-up expeditiously to ensure an anaplastic cancer is not missed at a treatable stage. Although thyroid cancer is more common in women, benign nodules are found proportionately more frequently than they are in men. Therefore, the risk of a nodule in a

man being cancerous is greater. The risk of cancer is greater in a single nodule compared to a multinodular goitre. This begs the question what is a multinodular gland? We would all agree in the case of a large nodular goitre, but the surgeon or pathologist directly inspecting the gland can see, or feel, nodules which cannot be felt through tissues of the neck. In addition, sonography shows small, impalpable nodules, often less than 5 mm. Should these be incorporated into the definition of multinodular goitre? At this time there is insufficient data to be certain.

When a nodule is hard and fixed to surrounding structures, it is likely to be malignant. Riedel's thyroiditis is very hard and can be fixed, but this condition is so rare that it should not be a prominent differential diagnosis. Hashimoto's thyroiditis can rarely cause fixation, but this possibility should be left for the pathologist to determine. When there is hoaresness due to vocal cord paralysis on the same side as a thyroid nodule, the inference is that the nodule is malignant. Cerise *et al.* [22] found this in 6 of 10 patients. However, in the remaining 4 vocal cord paralysis was due to benign lesions. I can confirm that a benign nodule can cause hoarseness but, nevertheless, with this symptom the nodule should be assumed to be malignant and no test short of surgery should be accepted. When there is significant enlargement of cervical lymph nodes in a patient with a thyroid nodule, it is probable that the nodule is cancerous and the nodal enlargement due to metastases. Benign conditions, such as Hashimoto's thyroiditis and Graves' disease, can very occasionally cause reactive (presumed immunological) enlargement of nodes, but the clinical setting would be different and a single nodule unlikely to be present, although Hashimoto's thyroiditis can present as a solitary nodule. A family history of proven benign nodular thyroid disease is reassuring. In contrast, a family history of medullary cancer in a patient with a new nodule must raise the probability of that diagnosis.

The clinical findings as described above point strongly to a diagnosis of cancer, but they are relatively uncommon. In most patients with a thyroid nodule there are no features of concern apart from the nodule itself. In this latter group, Miller [9] quotes the incidence of cancer to be 4%. These patients need further tests to determine which ones are at risk and should be referred for operation.

7.4 TESTING THYROID FUNCTION

Most patients with thyroid nodules are euthyroid and this can be confirmed by TSH or FT_4, or both of these tests. A proportion of patients with autonomous nodules are hyperthyroid, and in them there is an increase in T_3 toxicosis [23, 24]. Therefore, if there is clinical evidence of hyperthyroidism, or if it is known that the nodule is hot on ^{123}I scintigram, or if TSH is found to be suppressed, it is helpful to measure T_3. When there is suspicion of hypothyroidism, the diagnosis is confirmed by TSH and FT_4. Thus in almost every situation TSH and FT_4 define the thyroid status with precision.

7.5 INVESTIGATIONS

The information in the following sections can be complemented by reviewing the corresponding sections in Chapter 3, where the more practical aspects of the tests are described and additional references are provided.

7.5.1 RADIONUCLIDE SCINTIGRAPHY

The reason for obtaining a scintigram is to show whether the nodule is functioning or not. Functioning nodules concentrate more radioiodine than normal thyroid, hypo- or non–functioning, nodules concentrate less. Functioning nodules are called 'hot'

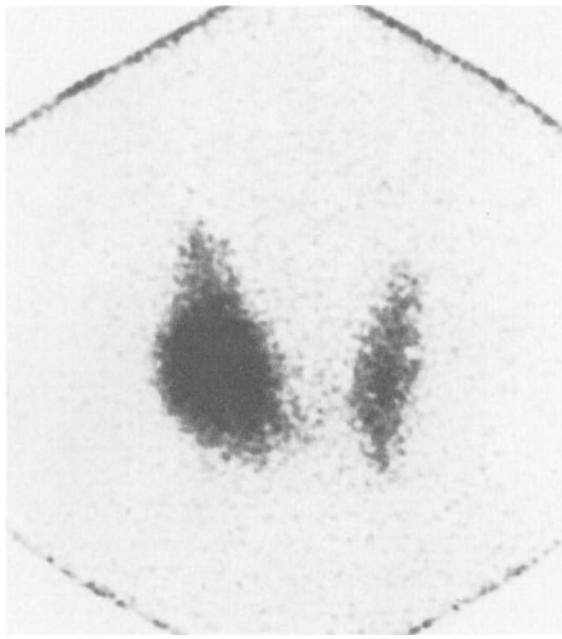
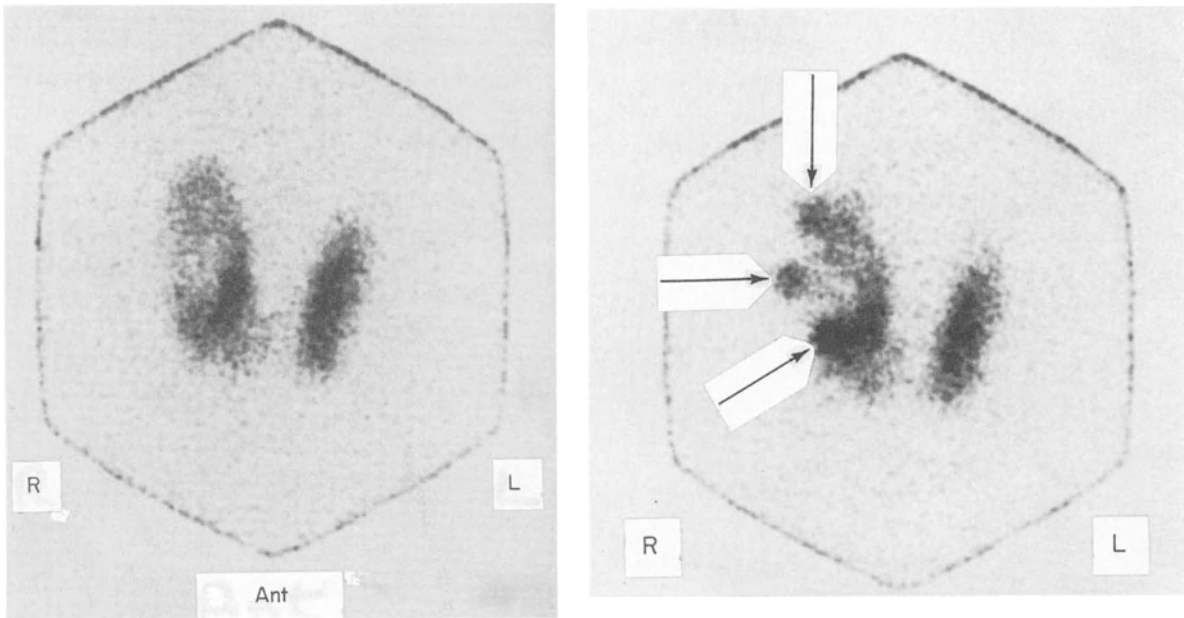


Figure 7.1 Thyroid scintigram made 3 hours after an oral dose of 200 μCi ^{123}I. The patient had a mobile right-sided nodule and she was clinically and biochemically euthyroid. The nodule is hyperfunctional since there is more uptake than in the surrounding thyroid. However, there is not total suppression of normal tissue. For complete evaluation it is necessary to use a radioactive marker placed on or around the nodule to demonstrate that what is felt and what is seen are one and the same.

nodules, non-functioning nodules are called 'cold' nodules. Figure 7.1 shows a hot nodule which has not suppressed the surrounding thyroid. Figure 7.2(*a*) shows a cold nodule in the right lobe, and Figure 7.2(*b*) shows the same nodule with a cobalt marker placed on the palpable nodule, demonstrating that the clinical lesion was cold on the scan. These are included as examples for the reader who has not reviewed Chapter 3. Experience dictates that a hot nodule is virtually never malignant. There are a few reports of malignancy in hot nodules [25, 26], and these are discussed and referenced in full in Chapter 5. The exact incidence of cancer in hot nodules is not known, largely because many of the reports do not provide information about how many hot nodules were investigated to find a cancer. A single cancer per 200 hot nodules is a reasonable interpretation from the literature. It can be difficult to differentiate a small hot nodule from adjacent thyroid, and it is important for the nuclear medicine physician to palpate the nodule and apply markers and/or use oblique and lateral images to ensure that there is no doubt that the palpable nodule and scan findings correspond. Unfortunately, the results of scintigraphy are disappointing in two main respects. Firstly, although the majority of thyroid nodules are benign, and although almost all hot nodules are benign, most thyroid nodules are not hot on scan. Secondly, the separation of scan results into hot or cold is not always easy in practice. As a result, in the literature there are reports ranging from hot, functional, warm, lukewarm, hypofunctional, to cold. In Chapter 3. I attempted to develop the thesis that every attempt should be made to answer the question: Has the nodule more or less radioiodine than the surrounding thyroid? If the former it is hot, and in the latter case it is cold. By these criteria about 10% of nodules are hot; therefore, 90% are cold.

Everything that has been said concerning the care of ensuring the clinical and scan findings correspond apply to the study of cold nodule. The reader who is following the numbers may well say that the scan results are not likely to determine whether a nodule is malignant and I would agree. However, if the scan is done first and if it shows unequivocally that the nodule is hot, the clinician and patient then do not need to be concerned about the risk of cancer.

The best instrument for thyroid scintigraphy is the gamma camera with a pin-hole collimator. The best radionuclide is ^{123}I. There are sufficient disparate results when ^{99m}Tc is compared with ^{123}I in the same



(a) (b)

Figure 7.2 (*a*) Thyroid scintigram 3 hours after 200 μCi ^{123}I in a patient with a solitary nodule in the lateral aspect of the middle of the right lobe. The nodule is hypofunctional (cold), i.e. it has less uptake of radioiodine than surrounding thyroid. (*b*) shows markers placed around the nodule and superimposed on the cold spot. The positions are of the radioactive markers are shown by arrows.

patient [27–29] with cancers appearing hot with the former radiopharmaceutical, to discourage use of ^{99m}Tc. In an extensive review of the literature, Ashcraft and Van Herle [30] calculated that on ^{123}I scan cancer was the cause of 16% of cold nodules (708 out of 4457 cases) and 9% of hypofunctioning nodules (49 out of 554 cases). If we add these together, 15% of the entire group of nodules with less uptake than normal thyroid were malignant and 85% were benign. In the combined series, only 5% of nodules were hyperfunctioning. Although there is the problem of ensuring that the same criteria were used by all authors in the interpretation of scintigrams, and that the instrumentation and radiopharmaceuticals were uniform, or state of the art, the data is important. These results indicate that scintigraphy does not add much diagnostic help to clinical evaluation.

7.5.2 SONOGRAPHY

There have been remarkable advances in sonographic instrumentation, and the resolution produced by state-of-the-art, real-time units is magnificent. Axial resolution of the order of 1 mm and lateral resolution of 2 mm can be obtained. There is no ionizing radiation, no patient preparation and it is not necessary to stop thyroid medications, or to wait for iodine contrast agents to be excreted. The test can be done during pregnancy. In spite of these great attributes, sonography lacks the ability of differentiating a benign from a malignant nodule. It can reliably differentiate a cystic lesion from a

solid one. If the cyst has a well visualized capsule, a homogeneously empty cavity and if the sound transmission is augmented behind the lesion, by these criteria the lesion has a very low chance of being malignant (about 2%). However, in a study of 146 nodules these criteria were met once (0.75%) [31]. This result is considerably lower than 18.9% derived by Ashcraft and Van Herle [4] from 17 published series. Some of the publications were by the same authors, and it is not clear if cases were included more than once, or if the patients were consecutive and unselected for the test. From the combined data, the average probability of a nodule being cystic was approximately 10%. The composite review determined that a solid lesion was cancerous in 21% of patients, a mixed solid cystic lesion cancer in 12% and, surprisingly, cancer was found in 7% of cystic lesions sent to surgery. There may have been additional factors which prompted referral of patients with cystic nodules for operation. Based on these data, ultrasound is not valuable in reaching the decision to operate on a thyroid nodule. One sign which is quoted as favouring benignity, is the 'halo sign' where a rim of tissue separates the nodule from surrounding thyroid. This is thought to represent a capsule produced by slow, steady, even growth of a benign lesion. Simeone *et al.* [31] found a halo in 43 of 116 benign nodules (37%), and only 2 out of 17 malignant nodules (12%). There are other reports of cancer giving this appearance (32).

Because of its excellent resolution, sonography demonstrates in some patients that a single, clinically palpable nodule is one of many sonographically visible nodules, and the most likely diagnosis is multinodular goitre. The clinical differentiation is important since the risk of cancer is less in a multinodular gland, but it is yet to be determined whether this dogma holds true if the other nodules are not palpable. I have found ultrasound of value in the occasional patient in whom lymph node metastases are the presenting complaint, and there is no palpable nodule in the thyroid. Visualizing a discrete nodule in the ipsilateral lobe as the nodal lesion strengthens the decision to operate on the thyroid. I have to admit that an impalpable nodule can occasionally be palpated in retrospect when its precise position has been defined by sonography. Apart from these situations, sonography is not cost effective in selecting patients with single nodules for thyroid surgery [33].

7.5.3 FREQUENTLY USED WORK-UP

Until recently, the routine evaluation of a thyroid nodule involved ordering a scintigram and sonogram. Not infrequently, both tests were ordered simultaneously and both done irrespective of the result of the other. Even now, this approach is common. In Figure 7.3 I have selected a population of 100 patients, each with a single thyroid nodule. I assume *a priori* that 90 of the nodules are benign and 10 are malignant. There are 10 hot nodules, none of which are malignant and, similarly, there are 10 benign cysts. Before testing it is not known which of the nodules are hot or cold, or solid or cystic. A cystic nodule cannot appear hot and, likewise, a hot nodule cannot be cystic. From the figure it can be seen that by starting with scintigram, 10% of patients who have a hot nodule have only one test and they are excluded from further concern of malignancy and are managed for hot nodule *per se*. All 90 patients with a cold nodule have an ultrasound, and of these 10 who have a pure cyst are labelled at low risk for cancer. Therefore, 80 of the 100 have a solid cold lesion and are considered at risk for cancer. These 80 patients are referred to surgery and 10 cancers diagnosed. If sonography is the first test (Figure 7.4), the same final result is found, although 10 patients who have a cystic nodule do not have scintigraphy. Both of these approaches fail badly in selecting the

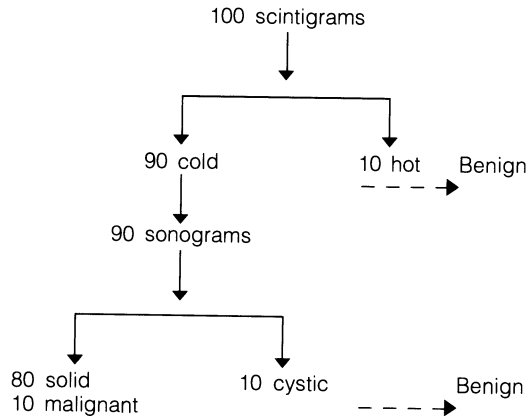


Figure 7.3 Thyroid nodule scintigram/sonogram. In 100 patients with a thyroid nodule, assume *a priori* that 10 nodules are cancer and 90 benign. Also assume 10 nodules are hot on scintigram and 10 are pure cysts. Also assume there are no cancers in hot nodules or in cysts. In this analysis scintigram is done as the first test. Therefore a total of 190 tests are done to improve the ratio of thyroid cancer to thyroid nodule from 1/10 to 1/8. If all patients with cold solid nodules are referred for operation, 10 will have cancer and 70 a benign nodule.

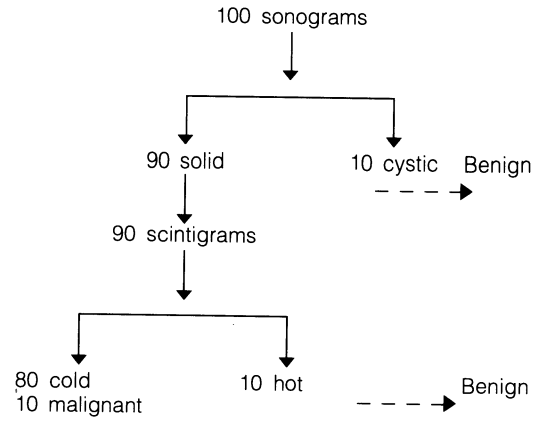


Figure 7.4 Thyroid nodule sonogram/scintigram. In 100 patients with a thyroid nodule assume *a priori* that 10 nodules are cancer and 90 benign. Also assume 10 nodules are hot on scintigram and 10 are pure cysts. Also assume there are no cancers in hot nodules or in cysts. In this analysis sonogram is done as the first test. Therefore a total of 190 tests are done to improve the ratio of thyroid cancer to thyroid nodule from 1/10 to 1/8. If all patients with cold solid nodules are referred for operation, 10 will have cancer and 70 a benign nodule.

high-risk patient. This is because the tests have low specificity and because the prevalence of cancer in solitary nodules is low.

7.5.4 TISSUE DIAGNOSIS

Of the techniques used to obtain tissue for pathological analysis, the one which has gained widest acceptance is FNA [34–40]. The techniques are described in Chapter 4. There is now abundant data to support this test and to counter the main concerns that it would track cancer cells, and that the small specimen would not be representative. It is important that there is sufficient material for the pathologist to study. Therefore, several passes have to be made and Hamburger and Hamburger [41] state that six fragments should be seen. In most series, about 5–10% of specimens are unsatisfactory and the aspiration should be repeated. Some authorities have written that the clinician doing the procedure should do at least 10 aspirates a week to maintain the skill [36]. Miller [9] has written that the first 1000 cases are necessary for learning! These statements would, by definition, cause all cases to be referred to a few centres and fewer and fewer practitioners would have this valuable test at hand. There is data from a non-academic setting showing equally successful results [42].

It is customary to classify the results into three categories: probable cancer (high risk), possible cancer (intermediate risk or suspicious), and benign (low risk). Miller *et al.* [35] using this approach found 107 of 132 high risk patients had cancer, and a further 6 had atypical adenomas, or Hurthle cell lesions. Therefore, 86% of the patients did require surgery. For one reason or another, 60 patients in the low-risk group had surgery and only 1 had cancer. Therefore,

the test was valuable in both positive predictive and negative predictive roles. Unfortunately, the intermediate-risk group is not so well defined. In an update from the same series. 2500 patients had FNA [41]. Using the same criteria, 218 out of 284 probably malignant by FNA had cancer, but only 16 out of 149 possibly malignant had cancer. Of 433 patients referred for operation on the basis of FNA result, 234 had cancer (54%). As an aside, the incidence of proven cancer was 234 out of 2500 cases, or 9.4%, which is extremely close to the 10%, which I chose for the analysis presented above.

Three hundred patients described by Colacchio *et al.* [43] had FNA and adequate tissue was obtained in every one. Final diagnosis was based on surgical specimen in 80 patients, large-needle biopsy in 170, and follow-up in 50. Of 22 in the 'probable cancer' group, 19 did have cancer (86%), whereas, only 3 out of 248 (1.2%) with benign cytology were subsequently found to have cancer. The overall incidence of cancer was 7.3%.

Miller *et al.* [44] obtained satisfactory aspirates in 95% of their 136 patients who were studied prospectively. Five aspirates were malignant and all 5 patients had cancer proven at surgery. Twenty-nine aspirates were suspicious, or showed follicular neoplasm, and 21 of the patients had surgery. Two had cancer and 15 of the lesions were follicular neoplasms, which are impossible to differentiate from follicular cancer by FNA. Two patients with benign aspirates had surgery and the lesions were proven to be benign. In this series, the incidence of cancer was 5.4%.

Hamberger *et al.* [45] used three cytological categories: malignant, suspicious and benign. They studied 1970 patients. All 98 with malignant aspirate had cancer. Of 233 with suspicious cytology, 60 had cancer (26% of this group). In total, 158 patients had proven cancer (8% of the total), and of those referred to operation 45% had cancer.

In their analysis of published results of FNA, Ashcraft and Van Herle [30] studied eight series from which all patients had surgery. None of the results I reviewed above are in their analysis. Eight hundred and forty-eight patient with benign cytology had surgery, and 22 cancers were found (2.6%). In contrast, 51% of the suspicious/malignant categories were malignant in 482 patient. The authors did not subdivide this group.

In summary, FNA is a simple, relatively non-invasive procedure that provides extremely valuable clinical information. An experienced cytopathologist can stratify the aspirates into high risk, of which 80–100% will be proven to be cancer, and low risk, in which about 2% have cancer and will be false negatives. There is an intermediate group which had defied all attempts to clarify it [46, 47]. In this category, some 15–30% have cancer. Depending on the incidence of cancer in the entire series, and the criteria used by the cytopathologist, the numbers in each category will differ. Assuming that 10% of the nodules are malignant, the analysis is shown in Figure 7.5.

7.5.5 BEST USE OF INVESTIGATIONS IN PRACTICE

The analysis of results of scintigraphy, sonography and FNA show that none is absolute in defining the pathology in every nodule. However, FNA is substantially more accurate than the first two tests. Figures 7.3 and 7.4 how how combined scintigraphy/sonography make little impact in the yield of cancers found at operation, if the criteria to operate is a single cold nodule. The analysis is based on the assumptions that 10% of nodules are malignant and that neither hot nodules, nor pure cysts contain cancer. None of these is absolutely true, but that does not detract from the thesis that even using these tests optimally, the probability that a nodule is malignant is increased from

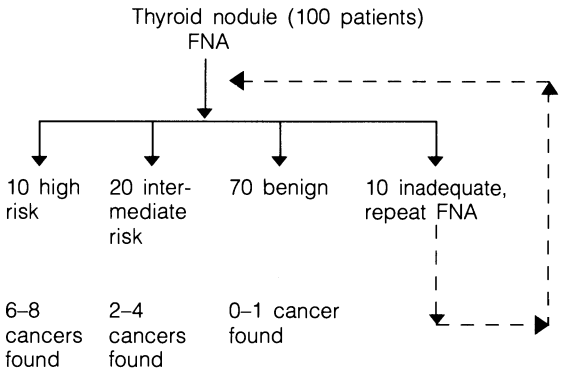


Figure 7.5 Thyroid nodule FNA. Assume *a priori* that the incidence of cancer in these 100 thyroid nodules is 10% and assume that a repeat aspirate in 10 patients gives adequate material for interpretation. The incidence of cancer in the high-risk category is 60–80%, in the intermediate 10–20% and in the low-risk group about 1–2%. If all the patients in the first two groups are operated on, the incidence of cancer is 33%. If there is some selectivity in patients in the intermediate group and only half have surgery, the incidence of cancer at surgery is 50%.

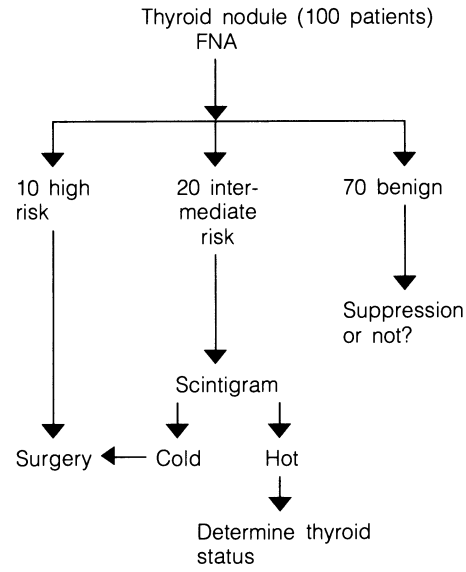


Figure 7.6 Thyroid nodule, further evaluation.

the *a priori* number of 1/10 to 1/8. This means that 80 patients would be referred to surgery to find 10 cancers. If the sequence of testing is reversed the same net result is obtained.

Some have recommended that FNA be done on solid cold nodules. However, this approach would mean that all patients would have either scintigraphy or sonography. Almost all would have a second test (the one which they did not have first), and then 80% would have FNA. When a clinician does FNA it is somewhat irrelevant if the nodule is solid or cystic; if it cystic this is quickly apparent. Therefore, why do the sonogram? Blum [48] believes that sonography helps in directing aspiration to the optimal sites. Since most physicians who do FNA do not use ultrasound guidance, this is of limited value. If after aspiration of cyst fluid there is palpable tissue, this should be rebiopsied. Therefore, we have removed sonography from the work-up as a routine test. Let us now consider scintigraphy. Since about 90% of nodules are cold, why not aspirate all nodules first? This should produce results similar to those in Figure 7.6, which allows an immediate management decision in 70–80% of patients. In 10%, the decision is to operate, and in 60–70% not to operate. As discussed, there remains a significant percentage of suspicious lesions and some of these are malignant. If all patients with suspicious cytology are referred for surgery, the incidence of cancer in surgically treated patients is about 1 in 3. Although this is substantially better than other approaches, it is not perfect. The patients with suspicious cytology have to be evaluated individually. Most of the reports are of follicular neoplasm, and they turn out to be follicular adenomas, but without the entire lesion to examine it is not possible for the pathologist to determine if there is angio or capsular invasion. Some of these lesions are hot on scintigram and, therefore, at low risk for cancer, so ^{123}I scan can be introduced selectively in this particular setting. In

addition, the pathologist can sometimes move to one or other side of the fence, and help the clinician with the decision whether to operate. When these steps are taken, the number of patients referred for operation can be reduced but, hopefully, the number of cancers found at surgery remains the same and no patients with cancer are excluded. This accounts for the result discussed under tissue diagnosis of cancer in 1 out of 2 of patients referred to surgery on the basis of FNA.

It is hoped that the clinician using such an approach can convince his or her surgical colleagues that by the time patients are referred for operation the data strongly support that there is a high risk of cancer. As a result the operation should be appropriate for that condition. This is discussed in detail in the next chapter, but in brief should be ipsilateral lobectomy and contralateral subtotal lobectomy.

7.6 MANAGEMENT OF CYSTIC NODULES

Some cysts disappear spontaneously. Also after aspiration of a cystic nodule, the lesion may never recur [49]. In one series of 141 patients, this happy outcome was found in 63 (45%) [50]. In a second report, 14 out of 35 patients (40%) were cured by one aspiration [51]. More than 50% recur and sometimes the speed of fluid reaccumulation is remarkable, and I have sent a patient home cured, only to find the lesion unchanged 24 hours later. The cyst can be reaspirated, but how many times? There is no published data to provide a definitive answer. I routinely send the cyst fluid to pathology where it is spun down and examined cytologically. Frequently, it contains macrophages with engulfed haemosiderin, presumably from haemorrhagic degeneration, debris and squames. These are not sufficient to establish that it is benign. Therefore, if there are several recurrences and the pathology is not certain, it is reasonable to remove the nodule. One of my colleagues believes that the second aspiration should be done with a larger-bore needle to make a bigger puncture in the cyst capsule; I regret I have to data to substantiate this. There are reports of successful permanent cure by instilling tetracycline into the cyst cavity. The first report I could find was of a single case [52]. There followed a report of cure of 7 out of 9 [53] and 10 out of 10 patients [54]. In each case, the concentration of tetracycline used was 100 mg/ml in 0.9% saline. In general, if the cyst was small, 1 ml of this preparation was instilled after the cyst had been drained, and 2 ml or more in the case of large cysts. These results appear very promising, but a recent controlled trial of tetracycline versus saline showed no difference in outcome [55]. Fourteen out of 30 treated with saline were cured, compared with 10 of 23 who received tetracycline (47% versus 43%, P = NS).

The fluid varies in colour from pale straw to almost black. Most agree that the colour does not provide any diagnostic help in predicting malignancy. When clear, water-like fluid is obtained, the source is likely to be a parathyroid cyst. If there is any doubt about the organ of origin of the cyst, this can be clarified by measuring thyroid and parathyroid hormone levels on the aspirate [51]. In practice, this is not used often. It could be hypothesized that prescription of thyroid hormone in a dose sufficient to suppress thyroid function would reduce the chance of recurrence. This does not seem to be the case if the thyroid is prescribed after the aspiration, because Clark *et al.* [51] prescribed thyroxine and had a 60% recurrence, and Sarda *et al.* [50] had a 53% recurrence without suppressive therapy. It is perhaps more logical to reduce thyroid function before aspiration, but I know of no controlled study in which the thyroxine was prescribed for a sufficient length of time to suppress thyroid function and then aspiration done. Clearly, this could only be done if there was

prior knowledge that the nodules were cystic.

Therefore aspiration, if it is the first test for a nodule, would also be used for the treatment of a thyroid cyst as well as for diagnosis. If possible, all fluid should be withdrawn. Should recurrences be troublesome, or the pathology in doubt, surgery is advised. In selected cases, instillation of a sclerosant could be considered, but the data would not support its use in every patient.

7.7 ROLE OF THYROID SUPPRESSION

There are data from many sources indicating that prescription of thyroid medication is a useful test in evaluating thyroid nodules (56–59). The rationale is that malignant nodules are not under normal control, therefore, they will not shrink when thyroid is given to suppress TSH. Alternatively, benign nodules are more physiological and would be more likely to disappear. The literature has been reviewed by Ashcraft and Van Herle [30] and Molitch *et al.* [60]. The percentage of nodules suppressed ranges from 9% [59] to 69% [56]. This disparity is marked. There are three major problems with older publications which could explain the differences. There was no tissue diagnosis, there was no simple method of ensuring TSH was suppressed, and there was no objective method of proving the nodule had shrunk. There are some lesions that shrink with considerable consistency, such as lymphocytic thyroiditis, but others, as discussed below, do not change. In addition, there are well-documented cases of thyroid cancer which regress with adequate thyroid medication [30, 61]. Molitch *et al.* [60] analysed the chance of regression of a benign versus a malignant nodule based on a review of the literature, and found almost no difference. On average, 16% of malignant and 22% of benign lesions were suppressible.

Recently, Gharib *et al.* [62] demonstrated in a double-blind study comparing thyroxine with placebo, that biopsy-proven colloid nodules did not regress with TSH suppression. It is important to note that only one pathology was studied, and the results might not be exactly the same in patients with other conditions. Nevertheless, the investigators had sensitive TSH measurements, therefore suppression was documented, and they had ultrasound measurement of nodules as objective proof of changes in dimension.

In summary, thyroid medication to suppress TSH is not a useful test to differentiate a benign from a malignant nodule, because the sensitivity is moderate and the specificity poor. It should not be used to determine management in a patient with a thyroid nodule. In contrast, if the pathology of the nodule is benign, should thyroxine be prescribed in an attempt to cause regression? The data presented indicates that in colloid nodule this treatment is unlikely to succeed. If FNA shows lymphocytic thyroiditis, thyroxine is likely to help, especially if TSH is above normal.

There is a potential problem of prescribing thyroxine based only on a report of benign cytology from FNA. If the lesion is an autonomous, non-suppressible hot nodule, the patient can be rendered hyperthyroid by the addition of thyroxine to thyroid hormones secreted endogenously. Therefore, it is recommended that either sensitive TSH or ^{123}I scintigram, or both, be ordered prior to starting treatment. When TSH is suppressed there is no point in trying to suppress it further. Also, when the nodule is hot and TSH measureable, and a decision is made to start thyroxine, that therapy should be prescribed with caution, and appropriate close follow-up arranged to ensure that the patient is not overtreated.

7.8 SUMMARY

Thyroid nodules are extremely common, whereas thyroid cancer is not. The single

best way of establishing the clinical decision of whether to operate is FNA, since this establishes a tissue diagnosis. Many, including myself, recommend this as the first test. This test is not perfect because 15–30% of aspirates are reported as suspicious lesions (mostly microfollicular neoplasms). Van Herle *et al.* [36] have shown that FNA is the most cost effective approach. Cost effectiveness is easier to demonstrate in a population than in the individual, and there is still an important role for the clinician. I do not, however, subscribe to the nihilistic view of Molitch *et al.* [60] that 'the decision to operate, suppress or aspirate is thus a "tossup"'. To operate on all patients with thyroid nodules is certain to cause more harm than benefit, and to attempt to suppress all nodules will be largely without benefit and, in some cases, harmful.

KEY FACTS

- Thyroid nodules are very common.
- Most thyroid nodules are benign.
- Most malignant nodules have an excellent prognosis if treated appropriately.
- It is important to differentiate nodules that are malignant from those that are benign.
- The most cost effective method of differentiating a benign from a malignant nodule is fine-(thin)-needle aspiration.
- Fine-needle aspiration has excellent sensitivity and specificity.
- The best radionuclide for scintigraphy is ^{123}I.
- Nodules which appear 'hot' on ^{123}I scintigraphy are almost always benign.
- ^{99m}Tc scintigraphy of nodules can give disparate results compared to ^{123}I.
- Usually, cancers are cold on ^{123}I scintigraphy, but most cold nodules are benign.
- Scintigraphy is sensitive but very nonspecific.
- Thyroid nodules which are pure cysts on ultrasound are almost always benign.
- Pure cysts are very rare.
- Most cancers appear as solid or mixed solid lesions on ultrasound, but most solid or mixed lesions are not cancers.
- Ultrasound is sensitive, but very nonspecific.

REFERENCES

1 Vander, J.B., Gaston, E.A. and Dawber, T.R. (1954) Significance of solitary non toxic thyroid nodules: preliminary report. *N. Engl. J. Med.*, **251**, 970–3.

2 Vander, J.B., Gaston, E.A. and Dawber, T.R. (1968) The significance of nontoxic thyroid nodules. *Ann. Intern. Med.*, **69**, 537–40.

3 Rojeski, M.T. and Gharib, H. (1985) Nodular thyroid disease: evaluation and management. *N. Engl. J. Med.*, **313**, 428–36.

4 Ashcraft M.W. and Van Herle, A.J. (1981) Management of thyroid nodules: 1. History and physical examination, blood tests, X-ray tests, and sonography. *Head Neck Surg.*, **3**, 216–30.

5 Mortensen, J.D., Woolner, L.B. and Bennett, W.A. (1955) Gross and microscopic findings in clinically normal thyroid glands. *J. Clin. Endocrinol. Metab.*, **15**, 1270–80.

6 Katz, A.D. and Bronson, D. (1978) Total thyroidectomy. The indications and results in 630 cases. *Am. J. Surg.*, **136**, 450–4.

7 Greenspan, F.S. (1974) Thyroid nodules and thyroid cancer. *West J. Med.*, **121**, 359–65.

8 Hoffman, G.L., Thomson, N.W. and Heffron, C. (1972) The solitary thyroid nodule. *Arch. Surg.*, **105**, 379–85.

9 Miller, J.M. (1979) Perspective, in *Clinical-Pathology Evaluation of Thyroid Nodules. Handbook and Atlas*, (eds J.I. Hamburger, J.M. Miller and S.R. Kini), Southfield, Private Publication, pp. 87–91.

10 Cancer statistics (1990) *Ca-A Cancer J for Clinicians*, **39**, 9–26.

11 Beahrs, O.H. (1976) Indications for excision of the clinically solitary thyroid nodule, in *Controversy in Surgery*, (eds R.L. Varco and J.P. Delaney), Saunders, Philadelphia, pp. 153–8.

12 Cassidy, C.E. (1976) Treatment of the clinically solitary thyroid nodule with thyroid hormone, in *Controversy in Surgery*, (eds R.L. Varco and J.P. Delaney), Saunders, Philadelphia, pp. 143–52.

13 Hempelmann, L.H., Pifer, J.W., Burke, G.J. *et al.* (1967) Neoplasms in persons treated with

X rays in infancy for thymic enlargement: a report of the third follow-up survey. *J. Natl. Cancer Instit.*, **38**, 317–41.

14 Hempelmann, L.H. (1968) Risk of thyroid neoplasms after irradiation in childhood. *Science*, **160**, 159–63.

15 Favus, M.J., Schneider, A.B., Stachura, M.E. *et al.* (1976) Thyroid cancer occurring as a late consequence of head-and-neck irradiation: evaluation of 1056 patients. *N. Engl. J. Med.*, **294**, 1019–25.

16 Gonzalez-Villalpando, C., Frohman, L.A., Bekerman, C. *et al.* (1982) Scintigraphic thyroid abnormalities after radiation: a controlled study with ^{99m}Tc pertechnetate scanning. *Ann. Intern. Med.*, **97**, 55–8.

17 De Groot, L. and Paloyan, E. (1973) Thyroid carcinoma and radiation: a Chicago endemic. *JAMA*, **225**, 487–91.

18 Hamburger, J.I. and Stoffer, S.S. (1977) Late thyroid sequelae of radiation therapy to the upper body, in *Radiation-Associated Thyroid Carcinoma*, (eds L.J. De Groot *et al.*) Grune and Stratton, New York, pp. 17–31.

19 Murphy, E.D., Scanlon, E.F., Swelstad, J.A. *et al.* (1977) A community hospital thyroid recall clinic for irradiated patients, in *Radiation-Associated Thyroid Carcinoma*, (eds L.J. De Groot *et al.*), Grune and Stratton, New York, pp. 35–40.

20 Maxon, H.R., Saenger, E.L., Thomas, S.R. *et al.* (1980) Clinically important radiation-associated thyroid disease: a controlled study. *JAMA*, **244**, 1802–5.

21 Maxon, H.R., Thomas, S.R., Saenger, E.L. *et al.* (1977) Ionizing irradiation and the induction of clinically significant disease in the human thyroid gland. *Am. J. Med.*, **63**, 967–78.

22 Cerise, E.J., Randall, S., Oschner, A. (1952) Carcinoma of the thyroid and nontoxic nodular goiter. *Surgery*, **31**, 552–61.

23 Shimaoka, K. (1973) Toxic adenoma of the thyroid with triiodothyronine as the principal circulating thyroid hormone. *Acta Endocrinol.*, **43**, 285–93.

24 Popma, B.H., Cloutier, M.D. and Hayles, A.B. (1973) Thyroid nodule producing T_3 toxicosis in a child. *Mayo Clin. Proc.*, **48**, 273–5.

25 Nagai, G.R., Pitts, W.C., Basso, L., Cisco, J.A. and McDougall, I.R. (1987) Scintigraphic hot nodules and thyroid cancer. *Clin. Nucl. Med.*, **12**, 123–7.

26 Sandler, M.P., Fellmeth, B., Salhany, K.E. and Patton, J.A. (1988) Thyroid carcinoma masquerading as a solitary benign hyperfunctioning nodule. *Clin. Nucl. Med.*, **13**, 410–15.

27 Steinberg, M., Cavalieri, R.R. and Choy, S.H. (1970) Uptake of technetium 99m-pertechnetate in a primary thyroid carcinoma: need for caution in evaluating nodules. *J. Clin. Endocrinol. Metab.*, **31**, 81–4.

28 Turner, J.W. and Spencer, R.P. (1976) Thyroid carcinoma presenting as a pertechnetate 'hot' nodule, but without ^{131}I uptake: case report. *J. Nucl. Med.*, **17**, 22–3.

29 Usher, M.S. and Arzoumanian, A.V. (1971) Thyroid nodule scans made with pertechnetate and iodine may give inconsistent results. *J. Nucl. Med.*, **12**, 136–7.

30 Ashcraft, M.W. and Van Herle, A. (1981) Management of thyroid nodules. II: Scanning techniques, thyroid suppressive therapy, and fine needle aspiration. *Head Neck Surg.*, **3**, 297–322.

31 Simeone, J.F., Daniels, G.H., Mueller, P.R. *et al.* (1982) High-resolution real-time sonography of the thyroid. *Radiology*, **145**, 431–5.

32 Propper, R.A., Skolnick, M.L., Weinstein, B.J. *et al.* (1980) The nonspecificity of the thyroid halo sign. *J. Clin. Ultrasound*, **8**, 129–32.

33 Abel-Nabi, H., Falko, J.M., Olsen, J.O. *et al.* (1984) Solitary cold thyroid nodule: cost-ineffectiveness of ultrasonography. *South Med. J.*, **77**, 1146–8.

34 Miller, J.M., Hamburger, J.I. and Kini, S.R. (1979) Diagnosis of thyroid nodules: use of fine-needle aspiration and needle biopsy. *JAMA*, **241**, 481–4.

35 Miller, J.M., Hamburger, J.I. and Kini, S.R. (1980) The impact of needle biopsy on the preoperative diagnosis of thyroid nodules. *Henry Ford Hosp. Med. J.*, **28**, 145–8.

36 Van Herle, A.J., Rich, P., Ljung, B-M.E. *et al.* (1982) The thyroid nodule. *Ann. Intern. Med.*, **96**, 221–32.

37 Walfish, P.G., Hazani, E., Strawbridge, H.T.G. *et al.* (1977) Combined ultrasound and needle aspiration cytology in the assessment and management of hypofunctioning thyroid nodule. *Ann. Intern. Med.*, **87**, 270–4.

38 Esselstyn, C.B. and Crile, G. Jr (1978) Needle aspiration and needle biopsy of the thyroid. *World J. Surg.*, **2**, 321–9.

39 Prinz, R.A., O'Morchoe, P.J., Barbato, A.L. *et al.* (1983) Fine needle aspiration biopsy of thyroid nodules. *Ann. Surg.*, **198**, 70–3.

40 Ramacciotti, C.E., Pretorius, H.T., Chu, E. *et al.* (1984) Diagnostic accuracy and use of aspiration biopsy in the management of thyroid nodules. *Arch. Intern. Med.*, **144**, 1169–73.

41 Hamburger J.I. and Hamburger, S.W. (1986) Fine needle biopsy of thyroid nodules: avoiding the pitfalls. *New York St. Med. J.*, **86**, 241–19.
42 Asp, A.A., Georgitis, W., Waldron, E.J. *et al.* (1987) Fine needle aspiration of the thyroid: use in an average health care facility. *Am. J. Med.*, **83**, 489–93.
43 Colacchio, T.A., Lo Gerfo, P. and Feind, C.R. (1980) Fine needle cytologic diagnosis of thyroid nodules: review and report of 300 cases. *Am. J. Surg.*, **140**, 568–71.
44 Miller, T.R., Abele, J.S. and Greenspan, F.S. (1981) Fine-needle aspiration biopsy in the management of thyroid nodules. *West J. Med.*, **134**, 198–205.
45 Hamberger, B., Gharib, H., Melton, L.J. III, *et al.* (1982) Fine-needle aspiration biopsy of thyroid nodules: impact on thyroid practice and cost of care. *Am. J. Med.*, **73**, 381–4.
46 Gharib, H., Zinsmeister, A.R., Grant, C.S. *et al.* (1984) Fine-needle aspiration biopsy of the thyroid: the problem of suspicious cytologic findings. *Ann. Intern. Med.*, **101**, 25–8.
47 Block, M.A., Dailey, G.E. and Robb, J.A. (1983) Thyroid nodules indeterminate by needle biopsy. *Am. J. Surg.*, **146**, 72–8.
48 Blum, M. (1984) The diagnosis of the thyroid nodule using aspiration biopsy and cytology. *Arch. Intern. Med.*, **144**, 1140–2.
49 Crile, G. Jr (1966) Treatment of thyroid cysts by aspiration. *Surgery*, **59**, 210–12.
50 Sarda, A.K., Bal, S., Gupta, S.D. *et al.* (1988) Diagnosis and treatment of cystic disease of the thyroid by aspiration. *Surgery*, **103**, 593–6.
51 Clark, O.H., Okerlund, M.D., Cavalieri, R.R. *et al.* (1979) Diagnosis and treatment of thyroid, parathyroid, and thyroglossal duct cysts. *J. Clin. Endocrinol. Metab.*, **48**, 983–8.
52 Ryan, W.G., Schwartz, T.B. and Harris, J. (1983) Sclerosis of thyroid cyst with tetracycline. *N. Engl. J. Med.*, **308**, 157.
53 Treece, G.L., Georgitis, W.J. and Hofeldt, F.D. (1983) Resolution of recurrent thyroid cysts with tetracycline instillation. *Arch. Intern. Med.*, **143**, 2285–7.
54 Edmonds, C.J. and Tellez, M. (1987) Treatment of thyroid cysts by aspiration and injection of sclerosant. *Br. Med. J.*, **295**, 529.
55 Hegedus, L., Hansen, J.M., Karstrup, S. *et al.* (1988) Tetracycline for sclerosis of thyroid cysts: a randomized study. *Arch. Intern. Med.*, **148**, 1116–18.
56 Astwood, E.B., Cassidy, C.E. and Aurbach, G.D. (1960) Treatment of goiter and thyroid nodules with thyroid. *JAMA*, **174**, 459–64.
57 Blum, M. and Rothschild, M. (1980) Improved nonoperative diagnosis of solitary 'cold' thyroid nodule. Surgical selection based on risk factors and three months of suppression. *JAMA*, **243**, 242–5.
58 Greenspan, F.S. (1974) Thyroid nodules and thyroid cancer. *West J. Med.*, **121**, 306–10.
59 Liechty, R.D., Stoffel, P.T., Zimmerman, D.E. *et al.* (1977) Solitary thyroid nodules. *Arch. Surg.*, **112**, 59–61.
60 Molitch, M.E., Beck, J.R., Dreisman, M. *et al.* (1984) The cold thyroid nodule: an analysis of diagnostic and therapeutic options. *Endocrin. Rev.*, **5**, 185–99.
61 Hill, L.D., Beebe, H.G., Hipp, R. *et al.* (1974) Thyroid suppression. *Arch. Surg.*, **108**, 403–5.
62 Gharib. H., James, E.M., Charboneau, J.W. *et al.* (1987) Suppressive therapy with levothyroxine for solitary thyroid nodules: a double-blind controlled clinical study. *N. Engl. J. Med.*, **317**, 70–5.

CHAPTER EIGHT

Thyroid cancer

8.1 INTRODUCTION

Thyroid cancer is the commonest endocrine cancer and is the twenty-fifth most common cancer in the USA. In 1991, it is estimated there will be about 12300 new cases (9050 women and 3250 men) in the USA. About 1000 patients die each year from thyroid cancer [1]. It has been said that, gram for gram, thyroid cancer causes more controversy than any other cancer. Major controversies centre round how much thyroid should be removed at operation [2–4], and about the role of adjuvant therapies, including radioiodine. Thyroid cancer is not a single disease; 70–90% of patients in the USA have differentiated cancer, which generally has an excellent prognosis. Because of the good outcome, it is necessary to treat and follow a large population of patients for many years before statistically sound conclusions can be reached [5–8]. It is clear that in many patients a good outcome can be predicted at time of presentation. However, in those who inevitably have a good prognosis, it is easy for clinicians to take credit for this and assume that their management was responsible. There have been no randomized prospective trials to evaluate controversial issues [9], but there are now good retrospective studies with meaningful numbers of patients who have been followed for sufficiently long, and important conclusions can be drawn.

In contrast, there are thyroid cancers that are among the most, if not the most, lethal. They are uncommon and so deadly that few clinicians see enough patients and follow them long enough to judge whether treatments are influencing the outcome.

The aim of this chapter is to provide a classification of thyroid cancers, and to discuss each individually. Controversial aspects will be addressed, and hopefully clarified, and a synthesis of the literature and personal experience presented. The reader may not accept the approach to management, but should have sufficient data to reason why.

8.2 CLASSIFICATION OF THYROID CANCERS

The vast majority of thyroid cancers arise from the follicular cells, and between 70–90% of these are papillary or follicular, and are differentiated. Table 8.1, which is modified from the American Thyroid Association classification [10], lists the types, and Table 8.2 shows representative percentages of various pathological types from several published series. About 55–65% are papillary, and this category includes mixed papillary-follicular cancer, since both have identical biological characteristics. About 15–25% are follicular, and included in this category are Hurthle cancers and clear-cell cancers. These last two merit separate discussion from follicular cancer, since their treatment and prognosis are less satisfactory. The last cancer which arises from follicular epithelium is the undifferentiated, or anaplastic cancer, which accounts for 5–15% of cases. These are usually subdivided into giant- or spindle-cell varieties. However, the prognoses are equally terrible so this pathological differentiation is not important clinically. In the

Table 8.1 Classification of thyroid cancers

Cell type	*Cancer type*	*Variants*
Follicular	Papillary	Papillary-follicular
		Follicular variant of papillary
	Follicular	Hurthle
		Clear cell
	Anaplastic	Giant/spindle cell
Parafollicular	Medullary	Sporadic
		MEN IIa
		MEN IIb
		Familial non-MEN
Lymphoid	Lymphoma	Non Hodgkin's
		Hodgkin's
		Plasmacytoma
Miscellaneous	Haemangioendothelioma	
	Connective tissue cancers	
Metastases	Kidney	
	Breast	
	Lung	
	Melanoma	
	G-I tract	

Table 8.2 Types and frequencies of thyroid cancers in five USA and two European series (UK and Switzerland)

		Percentage of lesions					
Ref.	*No.*	*Pap.*	*Foll.*	*Diff.*	*Anapl.*	*Medull*	*Other*
1	1181	62	18	80	14	6	
7	964			82	13	4	
9	152	63	21	84	13	3	
28	195	54	26	80	10	1	9
35	337	67	24	91	3	6	
29	469	31	16	47	40	3	15
31	573	25	39	64	26	2	8

USA there has been a trend for less cancers to be follicular or anaplastic, and more to be papillary. There is data to support that anaplastic cancers arise from long-standing papillary lesions, and it is conceivable that early diagnosis and treatment of differentiated cancer is responsible for this trend, although a change in the natural history of the disease cannot be excluded. European series show a higher proportion of follicular and anaplastic cancers. All of these cancers are more common in women, but recently the proportion found in men is increasing. It is likely that external radiation, which is known to be a cause of some thyroid cancers, is one factor for the increased incidence in men.

Cancers of the parafollicular cells are called medullary cancer, and make up about 5% in most series. Twenty per cent of these are familial and are part of the syndrome of **multiple endocrine neoplasia** type IIa (MEN IIa), a very small percentage MEN IIb, and about 80% are isolated clinical findings.

A small proportion of malignancies arise from lymphoid and connective tissues. The most common of these is non-Hodgkin's lymphoma. In older publications, the lymphomas were classified as small-cell anaplastic cancers, but this is now known to be erroneous and special staining techniques show unequivocally that they are lymphoid cancers. The prognosis is quite different from anaplastic cancer.

The thyroid is an extremely vascular organ and, as anticipated, blood-borne metastases are found in it. Autopsy of patients dying from widespread cancer demonstrate that thyroid metastases are common. However, they are seldom important clinically. In contrast, certain cancers, in particular, renal, breast, lung and melanoma, can present as a clinically relevant mass in the thyroid and, occasionally, removal of the metastasis produces long-term survival.

Each of these is discussed separately, with most emphasis being given to the differentiated lesions.

8.3 DIFFERENTIATED THYROID CANCER: PAPILLARY

8.3.1 INTRODUCTION

Although papillary and follicular cancers are both considered to be differentiated, there

are sufficient differences for them to be discussed individually. Several publications group these together, but wherever possible I have attempted to separate the data. Papillary cancer includes mixed papillary-follicular and follicular variant of papillary cancer, since their biological behaviour and prognosis are identical. Fifty-five–65% of thyroid cancers are of this type.

8.3.2 AETIOLOGY

There is now abundant evidence, both in humans and in experimental animals, that radiation is an important cause of papillary cancer [11–14]. This topic is discussed in detail in Chapter 13, which covers all aspects of thyroid dysfunction after radiation. Goitrogens have produced thyroid cancer in experimental animals, most probably from continuous TSH stimulation of the follicular cells. In clinical practice, they play a very small aetiological role. Most data supports that cancers of the thyroid are more common in areas of iodine deficiency, but these findings have been refuted by a study comparing the prevalence of papillary cancer in an iodine-rich area (Iceland), and demonstrating that it was five times greater than that of an iodine-poor area (North East Scotland) [15]. The differences could not be attributed to radiation, autoimmune thyroid disease, or any other reasonable factor. However, the degree of iodine deficiency in Scotland is modest when compared to clinically relevant iodine deficiency, and this probably accounts for these disparate results.

The role of Hashimoto's thyroiditis in causing, or simply being associated with, papillary cancer is controversial, with authoritative arguments for and against [16, 17]. Whatever the truth, the data of Clark *et al.* [18] showed that the risk of cancer in patients with Hashimoto's thyroiditis was 25% in those with a solitary cold nodule, but there was no increased risk in those with diffusely enlarged glands and no dominant nodule. Some of the controversy is related to the presence of focal, or diffuse, lymphoid infiltration in up to 50% of patients with papillary cancer [19]. Patients with papillary cancer can have serological evidence of thyroid autoimmunity; we found that 15 out of 38 patients (39%) had positive antithyroglobulin titres [20]. These patients were in a prospective study comparing whole-body radioiodine scintigraphy with serum thyroglobulin levels for follow-up of treated thyroid cancer. The possible beneficial role of the immunological infiltrate in this cancer is also controversial, but in the large series from the Mayo Clinic the presence of Hashimoto's thyroiditis was a statistically good prognostic feature [6].

There are reports of carcinogens causing thyroid cancer in experimental animals [21]. Alcohol has also been implicated by increasing TSH secretion, but this has not been a factor in patients whom I have studied, many of whom are non-drinkers.

In summary, most papillary cancers are not caused by any easily recognized factor. A history of external radiation over the neck is an important factor, but is causal in only a small percentage of the total. Other factors are of minor clinical significance. I was surprised to consult on a young woman with a radiation-induced papillary cancer which was treated by surgery. Postoperatively, she developed an unsightly keloid scar, which was treated by external radiation therapy!

8.3.3 PATHOLOGY

Papillary cancer can occur in any part of the thyroid. Its size varies from an incidental microscopic finding, to lesions several centimetres in diameter. Increasing size is a bad prognostic factor. Cancers less than 1.5 cm have been called occult [22], but this term has been criticized and should be restricted to cancers found incidentally when operation is done for some reason other than removing thyroid cancer. A better term for

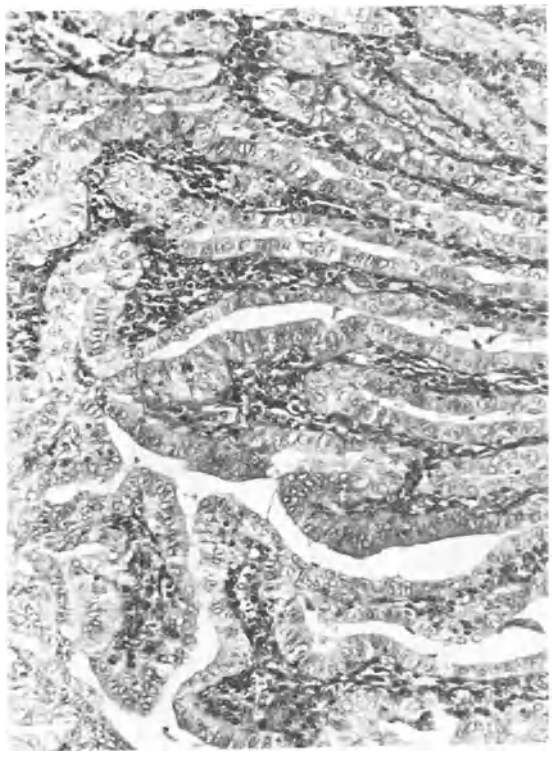


Figure 8.1 Typical appearance of papillary carcinoma. The cells are arranged in fronds with a delicate central core of vessels and connective tissue.

small cancers is 'minimal lesion'. The cancers are then classified as intrathyroidal and extrathyroidal, depending on whether they are restricted to the gland or have extended through the capsule. The cancers vary in colour, are firm to hard in consistency, and can be cystic in parts. Cystic degeneration of metastases in lymph nodes is common. Microscopic metastases to regional nodes are present in about 50% of patients at the time of the first surgery. The cancers do not have a true capsule, but form a pseudocapsule by slowly compressing normal tissues as they grow slowly. These cancers are multifocal in 20–80% of cases [23, 24], especially if the cancer is radiation induced [25]. The non-dominant lesions should not be considered as having the same potential for growth and spread, since it is clear that the frequency of recurrence in patients who have residual thyroid postoperatively is 10–20% in most series.

Histologically, the epithelial cells are cuboidal and arranged in fronds with a delicate vascular core (Figure 8.1). In many, there is a follicular component and even when this predominates, the mixed lesion is called papillary cancer. The cell nuclei have a characteristic ground-glass appearance, and they are sometimes like the eyes of 'Orphan Annie', and are given that name. Intranuclear inclusions are characteristic (Figure 8.2). Psammoma bodies are typical, but are not restricted to this cancer. In cases where the follicular cells are tall, the prognosis is less satisfactory [26].

8.3.4 CLINICAL PRESENTATION

Papillary thyroid cancer usually presents as a solitary thyroid nodule. Evaluation and management of thyroid nodules is discussed in Chapter 7, and is not repeated here. Papillary cancer usually presents as an asymptomatic nodule. When there is clinical evidence of invasion of the surrounding structures, such as the recurrent laryngeal nerve, the trachea, strap muscles of the neck, or oesophagus, the clinician should consider that the nodule is cancerous. Although microscopic lymph node metastases are found in up to 50% of patients, palpable lymph node enlargement is much less common and, *per se*, is not a common presentation. However, when papillary cancer is diagnosed in a cervical node, by far the most likely primary source is the thyroid and careful palpation of the thyroid precedes elaborate work-up for alternative primaries. Likewise, persistently enlarged neck nodes in a patient who has had external neck irradiation should prompt careful examination of the thyroid. Distant metastases in the

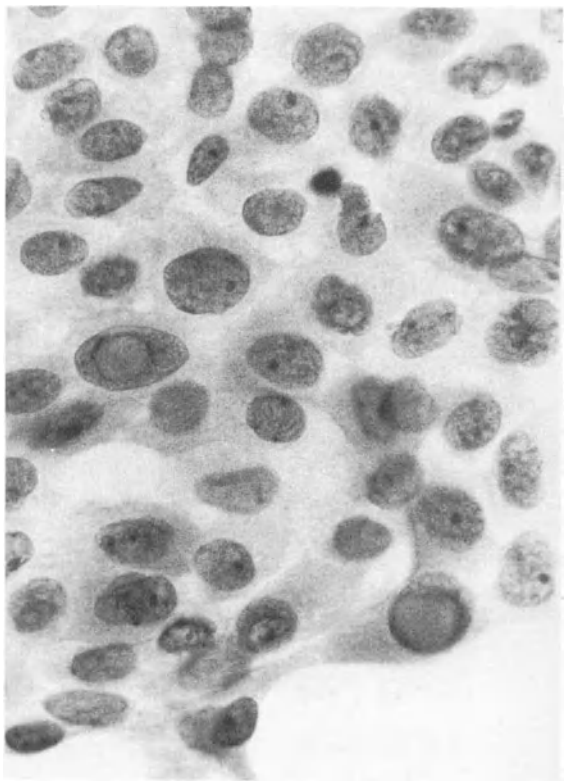


Figure 8.2 High power of papillary cancer showing intranuclear inclusions and 'Orphan Annie' appearance of some other nuclei.

lung, bones, liver, or brain are very rare presenting features, but when papillary cancer is diagnosed in one of these sites, and there is no obvious primary, the clinician should focus on the thyroid. Although numerically this is an unlikely primary, it is one of the few cancers where a reasonable prognosis can occur even in the presence of metastases. It is extremely rare for a minimal cancer to spread distantly. Therefore, in the case of widespread metastases, the primary cancer in the thyroid is palpable. There are a very few exceptions to this rule [6], and I have seen one patient with pleural metastases in whom the primary thyroid cancer of 1 mm was discovered on thin sectioning of the thyroid. This was done because the easily palpable lump thought to be the primary was found to be benign. Therefore, if a nodule is not felt, it is unlikely that the thyroid is the site of the primary lesion, but most authorities would advise an ultrasound to exclude this more objectively.

Almost without exception, patients with papillary cancer are euthyroid. The few reports of hyperthyroidism caused by thyroid cancer are in patients with widespread follicular cancer, or large hyperactive primary follicular lesions, and these are discussed under follicular cancer. Papillary cancer is found in patients of all ages, but the average is 35–45 years (Table 8.3) [3, 6, 27–29], and it is about 2–3 times more common in women.

8.3.5 MANAGEMENT

It is hard to discuss treatment without discussing prognosis first. This may seem paradoxical, but the outcome is dictated by a few simple factors not directly related to therapy. Therefore, with knowledge of these factors, the clinician can predict which patients will do well and treat them conservatively. In contrast, when the patient falls into a poor-risk category, a more radical treatment is prescribed. Prognostic factors are discussed in detail below, but it is important to recognize that the following factors are extremely important in relation to the risk of dying from the cancer, as well as having recurrent disease. Table 8.4 lists these factors and indicates their importance in five large series [3, 5, 6, 27, 30]. Young patients almost never die from papillary cancer, but patients who get this disease in later life are at considerable risk. Women have a better prognosis than men. The risk of death increases with the size of the primary cancer, and deaths almost never occur if the primary lesion is 2 cm or smaller. Extension into surrounding structures worsens prognosis, as does the presence of distant metastases, especially lesions to the bone or brain. As a result, a

Table 8.3 Prognostic features in papillary cancer

Ref.	*No.*	*Age*	*Gender*	*Size*	*Extr. lymph thyr. mets*		*Dist. histol. mets.*	
3	693	+	+	+	+	–	+	NA
5	546	+	+	NA	NA	+	+	NA
6	859	+	+	+	+	–	+	+
27	241	+	+	+	+	–	+	–
44	600	+	+	+	+	–	+	+

NA = Not available from text.

Table 8.4 Clinical demographics of patients with papillary thyroid cancer

Reference	*Number*	*Women %*	*Men %*	*Age (years)*
3	693	63.8	36.2	32.3
6	859	67.9	32.1	43.6
27	241	72.2	27.8	41.3
28	157	67.5	32.5	45.0
29	147	72.1	27.9	45.6

25-year-old woman with an intrathroidal cancer of 1.5 cm has an excellent prognosis, and treatment must not cause any long-term complication. In contrast, a 65-year-old man with a 4 cm cancer and spinal metastasis has a very bad prognosis, and therapy should be more radical in an effort to ablate all cancer.

8.3.6 SURGICAL TREATMENT

Surgical removal of the cancer is fundamental. Surgical opinion varies from removing only the cancer, the lobe containing the cancer, the lobe and isthmus, the lobe, isthmus and part of the contralateral lobe, to total thyroidectomy. The first is inadequate and is not considered further. Those who favour total thyroidectomy [32–35] develop the following supportive arguments. Many papillary cancers are multifocal (up to 80%), and it defies good surgical practice to leave known, albeit microscopic, cancer behind. Also, if a surgeon can remove one lobe at low risk, why not both lobes? In addition, when radioiodine therapy is given postoperatively, it is advantageous to have all normal thyroid removed. Opponents to total thyroidectomy counter that the risk of recurrence from lobectomy, or subtotal thyroidectomy, is not much greater than after total thyroidectomy. Therefore, that problem is more theoretical than real. They indicate that total thyroidectomy carries a risk of complications, which is considerably higher than the risk of lobectomy multiplied by 2. Finally, they counter that radioiodine can be prescribed even when there is some residual normal thyroid left after operation. Let us analyse the results of various operations, including recurrence rates, deaths from cancer and complications, to help determine the optimal approach.

In his analysis of 693 patients, Mazzaferri [3] found that the extent of an operation did not influence the outcome in patients with cancers smaller than 1.5 cm. This reference is the latest of a sequence of important publications; in this specific article there are more patients and longer follow-up, and the statistical conclusions are slightly different from those in the original paper, which was published in 1977 [36]. If the cancer is larger than 1.5 cm, total thyroidectomy is followed by fewer recurrences than subtotal thyroidectomy: 11.3% of 362 patients versus 22.0% of 315 patients ($P<0.004$). Permanent hypoparathyroidism occurred in 9.2% of the former group, and 0 out of 237 in the latter. Because of the improved recurrence rate, Mazzaferri and his colleagues [3, 36, 37] recommend total, or near total, thyroidectomy for lesions of 1.5 cm or greater. Rossi *et al.*

[38] advise bilateral subtotal thyroidectomy. After a median follow-up of 13 years in 239 patient, the recurrence rate was 12%, and 8% of their patients died. With this lesser operation, complications were greatly reduced with only 1 case of permanent hypoparathyroidism (0.4%), and 1 with unilateral vocal cord paralysis (0.4%). These results contrast with those of Harness *et al.* [35] who found 4.0% permanent hypoparathyroidism and 2.5% vocal cord paralysis in 430 patients who had total thyroidectomy. In another investigation of 706 patients with either papillary (81.3%) or follicular (18.7%) cancer, there were fewer recurrences in those who had total thyroidectomy than subtotal thyroidectomy or lobectomy [39]. The percentages were 15%, 28% and 25% respectively. However, after total thyroidectomy, 7% had unilateral vocal cord paralysis and 12.8% were hypoparathyroid. In a smaller group of patients, Starnes *et al.* [9] found a twenty-fold increase in complications after total thyroidectomy compared to lesser procedures, and these authors conclude 'total ipsilateral lobectomy, isthmectomy, and subtotal contralateral lobectomy is the treatment of choice for papillary, mixed papillary-follicular and follicular thyroid carcinoma'. Crile *et al.* [40] support this view and state that total thyroidectomy should be reserved for patients less than 7 years, or older than 44 years who have extensive bilateral disease, or distant metastases, provided the operation can be done safely. Likewise, Hay *et al.* [41] in reviewing the surgical experience in 859 patients at the Mayo Clinic report, 'we continue to recommend ipsilateral total lobectomy and contralateral subtotal lobectomy as an appropriate primary surgical treatment of papillary thyroid carcinoma'. These physicians have accepted that the complications from total thyroidectomy are sufficiently common and troublesome that they outweigh the slight reduction in recurrences, which can usually be treated successfully by a second operation.

What about the benefit of total thyroidectomy to the nuclear medicine physician who plans to treat the patient with radioiodine? I have only seen one absolutely negative whole-body ^{131}I scan in patients after thyroid surgery, even in cases where the operative note indicates total thyroidectomy was done. Attie *et al.* [34] measured the uptake of ^{131}I in 140 patients who had undergone total thyroidectomy, and 90 of these patients had values of 0.6% or greater. Therefore, there was significant thyroid left in 64% of patients. If it is accepted that total thyroidectomy cannot be achieved, and if it is accepted that significant troublesome permanent complications are more common after this procedure, there are strong reasons to accept the advice of the surgeons quoted above and the view of Cady [42]: 'overall, a policy of total thyroidectomy for thyroid cancer is doomed to failure since it provides no greater solution to the problem of thyroid cancer and does it at higher risk of major complications'.

One particularly difficult situation involves the patient who has had a lobectomy for an apparent benign nodule, interpreted as such on frozen section during the operation. The permanent slides show the lesion is carcinoma. The question arises of reoperating on the 3rd or 4th postoperative day to complete the procedure, or of ablating the residual thyroid with radioiodine, or to do nothing extra. It is not possible to give a single correct answer. If the primary lesion is single, intrathyroidal and the patient less than 45 years, the probability of recurrence is very low, and a second operation is not advised. None of 57 patients in one series who had lobectomy had a recurrence or died [38]. If there is evidence of metastases, and it is anticipated that radioiodine will be prescribed, subtotal lobectomy can be undertaken. Alternatively, the remaining lobe can be ablated with one dose of radioiodine, and the metastases treated with a second dose after several months. A repeat operation

allows the remainder of the thyroid to be examined pathologically and it expedites matters, but there is an increased risk of complications from this approach. On balance in this setting, reoperation is preferable. It is hoped that increased reliance on fine-needle aspiration of nodules preoperatively will result in surgeons accepting that patients referred for thyroidectomy for a nodule have a high probability of cancer, and the operation should be planned accordingly. There is now data to support that the accuracy of cytological interpretation of thyroid pathology on an adequate specimen by fine-needle aspiration is superior to frozen section interpretation of thyroid pathology (see Chapter 7). However, when thyroid tissue is seen on frozen section in lymph nodes, the diagnosis is unequivocally cancer, and this should be an indication to consider contralateral subtotal lobectomy.

Although spread of papillary cancer to regional lymph nodes is common, there is no place for radical neck dissection; it does not improve survival [41] and it adds troublesome complications [43]. It is very disturbing to consult on a young patient who has no evidence of cancer, but is physically troubled and markedly self-conscious about drooping and loss of function of the shoulder due to sacrifice of the spinal accessory nerve and/or marked asymmetry of the neck due to removal of the sternocleidomastoid muscle. As an aside, when the spinal accessory nerve is damaged, there is atrophy of the trapezius muscle to such a degree that the scapula is perceived as an abnormal swelling, and I have seen several patients who thought they felt metastases in that site. Lymph nodes which are obviously involved should be removed by 'berry picking' or modified neck dissection planned to preserve the above structures and the jugular vein. There is conflicting data of the prognostic significance of metastatic spread to lymph nodes in this cancer. Most series show no increase in mortality, and Cady *et al.* [44] showed an improved outcome when the nodes were involved. This view was criticized by Harwood *et al.* [45], who demonstrated that nodal involvement was commoner in younger patients, and since age is the most important single determinant of survival, patients with positive nodes have to be compared to properly matched controls. By doing that, they found positive nodes to be a poor prognostic factor. Nevertheless, the long-term importance of metastases to regional nodes is much less than age, sex, size of cancer, extrathyroidal spread and distant metastases.

An interesting study was conducted by Kozol and Numan [46]. They polled board certified surgeons and asked them what operation would be advised for a patient with a papillary cancer greater than 5 cm. Of the 100 surgeons who responded (50% response rate), 3 recommended lobectomy, 28 lobectomy plus isthmusectomy, 43 subtotal thyroidectomy and 26 total thyroidectomy. Clearly, there is no unanimity of opinion. There are other risks from thyroidectomy including death. This is significantly more common in patients older than 70 years (0.66%) compared with 0.02% in patients less than 50 years [47]. The mortality of 0.7% from 407 operations reviewed by Max *et al.* [48] was accounted for by pre-existing illness in the patients who died but, nevertheless, is a sobering statistic. Haematoma, wound infection and Horner's syndrome from damage to the cervical sympathetic chain are rare complications. It is not my role to discuss the pros and cons of general versus local anaesthesia for thyroid surgery, but simply to comment that local anaesthesia is appropriate for the patient who is a bad risk for general anaesthesia, but in whom surgery is necessary. There have been remarkable changes in the postoperative care of patients over the last 20 years. In the past, patients were kept in hospital for 7–10 days; now the trend is to discharge them on the first postoperative day provided there are

no complications. There are recent reports of same-day thyroidectomy, including one series of 48 patients, 3 of whom had differentiated cancer [49]. My personal preference would be for at least one night in hospital.

In summary, the consensus of opinion is that ipsilateral lobectomy and contralateral subtotal lobectomy is the optimal operation for papillary cancer. In patients who are younger than 45 years and have a single intrathyroidal cancer of less than 3 cm, ipsilateral lobectomy and isthmusectomy is adequate, but less desirable. There is no benefit from total thyroidectomy which, in practice, is difficult to achieve and is associated with a significant increase in troublesome complications.

8.3.7 ADDITIONAL THERAPIES

Having brought the patient through the operation, hopefully with no complications, the role of additional treatment arises. This always includes thyroxine and, in selected patients, radioiodine ^{131}I. Very seldom is it necessary to prescribe external radiotherapy, or chemotherapy. Each of these is discussed individually. Patients who have occult thyroid cancer, i.e. cancer less than 1 cm in size, found serendipitously when the thyroid is removed for some other reason, do not require radioiodine or other anticancer therapies. They should also not be subjected to repeat operation to complete total thyroidectomy. Their management should be that of the primary condition after operation as if no cancer had been present.

8.3.8 SUPPRESSIVE THERAPY WITH THYROXINE

Thyroid replacement is a basic part of treatment, because the patient is likely to be thyroid deficient when subtotal thyroidectomy has been done. In addition, differentiated thyroid cancers are usually TSH dependent, and sufficient thyroxine should be prescribed to suppress TSH. Many experts have seen papillary cancer shrink when TSH is suppressed [50]. There are reports of pulmonary lesions disappearing or stabilizing with this treatment alone [51]. There is experimental evidence in animals to support this [52]. The corollary is that metastases can grow when thyroxine is stopped in preparation for whole-body radioiodine scintigraphy, although in practice clinical problems are uncommon. Mazzaferri *et al.* [3] showed that patients treated with thyroxine had a statistically better outcome. In contrast with this long-held dogma, Cady *et al.* [53] did not find this to be stastistically significant in producing a better prognosis. Their conclusions have been criticized by Crile [54]. It is recommended that sufficient thyroxine is prescribed to suppress TSH. The dose of thyroxine necessary to achieve this depends on the weight of the patient, and will usually be in the range of 100–300 μg/day (approximately 2 μg/kg). The clinician should ensure that TSH is suppressed by measuring it with a new sensitive assay. It has been recommended that TRH test should be done to prove that there is no rise in TSH [55, 56], but this is not necessary. When distant lesions continue to grow in spite of suppressed TSH, alternative therapy has to be considered.

8.3.9 RADIOIODINE THERAPY

As an aid to determine which patients are treated with radioiodine, I try to separate those patients who have intrathyroidal papillary cancer from those who have extension into adjacent tissues, or who have metastases. The last two have a statistically greater chance of dying from the cancer, and in them it makes sense to ablate all functioning thyroid, both normal and malignant. On occasion, this separation is not obvious without performing a diagnostic scan. However, in most patients it is. The surgeon and

pathologist define whether there is extension through the capsule of the thyroid and whether there are lymph node metastases. Distant metastases may be recognized on chest radiograph, or suspected by symptoms of bone pain or persistent headache. Fortunately, distant metastases at presentation are not common. The best method of ablation is with radioiodine ^{131}I. This radionuclide is trapped and organified like inorganic iodine, and it emits beta particles which are destructive locally over a distance of several millimetres. Using this radionuclide, it is possible to deliver a very intense radiation dose to thyroid tissue without causing damage to adjacent normal tissues. ^{131}I also emits gamma rays which can be used for scintigraphy. Therefore, the distribution of the therapy can be predicted by a test dose, and approximate calculations of radiation from a therapeutic dose are made, based on size of lesions and their uptake of the tracer. It is possible to deliver tens of thousands of rads to some cancers, and this this contrasts with external beam therapy where about 6000 rad (60 Gy) is the limiting dose, because higher doses cause permanent damage to normal structures, such as the oesophagus, spinal cord, etc.

For diagnostic scintigraphy, thyroxine is stopped for a minimum of 4 weeks. This is to ensure that TSH rises. It is important to measure TSH to prove it is elevated. Edmonds *et al.* [57] found TSH to be greater than 30 μU/ml in athyreotic patients at 4 weeks, and we found a mean value of 129 μU/ml in our patients [20]. Beierwaltes *et al.* [58] recommends stopping thyroxine for 6 weeks, but gives no TSH values. Alternatively, thyroxine is stopped and replaced by L triiodothyronine for 4 weeks and then the triiodothyronine stopped for 2 weeks [59, 60]. The usual dose of L triiodothyronine is 50–100 μg/day, and it is best prescribed in divided doses due to its relatively short half-life. This approach is said to reduce the period of hypothyroidism experienced by the patient. I have not been impressed by any difference, and some care should be taken when introducing the L triiodothyronine, since the serum thyroxine will not fall for several days and transient hyperthyroidism can be produced by the addition of T_3 to T^4. A dovetailing of the medications, tapering L thyroxine and starting L triiodothyronine in half the final dose, prevents this, but is more complicated and takes longer. When the logic for using L triiodothyronine is questioned, there is really no advantage since the half-life of T_4 is 7 days and hypothyroidism is not apparent until the third week of abstinence, whereas the half-life of T_3 is 24–36 hours and hypothyroidism occurs for the same length of time before testing. The patient should not be given radiographic contrast and should not take iodine-containing medications. Several authorities recommend a low-iodine diet [61, 62]. I recommend reduced intake of seafood and flour products, and avoidance of vitamin and mineral supplements containing iodine. Others have used diuretics to lower plasma inorganic iodine in order to enhance trapping of radioiodine by the cancer [63]. Hamburger [64] encountered a severe complication when he used mannitol, and this is not recommended. I have not used diuretics.

Other investigators have used exogenous bovine TSH by injection, 10 units daily for 3 days, in an effort to augment radioiodine uptake [2]. This material is not human TSH, and it can cause allergic reactions [65]. In addition, it has a short half-life of approximately 1 hour, and its use is not encouraged. If exogenous TSH is employed and the scintigram is negative, the procedure has to be repeated correctly. Therefore, it is better to use the endogenous TSH protocol as described first.

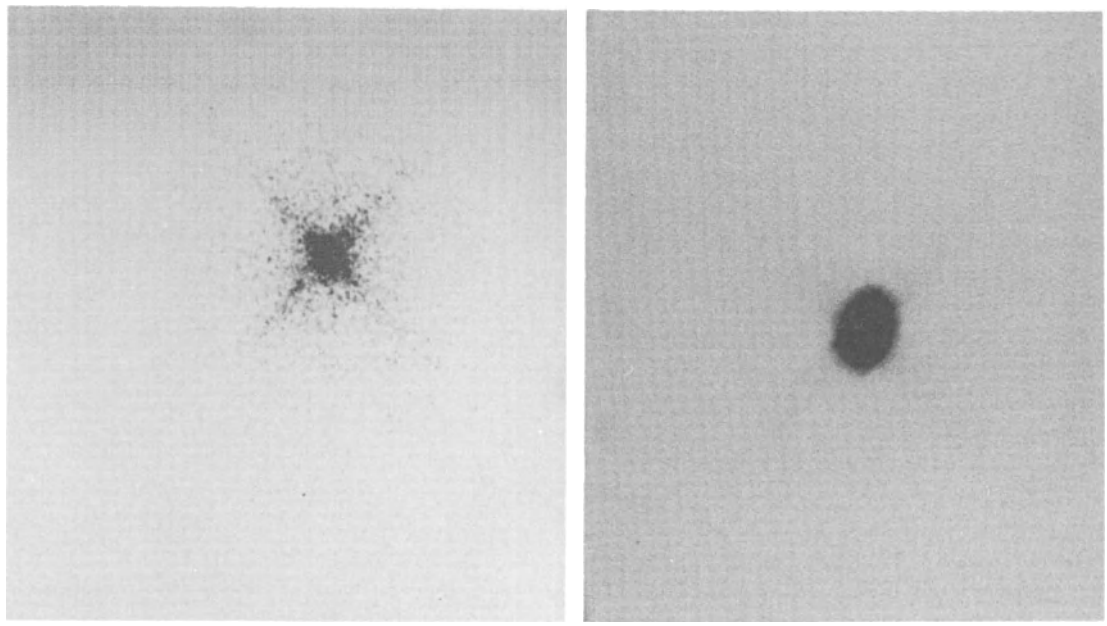
In those patients who have only had a lobectomy, the clinician should not expect a rise in TSH at the time of the first scintigram. Nevertheless, the residual normal thyroid will trap iodine and, if there is an

indication to treat, the lobe can be ablated with a therapeutic dose of ^{131}I. Treatment of distant lesions with radioiodine has to await ablation of normal thyroid, and cannot be undertaken for several months.

There is debate about the optimum dose of ^{131}I for total-body scintigraphy. The dose ranges from 500 μCi to 30 mCi. Those who use larger doses indicate that more lesions are detected in some patients, and in other patients the only lesions seen are with the higher dose. It is true that if scans are done several days after a therapy dose, lesions are picked up that were not imaged with the diagnostic scanning dose [66, 67]. However, it is unlikely that these lesions accumulate sufficient radioiodine to respond to therapy. Therefore, it is a moot point whether they are seen on the diagnostic scan with 30 mCi, or not. The fact that they are seen on the therapy scan usually means that they will require a second therapy dose at a later date. I prescribe 2 mCi and, routinely, obtain anterior and posterior whole-body scans with a spot view over the neck and upper chest using a gamma camera with appropriate collimators for the high energy of the gamma rays of ^{131}I (366 Kev). The spot view can be obtained with a standard collimator, or a pin-hole collimator. I routinely measure the uptake in neck lesions and, frequently, in distant metastases as well. Henk *et al.* [68] and Beckerman *et al.* [69] have presented data in favour of waiting 72 hours between giving the test dose and scanning, but there is no real difference between 48 and 72 hours, so any time within these limits is acceptable. There is no study comparing ^{123}I with ^{131}I for this purpose. The 13 hour half-life of the former would require a substantial dose to be administered if scans are to be made after 48 hours. In addition, because the energy of the gamma rays of ^{131}I are higher, it would be difficult to make images with ^{121}I, when ^{131}I had been used first. Therefore, it is difficult to plan a comparative study of ^{123}I with ^{131}I in which the order of administration is randomized, ^{123}I would always have to be studied first. Figure 8.3(*a*) shows a whole-body scan with uptake in residual thyroid, and Figure 8.3(*b*) shows a spot view of the neck.

Abnormal sites of uptake distant from the thyroid bed which concentrate radioiodine should be considered for treatment, as should residual thyroid when it is known that there is invasion into surrounding tissues. Figure 8.4 shows diagrammatically how I stratify the patients.

There is a second 'form of treatment' which involves ablating 'normal' thyroid postoperatively (Figure 8.5). The tissue is usually normal, but could conceivably contain microscopic foci of cancer. This is a very controversial issue. There are thyroidologists who ablate residual thyroid routinely, and they argue that it is not possible to determine whether there are microscopic foci of cancer, or whether there are functioning metastases until all normal thyroid has been removed. This is similar to the argument in favour of total thyroidectomy. The clinician should look critically at the simple prognostic factors and make a judgement whether it is likely that ablation of residual thyroid can improve prognosis. In a 25-year-old woman with a 2 cm intrathyroidal cancer this is unlikely. Therefore, an ablative dose should not be given. In contrast, if the patient is 65 years old and has a 5 cm cancer, there is reason to believe that ablation of all thyroid should improve the outcome. When a decision is made to ablate normal residual thyroid, this has to be thought of as different from treatment of cancer *per se*. The term prophylactic radioiodine therapy has been used, but even this is incorrect and I use the term thyroid remnant ablation. How much ^{131}I is necessary for thyroid remnant ablation? There has been a trend to prescribe 30 mCi (actually 29.9 mCi) but, of course, the main reason for choosing this particular dose is to allow the therapy to be given on an outpatient basis.



(a) (b)

Figure 8.3 (*a*) Whole-body scan 72 hours after 2 mCi of ^{131}I. The patient had subtotal thyroidectomy 4 weeks previously, and had been given no thyroxine postoperatively. Intense uptake is noted in the region of the thyroid bed, but no evidence of local or distant sites of uptake. Note that with the high energy of the gamma rays of ^{131}I there can be a 'star' effect. In (*b*) which is a spot view of the neck in the same patient, the artifactual star is no longer seen. This also shows uptake in the region of the thyroid bed and is probably normal thyroid.

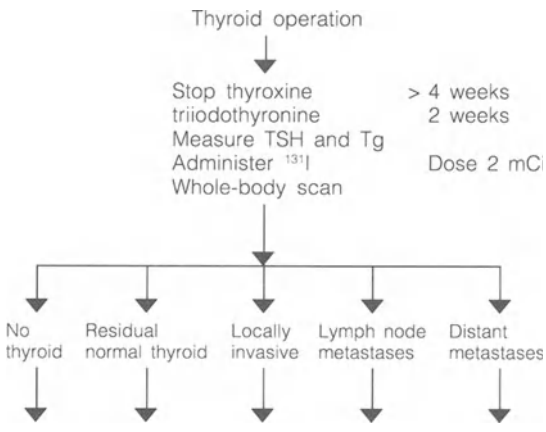


Figure 8.4 Flow diagram for management of a patient with papillary cancer after operation.

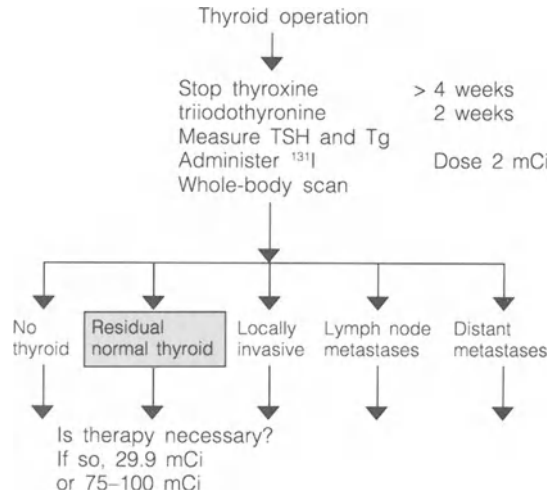


Figure 8.5 Remnant ablation.

In some series, 30 mCi is not as successful as larger doses (75–100 mCi) in ablating residual thyroid. Therefore, treatment of metastases is delayed and the patient may in fact be subjected to a greater cumulative radiation dose in the long term. The literature is not particularly helpful in formulating a uniform protocol. In the first report, 30 mCi successfully ablated 21 out of 36 (58%) residual thyroids, whereas higher doses were successful in 18 out of 28 cases (64%) [70]. The authors concluded that 30 mCi was as valuable. Ryo [71] criticized this publication since it lacked objective evidence of uptake, or volume of thyroid being treated. In contrast, Kuni and Klingensmith [72] did not achieve ablation of residual thyroid in any of 13 patients with low-dose therapy. Siddiqui *et al.* [73] were successful in only 1 out of 10 patients, and they felt low-dose therapy was not justified. It is difficult to compare these reports because the stage of the disease, the volume of the residual thyroid, the measurement of uptake, and the criteria for a negative scan, are not defined. Ramaciotti *et al.* [74] did measure uptake, and on this basis were successful in treating normal residual thyroid in 9 out of 15 patients. Even better results were reported by DeGroot and Reilly [75], with 15 out of 18 cured by 30 mCi and all 21 patients by 50 mCi. These workers ablated thyroid if the primary cancer was greater than 1 cm, or if there was a history of neck irradiation, or if the cancer was multifocal, in addition to those with metastases or invasion. This would be almost every case. They do give information about the stage of disease, but not the criteria for a negative post-treatment scan. Snyder *et al.* [76] treated 69 patients with 29 mCi and completely ablated the remnants in 42 patients, and almost totally ablated an additional 14 (82% of the total group). They found there was no relation to radioiodine uptake in the remnant, the volume of residual thyroid, or the calculated radiation dose. Equally important, they found that successful ablation did not protect the patient from developing metastases. Unfortunately, visual inspection was used to determine if 'a remnant was suitable for treatment'. In an undefined number of patients in whom uptake was measured, no therapy was prescribed if the value was less than 1%. I have used a lower cut-off at 0.3%. Figure 8.6 shows whole-body ^{131}I scintigrams postremnant ablation in the patient whose pretreatment scan is shown in Figure 8.3. I have not treated patients with radioiodine unless a diagnostic scan immediately before showed uptake. Blind treatment seems to me to be just that.

The reader is left puzzled. Should 30 mCi be prescribed for thyroid remnant ablation? Firstly, a decision should be made whether this treatment is necessary. In patients under 45 years with a cancer 3 cm or greater, it is justifiable to prescribe this amount. A repeat scan several months later may show total ablation, in which case no additional radioiodine treatment is prescribed. If the repeat scan shows no uptake in the neck but does show metastases, these would be treated with a larger dose of radioiodine (see below). If there is still residual uptake in the same area in the neck, a second dose of 30 mCi can be prescribed. In older patients, or when there is a reason to hope for rapid definitive ablation, a larger therapy dose of 75–100 mCi can be given. Unfortunately, there is no guarantee that this will be successful. The role of adequate subtotal thyroidectomy is stressed, since if there is only a small volume of normal thyroid and there are functioning metastases, the latter are usually seen on total-body scintigraphy, in which case a large therapy dose would be prescribed at the onset.

When there is abnormal uptake in distant sites, it is worth attempting therapy with a large dose of radioiodine. Figure 8.7 shows an anterior whole-body scan in a woman who had extensive functioning metastases. Some effort should be made to quantitate the uptake and to determine the mass of

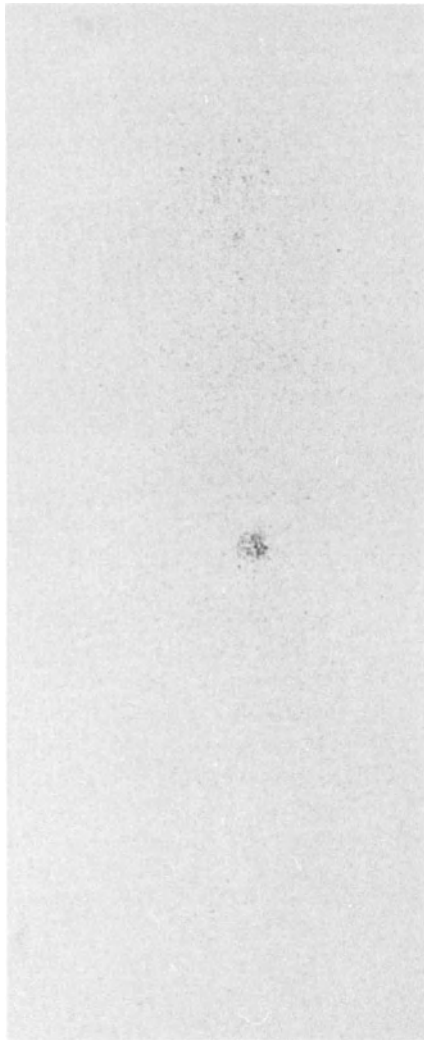


Figure 8.6 Follow-up anterior whole-body scan 72 hours after 2 mCi ^{131}I in a patient treated previously with surgery and ^{131}I. The patient has been off thyroxine for 4 weeks. A faint shadow of the body is seen with a trace of uptake in the neck and more uptake in the low pelvis due to excretion of the tracer.

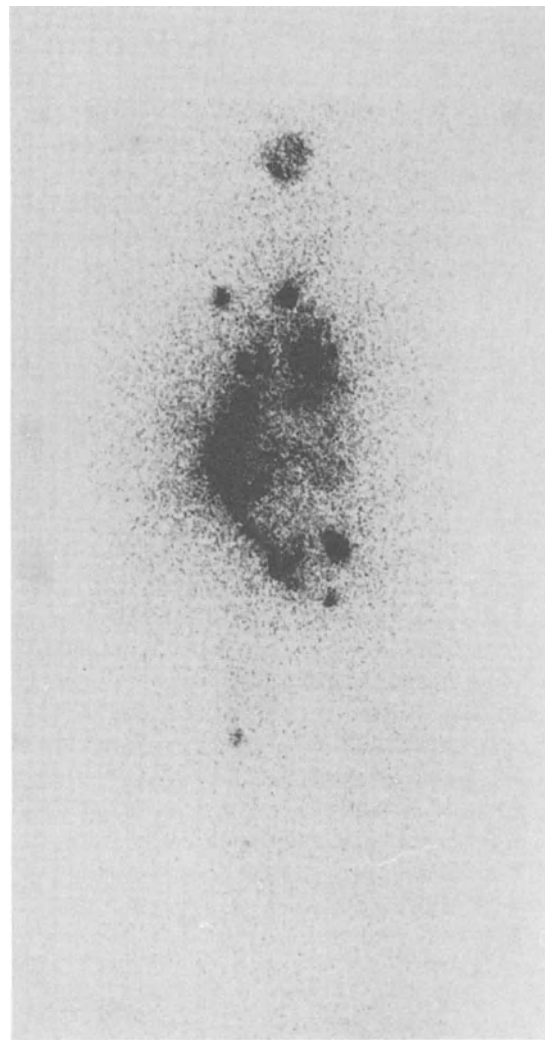


Figure 8.7 Whole-body scan (anterior projection) in a patient with widespread functioning metastases in the skull, lungs, liver, pelvis and right femur. The scan was made 72 hours after 2 mCi ^{131}I. There is uptake in the bowel due to excretion of radioiodine.

cancer by other methods including roentgenograms, CT (*without iodine contrast*), NMRI, or ultrasound. This is not always possible because the lesions can be so small that they are below the resolving capacity of these procedures. Maxon *et al.* [77] have attempted to quantitate the prescribed therapy, and have shown that a dose of 30 000 rad for thyroid remnant ablation and 8000 rad to metastases improved the rate of re-

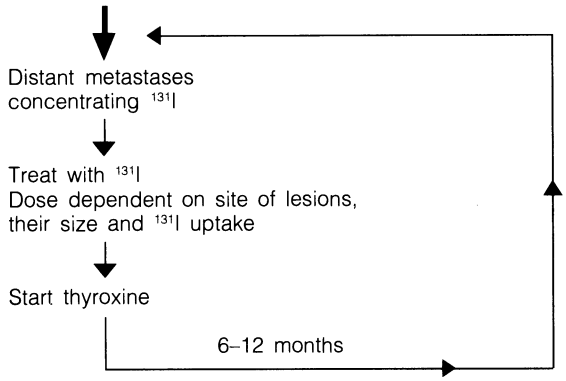


Figure 8.8 Flow diagram for the management of a patient with distant metastases.

sponse to therapy. When uptake at any site is less than 0.3% of the administered dose, therapy is unlikely to be successful. Figure 8.8 shows the protocol for treating distant metastases.

When there are pulmonary lesions, the dose administered is 100–150 rad. Diffuse pulmonary lesions which are not seen on chest X-ray are the easiest to ablate [78]. There are many reports of these lesions detected only by radioiodine scintigraphy [79, 80], and Figure 8.9 shows the scan in a young woman postoperatively and which shows diffuse pulmonary uptake of ^{131}I as well as functioning metastases in lymph nodes. There has been concern that radioiodine would damage normal pulmonary epithelium, but the local dosimetry does not support this conclusion. There are two reports of this [81, 82], but in the former case there was 50% uptake of the therapy dose in the lungs. In my experience, this is more than an order of magnitude than the usual case. Cannon-ball metastases to the lungs are less easy to ablate, but considerable success is possible provided the lesions trap radioiodine (Figure 8.10). Massin *et al.* [83] reported on 58 patients with pulmonary metastases from a total population of 831 patients (7%) with differentiated thyroid

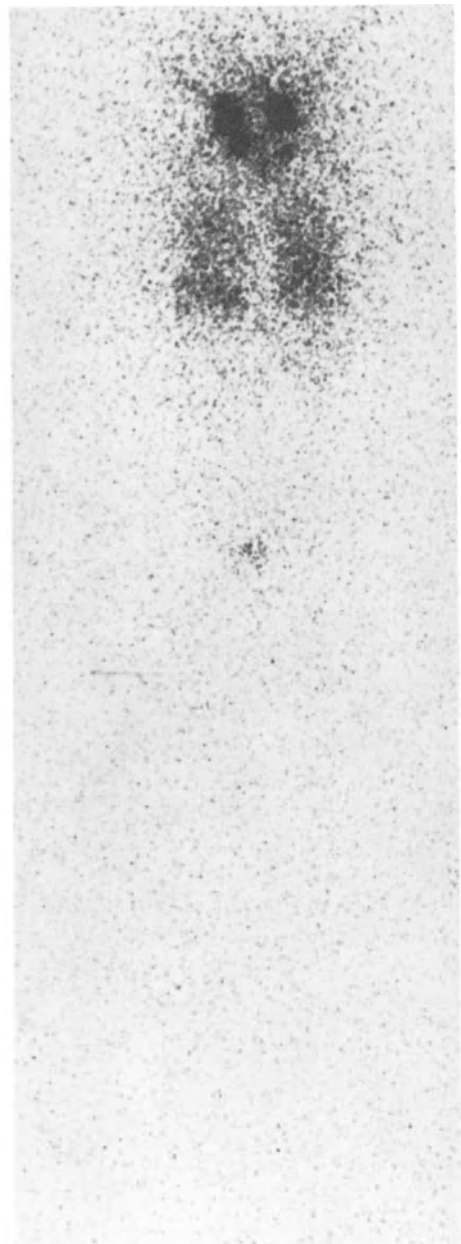


Figure 8.9 Whole-body scan made 72 hours after 2 mCi ^{131}I, which shows functioning cervical nodal metastases as well as diffuse pulmonary uptake. A chest roentgenogram was normal and the patient has diffuse 'microscopic' functioning metastases to the lungs.

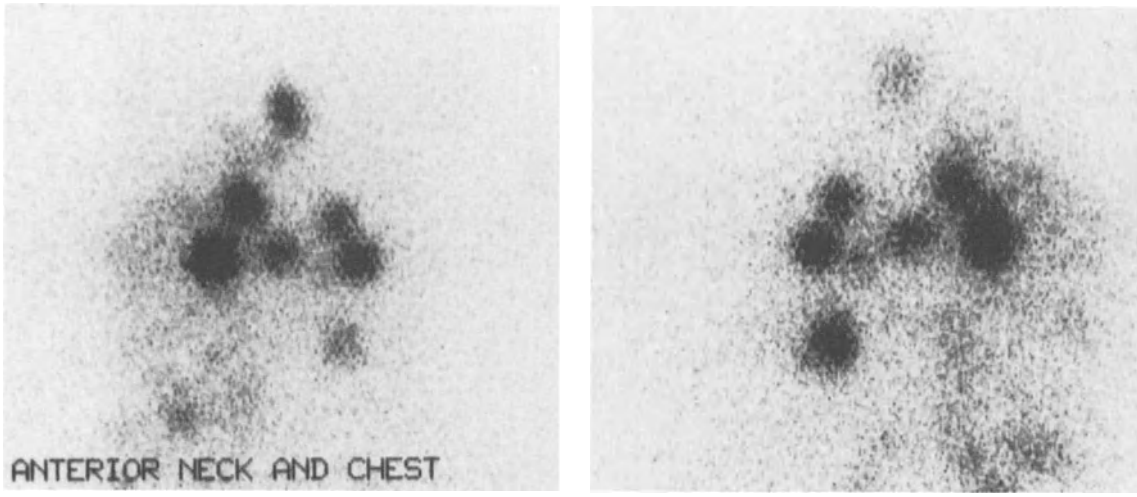


Figure 8.10 Anterior and posterior spot views of the lungs showing multiple areas of focal uptake of ^{131}I. This is typical of 'cannon-ball' metastases.

cancer. Their series included both papillary and follicular cancers, and they found that 5% of the former and 10% of the latter metastazised to the lungs. Thirteen of the 14 patients with micronodular disease had papillary cancer and 12 of the lesions concentrated radioiodine. The 8-year survival in these patients was 77%, compared with 18% for those with macronodules. Only 1.3% of patients who had total thyroidectomy and postoperative radioiodine developed pulmonary lesions, compared with 11% who had partial thyroidectomy. It appears that both the surgery and the radioiodine had a role in the reduction, because both total thyroidectomy alone and partial thyroidectomy plus radioiodine had an intermediate incidence. Neither produced as low a percentage as both together. Samaan *et al.* [84] found pulmonary metastases in 101 out of 1127 patients (9%). They also found the incidence of pulmonary metastases was less in those who had a total thyroidectomy (5%), compared with 9% for those who had a lesser operation. They also found that the prognosis was better in those with small lesions which concentrated radioiodine. Somewhat surprisingly, 42% of the patients had abnormal chest X-rays but normal scans, and only 10% had the converse. There is no information on how the diagnosis was established in the former patients. In both of these reports, young patients did better and, in both, radioiodine ablation improved the prognosis. The fact that lesions are not imaged on a repeat scan does not necessarily imply that they have been ablated. An alternative explanation is that they are no longer able to trap iodine, perhaps because of dedifferentiation. Nevertheless, a negative follow-up scan with a benign clinical course and undetectable thyroglobulin are good evidence of successful therapy.

The majority of bony metastases occur in the axial skeleton. They are more difficult to eradicate and, in the experience of some, are never entirely cured. I successfully treated a 30-year-old man who had several recurrences of differentiated cancer in the cervical lymph nodes. When he was referred for consideration for radioiodine therapy, the initial whole-body scintigram showed uptake in the left side of the thorax. Full lung tomograms were negative, and a ^{99m}Tc diphos-

phonate bone scan showed a lesion in a rib which corresponded to the hot spot on the radioiodine scan. He was treated with 100 mCi ^{131}I (a smaller dose than I would currently use), and is free of disease and has undetectable thyroglobulin after 13 years. In spite of pessimism about curing skeletal metastases, their growth can frequently be halted or reversed. Bone metastases are more common in patients with follicular cancer, but are found rarely when the pathology is papillary. The lesions are osteolytic on a radiograph, and not all are seen on standard bone scintigraphy. Castillo *et al.* [85] were unable to image 59% of lesions with ^{99m}Tc diphsophonate bone scan that were seen on a total-body iodine scan, or a radiograph. It is also my impression that although some of the skeletal lesions are difficult to image, with the latest ^{99m}Tc compounds and high-resolution gamma cameras, most are seen, albeit faintly (Figure 8.11). The prognosis in patients with skeletal metastases is poor. Harness *et al.* [86] treated 10 patients with radioiodine and, although 7 died, all 10 survived for at least 5 years. The authors were encouraged by the palliation from radioiodine. Hepatic metastases from papillary cancer are extremely rare, but for continuity this is discussed here. In general, when the liver is involved with thyroid metastases, there is widespread disease with nodal, pulmonary and skeletal lesions. Figure 8.7 shows a whole-body scan in a woman who originally did have isolated hepatic metastases, which responded partially to radioiodine therapy, although several years later she developed skeletal and brain lesions as shown. Diffuse hepatic uptake is usually due to concentration of radiolabelled hormones in the liver.

Fortunately, brain metastases are very rare. Their treatment is problematic because they are usually symptomatic, causing headache and vomiting, and there is concern that stopping thyroxine and allowing TSH to rise will stimulate further growth of the

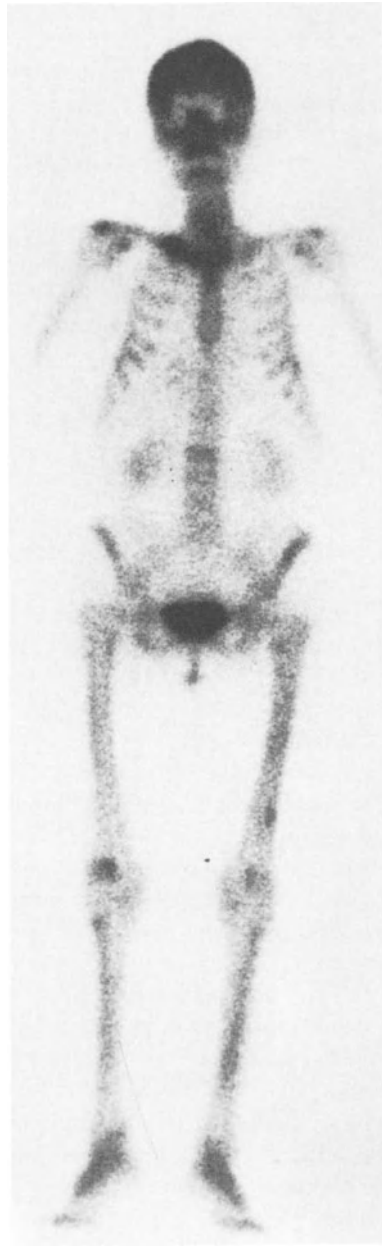


Figure 8.11 ^{99m}Tc diphosphonate bone scan in a patient with known metastases in the right clavicle (well seen) and left femur (not well seen).

lesion. In patients I have treated, I felt it was inadvisable to take this approach and the patients were treated by external radiation therapy with remission, but subsequent death from both brain lesions and widespread disease. If the brain lesion is single and in a non-critical part of the brain, it might be possible to resect it. There are two case reports of patients with cerebral metastases having catastrophic events shortly after ^{131}I therapy. The first had a stroke on the 4th day after 135 mCi of ^{131}I and was found at surgery to have a haemorrhagic metastasis [87]. The second developed symptoms which were attributed to radiation sickness 12 hours after 200 mCi [88], although that seems somewhat unlikely because the radiation delivered over that time would not be sufficient to cause this syndrome. Whether the radioiodine or the TSH stimulus was causal is not certain, but clearly in this setting the clinician must use considerable judgement to reach the decision of whether to stop thyroxine and treat the patients with radioiodine. A similar situation is found when a spinal metastasis abuts on the spinal cord; there are reports, and I have experience, of neurological worsening, which most probably was due to cancer growth under TSH stimulation [89, 90]. In some cases like this, radioiodine is the most appropriate therapy, but this should be planned in collaboration with the neurosurgeon and radiation oncologist, so that emergent steps can be taken if complications occur.

The prognosis in patients who have extension of the cancer out of the thyroid into strap muscles or trachea is worse, and residual tissue should be ablated with radioiodine. This is not thyroid remnant ablation, but destruction of tissue that is almost certainly cancerous. In this situation, a dose of 75–100 mCi ^{131}I is recommended. The most contentious problem is whether to treat the patient with positive uptake in lymph nodes with radioiodine. The debate about the prognostic significance of metastases to lymph nodes has been presented. This is not a major bad prognostic factor. It is my policy to treat positive nodes which are impalpable with radioiodine, and to advise surgical removal of those that are palpable. The protocol for treatment with radioactive iodine is shown in Figure 8.12, and is similar to that for distant metastases, except the therapy dose is usually 100 mCi.

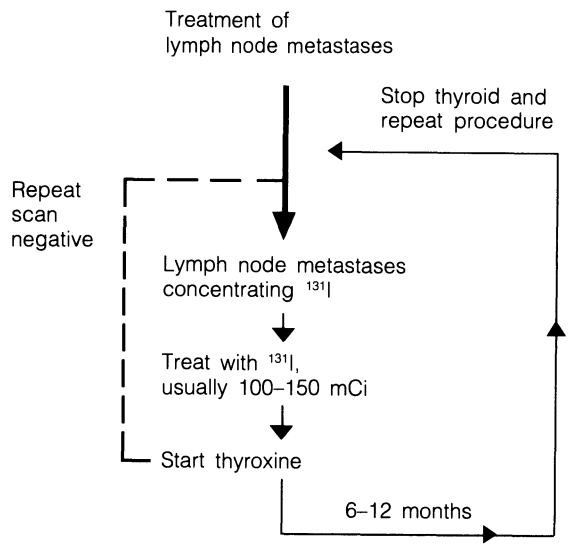


Figure 8.12 Flow diagram for the treatment of functioning metastases to the lymph nodes.

A repeat scan 7–10 days after the therapy dose is valuable to prove that the treatment localized where desired. As stated above, a scan of the therapy dose sometimes demonstrates lesions that were not seen on the test scan [66, 67]. The scan will also show diffuse uptake of radioiodine in the liver in those patients in whom there is enough functioning tissue to produce radiolabelled thyroid hormones. The diffuse uptake is due to metabolism of radiolabelled hormones in the liver, and should not be interpreted as metastases [91–93].

The use of diuretics and low-iodine diets to augment uptake in metastases has been presented. An alternative approach, which

has not been used extensively and which I have not used, is to prescribe lithium to prevent the release of iodine from the thyroid. The original report by Gershengorn *et al.* [94] was not encouraging, because of the high whole-body and marrow radiation from ^{131}I. A more recent study in 18 patients showed that the half-life of radioiodine in metastases was increased after 7 days of lithium carbonate in a dose range of 400–800 mg daily [95]. However, there was no increase in the retention time in a normal thyroid. The experimental design resulted in the measurements with adjuvant lithium always postdating the non-lithium measurement, so the effect of protracted hypothyroidism on the outcome could not be excluded.

Not all papillary cancers concentrate iodine and even when the test is done properly and TSH is high, about 10% of cancers are not visualized. There are a very few false-positive results provided the normal distribution of iodine is remembered (Chapters 2 and 3). There are case reports of uptake in inflammatory lung disease [96], Meckel's diverticulum [97] and renal cyst [98].

8.3.10 SIDE-EFFECTS AND COMPLICATIONS OF ^{131}I THERAPY

The intense radiation dose delivered to the thyroid can cause radiation thyroiditis with acute pain and tenderness over the thyroid. The pain can be referred to the jaw, ear, or teeth on the side where the remnant of thyroid remains. This complication is rare, but the patient should be warned about it. It usually occurs 7–14 days after treatment. There is a spectrum of severity; some patients only require simple analgesics like aspirin, but in severe cases it is necessary to prescribe stronger analgesics and prednisone (30–40 mg) for about 2 weeks. One patient I treated when this occurred became hyperthyroid as a result of disruption of the gland and required propranolol for several weeks. There is very little chance of causing thyroid storm, but if the patient is hyperthyroid due to widespread metastatic cancer (see follicular cancer), it is justifiable to pretreat with an antithyroid medication for a few weeks; but that treatment has to be stopped before administering radioiodine. Beta-blockers would be prescribed to treat hyperthyroid symptoms. Many patients report a change in taste, days to weeks, after therapy, more often when 100 mCi or more is prescribed. Allweiss *et al.* [99] in an analysis of treated patients found that sialadenitis is more common than most have believed. Ten out of 87 patients developed this. The complication occurred as early as 1 day, and 9 of the 10 had symptoms within 3 weeks of therapy. It was not uncommon for the symptoms to last as long as 1–2 years. Edmonds and Smith [100] also found pain in the salivary glands, usually the parotid, in 10% of their patients, and this complication could be delayed for months to years after therapy. I have suggested that patients suck lemon sweets for several days to encourage the flow of saliva, but have not conducted a trial to determine its benefit.

Growth of the cancer under TSH stimulation has been discussed. When a complication occurs in hours or days after treatment, the temporal relationship incriminates either the treatment, or the preparation for treatment. Whenever there is evidence of differentiated thyroid cancer in a fixed space where accelerated growth would be critical, considerable judgement must be used before embarking on this treatment.

The parathyroid glands receive a significant radiation dose from ^{131}I, but there are few reports of hypoparathyroidism resulting from this treatment. Recently, Glazebrook [101] undertook a study to determine parathyroid reserve in patients who had received radioiodine. The stimulus for the investigation was a patient who developed tetany 20 months after receiving 100 mCi ^{131}I.

Glazenbrook concluded that 58% of patients treated postoperatively with radioiodine were subclinically hypoparathyroid, but since these patients were statistically different before ^{131}I, it is likely that surgery, not radioiodine, was causal. In practice, hypoparathyroidism is not a complication. Nevertheless, further investigations using parathyroid hormone measurements before and after surgery and after radioiodine seem justified.

The major theoretical problems of radioiodine relate to long-term complications. This is important since many of the patients are young and their prognosis treated by operation and thyroxine alone is good. Potential complications include induction of a more aggressive form of thyroid cancer, and induction of cancers in organs which are the sites of highest radiation doses from radioiodine, in particular the stomach, salivary glands, kidney and bladder, plus the marrow whose cells are radiosensitive. Potential risk to children born to patients who have been treated with radioiodine must be considered.

There are reports of differentiated cancers becoming anaplastic after radioiodine, but more cases transform *de novo* [102]. This topic is developed in depth in the section on anaplastic cancer. If the goal of treatment is to ablate all thyroid tissue, both malignant and normal, and this is achieved, anaplastic change cannot occur. Therefore, if radioiodine is recommended in a specific patient, adequate single-dose treatment should be attempted. This is somewhat different from ablation of a normal remnant which is discussed above. Several large series show no increased risk of second malignancies that could be attributed to radioiodine [103, 104]. However, the data of Pochin [105] supported the thesis that acute leukaemia (three cases) was found more often than expected, but this complication was found after cumulative doses of more than 1050 mCi. His protocol involved therapy doses given repeatedly at intervals of a few months, and few therapists prescribe doses as frequently, or as large as these. Residual thyroid can be ablated with 1 or 2 therapies, and although distant metastases can be difficult to ablate, the interval between therapies should not be less than 6 months and, preferably, 1 year. When there is a life-threatening concern about the cancer, it is justifiable to prescribe a cumulative dose greater than 1050 mCi. The patients treated by Pochin have been analysed further by Edmonds and Smith [100]. The three patients who developed leukaemia did so in 1957, and were the last in this series to develop this complication. Leukaemia occurred within 3 years of therapy. The number is greater than the expected incidence of 0.25% ($P = 0.002$). Brinckner *et al.* [106] found two cases of acute myelogenous leukaemia in 194 patients treated with radioiodine, which contrasted with 0.097 expected. From the literature, they present 10 patients with a denominator of just less than 500 patients. They conclude that ^{131}I is appropriate for differentiated metastatic cancer, but is not without risk. One patient I treated developed stage IV immunoblastic lymphoma 9 years after her first therapy dose. She received a total of 400 mCi over 3 years.

Edmonds and Smith [100] found 6 patients with breast cancer, which was just statistically more than the 2.53 expected ($P = 0.044$). There were 3 bladder cancers compared to 0.46 expected ($P = 0.012$). Bladder cancers did not occur until 14–20 years after treatment. Cancers of the salivary gland, stomach and other sites were not increased. They conclude the 'benefits of therapy do not appear to be outweighed by long-term harmful effects'.

One series showed no difference in genetic risk to offspring of 33 treated patients [107]. The treated patients were 14.6 years average age at the time of therapy, received

an average of 196 mCi, and were followed for 18.7 years. This data is heartening, but more information is necessary before a final conclusion can be reached. Several patients I have treated with large doses have had normal offspring and, generally, I advise them to wait one year before conceiving, although there is no data to support this delay. Handlesman *et al.* [108] described a 32-year-old man who became azoospermic after 350 mCi ^{131}I. The gonadal dose was estimated between 175–525 rad. They showed a positive correlation between the ^{131}I dose and FSH level, and an inverse relation of dose and sperm density. Small testes and azoospermia was described in a teenager who received 350 mCi (radiation dose to the testes was calculated to be in the range of 175–350 rad) [109], and Edmonds and Smith [100] describe a similar patient, but contrast him with two who received larger doses and fathered normal children. A prospective study would be of value.

Concern about radioiodine for pulmonary metastases has been discussed [81], but it is more likely that impaired lung function results from residual cancer than radiation, since pulmonary function is usually normal when there is no evidence of cancer.

Serious, long-term complications of radioiodine are not common, but they are not zero. Therefore, because differentiated cancer has a good prognosis, this treatment should not be used indiscriminately. If young patients are to be treated, the lowest dose which is expected to be successful should be used. In patients with distant metastases, therapy should not be withheld because of concern of complications, as the cancer poses a greater risk.

8.3.11 RESULTS OF ^{131}I THERAPY

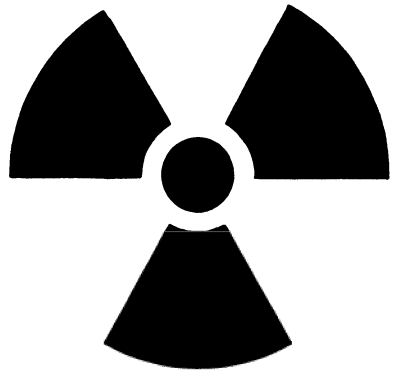
There are no controlled, randomized trials comparing radioiodine with no radioiodine in patients with the same stage of disease, the same surgery and similar age and sex distribution. Those who believe that it improves the prognosis point to their long-term results, and those who do not think it is beneficial point to theirs. In the patients analysed by Mazzaferri [3] and Mazzaferri and Young [36], there were fewer recurrences in patients treated with radioiodine (6.4% v. 13.1%), yet these patients had more extensive local disease and cervical node metastases at presentation. Therefore, the benefit of radioiodine might be greater than is apparent from the numbers. There are no criteria on why these patients received radioiodine, or not. Eighty-seven per cent received less than 200 mCi and 98% less than 300 mCi.

Leeper [110] reported on the use of ^{131}I in 46 patients, 25 with papillary cancer, who had distant metastases. For controls he used patients whose cancers did not concentrate ^{131}I. This is flawed since these latter cancers, by definition, have a different biological behaviour from those that trap radioiodine. Patients less than 40 years of age with papillary cancer were benefited, and the mean dose prescribed was 470 mCi. In the analysis of 333 patients treated at the University of Michigan, 36 had lung or bone metastases, and 28 of these had papillary cancer. The mortality in the series was 28% at 15 years, which the authors compare with a 75% 5-year mortality from a different centre. They have also compared the outcome with a historical control group from their own institute who were operated on, but did not receive radioiodine [111]. The radioiodine was shown to improve the prognosis, but this type of comparison is also flawed since many factors could have changed with the passage of time. In the prospective treatment group of 54 patients treated by Krishnamurthy and Blahd [112], those patients in whom complete ablation was achieved survived with no serious complications. In summary, although most therapists are

convinced that radioiodine therapy improves survival, there is no controlled study to confirm this. The data available suggests that those with distant lesions are helped and that ablation of residual thyroid reduces the recurrence rate somewhat.

8.3.12 RADIATION PROTECTION AND SAFETY [113]

Women in the childbearing age should have a negative pregnancy test before radioactive iodine is prescribed. This is best done using serum beta HCG. After treatment, patients are a radiation source from which their relatives and the public should be protected. The NRCP regulations recommend a limit of 5 rem/year whole-body radiation for radiation workers and for family members over 45 years. The limit to non-radiation workers and younger family members is 0.5 rem-year. It is recommended that patients receiving 30 mCi or greater should be admitted to hospital. If one centre treats a substantial number of patients as in-patients, there should be a room designated for these patients. The room should be at the end of a corridor with two free walls and only one wall adjacent to another patient room [114]. The patient in the adjacent room should be older than 45 years. The common wall can have lead shielding incorporated, or a lead shield can be placed between the treated patient and the wall. It is preferable that the patient sleeps at the far end of the room and wall fixtures, call button and oxygen outlets should be placed accordingly. When the patient is admitted, a special form should be posted on the outside of the room door (Figure 8.13). The patient should wear a wrist band indicating that radioactivity has been prescribed. The nurses should wear radiation dosimeters and none should be pregnant. Rubber gloves should be used by nurses when they are in contact with the patient. It is better to administer the therapy in the patient's hospital room, because it is easier to transport the dose well shielded in a lead pig than it is to transport a radioactive patient. The patient should sign informed consent that the nature of the treatment has been explained and potential problems discussed. A form giving information on safely measures to be taken after discharge is prudent. The treatment can be given in liquid or capsule form. New dispensing systems for the liquid do not cause as much risk of release of vaporized radioiodine as old systems. Capsules reduce this risk [115], but the cost of preparing capsules is so expensive that I use liquid for cost reasons alone. The technologist or physician responsible for giving the treatment must explain to the patient what to do, and must wear rubber gloves. The treating physician should be in attendance. Once treated, the patient must remain in the special room until released by the physician. Showers are allowed. The patient should drink at least 8 ounces of fluid hourly for 8–10 hours, and micturate at least every 2 hours, to speed the excretion of untrapped radioiodine and to reduce radiation to the urinary tract. There should be instructions about how long nurses and visitors can be in contact with the patient, and the office and home phone number of the responsible physician should be on record in case a problem arises. Since the urine is extremely radioactive, it should not be collected, and great care should taken to avoid spillage or splashing. Large, plastic waste containers should be in the room to collect non-reusable materials, and meals should be delivered on paper plates, which are collected by the person responsible for radiation safety. Bed clothes are placed in plastic bags and retained until radioactivity has decayed. Generally, the patients are healthy and require a minimum of laboratory tests. When blood or urine tests are planned, they should be obtained before the radioiodine is prescribed. Elective surgery should not be planned in these patients, but emergency surgical procedures must be done as



CAUTION

RADIOACTIVE MATERIALS

VISITING TIME CONTROLLED

VISITORS CHECK AT NURSING STATION BEFORE ENTERING ROOM
VISITANTES DEBEN DE REPORTAR A LA ESTACION DE ENFERMERAS ANTES DE ENTRAR AL CUARTO

Attending Physician: _____
Phone: Days _____ Nights: _____
RADIATION SAFETY OFFICE AT ANY TIME CALL

Patient's Name _____

Med # _____

CAUTION
RADIOACTIVE MATERIAL

Iodine-131 Therapy

mCi _____

Administered _____
(date)

INSTRUCTIONS:

1) This patient has received a therapeutic dose of radioactivity which could present hazards.
2) Consult "Physician's Orders for Patients Who Have Received Radioactive Iodine-131 Therapy" form enclosed in this record and the "Radiation Protection Guide for Hospital Staff."
3) All precautions expire 45 days after date administered (see above).

Figure 8.13 Example of a notice to be posted on the door of a patient who has been hospitalized for treatment with 30 mCi or more of ^{131}I.

expeditiously as possible, and sponges, specimens and instruments labelled as radioactive and handled as such. Instruments should be free of radioactivity before reuse.

A patient treated with 100 mCi emits 22 mrem/hour at 1 metre. When the retained dose is less than 30 mCi, or the emitted radiation 8 mrem/hour at 1 metre, the patient can be released from hospital. Once the retained dose is 8 mCi or less (emitted radiation 1.8 mrem/hour), no special precautions are necessary. Jacobson *et al.* [116] have measured whole-body and thyroid radiation in family members. They found a range of whole-body exposure of 0.17–126 mrem/day. Thyroid doses ranged from 4–1330 mrem. They found the telephone mouthpiece was the hottest surface and, as a result, we cover the mouthpiece of the phone in the hospital room with thin plastic, such as Seran wrap.

Personnel involved in radioactive iodine therapies should have counts made over their thyroids to ensure there has been no inhalation of radioactivity. Clearly, this form of treatment should be under the control of a physician trained in therapy with unsealed radionuclides and radiation safety.

8.3.13 PROGNOSIS

Prognosis falls into two categories: firstly the recurrence rate and, secondly, and more importantly, the death rate. Not all publications separate these, and to a degree the two factors are interrelated. Important factors for both are increasing age, male sex, large primary cancer, distant metastases and dedifferentiated pathology. Less important factors are lymph node metastases and the presence of Hashimoto's thyroiditis. Table 8.2 lists the role of these in several published series. Hay *et al.* [41] have developed a formula which can be used to determine *a priori* the prognosis. The mathematical basis for the formula comes from results of their multivariant analysis of the outcome in 860 patients. The factors used are Age, Grade (histological), Extent and Size (AGES). Prognostic score = (0.05 × age in years if the patient is 40 years old or more, 0 if less than 40), plus (1 if the histology is grade 2, or +3 if the histology grade is 3 or 4), plus (1 if there is extrathyroidal spread or +3 if there is distant spread), plus (0.2 × maximum diameter of the primary cancer in cm). In this analysis, a score of 3.9 or less was associated with a 25-year cancer mortality of 2%! A score from 4.0–4.99 had a 24% mortality after the same length of follow-up, and a score of 5.0–5.99 a mortality of 49%, and 93% of those with a score of 6.0 or more died as a result of the cancer. Clearly, any adjuvant therapy should be recommended in the last groups, not the first.

8.3.14 TREATMENT OF CANCER THAT DOES NOT ACCUMULATE ^{131}I

About 10% of histologically well-differentiated thyroid cancers do not accumulate a meaningful quantity of ^{131}I, even when the patient has been off thyroxine and has a marked TSH stimulus. Painful bone lesions which do not trap iodine should be treated using external radiation therapy. Progressive widespread metastatic disease should be treated with systemic chemotherapy. Otherwise, if the patient is asymptomatic, the only treatment is suppressive doses of thyroxine for life.

8.3.15 EXTERNAL RADIATION THERAPY

There is a very limited role for external radiation therapy in the primary treatment of differentiated thyroid cancer. If metastases accumulate ^{131}I, this form of radiation treatment is preferable because a higher radiation dose can be delivered more selectively. Whenever there is residual thyroid cancer in the neck which is not controlled with TSH suppression and which does not trap iodine, external radiation therapy can be used. There are reports of its use in place

of radioiodine, with fair results [117], but in any publication about therapy the other prognostic factors have to be evaluated since they frequently dictate the outcome. I consulted and treated a young man whose papillary cancer had been treated postoperatively (lobectomy) with high-dose external radiation. When he developed distant metastases and was referred for radioiodine therapy, a diagnostic whole-body ^{131}I scintigram showed normal uptake in the residual lobe, which was subsequently totally ablated with ^{131}I. He died of widespread thyroid cancer and is the only patient less than 45 years old who has done so in my experience. There are reports of external radiation given before ^{131}I causing a bad outcome [118]. This case demonstrates that normal and malignant thyroid are resistant to fairly high doses of radiation, 7000 rad in this case, and that internal radiation from ^{131}I can deliver a higher dose.

8.3.16 CHEMOTHERAPY FOR DIFFERENTIATED THYROID CANCER

Because most patients with differentiated thyroid cancer have a good prognosis, especially if treated by the appropriate operation, oral thyroxine and, in selected cases, radioiodine, there is a very limited role for anticancer chemotherapy. Gottlieb and Hill [119] presented the results of treatment with Adriamycin in 28 patients with differentiated thyroid cancers. Twelve patients had papillary cancer, 6 follicular, 9 Hurthle and one unclassified. Twenty-one had neck involvement, the same number pulmonary metastases, and 9 had bone metastases. In every patient, the disease was progressive and was considered to be untreatable with standard therapies. Ten had a partial remission (36%), and their survival was superior to those in whom the cancer continued to grow. Shimaoka and Reyes [120] treated 14 patients with Adriamycin 60–90 mg/m^2 at 3–4-week intervals. One patient had a complete remission and 4 others a partial remission. Hellman *et al.* [121] used combined chemotherapy with Adriamycin 40 mg/kg on day 1, melphalan 6 mg/m^2 orally from day 3 to day 6, vincristine 2 mg intravenously and bleomycin 15 mg intramuscularly on day 15 of a 28-day cycle. Eight cycles were prescribed, then melphalan was given monthly for a year. Four patients with progressive limited disease had a complete remission, and 3 with widespread disease a partial remission.

Cisplatinum, or a combination of cisplatinum and Adriamycin, are under investigation, but results in reasonable numbers of patients are not available. Whatever chemotherapy is used, it is important that an oncologist is responsible for the management of the patient, and the decision about when to introduce chemotherapy is a joint one with the patient and thyroidologist. This therapy should not be used when there is no evidence of progressive disease.

8.3.17 THYROGLOBULIN AS A TUMOUR MARKER

Serum thyroglobulin is a very valuable marker for differentiated thyroid cancer. The topic is introduced in Chapter 3. Many researchers have shown that increased levels correlate with recurrent or metastatic disease, and absent thyroglobulin with successful ablation of all thyroid tissue [122–129]. In our experience, the results are very valuable but are different depending on whether the patient is taking thyroxine, or not. They also depend on whether a significant amount of normal thyroid is left postoperatively. In those patients who had total thyroidectomy and are taking suppressive doses of thyroxine, the sensitivity is 97% and specificity 96% [129]. In those with residual thyroid, the specificity falls to 87%, but the sensitivity is still excellent at 97%. When the patient stops thyroxine and thyroid tissue, both

benign and malignant, is stimulated by TSH, the results are less impressive but still clinically valuable. The sensitivity in those with no thyroid tissue is 75%, and in those with residual thyroid 94%. The specificities are 95% and 71% respectively. Clearly, there are both false negatives and false positives, and readers should not be overly concerned by case reports of proven metastatic disease associated with normal thyroglobulin [130]. When evaluated along with careful clinical examination and a whole-body radioiodine scan, the clinician has three objective methods of follow-up.

I suggest the following approach in patients who are thought to have total thyroid ablation, either by surgery alone, or by surgery and radioiodine. When total-body ^{131}I scintigraphy is done to prove that ablation has been achieved, stop thyroxine for at least 4 weeks, draw blood just prior to administering the tracer dose of ^{131}I and measure TSH and thyroglobulin. If the scan is negative and thyroglobulin undetectable, complete ablation is virtually assured. Restart thyroxine and use clinical examination and thyroglobulin measurements while the patient is on thyroxine to follow the course of the disease. If thyroglobulin becomes detectable at any time, stop thyroxine and repeat the radioiodine scan.

If the scan is abnormal yet thyroglobulin unmeasurable, the patient would be treated with ^{131}I to ablate the abnormality but, in this situation, thyroglobulin will not provide a good index for follow-up. This is uncommon. When the opposite is found, a negative scan with positive thyroglobulin, the clinician is perplexed since there is probably cancer but its site is not known. Whole-body ^{201}Tl scintigraphy can help to define the abnormal site which, if it is to be treated, will require surgery or external radiation since it does not concentrate radioiodine.

In patients who had a lesser thyroid operation and a decision made simply to treat with thyroxine, I do not do radioiodine scans because the residual thyroid will be imaged and little else. In these patients thyroglobulin is helpful, but a normal result in our experience is up to 10 ng/ml, and not undetectable as in the former situation.

8.3.18 WHOLE-BODY THALLIUM SCINTIGRAPHY

There is growing evidence that ^{201}Tl is a valuable additional imaging agent for thyroid cancer. It is not specific; however, it has the great advantage that the study can be done without stopping thyroxine. If sufficient data supports that this scan always gives the same result as radioiodine, the ^{201}Tl scan would be done first and, if negative, the patient would not have to stop thyroxine. When the ^{201}Tl scan is positive, a radioiodine scan would be ordered as a preliminary to determine if treatment with radioiodine should be administered. The data of Brendel *et al.* [131] speaks against this possibility. This is also presented in Chapter 3.

8.4 DIFFERENTIATED THYROID CANCER: FOLLICULAR

This cancer is discussed separately because the pathology, behaviour and prognosis are different from papillary cancer [132]. Not all experts agree on the distinction and argue that the poorer prognosis is attributed to the patients being older.

8.4.1 AETIOLOGY

There is only a minor association with prior head and neck radiation causing follicular cancer. In a significant number of cases the lesion arises in a multinodular goitre, but it is not clear if the cancer arises there *de novo*,

or whether malignant transformation occurs. The incidence of follicular cancer is decreasing in the USA [133, 134], and this has been attributed to increased iodine in the diet, and hence less multinodular goitre. Coincidentally, the percentage of papillary cancers is increasing.

8.4.2 PATHOLOGY

This section deals with pure follicular cancer. Hurthle cell tumours, which are considered as a variant of follicular cancer, are discussed separately below. The cancer is usually well circumscribed when small but, as it enlarges, it invades both the vessels and the capsule of the gland. It is pink in colour, and can occur at any place in the thyroid, although it is said to be rare in the isthmus. Histologically, it consists of microfollicles with small amounts of colloid (Figure 8.14). There are no papillae and no psammoma bodies. When there are classic features of follicular cancer, but the nuclei have a ground-glass appearance, the lesion is classified as a follicular variant of papillary cancer and the lesion behaves like papillary rather than follicular cancer [135]. Pure follicular cancer has a greater tendency to metastasize by the blood to the bones, lung, liver and brain than papillary cancer, and less tendency to spread via the lymphatics to regional nodes. Histological evidence of marked capsular invasion or vascular invasion are important, since they are each bad prognostic features (Figure 8.15). Sometimes it is difficult to differentiate an atypical follicular adenoma from a well-differentiated follicular carcinoma, but minor degrees of angioinvasion clinch the latter diagnosis. Even after careful evaluation of multiple sections, the issue can be unsettled and only the appearance of metastases at a later date establishes the true nature of the lesion. Most now agree that separating well-differentiated follicular cancer from moderately well-differentiated is prognostically important.

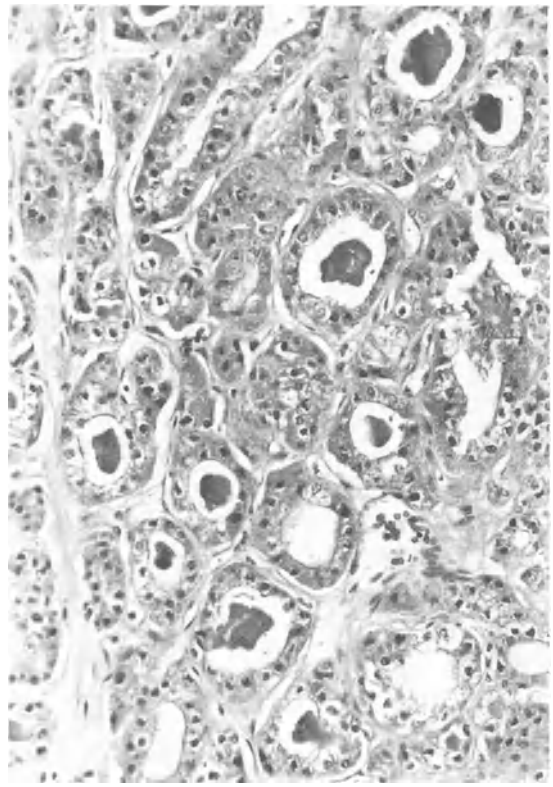


Figure 8.14 Histology of follicular carcinoma.

8.4.3 CLINICAL PRESENTATION

The usual presentation is a nodule in the thyroid. In most series, 65–80% are women and the average age range is from 45–55 years [132–134, 136]. Most patients are euthyroid, but there are a small number of reports of hyperthyroidism due to widespread metastases secreting excess thyroxine [137–139] or very rarely a huge primary lesion hypersecreting [140]. Because of the propensity for angioinvasion, the cancer can grow along the great vessels of the neck and cause superior vena cava syndrome [141, 142].

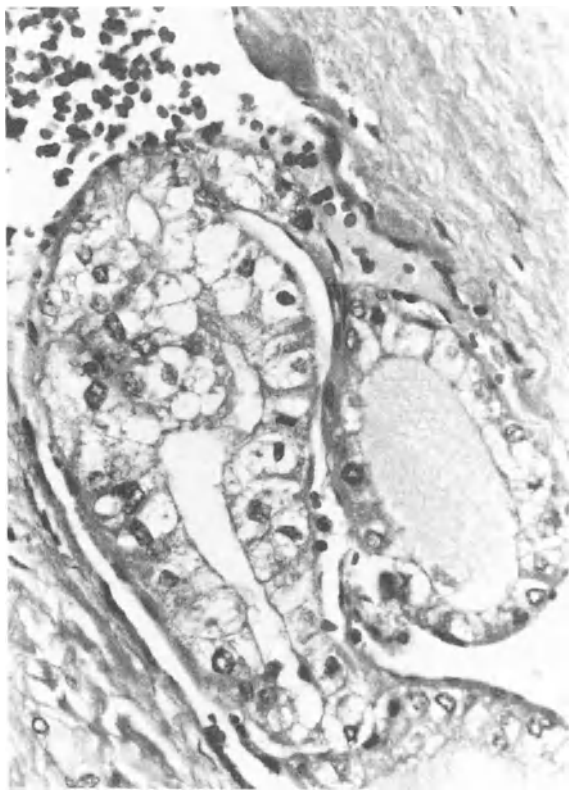


Figure 8.15 Intravascular extension of follicular cancer.

8.4.4 TREATMENT

Surgery is the main form of treatment for this cancer. The correct operation is near total thyroidectomy, but as stated above, even after total thyroidectomy, residual tissue is usually apparent on whole-body imaging with radioiodine [143]. The role of radioiodine is more clearly established in the case of follicular cancer, although even here there is no uniform opinion [143]. Certainly, if there is pathological evidence of angio- or capsular invasion, residual thyroid should be ablated with 75–100 mCi ^{131}I. A repeat scan 6–12 months later is done to look for functioning metastases which, if present, are treated with a second dose of ^{131}I. When radioiodine is used in the rare patient with follicular cancer who is hyperthyroid, pretreatment with antithyroid drugs is recommended to prevent thyroid storm [144]. The usual dose to treat metastases is 150–200 mCi ^{131}I, but Leeper [1] has demonstrated that larger doses can be given provided dosimetric calculations from the preliminary test dose show that the blood will receive less than 200 rad, and that retention at 48 hours is not greater than 80 mCi. Using this protocol in 150 patients, he has not seen fatal marrow aplasia, leukaemia, or pulmonary fibrosis. I have never used more than 200 mCi for a single treatment.

The principles for the use of radiation therapy and chemotherapy are the same as for progressive papillary cancer.

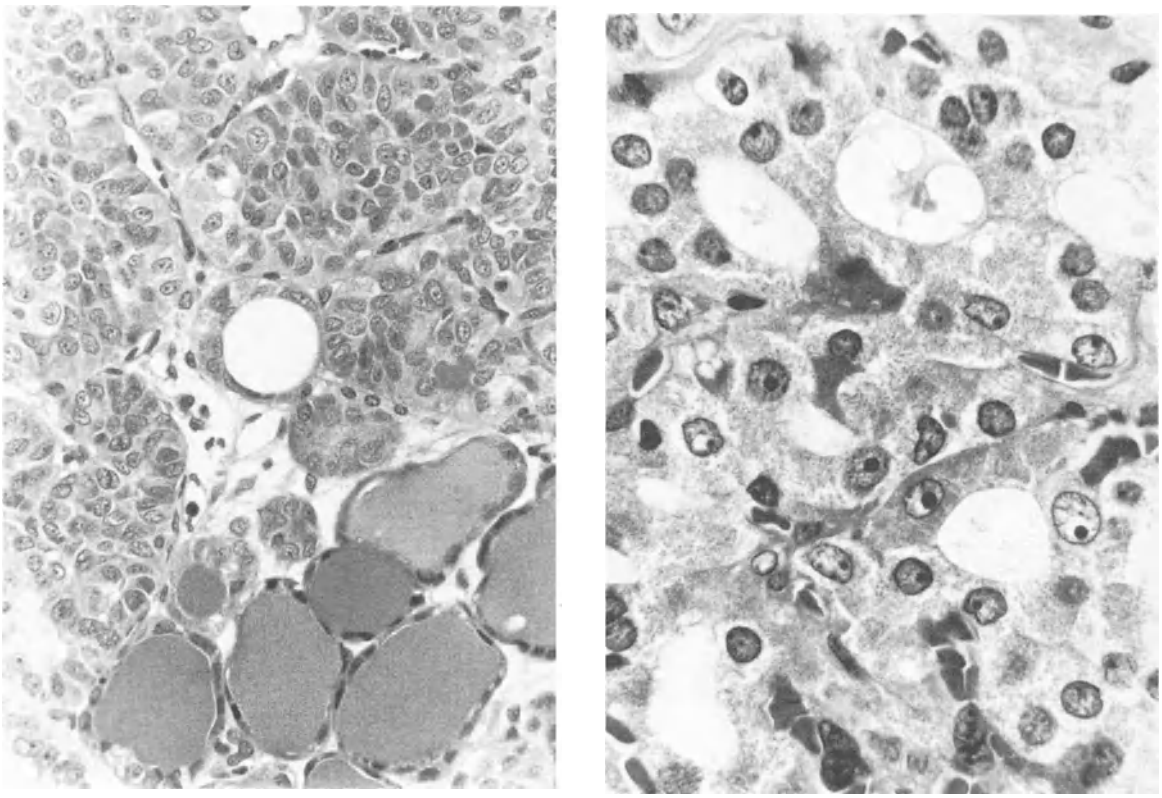
Thyroglobulin as well as total-body ^{131}I scintigraphy are used for determining whether the patient is free from cancer, or not.

8.4.5 PROGNOSIS

The overall prognosis in patients with follicular cancer is inferior to that in patients with papillary cancer. Several factors are associated with a bad prognosis, and of these the most important are extrathyroidal extension of the cancer, distant metastases, the large size of the primary lesion, nodal metastases, and old age of the patient [133, 134, 136]. Extensive angioinvasion is significant, but hard to separate from local invasion and distant metastases.

8.5 DIFFERENTIATED THYROID CANCER: HURTHLE CELL

Hurthle cells, also called Askanazy cells, are large oxyphil cells (Figure 8.16). These cells also occur in the thyroid in a variety of conditions, including Hashimoto's thyroiditis and Graves' disease, in addition to neoplasia. There is now no doubt that this is a follicular cell with abundant mitochondria



(a) (b)

Figure 8.16 (*a*) A low-power photomicrograph of a Hurthle cell lesion in upper three-quarters of the picture and normal thyroid below for comparison. To prove this lesion is cancerous requires evidence of capsular invasion, vascular invasion or the presence of metastases. (*b*) A high-power photomicrograph of the Hurthle cells with abundant dark cytoplasm.

[145]. Therefore, Hurthle cell cancers are variants of follicular cancer. It is necessary for there to be evidence of metastases, or angio- or capsular invasion before this diagnosis is made. The cancer occurs in slightly older age (mean age 55.5 years in 29 patients [145]) than pure follicular cancer, and the ratio of women to men is 2 to 1. The cancer is more prone to spread locally than follicular cancer, but distant spread occurs as well. Because there are few large series, it is difficult to establish optimal therapy. However, near total thyroidectomy is advised when there is definite evidence that the lesion is cancerous. Postoperatively, thyroxine is prescribed but there is seldom evidence that radioiodine is taken up by metastases, so this therapy is not prescribed. A repeat operation is done for local recurrence. Symptomatic distant lesions are treated by surgery if they can be resected or debulked without serious complications. Alternatively, external radiotherapy is given. Ten of the 29 patients studied by Watson *et al.* [146] died of their cancer and bad prognostic features were lymph-node

metastases, high-grade histology and local invasion. No patients had distant metastases at presentation, but this has previously been shown to be bad.

8.6 DIFFERENTIATED THYROID CANCER: CLEAR CELL

I am not certain whether this should be classified with follicular or anaplastic cancer. It is rare and has a bad prognosis. The only case I have seen had a metastasis to the ilium, which concentrated radioiodine, hence I have placed the discussion here. It is difficult on occasion to determine if this is a primary thyroid cancer, or if it is a metastasis from a clear-cell cancer of the kidney [146, 147]. If the lesion stains with antithyroglobulin, it is of thyroid origin. When diagnosed early, near total thyroidectomy is advised. In the case of metastatic spread, testing can be done to determine if the cancer traps sufficient radioiodine to advise this therapy. Otherwise, radiation and/or chemotherapy are prescribed depending on the position and extent of spread [148].

8.7 DIFFERENTIATED CANCERS IN EXTRATHYROIDAL SITES

8.7.1 CANCER IN THYROGLOSSAL DUCT OR CYST

Thyroid cancer in the thyroglossal duct or cyst is rare and usually not diagnosed preoperatively. The surgeon and patient are surprised to learn that a routinely removed thyroglossal cyst contains cancer. On occasion, hardness of the cyst or associated lymphadenopathy alert the clinician to the possibility of this diagnosis. Jaques *et al.* [149] and other investigators [150–152] have reviewed the literature and added cases, and in total about 70 cases have been described. Ninety per cent are papillary cancers [153], but unlike papillary cancers arising in the thyroid, only about 10% of these have metastases to regional lymph nodes. This might be an underestimate since nodes are not sampled routinely in the surgery of thyroglossal cyst. There is an increased ratio of women (2 to 1) and the age range is 30–60 years. There is one report of a case occurring after neck irradiation [154]. The condition has an excellent prognosis and the operative procedure for the thyroglossal cyst (**Sistrunk operation**) is all that is required in most patients. Since a small proportion of these cancers are thought to arise in the thyroid and migrate upwards through the thyroglossal duct, it is important to palpate the thyroid carefully to ensure there is no mass. It is probably correct to obtain a thyroid scintigram or ultrasound, and if these and clinical findings are normal, most authorities recommend prescribing thyroxine in a dose sufficient to suppress TSH. It could be argued that if the thyroid is normal and the cancer arose *de novo* in the ectopic site, no additional therapy would be required, but caution usually dictates the former approach. The small number of cases does not allow sweeping recommendations to be made. I have seen this once in a 37-year-old woman in whom a thyroglossal cyst was removed for cosmetic reasons. It was made up entirely of papillary cancer. There was a tiny palpable nodule in the lower left of the thyroid, which was hot on ^{123}I scintigram. After considerable discussion a decision was made not to operate on the thyroid. She remains well with the tiny nodule unchanged 12 years later.

8.7.2 CANCER IN STRUMA OVARII

Struma ovarii is a rare tumour which is usually diagnosed by the pathologist when an ovarian tumour is removed. It is a teratoma in which thyroid tissue makes up the majority of the lesion. About 0.5% of ovarian tumours are of this kind. The thyroid tissue is usually benign, although 19 cases of

malignant struma ovarii were found in the world literature up to 1983 [155]. Other ways in which this tumour can present include hyperthyroidism (Chapter 5) and ascites [156]. The number of cases with metastases is extremely small and the only patient I have treated presented with a solitary bony metastasis causing spinal cord compression. The ovarian tumour had been removed previously, but diagnosed as a benign lesion. With pathological proof that the spinal lesion was follicular cancer, a review of the original showed it was malignant (a difficult diagnosis because the usual criteria for malignancy are hard to apply in teratoma, where various tissues are intermingled). The treatment is similar to that of thyroid cancer. The primary lesion should be removed. Because there are a small number of reports of bilateral tumours, annual gynaecological examination is advised. When there is no evidence of metastases this is adequate. When metastases are present they can be treated with radioiodine, but before this is possible, the normal thyroid has to be removed by surgery. This also ensures that the primary cancer is not in the thyroid. In the patient described, this was done and the spinal lesion treated with 2 doses of 200 mCi radioiodine at an interval of 1 year. At the time of writing, she is clinically free of disease, a total-body ^{131}I scan is negative and thyroglobulin undetectable [157].

8.8 UNDIFFERENTIATED CANCER: ANAPLASTIC

8.8.1 INTRODUCTION

Fortunately, this cancer is rare. It accounts for 5–15% of thyroid cancers in most of the large published series in the USA (approximately 500 new cases per year). The incidence is higher in Europe. It is probably the most rapidly lethal of all cancers, few patients survive 6 months from the time of diagnosis and, therefore, it accounts for a substantial proportion of thyroid cancer deaths.

8.8.2 AETIOLOGY

There is considerable circumstantial evidence that anaplastic cancer arises from preexisting differentiated thyroid cancer or, in some cases, long-standing goitre. In one series of 84 patients, 74 had one or other of these factors [158]. It has been suggested that previous external or ^{131}I radiation for differentiated cancer increases the risk of anaplastic transformation [159], but since this transformation can occur without radiation the association is not absolute. Kapp *et al.* [102] reported two cases, one after external radiation, the other after ^{131}I for treatment of differentiated thyroid cancer, and they reviewed the world literature. Of 135 cases of differentiated cancer that progressed to anaplastic, 35 had prior radiation (mostly ^{131}I) and 100 had not. In another series, no cases had this association [160], and the chance of transformation occurring after ^{131}I is determined to be less than 5%. Clearly, if the radioiodine ablates all malignant tissue, this sequence cannot occur and whenever I have encountered such transformation, there was residual thyroid cancer which could not be ablated.

8.8.3 PATHOLOGY

Anaplastic cancers are classified as giant or spindle. Adenosquamous cancers are probably anaplastic, as are sarcomas which are so anaplastic that they are interpreted as sarcoma rather than carcinoma. In the past, there was a category of small-cell anaplastic cancer, but in retrospect these are either lymphoma or medullary cancer without amyloid. This misinterpretation accounts for the relatively better prognosis in patients with this pathology (small-cell anaplastic carcinoma), and it makes comparison of prognosis in different series difficult since

patients with different diseases are compared. In true anaplastic cancer, the cells are large, bizarre, often multinucleated with hyperchromatic nuclei (Figure 8.17). Standard histological staining techniques with antibodies (usually monoclonal antibodies) against thyroglobulin make it possible to prove the origin of the cells with considerable accuracy [161, 162]. Nevertheless, when the cells are extremely dedifferentiated, they do not make thyroglobulin.

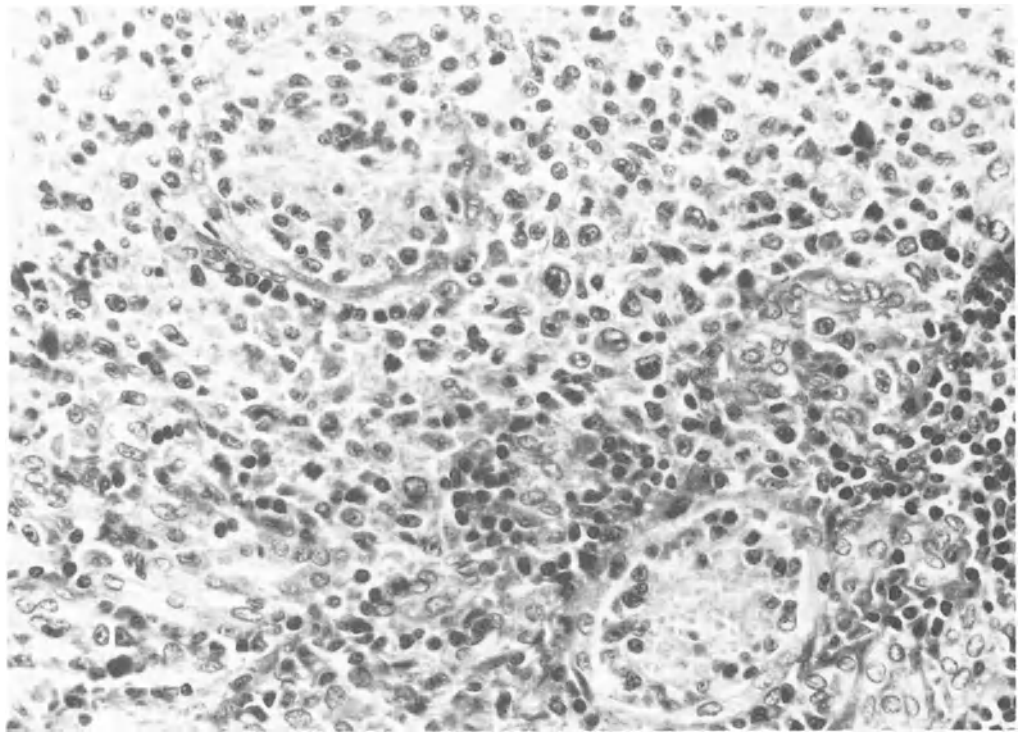
8.8.4 CLINICAL PRESENTATION

Most of the patients are older than 60 years and there is a slight increase in women (Table 8.5). The symptoms include a rapidly enlarging neck mass, breathlessness, choking, hoarseness and dysphagia. Carcangiu *et al.* [160] describe the three D's, dysphagia, dyspnoea and dysphonia. Although lymph node metastases are very common early (80%), and distant metastases have occurred in about 50% by presentation, it is the dramatic primary cancer that predominates. There is early extension into midline structures. The diagnosis can be made with considerable accuracy from the bedside. The patient has a rock-hard thyroid mass which is fixed, and has difficulty speaking and breathing. Stridor can be present. This cancer can cause obstruction of the superior vena cava. Occasionally, the cancer is found by the pathologist in a surgically removed nodule when there has been no clinical suspicion of anaplastic cancer. If the lesion is small and removed completely, a very fortunate circumstance, this is the only hope of long-term survival.

8.8.5 INVESTIGATIONS, TREATMENT AND PROGNOSIS

Because of the rapid onset of the disease and its terrible prognosis, early tissue diagnosis is important. There is no role for scintigraphy or ultrasound in a patient with stridor. A chest radiograph with views of the thoracic inlet help to define encroachment on the trachea and whether there are pulmonary metastases. A CT scan of the neck and thorax give more information about these, and should be ordered as an emergency. In this clinical situation, it is legitimate to use iodine contrast, since if the diagnosis is anaplastic cancer there is no role for radioiodine and, if not, waiting 4–6 weeks until the iodine is excreted is acceptable. If, as is usually the case, it is thought that the cancer is unresectable diagnosis might be made by needle aspiration, or limited open biopsy. On the other hand, if a needle aspirate of a less sinister lesion shows anaplasia and clinically and radiologically there is no evidence of invasion, complete surgical excision should be done. This is the only hope of long-term survival. Aldinger *et al.* [158] reported a mean survival rate of 5.4 years for three patients in whom the disease was confined to the thyroid and surgically removable, compared with 4.8 months in 81 patients with more advanced disease. Since the patient usually has far advanced local and/or distant metastases when first seen, the physician and patient have to accept the disease is incurable. To emphasize this, in addition to the figures above, Carcangiu *et al.* [160] report that 82% of the patients they followed died within 1 year, and the mean survival rate in another large series was 4 months [4]. Casterline *et al.* [163] felt that survival for longer than 2 years was sufficient to warrant a case report, and they summarized the results of 10 publications, and showed that the 2 year survival in 420 patients was 2.6%. It is difficult for one centre to develop meaningful, controlled protocols because this cancer is not common, the progression is so rapid, and the patients elderly and frail and unable to tolerate severe therapeutic regimes. There is a consensus that high-dose external radiation should be coupled with chemotherapy. The radiation dose recommended is 5000–6000 rad and various fractions, such as

(a)



(b)

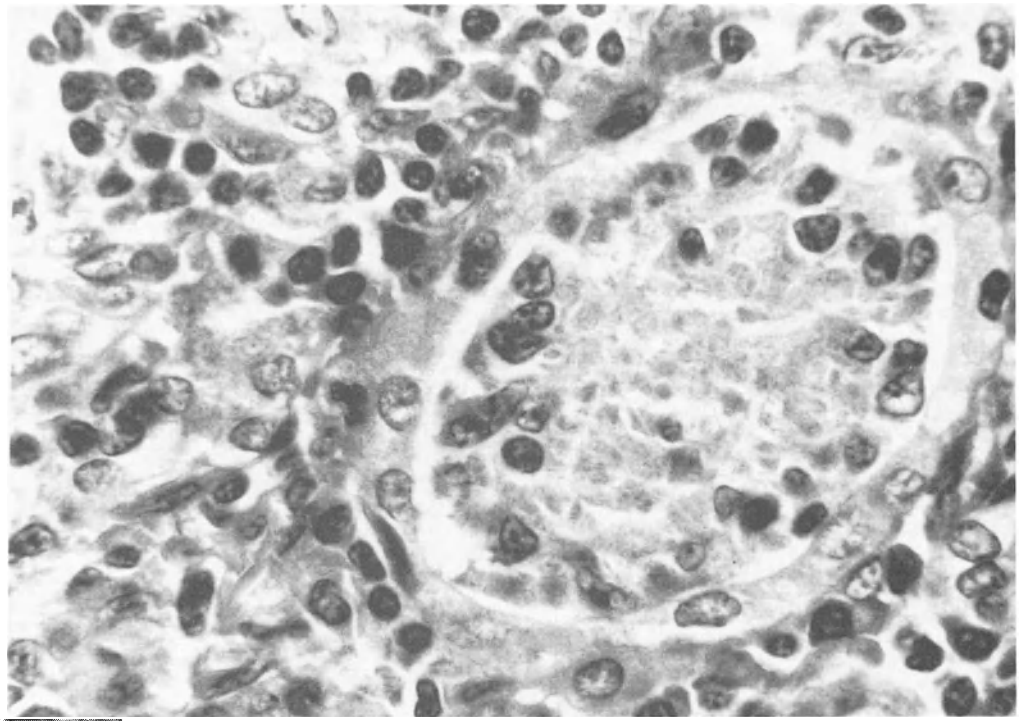


Figure 8.17 (*a*) Low-power photomicrograph and (*b*) high-power photomicrograph of an anaplastic carcinoma showing the loss of follicular architecture, bizarre cell shape and multiple mitotic figures.

Table 8.5 Patient characteristics in anaplastic cancer of the thyroid

Reference	*Number*	*Average age (years)*	*Ratio women to men*
162	26	66	2.7/1
158	84	64	1/1.5
160	70	67	3.1/1

200 rad per day, or 160 rad twice daily, or 100 rad 4 times a day have been prescribed. The chemotherapy should include Adriamycin [164, 165], which has been shown to be the most effective single agent and, frequently, this is combined with cis-platinum. Even with combined therapy the prognosis is terrible. Aldinger *et al.* [158] reported success in 4 out of 14 patients with combined surgery, radiation and chemotherapy, 1 out of 16 with surgery alone, 1 out of 7 with surgery and radiotherapy, and 0 out of 7 with surgery and chemotherapy. In spite of early shrinkage of the cancer with chemotherapy, it grows back relentlessly and causes death by local invasion. Occasionally, chemotherapy causes sufficient reduction in size of the primary lesion to make it possible to consider surgical excision [166]. If the patient is in respiratory distress, tracheostomy is necessary but this can be technically difficult because of the extent and site of the malignancy. There has to be cooperation of thyroidologist, surgeon, radiation therapist and oncologist, and because of the dreadful nature of the disease, the patient must be given adequate relief of suffering with strong analgesics and sedatives, and support for the family.

8.9 MEDULLARY CANCER

8.9.1 INTRODUCTION

Medullary cancer accounts for about 5–10% of thyroid cancers (Table 8.1). Sizemore [167] found it in a progressively increased proportion, up to 21%, but this was due to familial cases diagnosed at an early stage by screening (see below). Hazard *et al.* [168] identified this as a separate cancer in 1959, in a paper describing 21 cases. Prior to then, these cancers were classified as anaplastic. Correctness of diagnosis is extremely important, because about 20% of medullary cancers are familial, and because the prognoses of the two diseases is different, anaplastic cancer causing inevitable death in a few months. The concept that medullary cancer arises from parafollicular cells which secrete calcitonin was proposed by Williams in 1967 [169], and the following year, three groups reported on patients with this disease in whom extremely high concentrations of calcitonin were found in the cancers [170–172] and subsequently in the blood [173].

Medullary cancer can occur sporadically, or it can be familial. The familial are subdivided into three types: firstly multiple endocrine neoplasia type IIa (MEN IIa), secondly type IIb and, lastly, familial non-MEN medullary cancer. MEN IIa includes a constellation of medullary cancer, phaeochromocytoma, and hyperparathyroidism, and is also called **Sipple's syndrome** [174]. MEN IIb has the first two features plus a characteristic facial appearance, Marfanoid features, and mucosal neuromas [175]. Non-MEN familial cancer does not have the additional features. All are transmitted as an autosomal dominant.

8.9.2 PATHOLOGY

The cell of origin is the parafollicular or C cell which lies between follicles. They do not abut on colloid, have no microvilli and they contain dark, secretory granules [176]. The cells can be demonstrated with peroxidase-labelled anticalcitonin antibodies. They secrete calcitonin which can be used as a serum marker to detect the cancer, and to determine the success of surgical treatment [177,

178]. In familial cases diagnosed early by provocative tests designed to stimulate release of calcitonin, there is a spectrum from C cell hyperplasia to frank malignancy. This is not seen in sporadic cases. The cells are round, polyhedral and pleomorphic, and are present in sheets. There are no papillary or follicular elements in the classic case, although there are a few reports of cancers which do contain both malignant follicular and parafollicular elements [179, 180]. These are difficult to explain since it implies malignant transformation of two cell types with different embryonic development. A characteristic finding is amyloid in primary and secondary lesions. There is amino acid homology between amino acids 9–19 of calcitonin and amyloid, and the C cells appear to secrete amyloid. It can be important to do Congo red staining to aid with diagnosis. The cancers are unencapsulated and hard, and they are multifocal in about 20% of sporadic cases and 90% of the familial. A typical pattern in the familial cancers which have not been treated at an early stage, is bilateral cancers at the lateral aspect of the junction of the upper and middle thirds of the thyroid. In Ibanez's [181] series, 7 out of 9 familial cases were bilateral. Lymph node metastases are found in 50–80% of patients, and are more frequent in the central rather than lateral nodes. Nodal metastases in the mediastinum have been found in 20–30% of patients at the first operation. Blood-borne metastases are found in lung, liver and bone in descending frequency, and other organs are involved rarely. The pathological features have been described in depth in several reviews [181–183].

Patients with MEN IIa and b can have phaeochromocytoma. This was the case in 15 out of 31 cases in the series of Saad *et al.* [184] and 12 out of 29 cases described by Chong *et al.* [185]. The adrenal cancers are bilateral in about 50% of patients [186], and can be malignant. Hyperplasia of adrenal medullary cells has been encountered in patients with medullary cancer, as has C cell hyperplasia in patients with phaeochromocytoma [187]. Just as 80% of medullary cancers are sporadic, the same percentage applies to sporadic phaeochromocytoma. Extra-adrenal as well as intra-adrenal phaeochromocytomas have been described in one patient [188].

8.9.3 CLINICAL PRESENTATION

Medullary cancer is found in equal numbers in men and women [167, 184]. Patients can be any age, but sporadic ones are discovered most frequently in the 40–50 year range and familial cases earlier, usually between 15–30 years, especially if screening tests are carried out. In sporadic cases, the most frequent presentation is a thyroid nodule. Not infrequently, the specific diagnosis is not suspected preoperatively, and surgery is for a clinically suspicious cold nodule. With more extensive use of fine-needle aspiration to obtain a tissue diagnosis in thyroid nodules, the diagnosis should be established preoperatively. This is important because it allows planning of the optimal surgical procedure, namely, total thyroidectomy. It is not clinically useful to measure calcitonin in every patient with a thyroid nodule with the intention of diagnosing medullary cancer. About 30% of patients with medullary cancer have troublesome diarrhoea and this symptom, if persistent in a patient with a thyroid nodule, should raise the probability of medullary cancer. Diarrhoea is thought to be due to a secretory product of the cancer, which, in addition to calcitonin, can produce 5-hydroxytryptamine, histamine, prostaglandins, CEA, vasoactive peptide. ACTH, corticotrophin releasing factor and other vasoactive materials (167, 182, 189). In general, these would not be looked for routinely, but the clinician should be alert to symptoms which could be due to humoral secretions. In familial cases, hypertension from coexisting phaeochro-

mocytoma might be present. The clinician should examine the patient carefully to determine the extent of the cancer and for the presence of regional lymph node involvement.

8.9.4 INVESTIGATIONS

(a) Calcitonin

Calcitonin is a 32 amino acid peptide of molecular weight 3400. It is a valuable tumour marker both to diagnose medullary cancer, and to follow the response to treatments. There are some drawbacks with this measurement. Firstly, the assay is not particularly sensitive and there is overlap between normals and 'low' abnormals, therefore, false negatives are found. Secondly, certain non-medullary cancers, in particular oat-cell of lung, breast and pancreas, also secrete calcitonin [190, 191]. Thirdly, the levels of calcitonin fluctuate considerably even from clearly abnormal to normal. With these considerations in mind, the following approach is proposed for patients in whom the diagnosis is suspected.

Measure calcitonin in a venous blood sample; if the result is elevated the diagnosis is very likely and patient should have tests to exclude phaeochromocytoma.

If the calcitonin level is normal, provocative tests should be conducted, especially in family members who are being screened for asymptomatic disease. Of the provocative tests, the two which have been most reliable are the short calcium infusion and the pentagastrin tests [192]. The patient should be fasted and the tests should be done under continuous medical observation.

Calcium 2 mg/kg is injected rapidly, or 3 mg/kg is infused over 10 minutes and blood samples taken over 15 minutes. Alternatively, pentagastrin is injected intravenously in a dose of 0.5 μg/kg and blood samples drawn at 0. 1, 2, 5 and 10 minutes. Sizemore and Go [193] found a rise in calcitonin of 5–36-fold over basal levels in patients, and Sizemore [167] prefers this test because it has a higher sensitivity. Some patients suffer transient epigastric or substernal discomfort shortly after injection of the pentagastrin.

Neither of these tests is perfect, and there are reports of disparate results in a small proportion of patients. Therefore, if one of the tests is negative yet the clinical suspicion persists, the other test should be undertaken. To overcome this, Wells *et al.* [194] recommend combining calcium infusion (2 mg/kg) followed by pentagastrin 0.5 μg/kg with multiple blood samples over 15 minutes.

(b) Imaging tests

Several radiopharmaceuticals have been found to localize in primary and metastatic medullary cancer. Some of these were introduced in Chapter 3. Thallium–201 was first recognized to localize in medullary cancer in 1980 [195], and Hoefnagel *et al.* [196] correctly localized 11 out of 12 lesions. The test requires no preparation, 2.0 mCi of ^{201}Tl as thallous chloride are injected intravenously and whole-body imaging started after 10 minutes. The major role of ^{201}Tl is in searching for cancer in patients with persistently elevated calcitonin.

Radioiodinated metaiodobenzylguanidine (MIBG), which has been a very successful in imaging phaeochromocytoma [197] and has also been used to treat metastatic lesions [198], was found serendipitously to localize in medullary cancer [199], and subsequent reports confirm that it localizes in some, but not all, lesions [200, 201]. The test has a significant false-negative rate. However, when there is intense uptake in a site deemed to be unresectable, consideration should be given to therapy with ^{131}I-MIBG (100 mCi has been prescribed [196]).

Pentavalent ^{99m}Tc **dimercaptosuccinate** (DMSA) was first shown to image medullary cancer in 1984 [202], and subsequent reports have been favourable [203, 204]. The role of this radiopharmaceutical is similar to ^{201}Tl.

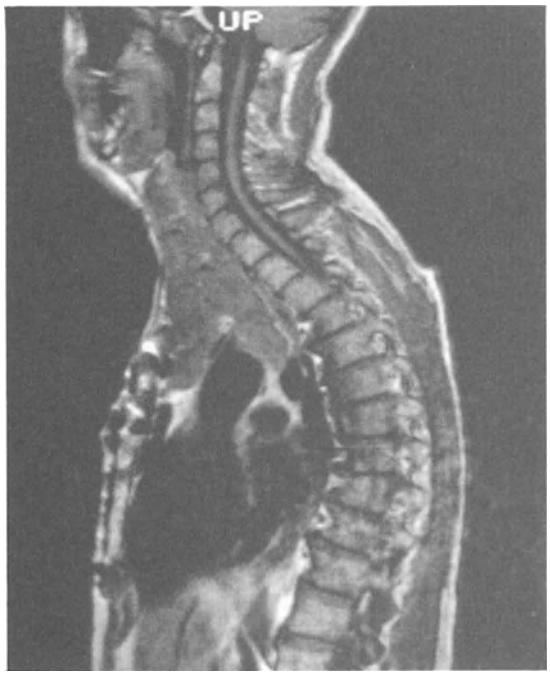


Figure 8.18 Sagittal section of a NMRI scan through the lower head, neck, and upper trunk in a patient with extensive nodal metastases from medullary cancer. Abnormal nodes are seen throughout the neck and upper mediastinum.

Five to 10 mCi are injected intravenously and whole-body images made 2 hours later.

Specific monoclonal antibodies to calcitonin have been used in experimental animals [205] and in patients [206]. Both whole antibody and fragments $F(ab')_2$ have been used. It is too early to define their role in diagnosis and treatment at the time of writing.

Standard imaging techniques which are not tumour specific are used to stage the cancer: chest roentgenogram and CT or NMRI of the thorax for pulmonary metastasis and mediastinal nodal involvement, skeletal scintigraphy and CT or liver scintigraphy to evaluate the bones and liver respectively. Figure 8.18 shows a NMRI scan in patient with extensive neck and mediastinal nodal metastases.

8.9.5 TREATMENT

Total thyroidectomy is the treatment of choice [167, 184]. If a lobectomy has been done before the diagnosis was established, a second operation should be undertaken to complete the procedure. The central lymph nodes from the hyoid to the innominate should be removed because they are frequently involved. If lateral cervical lymph nodes are found to be involved at operation, a modified radical dissection is advised. Although some authorities recommend this routinely, I do not. One of the prognostic factors in determining long-term survival is removal of all cancer at the first operation. In selected cases, external radiation therapy is used postoperatively; this has best results when there is a small tumour load, in the case of bulky residual disease it is not curative. The dose and port vary depending on the specific site of the cancer but, in general, 4500–5000 rad supervoltage is prescribed over 4–6 weeks. This should be prescribed by a radiation therapist with an interest and knowledge of the disease and its natural history.

There are isolated reports of ^{131}I being used to treat medullary cancer [206–208]. The cells do not trap iodine. It has been hypothesized that small foci of medullary cancer surrounded by normal thyroid would receive sufficient radiation from ^{131}I in the normal tissue to be sterilized. When total thyroidectomy is done, there is little role for ablating residual thyroid because the uptake of ^{131}I is so small that lethal radiation damage to adjacent cancer is not likely to occur. In larger series, the recurrence and death rates are not reduced in those treated with radioiodine, and this therapy is not recommended.

When the diagnosis of medullary cancer is known preoperatively, it is prudent to screen for phaeochromocytoma by measuring urinary catecholamines. When phaeochromocytoma and medullary cancer

coexist, the former should be treated first. All the usual preoperative and intraoperative care for a patient at risk for unexpected adrenergic crisis should be in place. The thyroidectomy is done when that risk has been removed. All patients should be put on thyroxine postoperatively simply because they need it, but unlike the situation with differentiated cancers, this therapy does not suppress medullary cancer. Diarrhoea due to humoral secretions from unresectable metastases should be treated with standard medical measures including codeine, Lomotil and kaolin, and if these are not successful, a trial of nutmeg, which is a prostaglandin inhibitor, is suggested. In those patients with widespread metastases systemic chemotherapy has to be considered, but none is very effective. It is probable that specific treatment with radiolabelled antibodies will be used therapeutically in the future. Family members should be screened so that no early case is missed because cure can be anticipated at that time, whereas in advanced disease the prognosis is gloomy.

8.9.6 PROGNOSIS

The outcome depends on the stage of the cancer, the completeness of surgery, whether the cancer is sporadic or familial, and the age of the patient (young patients survive longer). Patients with MEN IIa do best, followed by sporadic cases, and the worst prognosis is found in patients with the rare MEN IIb. Overall survival in two large series at 10 years were 67% and 61% [167, 184].

8.10 LYMPHOMA OF THE THYROID

8.10.1 INTRODUCTION

The exact percentage of lymphomas presenting in the thyroid is difficult to determine because most publications to not discuss the total number of lymphomas seen, only those cases diagnosed in a thyroid mass. It is also difficult to determine what percentage of thyroid malignancies are lymphomas for the same reason. Hamburger *et al.* [209] found 30 cases out of 389 with thyroid cancer (7.7%), and these were diagnosed from 4200 patients with a thyroid nodule, most of whom had fine-needle aspiration for tissue diagnosis. If this is representative, the frequency of primary lymphoma in the thyroid is similar to medullary or anaplastic cancer.

It is now recognized that a significant proportion of cancers which were classified as small-cell anaplastic cancers are, in fact, primary lymphomas [210, 211]. In most series, the predominant lymphoma is diffuse histiocytic (**Rappaport Classification** [212]), but there are reports of T-cell lymphoma, plasmacytoma [213, 214] and Hodgkin's disease [215]. In the experience of my radiation therapy colleagues, this is a rare presentation for lymphoma, accounting for 1.3% of cases [216]. Burke *et al.* [217] provide evidence that there is a pathological gradation from Hashimoto's thyroiditis (chronic lymphocytic thyroiditis) to lymphoma, and they found this in 27 of 35 cases where they could examine residual thyroid not involved with lymphoma. This association is recognized in 24–95% of published cases (Table 8.6) [216–218]. Hashimoto's thyroiditis is a very common clinical problem, and the frequency with which it progresses to lymphoma is not known. One patient in whom I made the diagnosis by fine-needle aspiration, confirmed by open biopsy, did have pathological evidence of chronic lymphocytic thyroiditis, but had no circulating antithyroid antibodies. Unfortunately, antibody studies in patients with lymphoma of the thyroid are usually lacking. Does Hashimoto's thyroiditis progress to lymphoma in a small percentage of patients, or is the thyroid limited in its response to the presence of cancers including lymphoma by mounting a lymphocytic response, like chronic lymphocytic thyroiditis? The lymphocytic response is also

Table 8.6 Demographics of patients with lymphoma of the thyroid

Reference	*Number*	*Women to men*	*Average age (years)*	*Hashimoto's thyroiditis (%)*
209	30	2.7/1	61	24
211	249	2.7/1	62	95
216	11	1.2/1	57	73
217	35	2.9/1	65	77
218	57	2.6/1	62	36
219	12	1.0/1	62	33
220	29	4.8/1	64	76
221	10	10/0	68	30
222	12	1.4/1	60	33
223	20	3.0/1	64	NA

seen in papillary cancer. Holm *et al.* [225] followed 829 patients with aspirate-proven chronic lymphocytic thyroiditis, and compared them with matched controls who had colloid goitre and with age- and sex-matched normal population. They found four cases of lymphoma of the thyroid [0.2%] in those with Hashimoto's thyroiditis, which was 67 times the expected frequency in the population. As stated earlier, a solitary nodule in a patient with Hashimoto's thyroiditis should be investigated in the same way as any solitary nodule.

8.10.2 CLINICAL PRESENTATION

The clinical features of lymphoma in the thyroid include thyroid mass, goitre, and a sudden increase in goitre size. The thyroid mass is hard, non-tender and non-fluctuant, and often fixed to surrounding structures. The average age of the patients is about 60 years, and there are about three women to each man (Table 8.6). The majority of patients are euthyroid, but when the entire gland is involved, the patient can be hypothyroid as was the case in 12 of 30 patients studied by Hamburger *et al.* [209]. Autoimmune thyroiditis could be an alternative cause of the hypothyroidism. There is one report of hyperthyroidism due to the lymphoma disrupting the follicles and releasing thyroid hormones into the circulation [226]. Hoarseness is described with higher frequency than in differentiated cancer, with a range from 10% [12] to 66% [219]. The incidence of dysphagia is also significant, ranging from 14–36% [217, 220]. The presence of these and/or stridor would suggest lymphoma or anaplastic cancer.

Investigations include needle aspiration of solitary nodule. However, this is one area where cytology can fail to provide the definitive answer and can be misleading. It can be difficult to differentiate chronic lymphocytic thyroiditis from lymphoma unless there is sufficient tissue to stain with monoclonal antilymphocyte antibodies to determine if the lesion is monoclonal and cancerous, or polyclonal and benign. In cases where uncertainty persists, open biopsy is essential. In stage 1, lymphoma in which the cancer is localized to the thyroid, lobectomy not only establishes the diagnosis but also can be curative, although external radiation therapy is usually advised. Thyroid scintigraphy and ultrasound seldom are helpful, but if the diagnosis is known from needle aspirate a whole-body ^{67}Ga scan is valuable in staging the extent of the disease. Once the diagnosis is certain, conventional investigations include chest roentgenogram, CT of the

chest and abdomen, lymphangiogram and bone marrow aspirate so that stage can be determined. This is important for appropriate therapy. In stage 1 and 2 disease, local radiotherapy to a dose of 4000 rad is sufficient, in stages 3 and 4, chemotherapy or combined radiation and chemotherapy are necessary. The management should be dictated by a radiation therapist or an oncologist experienced in treating patients with lymphomas.

The importance of establishing the correct diagnosis is that treatment and prognosis are quite different from anaplastic cancer of the thyroid. Seventy-five per cent of patients with lymphoma confined to the thyroid live 5 years or longer. A typical patient is described in the case records of the Massachusetts General Hospital [227].

8.11 METASTASES TO THE THYROID

Metastases from cancers of other organs are found in the thyroid in 1.9–26.4% of autopsies [228]. This large discrepancy is in part due to the tenacity of the pathologist and the frequency of sectioning the gland. Willis [229] found 5.2% and Shimaoka *et al.* 9.55% [230], and these percentages are probably more consistent with general experience. These lesions are incidental and of no clinical significance. McCabe *et al.* [228] in reviewing the literature found that 77% of metastases were from five primary sites, the breast, lung, melanoma, kidney and gastrointestinal tract. These data deal with autopsies. More important in clinical practice are finding metastatic cancer (1), in a solitary thyroid nodule in a patient with a known primary cancer, or (2) in a patient with no known cancer. In the first situation, cancer in a solitary nodule in a patient with a prior diagnosis of cancer is more likely to be due to a metastasis than to primary thyroid cancer; therefore, it is important to review the past history of cancer when evaluating a patient with a thyroid nodule. Ivy [231] described 19 patients in his total series of 30. In the entire group the sex distribution was virtually equal with 16 men and 14 women. As expected, 26 of the patients were 50 years of age or older. In 8 patients the primary site was found at the same time as the metastasis to the thyroid, and in 3 the true diagnoisis was not made for several months. Although the diagnosis was made at operation in 27 of the patients, the author makes the point that fine-needle aspiration as the first test should limit the need for surgery as a diagnostic test. The primary sites were the kidney in 12, breast in 6 and lung in 5 patients respectively. McCabe *et al.* [228] had very similar experience in 17 patients. Nine were women and 14 were 50 years of age or older. In 13 patients, the primary cancer was known, and in 4 it was diagnosed synchronously with the metastasis. None was diagnosed by fine-needle aspirate, although they also support this investigation. The prognosis in these patients is poor. Unless it is clear from other tests that the thyroid is the only site of metastasis, surgery is usually not advised. When surgery is done, procedures greater than lobectomy do not improve the prognosis. Most patients die within 12 months.

The cases discussed above are metastases in clinically relevant nodules and, remarkably, 34 out of 76 such cases have been due to renal cancer. There can be difficulty in differentiating clear-cell cancer of the kidney from follicular cancer, in particular, the clear-cell variety [232], but use of fat stains which are positive in the former and antithyroglobulin which labels the latter should make this differentiaton. Sometimes the kidney metastasis in the thyroid is the only secondary lesion and a lobectomy to remove the mass is followed by long-term survival [233]. A recent report has looked at the frequency of diagnosing metastases by fine-needle aspirate and found 4 in 68 consecutive patients, all of whom were known to

have a primary site [234]. I found 2 cases in my first 100 aspirates, both in patients with known cancer.

When a patient with a known cancer presents with a thyroid nodule, a fine-needle aspirate is advised. Thyroid scintigraphy and ultrasound usually do not add new information. If a metastasis is diagnosed, further work-up including a chest roentgenogram and a CT of the chest and abdomen would be ordered to determine whether there are other lesions. If not, a lobectomy is advised. When the aspirate shows primary thyroid cancer, treatment as outlined earlier in the Chapter is advised, provided the patient is expected to have a meaningful survival from the original nonthyroidal cancer. If the fine-needle aspirate is benign, no treatment is required apart from periodic follow-up. When metastatic cancer is diagnosed on aspirate of a thyroid nodule in a patient with no known primary cancer, it is necessary to determine the primary site. The frequency of a renal primary is stresssed, and ultrasound is the best noninvasive test. Careful skin examination looking for melanoma, chest roentgenogram and mammography in women should be considered. There is one report of Kaposi's sarcoma in a patient with AIDS [235] and this might become a more frequent occurrence.

KEY FACTS

- Three types of cancer arise from the follicular cell; papillary, follicular and anaplastic.
- Medullary cancer arises from the parafollicular C cell.
- There are about 12 000 new thyroid cancers in the USA each year.
- **Papillary** cancer is the commonest; it is slow growing and has the best prognosis.
- Many cases already have cervical nodal metastases at the time of diagnosis.
- In papillary cancer, good prognostic features are age <45 years, female gender, cancer <3 cm, intrathyroidal lesion, and the coexistence of autoimmune thyroid disease.
- Diagnosis is made clinically, and usually by FNA.
- Therapy is surgical (usually total lobectomy on side of lesion, isthmusectomy and subtotal lobectomy on contralateral side).
- Thyroxine is prescribed for life to suppress TSH.
- Radioiodine ^{131}I is administered to ablate functioning metastases.
- The role of ^{131}I to ablate normal remnants not fully defined; is in advised in selected cases where a poor prognosis anticipated.
- There is seldom a' role for external radiation or chemotherapy.
- **Follicular cancer** is much less common, and tends to metastasize haematogenously to the lung, bone, brain and liver.
- Diagnosis is made clinally and by FNA.
- It is treated by surgery, total lobectomy, isthmusectomy and subtotal lobectomy on the contralateral side (alternatively, a total thyroidectomy).
- ^{131}I is administered to ablate functioning metastases.
- Whole-body ^{131}I scintigraphy is valuable to define functioning lesions in both papillary and follicular cancer.
- Thyroglobulin is a good method of determining the effectiveness of therapy or recurrence of the disease.
- **Anaplastic cancer** is found in elderly patients.
- It is rapidly fatal due to local and distant involvement.
- No therapy is effective in advanced disease.
- Complete surgical removal is seldom possible.
- External radiation and chemotherapy are usually given, but are palliative at best.
- **Medullary cancer** can be isolated or part

of multiple endocrine syndromes which are familial.

- Calcitonin is a useful tumour marker and family members should be screened since early detection and therapy is optimal.
- Diagnosis is usually made clinically and by FNA.
- Treatment is total thyroidectomy and central lymph node dissection.
- ^{131}I is not valuable.
- Problem is measurable calcitonin without an obvious source.
- Imaging tests, such as ultrasound, CT, NMRI and ^{201}Tl, can be used to find residual cancer.
- Venous catheterization is sometimes used for calcitonin localization.
- **Lymphoma** arising in the thyroid accounts for about 5% of cancers.
- It is usually found in older women, often in pre-existing Hashimoto's thyroiditis.
- Diagnosis is made clinically and by FNA.
- Therapy depends on the stage of the disease; usually external radiation therapy and chemotherapy are administered.
- **Metastases** to the thyroid are rare as a presenting feature.
- Primary sites are usually the breast, lung, melanoma, kidney and gastrointestinal tract.

REFERENCES

1 Silverberg, E., Boring, C.C. and Squires, T.S. (1990) Cancer statistics 1990. *CA-A Cancer J for Clinicians*, **40**, 9–26.

2 Blahd, W.H. (1979) Treatment of malignant thyroid disease. *Semin. Nucl. Med.*, **9**, 95–9.

3 Mazzaferri, E.L. (1987) Papillary thyroid carcinoma: factors influencing prognosis and current therapy. *Semin. Oncol.*, **14**, 315–32.

4 Edmonds, C.J. (1979) Treatment of thyroid cancer. *Clin. Endocrinol. Metab.*, **8**, 223–42.

5 Tubiana, M., Schlumberger, M., Rougier, P. *et al.* (1985) Long-term results and prognostic factors in patients with differentiated thyroid carcinoma. *Cancer*, **55**, 794–804.

6 McConahey, W.M., Hay, I.D., Woolner, L.B. *et al.* (1987) Papillary thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. *Mayo Clin. Proc.*, **61**, 978–96.

7 Rossi, R.L., Nieroda, C., Cady, B. *et al.* (1985) Malignancies of the thyroid gland. The Lahey Clinic experience. *Surg. Clin. N. Am.*, **65**, 211–30.

8 Mazzaferri, E.L. (1988) Thyroid cancer: an overview. *Thyroid Today*, **1 (10)**, (ed. J.H. Oppenheimer).

9 Starnes, H.F., Brooks, D.C., Pinkus, G.S. *et al.* (1985) Surgery for thyroid carcinoma. *Cancer*, **55**; 1376–81.

10 Werner, S.C. (1969) Classification of thyroid disease. Report of the committee on nomenclature, the American Thyroid Association – Part 1. *J. Clin. Endocrinol Metab*, **29**, 860–2.

11 Duffy, B.J. Jr and Fitzgerald, P.J. (1950) Cancer of the thyroid in children: a report of 28 cases. *J. Clin. Endocrinol. Metab.*, **10**, 1296–308.

12 Favus, M.J., Schneider, A.B., Stachura, M.E. *et al.* (1976) Thyroid cancer occurring as a late consequence of head-and-neck irradiation: evaluation of 1056 patients. *N. Engl. J. Med.*, **294**, 1019–25.

13 Doniach, I. (1974) Carcinogenic effect of 100, 250 and 500 rad X-rays on the rat thyroid gland. *Br. J. Cancer*, **30**, 487–95.

14 DeGroot, L. and Paloyan, E. (1973) Thyroid carcinoma and radiation: a Chicago endemic. *JAMA*, **225**, 487–91.

15 Williams, E.D., Doniach, I., Bjarnason, O. *et al.* (1977) Thyroid cancer in an iodine rich area. A histopathological study. *Cancer*, **39**, 215–22.

16 Dailey, M.E., Lindsay, S. and Skahen, R. (1955) Relation of thyroid neoplasms to Hashimoto's disease of the thyroid gland *Arch. Surg*, **70**, 291–7.

17 Woolner, L.B., McConahey, W.M. and Beahrs, O.H. (1959) Struma lymphomatosa (Hashimoto's thyroiditis) and related thyroid disorders. *J. Clin. Endocrinol. Metab.*, **19**, 53–83.

13 Clark, O.H., Greenspan, F.S. and Dunphy, J.E. (1980) Hashimoto's thyroiditis and thyroid cancer: indications for operation. *Am. J. Surg.*, **140**, 65–70.

19 Meier, D.W., Woolner, L.B., Beahr, O.H. *et al.* (1959) Parenchymal findings in thyroidal carcinoma: pathological study of 256 cases. *J. Clin. Endocrinol. Metab*, **19**, 162–71.

20 McDougall, I.R. and Bayer, M.F. (1980) Follow-up of patients with differentiated

thyroid cancer using serum thyroglobulin measured by an immunoradiometric assay. Comparison with I–131 total body scans. *J. Nucl. Med.*, **21**, 741–4.

21 Cox, A.J. Jr, Wilson, R. and DeEds, F. (1947) The carcinogenic activity of 2-acetaminofluorene. Characteristics of the lesions in albino rats. *Cancer Res*, **7**, 647–52.

22 Woolner, L.B., Beahrs, O.H., Black, B.M. *et al.* (1961) Classification and prognosis of thyroid carcinoma: a study of 885 cases observed in a thirty year period. *Am. J. Surg.*, **102**, 354–87.

23 Black, B.M., Kirk, T.A. and Woolner, L.B. (1960) Multicentricity of papillary adenocarcinoma of the thyroid: influence on treatment. *J. Clin. Endocrinol. Metab.*, **20**, 130–5.

24 Clark, R.I. Jr., White, E.C. and Russel, W.O. (1959) Total thyroidectomy for cancer of the thyroid: significance of intraglandular dissemination. *Ann. Surg.*, **149**, 858–66.

25 Clark, O.H. (1980) Thyroid nodules and thyroid cancer: surgical aspects. *West. J. Med.*, **133**, 1–8.

26 Hawk, W.A. and Hazard, J.B. (1976) The many appearances of papillary carcinoma of the thyroid. *Clev. Clin. Quart.*, **43**, 207–16.

27 Carcangiu, M.L., Zampi. G., Pupi A. *et al.* (1985) Papillary carcinoma of the thyroid: a clinicipathologic study of 241 cases treated at the University fo Florence, Italy. Cancer, **55**, 805–28.

28 Wanebo, H.J., Andrews, W. and Kaiser, D.L. (1983) Thyroid cancer: some basic considerations. *Cancer J. for Clinicians*, **33**, 87–97.

29 Staunton, M.D. and Skeet, R.G. (1979) Thyroid cancer: prognosis in 469 patients. *Br. J. Surg.* **66**, 643–7.

30 Simpson, W.J., McKinney, S.E., Carruthers, J.S. *et al.* (1987) Papillary and follicular thyroid cancer: prognostic factors in 1578 patients. *Am. J. Med.*, **83**, 479–88.

31 Heitz, P., Moser, H. and Staub, J.J. (1976) Thyroid cancer: a study of 573 thyroid tumors and 161 autopsy cases observed over a thirty-year period. *Cancer*, **37**, 2329–37.

32 Clark, O.H. (1982) Total thyroidectomy: the treatment of choice for patients with differentiated thyroid cancer *Ann. Surg.*, **196**, 361–70.

33 Jacobs, J.K., Aland J.W., Ballinger, J.F. *et al* (1983) Total thyroidectomy: a review of 213 patients. *Ann. Surg.*, **197**, 542–8.

34 Attie, J.N., Moskowitz, G.W., Margouleff, D. *et al.* (1979) Feasibility of total thyroidectomy in the treatment of thyroid carcinoma: postoperative radioactive iodine evaluation in 140 cases. *Am. J. Surg.*, **138**, 555–60.

35 Harness, J.K., Fung, L., Thompson, N.W. *et al.* (1986) Total thyroidectomy: complications and technique. *World J. Surg.*, **10**, 781–6.

36 Mazzaferri, E.L., Young, R.L., Oertel, J.E. *et al.* (1977) Papillary thyroid carcinoma: the impact of therapy in 576 patients. *Medicine*, **56**, 171–95.

37 Mazzaferri, E.L. and Young, R.L. (1981) Papillary thyroid carcinoma: a 10 year follow-up report of the impact of therapy in 576 patients. *Am. J. Med.*, **70**, 511–18.

38 Rossi, R.L., Cady, B., Silverman, M.L. *et al.* (1986) Current results of conservative surgery for differentiated thyroid carcinoma. *World J. Surg.*, **10**, 612–22.

39 Samaan, N.A., Maheshwari, Y.K., Nader, S. *et al.* (1983) Impact of therapy for differentiated carcinoma of the thyroid: an analysis of 706 cases. *J. Clin. Endocrinol. Metab.*, **56**, 1131–8.

40 Crile, G. Jr, Antunez, A.R., Esselstyn, C.B. *et al.* (1985) The advantages of subtotal thyroidectomy and suppression of TSH in the primary treatment of papillary carcinoma of the thyroid. *Cancer*, **55**, 2691–7.

41 Hay, I.D., Grant, C.S., Taylor, W.F. *et al.* (1987) Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. *Surgery*, **102**, 1088–95.

42 Cady, B. (1986) Invited commentary. *World J. Surg.*, **10**, 786.

43 Sako, K., Marchetta, F.C., Razack, M.S. *et al.* (1985) Modified radical neck dissection for metastatic carcinoma of the thyroid: a reappraisal. *Am. J. Surg.*, **150**, 500–2.

44 Cady, B., Sedgwick, C.E., Meissner, W.A. *et al.* (1979) Risk factor analysis in differentiated thyroid cancer. *Cancer*, **43**, 810–20.

45 Harwood, J., Clark O.H. and Dunphy, J.E. (1978) Significance of lymph node metastasis in differentiated thyroid cancer. *Am. J. Surg.*, **136**, 107–12.

46 Kozol, R.A. and Numann, P.J. (1987) Surgery for thyroid cancer: recommendations versus reality. *Conn. Med.*, **51**, 643–4.

47 Foster, R.S. Jr (1978) Morbidity and mortality after thyroidectomy. *Surg. Gynecol. Obstet.*, **146**, 423–9.

48 Max, M.H., Scherm, M. and Bland, K.I. (1983) Early and late complications after thyroid operations. *South. Med. J.*, **76**, 977–80.

49 Steckler, R.M. (1986) Outpatient thyroidec-

tomy: a feasibility study. *Am. J. Surg.*, **152**, 417–19.
50 Crile, G. Jr (1966) Endocrine dependency of papillary carcinomas of the thyroid. *JAMA*, **195**, 721–4.
51 Starr, P. (1962) Pulmonary metastases of papillary cancer of the thyroid gland. Regression after nine year's of observation. *JAMA*, **180**, 978.
52 Maloof, F. (1955) The effects of hypophysectomy and of thyroxine on the radiation-induced changes in the rat thyroid. *Endocrinol.*, **56**, 209–14.
53 Cady, B., Cohn, K., Rossi, R.L. *et al.* (1985) The effect of thyroid hormone administration upon survival in patients with differentiated thyroid carcinoma. *Surgery*, **98**, 1171–8.
54 Crile, G. Jr (1986) A second opinion about thyroid hormone treatment. *Surgery*, **103**, 268–9.
55 Busnardo, B., Vangelista, R., Giarelli, M.E. *et al.* (1976) TSH level and TSH response to TRH as a guide to the replacement of treatment of patients with thyroid carcinoma. *J. Clin. Endocrinol. Metab.*, **42**, 901–6.
56 Hoffman, D.P., Surks, M.L., Oppenheimer, J.H. *et al.* (1977) Response to thyrotropin releasing hormone: an objective criterion for the adequacy of thyrotropin suppression therapy. *J. Clin. Endocrinol. Metab.*, **44**, 892–901.
57 Edmonds, C.J., Hayes, S., Kermode, J.C. *et al.* (1977) Measurement of serum TSH and thyroid hormones in the management of treatment of thyroid carcinoma with radioiodine. *Br. J. Radiol.*, **50**, 799–807.
58 Beierwaltes, W.H., Nishiyama, R.H., Thompson, N.W. *et al.* (1982) Survival time and 'cure' in papillary and follicular thyroid carcinoma with distant metastases: statistics following University of Michigan therapy. *J. Nucl. Med.*, **23**, 561–8.
59 Hilts, S.V., Hellman, D., Anderson, J. *et al.* (1979) Serial TSH determination after T_3 withdrawal or thyroidectomy in the therapy of thyroid carcinoma. *J. Nucl. Med.*, **20**, 928–32.
60 Goldman, J.M., Line, B.R., Armodt, R.L. *et al.* (1980) Influence of triiodothyronine withdrawal time on ^{131}I uptake postthyroidectomy for thyroid cancer. *J. Clin. Endocrinol. Metab.*, **50**, 734–9.
61 Maxon, H.R., Thomas, S.R., Chen, A. I-W. (1981) The role of nuclear medicine in the treatment of hyperthyroidism and well differentiated thyroid adenocarcinoma. *Clin. Nucl. Med.*, **6**, 88–98.
62 Maruca, J., Santner, S., Miller, K. *et al.* (1984) Prolonged iodine clearance with a depletion regimen for thyroid carcinoma: concise communication. *J. Nucl. Med.*, **25**, 1089–93.
63 Lakshmanan, M., Schaffer A., Robbins, J. *et al.* (1988) A simplified low iodine diet in I-131 scanning and therapy of thyroid cancer. *Clin, Nucl. Med.*, **13**, 866–8.
64 Hamburger, I. and Desai, P. (1966) Mannitol augmentation of ^{131}I uptake in the treatment of thyroid carcinoma. *Metabolism*, **15**, 1055–8.
65 Krishnamurthy, G.T. (1978) Human reaction to bovine TSH: concise communication. *J. Nucl. Med.*, **19**, 284–6.
66 Nemec, J., Rohling S., Zamrazil, V. *et al.* (1979) Comparison of the distribution of diagnostic and thyroablative I-131 in the evaluation of differentiated thyroid cancers. *J. Nucl. Med.*, **20**, 92–7.
67 Preisman, R.A. and Halpern, S. (1978) Detection of metastatic thyroid carcinoma after the administration of a therapeutic dose of 131-iodine. *Eur. J. Nucl. Med.*, **3**, 69–70.
68 Henk, J.M., Kirkman, S. and Owen, G.M. (1972) Whole-body scanning and ^{131}I therapy in the management of thyroid carcinoma. *Br. J. Radiol.*, **45**, 369–76.
69 Beckerman, C., Gottschalk, A. and Hoffer, P.B. (1974) Optimal time for ^{131}I total body imaging to detect metastatic thyroid carcinoma. *J. Nucl. Med.*, **15**, 477.
70 McCowen, K.D., Adler, R.A., Ghaed, N. *et al.* (1976) Low dose radioiodine thyroid ablation in postsurgical patients with thryoid cancer. *Am. J. Med.*, **61**, 52–8.
71 Ryo, U.Y. (1977) Low-dose and high-dose radioiodine in thyroid cancer. *Am. J. Med.*, **63**, 167.
72 Kuni, C.C. and Klingensmith, W.C. (1980) Failure of low doses of ^{131}I to ablate residual thyroid tissue following surgery for thyroid cancer. *Radiology*, **137**, 773–4.
73 Siddiqui A.R., Edmonson, J., Wellman H.H. *et al.* (1981) Feasibility of low doses of ^{131}I for thyroid ablation in postsurgical patients with thyroid carcinoma. *Clin. Nucl. Med.*, **6**, 158–61.
74 Ramacciotti, C., Pretorius, H.T., Line, B.R. *et al.* (1982) Ablation of nonmalignant thyroid remnants with low doses of radioactive iodine: concise communication. *J. Nucl. Med.*, **23**, 483–9.
75 DeGroot, L.J. and Reilly, M. (1982) Comparison of 30 and 50 mCi doses of iodine-131 for thyroid ablation. *Ann. Intern. Med.*, **96**, 51–3.

76 Snyder, J., Gorman, C. and Scanlon, P. (1983) Thyroid remnant ablation: questionable pursuit of an ill-defined goal. *J. Nucl. Med.*, **24**, 659–65.
77 Maxon, H.R., Thomas, S.R., Hertzberg, V.S. *et al.* (1983) Relation between effective radiation dose and outcome of radioiodine therapy for thyroid cancer. *N. Engl. J. Med.*, **309**, 937–41.
78 Freebberg, A.S., Ureles, A.L., Lesses, M.F. *et al.* (1950) Pulmonary metastatic lesion successfully treated with radioactive iodine. *JAMA*, **144**, 16–19.
79 Catz, B. and Starr, P. (1956) Cancer of the thyroid with metastases to the lungs: condition shown by scintigram in absence of definite X-ray findings. *JAMA*, **160**, 1046–7.
80 Turner, J.E. and Weir, G.J. Jr (1972) Pulmonary metastases from thyroid carcinoma detectable only by ^{131}I scan. Treatment and response. *J. Nucl. Med.*, **13**, 854–5.
81 Rall, J.E., Alpers, J.B., Lewallen, G.G. *et al.* (1957) Radiation pneumonitis and fibrosis: a complication of radioiodine treatment of pulmonary metastases from cancer of the thyroid. *J. Clin. Endocrinol. Metab.*, **17**, 1263–76.
82 Frazell, E.L. and Foote, F.W. (1958) Papillary cancer of the thyroid. A review of 25 years of experience. *Cancer*, **11**, 895–922.
83 Massin, J-P., Savoie, J-C., Garnier, H. *et al.* (1984) Pulmonary metastases in differentiated thyroid carcinoma: study of 58 cases with implications for the primary tumor treatment. *Cancer*, **53**, 982–92.
84 Samaan, N.A., Schultz, P.N., Haynie, T.P. *et al.* (1985) Pulmonary metastasis of differentiated thyroid carcinoma: treatment results in 101 patients. *J. Clin. Endocrinol. Metab.*, **65**, 376–80.
85 Castillo, L.A., Yeh, S.D.J., Leeper, R.D. *et al.* (1980) Bone scans in bone metastases from functioning thyroid carcinoma. *Clin. Nucl. Med.*, **5**, 200–9.
86 Harness, J.K., Thompson, N.W., Sisson, J.C. *et al.* (1974) Differentiated thyroid carcinomas: treatment of distant metastases. *Arch, Surg.*, **108**, 410–17.
87 Holmquest, D.L. and Lake, P. (1976) Sudden hemorrhage in metastatic carcinoma of the brain during treatment with iodine-131. *J. Nucl. Med.*, **17**, 307–9.
88 Datz, F.L. (1986) Cerebral edema following iodine-131 therapy for thyroid carcinoma metastatic to the brain. *J. Nucl. Med.*, **27**, 637–40.
89 Goldberg, L.D. and Ditchek, N.T. (1981) Thyroid carcinoma with spinal cord compression. *JAMA*, **245**, 953.
90 Shortliffe, E.H. and Crapo, L.M. (1982) Thyroid carcinoma with spinal cord compression. *JAMA*, **247**, 1566–7.
91 Maayan, M.L., Eisenberg, J., Lopez, E.M. *et al.* (1976) Hepatic visualization after ^{131}I in patients with thyroid carcinoma. *N. Engl. J. Med.*, **295**, 1258–9.
92 Zeissman, H.A., Bahar, H., Fahey, F.H. *et al.* (1987) Hepatic visualisation on iodine-131 whole-body thyroid cancer scans. *J. Nucl. Med.*, **28**, 1408–11.
93 Rosenbaum, R.C., Johnston, G.S., Valente, W.A. (1988) Frequency of hepatic visualization during I-131 imaging for metastatic thyroid carcinoma. *Clin. Nucl. Med.*, **13**, 657–60.
94 Gershengorn, M.C., Izumi, M., Robbins, J. *et al.* (1976) Use of lithium as an adjunct to radioiodine therapy of throid carcinoma. *J. Clin. Endocrinol. Metab.*, **42**, 105–11.
95 Pons, F., Carrio, I., Estorch, M. *et al.* (1987) Lithium as an adjuvant of iodine-131 uptake when treating patients with well-differentiated thyroid carcinoma. *Clin. Nucl. Med.*, **12**, 644–7.
96 Hoschl, R., Choy, D.H.-L. and Gandevia, B. (1988) Iodine-131 uptake in inflammatory lung disease: a pitfall in treatment of thyroid carcinoma. *J. Nucl. Med.*, **29**, 701–9.
97 Brachman, M.B., Rothman, B.J., Ramanna, L. *et al.* (1988) False-positive iodine-131 body scan caused by a large renal cyst. *Clin. Nucl. Med.*, **13**, 416–18.
98 Caplan, R.H., Gundersen, G.A., Abellera, M. *et al.* (1987) Uptake of iodine-131 by a Meckel's diverticulum mimicking metastatic thyroid cancer. *Clin. Nucl. Med.*, **12**, 760–2.
99 Allweiss, P., Braunstein, G.D., Katz, A. *et al.* (1984) Sialadenitis following I-131 therapy for thyroid carcinoma: concise communication. *J. Nucl. Med.*, **25**, 755–8.
100 Edmonds, C.J. and Smith, T. (1986) The long-term hazards of the treatment of thyroid cancer with radioiodine. *Br. J. Radiol.*, **59**, 45–51.
101 Glazebrook, G.A. (1987) Effect of decicurie doses of radioactive iodine-131 on parathyroid function. *Am. J. Surg.*, **154**, 368–73.
102 Kapp, D.S., Li Volsi, V.A., Sanders, M.M. (1982) Anaplastic carcinoma following well-differentiated thyroid carcinoma: etiological considerations. *Yale J. Biol. Med.*, **55**, 521–8.
103 Leeper, R.D. (1985) Thyroid cancer. *Med. Clin. N. Am.*, **69**, 1079–96.
104 Beierwaltes, W.H. (1978) The treatment of

thyroid carcinoma with radioactive iodine. *Semin. Nucl. Med.*, **8**, 79–94.
105 Pochin, E.E. (1969) Long-term hazards of radioiodine treatment of thyroid carcinoma, in *UICC Monograph Series Vol. 12, Thyroid Cancer*, (ed. C. Hedinger), Springer-Verlag., Berlin, pp. 293–304.
106 Brincker, H., Hansen H.S. and Andersen, A.P. (1973) Induction of leukaemia by ^{131}I treatment of thyroid carcinoma. *Br. J. Cancer*, **28**, 232–7.
107 Sarkar, S.D., Beierwaltes, W.H., Gill, S.P. *et al.* (1976) Subsequent fertility and birth histories of children and adolescents treated with ^{131}I for thyroid cancer. *J. Nucl. Med.*, **17**, 460–4.
108 Handelsman, D.J., Conway, A.J., Donnelly, P.E. *et al.* (1980) Azoospermia after iodine-131 treatment of thyroid carcinoma. *Br. Med. J.*, **281**, 1527.
109 Ahmed, S.R. and Shalet, S.M. (1985) Gonadal damage due to radioactive iodine (I^{131}) treatment for thyroid carcinoma. *Postgrad. Med. J.*, **61**, 361–2.
110 Leeper, R.D. (1973) The effect of ^{131}I therapy on the survival of patients with metastatic papillary or follicular thyroid cancer. *J. Clin. Endocrinol.*, **36**, 1143–52.
111 Varma, V.M., Beierwaltes, W.H., Nofal, M.M. *et al.* (1970) Treatment of thyroid cancer: death rates after surgery and after surgery followed by sodium iodide I-131. *JAMA*, **214**, 1437–42.
112 Krishnamurthy, G.T. and Blahd, W.H. (1977) Radioiodine I-131 therapy in the management of thyroid carcinoma: a prospective study. *Cancer*, **40**, 195–202.
113 National Council on Radiation Protection and Measurements (1970) Report No 37. *Precautions in the Management of Patients who have Received Therapeutic Amounts of Radionuclides.*
114 Greenfield, L.D., Herman, M.W. and Patrick, J. (1978) Radiation safety precautions with 131 iodine therapy. *Cancer Nursing*, **Oct**, 379–84.
115 Browning, E.J., Banerjee, K. and Reisenger, W.E. Jr (1978) Airborne concentration of I-131 in a nuclear medicine laboratory. *J. Nucl. Med.*, **19**, 1078–81.
116 Jacobson, A.P., Plato, A. and Toeroek, D. (1978) Contamination of the home environment by patients treated with iodine-131. *Am. J. Pub. Health*, **68**, 225–30.
117 Simpson, W.J. and Carrurthers, J.S. (1978) The role of external radiation in the management of papillary and follicular thyroid cancer. *Am. J. Surg.*, **136**, 457–60.
118 Carr, E.A. Jr, Dingledine, W.S. and Beierwaltes, W.H. (1958) Premature resort to X-ray therapy: a common error in treatment of carcinoma of the thyroid. *Lancet*, **78**, 478–83.
119 Gottlieb, J.A. and Hill, C.S. (1974) Chemotherapy of thyroid cancer with adriamycin. *N. Engl. J. Med.*, **290**, 193–7.
120 Burgess, M.A. and Hill, C.S. Jr (1978) Chemotherapy in the management of thyroid cancer, in *Thyroid Cancer*, (ed. L.D. Greenfield) CRC Press, West Palm Beach, pp. 233–45.
121 Hellman, D.E., Durie, B.G.M., Woolfenden, J.M. *et al.* (1980) Multidisciplinary management of carcinoma of the thyroid. *Arizona Med.*, **37**, 19–25.
122 Van Herle, A.J. and Uller, R.P. (1975) Elevated serum thyroglobulin: a marker of metastases in differentiated thyroid carcinomas. *J. Clin. Invest.*, **56**, 272–7.
123 Shlossberg, A.H., Jacobson, J.C.J. and Ibbertson, H.K. (1979) Serum thyroglobulin in the diagnosis and management of thyroid carcinoma. *Clin. Endocrinol.*, **10**, 17–27.
124 Tang Fui, S.C.N., Hoffenberg, R., Maisey, M.N. *et al.* (1979) Serum thyroglobulin concentrations and whole-body radioiodine scan in follow-up of differentiated thyroid cancer after thyroid ablation. *Br. Med. J.*, **2**, 298–300.
125 Charles, M.A., Dodson, L.E., Waldeck, N. *et al.* (1980) Serum thyroglobulin levels predict total body iodine scan findings in patients with treated well-differentiated thyroid carcinoma. *Am. J. Med.*, **69**, 401–7.
126 Blahd, W.H., Drickman, M.V., Porter, C.W. *et al.* (1984) Serum thyroglobulin, a monitor of differentiated thyroid carcinoma in patients receiving thyroid hormone suppression therapy: concise communication. *J. Nucl. Med.*, **25**, 673–6.
127 Black, E.G., Cassoni, A., Gimlette, T.M.D. *et al.* (1981) Serum thyroglobulin in thyroid cancer. *Lancet*, **2**, 443–5.
128 Bayer, M.F., McDougall, I.R. and Kriss, J.P. (1987) Retrospective study of serum thyroglobulin measurements performed in patients with differentiated thyroid carcinoma at the Stanford University thyroid clinic between 1979 and 1985, in *Thyroglobulin and Thyroglobulin Antibodies in the Follow-up of Thyroid Cancer and Endemic Goiter*, (eds M. Hufner and C. Reiners), Georg Thieme Verlag, Stuttgart, pp. 104–11.
129 Moser, E., Fritsch, S. and Braun, S. (1988) Thyroglobulin and ^{131}I uptake of remaining thyroid tissue in patients with differentiated

carcinoma after thyroidectomy. *Nucl. Med. Comm.*, **9**, 262–6.

130 Miller, J.H. and Marcus, C.S. (1988) Metastatic papillary thyroid carcinoma with normal serum thyroglobulin level. *Clin. Nucl. Med.*, **13**, 652–3.

131 Brendel, A.J., Guyot, M., LeFort, G. *et al.* (1988) Thallium-201 imaging in the follow-up of differentiated thyroid carcinoma. *J. Nucl. Med.*, **29**, 1515–20.

132 LiVolsi, V.A. (1978) Pathology of thyroid cancer, in *Thyroid Cancer*, (ed. L.D. Greenfield), CRC Press, West Palm Beach, pp. 85–141.

133 Harness, J.K., Thomson, N.W., McLeod, M.K. *et al.* (1984) Follicular carcinoma of the thyroid gland: trends and treatment. *Surgery*, **96**, 972–8.

134 Lang, W., Choritz, H. and Hundeshagen, H. (1986) Risk factors in follicular thyroid carcinomas. *Am. J. Surg. Pathol.*, **10**, 246–55.

135 Chen, K.T.K. and Rosai, J. (1977) Follicular variant of thyroid papillary carcinoma: a clinicopathological study of six cases. *Am. J. Surg. Pathol.*, **1**, 123.

136 Young, R.L., Mazzaferri, E.L., Rahe, A.J. *et al.* (1980) Pure follicular thyroid carcinoma: impact of therapy on 214 patients. *J. Nucl. Med.*, **21**, 733–9.

137 Federman, D.D. (1964) Hyperthyroidism due to functioning metastatic carcinoma of the thyroid. *Medicine*, **43**, 267–74.

138 Chapman, C.N., Sziklas, J.J., Spencer, R.P. *et al.* (1984) Hyperthyroidism with metastatic follicular thyroid carcinoma. J. Nucl. Med., **25**, 466–8.

139 Ober, K.P., Cowan, R.J., Sevier, R.E. *et al.* (1987) Thyrotoxicosis caused by functioning metastatic thyroid carcinoma. *Clin. Nucl. Med.*, **12**, 345–8.

140 Pont, A., Spratt, D. and Shinn, J.B. T_3 toxicosis due to nonmetastatic follicular carcinoma of the thyroid. *West. J. Med.*, **136**, 255–8.

141 Thomson, N.W., Brown, J., Orringer, M. *et al.* (1978) Follicular carcinoma of the thyroid with massive angioinvasion: extension of tumor thrombus to the heart. *Surg.*, **83**, 451–7.

142 Perez, D. and Brown, L. (1984) Follicular carcinoma of the thyroid appearing as an intraluminal superior vena cava tumor. *Arch. Surg.*, **119**, 323–6.

143 Discussion of reference 133 by various surgeons (1984) *Surg.*, **96**, 978–80.

144 Cerletty, J.M. and Listwan, W.J. (1979) Hyperthyroidism due to functioning metastatic thyroid carcinoma: precipitation of thyroid storm with therapeutic radioactive iodine. *JAMA*, **242**, 269–70.

145 Feldman, P.S., Horvath, E. and Kovacs, K. (1972) Ultrastructure of three Hurthle cell tumors of the thyroid. *Cancer*, **30**, 1279–85.

146 Watson, R.G., Brennan, M.D., Goellner, J.R. *et al.* (1984) Invasive Hurthle cell carcinoma of the thyroid: natural history and management. *Mayo Clin. Proc.*, **59**, 851–5.

147 Fisher, E.R. and Kim, W.S. (1977) Primary clear cell thyroid carcinoma with squamous features. *Cancer*, **39**, 2497–502.

148 Van Herle, A.J. and Uller, R.P. (1979) Thyroid cancer. Classification, clinical features, diagnosis and therapy, in *The Thyroid: Physiology and Treatment of Disease*, (eds J.M. Hershman and G.A. Bray), Pergamon Press, Oxford, pp. 505–31.

149 Jaques, D.A., Chambers, R.G. and Oertel, J.E. (1970) Thyroglossal tract carcinoma. A review of the literature and addition of eighteen cases. *Am. J. Surg.*, **120**, 439–46.

150 Page, C.P., Kemmerer, W.T., Haff, R.C. *et al.* (1974) Thyroid carcinomas arising in thyroglossal ducts. *Ann. Surg.*, **180**, 799–803.

151 Joseph, T.J. and Komorowski, R.A. (1975) Thyroglossal duct carcinoma. *Hum. Pathol.*, **6**, 717–29.

152 Banerjee, S.N., Ananthakrishnan, N., Veliath, A.J. *et al.* (1986) Papillary carcinoma in a giant lateral thyroglossal cyst. *Postgrad. Med. J.*, **62**, 849–51.

153 LiVolsi, V.A., Perzin, K.H. and Savetsky, L. (1974) Carcinoma arising in median ectopic thyroid (including thyroglossal duct tissue). *Cancer*, **34**, 1303–15.

154 Roses, D.F., Snively, S.L., Phelps, R.G. *et al.* (1983) Carcinoma of the thyroglossal duct. *Am. J. Surg.*, **145**, 266–9.

155 Pardo-Mindan, F.J. and Vazquez, J.J. (1983) Malignant struma ovarii: light and electron microscopic study. *Cancer*, **51**, 337–43.

156 Kempers, R.D., Dockerty, M.B., Hoffman, D.L. *et al.* (1970) Struma ovarii: ascitic, hyperthyroid, and asymptomatic syndromes. *Ann. Intern. Med.*, **72**, 883–93.

157 McDougall, I.R., Krasne, D., Hanberry, J.W., *et al.* (1989) Malignant struma ovarii presenting as paraparesis from a spinal metastasis. *J. Nucl. Med.*, **30**, 407–11.

158 Aldinger, K.A., Samaan, N.A., Ibanez, M. *et al.* (1978) Anaplastic carcinoma of the thyroid. A review of 84 cases of spindle and giant cell carcinoma of the thyroid. *Cancer*, **41**, 2267–75.

159 Shimaoka, K., Getaz, P.E. and Rao, U. (1979)

Anaplastic carcinoma of the thyroid: radiation associated. *New Y. St. J. Med.*, **79**, 874–7.
160 Carcangiu, M.L., Steeper, T., Zampi, G. *et al.* (1985) Anaplastic thyroid carcinoma. A study of 70 cases. *Am. J. Clin. Pathol.*, **83**, 135–58.
161 Nel, C.M.L., Van Heerden, J.A., Goellner, J.R. *et al.* (1985) Anaplastic carcinoma of the thyroid: a clinicopathologic study of 82 cases. *Mayo Clin. Proc.*, **60**, 51–8.
162 Shevro, J., Gal, R., Avidor, I. *et al.* (1984) Anaplastic thyroid carcinoma. A clinical, histologic and immunochemical study. *Cancer*, **62**, 319–25.
163 Casterline, P.F., Jaques, D.A., Blom, H. *et al.* (1980) Anaplastic giant and spindle-cell carcinoma of the thyroid. *Cancer*, **45**, 1689–92.
164 Kim, J.H. and Leeper, R.D. (1983) Treatment of anaplastic giant and spindle cell carcinoma of the thyroid with combination adriamycin and radiation therapy. A new approach. *Cancer*, **52**, 954–7.
165 Shimaoka, K., Schoenfeld, D.A., De Wys, W.D. *et al.* (1983) a randomized trial of doxorubicin versus doxorubicin plus cisplatinum in patients with advanced thyroid carcinoma. *Cancer*, **56**, 2155–60.
166 Spanos, G.A., Wolk, D., Desner, M.R. *et al.* (1982) Preoperative chemotherapy for giant cell carcinoma of the thyroid. *Cancer*, **50**, 2252–6.
167 Sizemore, G.W. (1987) Medullary cancer of the thyroid gland. *Semin. Oncol.*, **14**, 306–14.
168 Hazard, J.B., Hawk, W.A., Crile, G. Jr (1959) Medullary (solid) carcinoma of the thyroid: a clinicopathologic entity. *J. Clin. Endocrinol. Metab.*, **19**, 152–61.
169 Williams, E.D. (1967) Medullary carcinoma of the thyroid gland. *J. Clin. Pathol.*, **20**, 395–8.
170 Cunliffe, W.J., Black, M.M., Hall, R. *et al.* (1968) A calcitonin-secreting thyroid carcinoma. *Lancet*, **2**, 63–8.
171 Tashjian, A.H. and Melvin, K.E.W. (1968) Medullary carcinoma of the thyroid gland. Studies of thyrocalcitonin in plasma and tumor extracts. *N. Engl. J. Med.*, **279**, 279–83.
172 Tubiana, M., Milhaud, G., Coutris, G. *et al.* (1968) Medullary carcinoma and thyrocalcitonin. *Br. Med. J.*, **4**, 87–9.
173 Tashjian, A.H. Jr, Howland, B.G., Melvin, K.E.W. *et al.* (1970) Immunoassay of human calcitonin: clinical measurement, relation to serum calcium and studies in patients with medullary carcinoma. *N. Engl. J. Med.*, **283**, 890–5.
174 Sipple, J.H. (1961) The association of pheochromocytoma with carcinoma of the thyroid gland. *Am. J. Med.*, **31**, 163–6.
175 Cunliffe, W.J., Hudgson, P., Fulthorpe, J.J. *et al.* (1970) A calcitonin-secreting medullary thyroid carcinoma associated with mucosal neuromas, Marfanoid features, myopathy and pigmentation. *Am. J. Med.*, **48**, 120–6.
176 De Lellis, R.A. and Wolfe, H.J. (1981) The pathobiology of the human calcitonin (C)-cell: a review, *Pathology Annual Part 2, Vol 16*, Appleton-Century-Crofts, New York, pp. 25–52.
177 Goltzman, D., Pott, J.T. Jr, Ridgeway, E.C. *et al.* (1974) Calcitonin as a tumor marker: use of a radioimmunoassay for calcitonin in the postoperative evaluation of patients with medullary thyroid carcinoma. *N. Engl. J. Med.*, **290**, 1035–9.
178 Rougier, P., Calmettes, C., Laplanche, A. *et al.* (1983) The values of calcitonin and carcinoembryonic antigen in the treatment and management of nonfamilial medullary thyroid carcinoma. *Cancer*, **51**, 855–62.
179 Parker, L.N., Kollin, J., Wu, S-Y. *et al.* (1985) Carcinoma of the thyroid with a mixed medullary, papillary, follicular, and undifferentiated pattern. *Arch. Intern. Med.*, **145**, 1507–9.
180 Burt, A.D., MacGuire, J., Lindop, G.B. *et al.* (1987) Mixed follicular-parafollicular carcinoma of the thyroid. *Scot. Med. J.*, **32**, 50–1.
181 Ibanez, M.L. (1974) Medullary carcinoma of the thyroid gland, in *Pathology Annual*, (ed. S.C. Sommers), Appleton-Century-Crofts, New York, pp. 263–90.
182 Williams, E.D. (1981) Medullary carcinoma and other disorders involving calcitonin, in *Endocrinology*, vol 2, (ed. L.J. De Groot, *et al.*), Grune and Stratton, New York, pp. 777–92.
183 Woolner, L.B., Beahrs, O.H., Black, B.M. *et al.* (1961) Classification and prognosis of thyroid carcinoma. *Am. J. Surg.*, **102**, 354–87.
184 Saad, M.F., Ordonez, N.G., Rashid, R.K. *et al.* (1984) Medullary carcinoma of the thyroid: a study of the clinical features and prognostic factors in 161 patients. *Medicine*, **63**, 319–41.
185 Chong, G.C., Beahrs, O.H., Sizemore, G.W. *et al.* (1975) Medullary carcinoma of the thyroid gland. *Cancer*, **35**, 695–704.
186 Pont, A. (1980) Multiple endocrine neoplasia syndromes. *West. J. Med.*, **132**, 301–12.
187 Ram, M.D., Rao, K.N. and Brown, L. (1978) Hypercalcitoninemia, pheochromocytoma, and C-cell hyperplasia: a new variant of Sipple's syndrome. *JAMA*, **239**, 2155–6.

188 Marks, A.D. and Channick, B.J. (1974) Extra-adrenal pheochromocytoma and medullary thyroid carcinoma with pheochromocytoma. *Arch. Intern. Med.*, **134**, 1106–9.

189 Williams, E.D., Karim, S.M.M. and Sandler, M. (1968) Prostaglandin secretion by medullary carcinoma of the thyroid – a possible cause of the associated diarrhoea. *Lancet*, **1**, 22–3.

190 Milhaud, G., Calmette, C., Taboulet, J. *et al.* (1974) Hypersecretion of calcitonin in neoplastic conditions. *Lancet*, **1**, 462–3.

191 Coombes, R.D., Hillyard, C., Greenberg, P.B. *et al.* (1974) Plasma-immunoreactive-calcitonin in patients with non-thyroidal tumours. *Lancet*, **1**, 1080–3.

192 Hennessy, J.F., Gray, T.K., Cooper, C.W. *et al.* (1973) Stimulation of thyrocalcitonin secretion by pentagastrin and calcium in two patients with medullary carcinoma of the thyroid. *J. Clin. Endocrinol. Metab.*, **36**, 200–3.

193 Sizemore, G.W. and Go, V.L.W. (1975) Stimulation tests for diagnosis of medullary thyroid carcinoma. *Mayo Clin. Proc.*, **50**, 53–6.

194 Wells, S.A., Dilley, W.G., Farndon, J.A. *et al.* (1985) Early diagnoisis and treatment of medullary thyroid carcinoma. *Arch. Intern. Med.*, **145**, 1248–52.

195 Parthasarathy, K.L., Shimaoka, K., Bakshi, S.P. *et al.* (1980) Radiotracer uptake in medullary carcinoma of the thyroid. *Clin. Nucl. Med.*, **5**, 45–8.

196 Hoefnagel, C.A., Delprat, C.C., Zanin, D. *et al.* (1988) New radionuclide tracers for the diagnosis and therapy of medullary thyroid carcinoma. *Clin. Nucl. Med.*, **13**, 159–65.

197 Sisson, J.C., Frager, M.S., Valk, T.W. *et al.* (1981) Scintigraphic localization of pheochromocytoma. *N. Engl. J. Med.*, **305**, 12–17.

198 Sisson, J.C., Shapiro, B., Beierwaltes, W.H. *et al.* (1984) Radiopharmaceutical treatment of malignant pheochromocytoma. *J. Nucl. Med.*, **24**, 197–206.

199 Endo, K., Shiomi, K., Kasagi, K. *et al.* (1984) Imaging of medullary thyroid cancer with ^{131}I-MIBG. *Lancet*, **2**, 233.

200 Connell, J.M.C., Hilditch, T.E. and Elliott, A. *et al.* (1984) ^{131}I-MIBG and medullary carcinoma of the thyroid. *Lancet*, **2**, 1273–74.

201 Keeling, C.A. and Basso, L.V. (1988) Iodine-131 MIBG uptake in metastatic medullary carcinoma of the thyroid. *Clin. Nucl. Med.*, **13**, 260–3.

202 Ohta, H., Yamamoto, K., Endo, K. *et al.* (1984) A new imaging agent for medullary carcinoma of the thyroid. *J. Nucl. Med.*, **25**, 323–5.

203 Clarke, S.E.M., Fogelman I., Lazarus, C.R. *et al.* (1986) A comparison of ^{131}I-MIBG and ^{99m}Tc-pentavalent-DMSA for imaging patients with medullary cell carcinoma of the thyroid, in *Nuklearmedizin – Nuclear Medicine in Research and Practice*, (eds H.A.E. Schmidt and D. Emrich), Schattauer Verlag, Stuttgart, pp. 475–6.

204 Miyauchi, A., Endo, K., Ohta, H. *et al.* (1986) ^{99m}Tc(v) Dimercaptosuccinic acid scintigraphy for medullary thyroid carcinoma. *World J. Surg.*, **10**, 640–5.

205 Guilloteau, D., Baulieu, J-L., Besnard, J-C. (1985) Medullary-thyroid-carcinoma imaging in an animal model: use of radiolabeled anti-calcitonin $F(ab')_2$ and meta-iodobenzylguanidine. *Eur. J. Nucl. Med.*, **11**, 198–200.

206 Hellman, D.E., Kartchner, M., Van Antwerp, J.D. *et al.* (1979) Radioidine in the treatment of medullary carcinoma of the thyroid. *J. Clin. Endocrinol. Metab.*, **48**, 451–5.

207 Deftos, L.J. and Stein, M.F. (1980) Radioiodine as an adjunct to the surgical treatment of medullary thyroid carcinoma. *J. Clin. Endocrinol. Metab.*, **50**, 967–8.

208 Nusynowitz, M.L., Pollard, E., Benedetto, A.R. *et al.* (1981) Treatment of medullary carcinoma of the thyroid with I-131. *J. Nucl. Med.*, **23**, 143–6.

209 Hamburger, J.I., Miller, J.M., Kini, S.R. (1983) Lymphoma of the thyroid. *Ann. Intern. Med.*, **99**, 685–93.

210 Meissner, W.A. and Warren, S. (1969) Tumors of the thyroid gland, in *Atlas of Tumor Pathology*, second series, fascicle 4, Armed Forces Institute of Pathology, Washington DC.

211 Compagno, J. and Oertel, J.E. (1980) Malignant lymphomas and other lymphoproliferative disorders of the thyroid gland. A clinicopathologic study of 245 cases. *Am. J. Clin. Pathol.*, **74**, 1–11.

212 Rappaport, H. (1964) Tumors of the hematopoietic system, *Atlas of Tumor Pathology*, fascicle 8, section 3, Armed Forces Institute of Pathology, Washington DC.

213 Buss, D.H., Marshall, R.B., Holleman, I.L. *et al.* (1980) Malignant lymphomas of the thyroid gland with plasma cell differentiation (plasmacytoma). *Cancer*, **46**, 2671–5.

214 Chen, K.T.K., Bauer, V. and Bauer, F. (1986) Localized thyroid plasmacytoma. *J. Surg. Oncol.*, **32**, 220–2.

215 Gibson, J.M. and Prinn, M.G. (1986) Hodgkin's

disease involving the thyroid gland. *Br. J. Surg.*, **55**, 236–8.
216 Chak, L.Y., Hoppe, R.T., Burke, J.S. *et al.* (1981) Non-Hodgkin's lymphoma presenting as thyroid enlargement. *Cancer*, **48**, 2712–16.
217 Burke, J.S., Butler, J.J. and Fuller, L.M. (1977) Malignant lymphomas of the thyroid. A clinical pathologic study of 35 patients including ultrastructure observations. *Cancer*, **39**, 1587–602.
218 Devine, R.M., Edis, A.J. and Banks, D.M. (1981) Primary lymphoma of the thyroid: a review of the Mayo Clinic experience. *World J. Surg.*, **5**, 33–8.
219 Grimley, R.P. and Oates, G.D. (1980) The natural history of malignant thyroid lymphomas. *Br. J. Surg.*, **67**, 475–7.
220 Maurer, R., Taylor, C.R., Terry, R. *et al.* (1979) Non-Hodgkin's lymphoma of the thyroid gland. *Virch. Arch. A. Path. Anat. Histol.*, **383**, 293–319.
221 Schwarze, E-W., Papadimitriou, C.S. (1980) Non-Hodgkin lymphoma of the thyroid. *Path. Res. Pract.*, **167**, 346–62.
222 Sirota, D.K. and Segal, R.L. (1979) Primary lymphomas of the thyroid gland. *JAMA*, **242**, 1743–6.
223 Souhami, L., Simpson, J. and Carrurthers, J.S. (1980) Malignant lymphoma of the thyroid gland. *Int. J. Rad. Onc. Biol. Phys.*, **6**, 1143–7.
224 Rolf, S.L. (1980) Primary lymphomas of the thyroid and Hashimoto's thyroiditis. *J. Kentucky Med. Assoc.*, **78**, 263–6.
225 Holm, L-E., Blomgren, H. and Lowhagen, T. (1985) Cancer risks in patients with chronic lymphocytic thyroiditis. *N. Engl. J. Med.*, **312**, 601–4.
226 Shimaoka, K., Van Herle, A.J. and Dindogru, A. (1976) Thyrotoxicosis secondary to involvement of the thyroid with malignant lymphoma. *J. Clin. Endocrinol. Metab.*, **43**, 64–8.
227 Case Records of the Massachusetts General Hospital (1987) Case 15. *N. Engl. J. Med.*, **316**, 931–8.
228 McCabe, D.P., Farrar, W.B., Petkov, T.M. *et al.* (1985) Clinical and pathologic correlation in disease metastatic to the thyroid. *Am. J. Surg.*, **150**, 519–23.
229 Willis, R.A. (1931) Metastatic tumors in the thyroid. *Am. J. Pathol.*, **7**; 187–208.
230 Shimaoka, K., Sokal, J. and Pickren, J. (1962) Metastatic neoplasms in the thyroid gland. *Cancer*, **15**, 557–65.
231 Ivy, H.K. (1984) Cancer metastatic to the thyroid: a diagnostic problem. *Mayo Clin. Proc.*, **59**, 856–9.
232 Gault, E.W., Leung T.W.H. and Thomas, D.F. (1974) Clear cell renal carcinoma masquerading as thyroid enlargement. *J. Pathol.*, **113**, 21–5.
233 Thomson, J.A., Kennedy, J.S., Browne, M.K. *et al.* (1975) Secondary carcinoma of the thyroid gland. *Br. J. Surg.*, **62**, 692–3.
234 Watts, N.B. (1987) Carcinoma metastatic to the thyroid: prevalence and diagnosis by fine-needle aspiration cytology. *Am. J. Med. Sci.*, **293**, 13–17.
235 Krauth, P.H. and Katz, J.F. (1987) Kaposi's sarcoma involving the thyroid in a patient with AIDS. *Clin. Nucl. Med.*, **12**, 848–9.

CHAPTER NINE

Thyroiditis

9.1 INTRODUCTION

In this chapter, six thyroid disease are described. Each has an inflammatory pathology, but they are only loosely connected clinically and there is not a common aetiology. Table 9.1 lists these disorders and their eponyms and synomyms and probable causes. Hashimoto's thyroidities is extremely common in clinical practice, and it is said to be the most prevalent thyroid disease. In contrast, acute suppurative thyroiditis and Riedel's thyroiditis are rarities. Each syndrome is presented individually starting with the commonest.

Table 9.1 Classification of thyroiditis

Type	*Eponyms and synonyms*	*Aetiology*
Acute	Suppurative	Infective
Subacute	De Quervain's Granulomatous	Probably viral
Silent	Painless Postpartum Hyperthyroiditis Transient	Probably immunological
Hashimoto's	Chronic lymphocytic autoimmune	Immunological
Riedel's	Invasive fibrous	Unknown
Radiation		Radiation

9.2 HASHIMOTO'S THYROIDITIS

The original description of this type of thyroiditis was in four middle-aged Japanese women [1]. Although the age and sex are characteristic, this disease is found in all ages and both sexes. It is very common in Japan, but it is also very prevalent in North America and Europe. Most series show a preponderance of women with the ratio to men from 9 to 1 to as great as 25 to 1 [2, 3)]. In one large population study, the annual incidence in women was 69 to 100 000 [3]. The peak incidence is between 40–60 years. The original description of the pathology showed the thyroid to be infiltrated with lymphoid cells, and Hashimoto's thyroiditis was the first proven autoimmune disease. Witebsky *et al.* [4] produced experimental thyroiditis in animals by injecting them with thyroid antigens, and Roitt *et al.* [5] showed that antibodies against thyroid antigens were present in the circulation of patients with this diagnosis. Other synonyms, such as chronic lymphocytic thyroiditis, autoimmune thyroiditis and lymphadenoid goitre result from the pathological appearance and pathogenesis.

One of the important clinical questions is to define what constitutes a diagnosis of Hashimoto's thyroiditis. It is an autoimmune disease in which there is a goitre, evidence of humoral autoimmunity to thyroid antigens and characteristic lymphocytic infiltration of the thyroid. Frequently, other members of the family have autoimmune thyroid disease or circulating antithyroid antibodies. There would be no doubt about the diagnosis if the patient had all of the above features. However, would, or should, the finding of circulating thyroid antibodies in a middle-aged woman be sufficient to establish the diagnosis? For some that is enough, but such a finding is very common. In one

study in patients seen in general practice, 16.2% of women and 4.3% of men had antithyroglobulin antibodies [6]. I use the presence of a goitre plus thyroid antibodies to make the diagnosis. In contrast, Fisher *et al.* [7] require five markers: goitre, scintigraphic findings, increased TSH, thyroid antibodies and a positive perchlorate discharge test. I agree that TSH should be measured in all patients, but the result is usually normal; therefore, it need not be high to establish the diagnosis. It is not necessary to obtain a thyroid scintigram routinely and a perchlorate discharge test, although frequently abnormal, is definitely not required in practice.

Another vexed issue is the relationship to other autoimmune thyroid disease, in particular Graves' disease and primary hypothyroidism. If the patient is hyperthyroid, has a firm goitre and evidence of humoral autoimmunity, does she have Graves' disease or Hashimoto's thyroiditis? Fatourechi *et al.* [8] described 24 such patients and concluded that Graves' and Hashimoto's were part of the same disorder. Wyse *et al.* [9] described 10 patients with characteristic ophthalmopathy of Graves' disease, in whom biopsy of the thyroid (3 open and 7 needle biopsies) showed changes of Hashimoto's Some authors have used the term Hashitoxicosis to cover this overlap. I take a pragmatic approach which is related to thyroid status and the proposed treatment. If the patient is hyperthyroid, treatment will be for hyperthyroidism. Therefore, it is better to say the patient has Graves' disease, or autoimmune thyroid disease with hyperthyroidism. Similarly, when there is clinical evidence of infiltrative ophthalmopathy in a euthyroid patient with a firm goitre, the best diagnostic label would be euthyroid Graves' ophthalmopathy, because treatment will be direct at the eye disease. Likewise, if the patient has a diffuse, rubbery goitre and is euthyroid, Hashimoto's thyroiditis is the most appropriate designation. If the patient presents with hypothyroidism and has high levels of thyroid antibodies, the best term is primary hypothyroidism. It is important to recognize that giving a name to a disease does not infer knowledge of its aetiology: this terminology is used to allow clinicians to understand why certain treatments are proposed.

9.2.2 AETIOLOGY

There has been a large body of experimental evidence supporting the autoimmune nature of Hashimoto's thyroiditis. This will not to be presented in detail because it does not directly influence management. The thyroid autoantibodies are to various thyroid antigens, including thyroglobulin, thyroid microsomes and a second colloid antigen. Some patients have thyroid receptor antibodies (TRAb), others have growth-stimulating antibodies, and others have antibodies that inhibit these functions. A mixture of stimulating and inhibiting antibodies can be detected in the same patient. Very occasionally, antibodies are formed against T_4 and/or T_3. Those readers who are interested in the purported defect in immune regulation, which allows formation of these antibodies, are referred to Volpé [10, 11]. These reviews indicate the possible role of cellular immunity.

It might be hypothesized that some noxious agent, e.g. a virus, alters the antigenic structure of the gland so that the thyroid is no longer recognized as self. So far, evidence of a single causative factor has not been forthcoming, although the relationship of autoimmune thyroid disease to a prior high dose of external radiation to the anterior neck, which could alter thyroid antigenic structure, is recognized [12].

There is an association of Hashimoto's thyroiditis with certain tissue types. That form of Hashimoto's which most often results in atrophy of the thyroid (this goes on

to primary hypothyroidism) is associated with HLA-DR3 [13]. In contrast, HLA-DR5 is found more frequently in patients with the goitrous form of the disease [14]. The fact that these tissue characteristics are on the sixth chromosome fails to explain why women are more likely to get the disease. Perhaps oestrogen influences the expression of the gene.

Beierwaltes [15] has drawn attention to the linear relationship between the increasing intake of dietary iodine and the increasing frequency of Hashimoto's thyroiditis, and suggests that iodine is an aetiological factor. He argues that iodine in doses not dissimilar to those ingested in the USA (approximately 750 μg/day) causes a defect in organification, and that defect is characteristic of Hashimoto's thyroiditis. Whether the defect can cause Hashimoto's is less clear. Evans *et al.* [16], however, were able to produce thyroiditis in dogs by subcutaneous injection of iodine. Allen *et al.* [17] demonstrated that oral iodine could increase the incidence of lymphocytic thyroiditis in young rats with a genetic predisposition to develop this condition.

In summary, the evidence points to Hashimoto's thyroiditis being an organ-specific autoimmune disorder. The patient may be genetically predisposed and the gland might require an insult (viral, iodine, radiation, other?), which slightly alters its antigens and thyroid autoantibodies are formed. Some of these antibodies damage the gland and others influence its function. The final clinical picture will depend on the specific antibody milieu at any one time.

9.2.3 PATHOLOGY

The gland is enlarged, firm, often bosselated, or nodular and paler than normal. The pyramidal lobe is frequently enlarged. There is an infiltrate of lymphocytes and plasma cells between the thyroid follicles and, in places, these form lymphoid follicles with germinal centres. There is disruption of thyroid follicles and their number is reduced. The follicular cells have a variable appearance. They can be cuboidal or columnar when stimulated by TSH or other growth stimulators. Some of the hypertrophied follicular cells have an oxyphilic cytoplasm and are called Hurthle or Askanazy cells. There is a fibrous variant of the disease in which the thyroid is very firm, and there is marked overgrowth of fibrous tissue at the expense of thyroid follicles. In the atrophic variant, the gland is small and shrunken with few follicles. Woolner *et al.* [18] in an extensive review of 605 patients has provided the interested reader with an excellent reference. Usually the entire gland is involved, but these findings can be restricted to a lobe, or nodule, or even microscopically (focal thyroiditis).

9.2.4 CLINICAL PRESENTATION

The patient is most often female. She can be asymptomatic and a goitre is found at a medical examination, very often done for unrelated reasons. The goitre is rubbery to firm in consistency and it can be smooth, granular, bosselated, or lobular. In one series of 217 patients, 92% were firm or bosselated, and in 68% the entire gland was diffusely enlarged [7]. The goitre has discrete borders and does not invade surrounding structures.

As more nodules are subjected to needle aspiration, it has become apparent that Hashimoto's thyroiditis can present as a solitary nodule. Nevertheless, a solitary nodule in a thyroid which feels like a classic Hashimoto's should be investigated independently, because the incidence of cancer in such a solitary nodule is similar to that in a nodule in a normal gland. The patient is most often clinically euthyroid, 78% in the report of Fisher *et al.* [7], but the whole spectrum of thyroid function is reported from overt hypothyroidism (18%) through

subclinical hypothyroidism where the only abnormality is a high TSH, euthyroidism, and hyperthyroidism (4%). The nomenclature of those patients with abnormal thyroid function was addressed previously. In addition to subclinical hypothyroidism, there are other patients who have an exaggerated response to TRH. In general, there is nothing to be gained from doing the TRH test, since treatment would be prescribed for other criteria (see below).

Very rarely the thyroid is painful and tender, making the differentiation from subacute thyroiditis clinically difficult. The enlarged gland can produce pressure symptoms, including a feeling of heaviness in the neck, a strange sensation on swallowing, and even dysphagia, hoarseness and dyspnoea. It is not unusual to find cervical lymphadenopathy, whose presence is attributed to the immune process. If a patient has a nodular goitre, hoarseness and enlarged cervical lymph nodes, the most important disease to exclude is cancer, and all necessary steps should be taken to exclude that diagnosis, before attributing the symptoms and signs to Hashimoto' thyroiditis.

There are generally no systemic symptoms unless the patient is hypothyroid. To blame Hashimoto's for depression or allergies distracts the clinician from prescribing the optimal treatment for those disorders. It has generally been accepted that most patients with chronic lymphocytic thyroiditis become hypothyroid sooner or later. There is evidence from a large prospective study of randomly selected people from a community in England that is not the case. Those patients at most risk for developing hypothyroidism had significant elevations of thyroid antibodies and a slightly raised TSH. Five per cent of women with those two risk factors became hypothyroid each year for 4 years [19]. In another study, 5 out of 18 asymptomatic patients became hypothyroid in 4–39 months [20, 21]. It should be kept in mind that the English study looked at healthy, ambulant citizens, whereas, in practice, patients are more likely to have clinical problems, such as a goitre or compensated hypothyroidism. Therefore, these numbers might underestimate the frequency of progression to hypothyroidism. Most patients with the full clinical syndrome of primary hypothyroidism probably had Hashimoto's thyroiditis, provided destructive causes of hypothyroidism such as surgery and radioiodine therapy are excluded.

A lesser proportion of patients who have goitre and mild hypothyroidism go into remission [22], and some even become hyperthyroid [23]. These fluctuations can best be explained by changes in the amounts or activities of stimulating, inhibiting and growth antibodies.

The most important differential diagnosis is simple non-toxic goitre. The presence of high titres of thyroid antibodies points to a diagnosis of Hashimoto's. Since the therapies are similar, differentiation is not critical, although autoimmune thyroiditis is more likely to progress to hypothyroidism and associated immunological diseases are more frequent.

There is debate whether thyroid cancer is more common in patients with Hashimoto's thyroiditis or not. Certainly, many papillary cancers are accompanied pathologically by an infiltrate of lymphocytes which is identical to focal thyroiditis. In my experience, 40% of patients with papillary cancer have antithyroid antibodies [24]. However, this is different from Hashimoto's thyroiditis causing the cancer. The evidence supports no difference, e.g. Perzig [25] found cancer in 86 out of 364 patients with thyroiditis, and 216 out of 909 from his complete surgical series; both represent 24% of the denominator. Clark *et al.* [26] found 9 cancers in 75 patients with Hashimoto's thyroiditis. Seven were found out of 27 patients with a discrete solid nodule (25%) and only 2 out of 48 with a diffusely enlarged thyroid (4%). Most of the patients who had cancer would have

been diagnosed by standard evaluation of the solitary nodule. Lymphoma is found more often in association with autoimmume thyroiditis [27, 28], but the risk is so small that it does not warrant prophylactic thyroidectomy. Lymphoma of the thyroid is discussed in detail in Chapter 8.

Other autoimmune diseases are found more frequently. These include adrenal insufficiency, and the combination of primary hypothyroidism and hypoadrenalism is called **Schmidt's syndrome**. Doniach *et al.* [29] found gastric antibodies in 30% of patients with autoimmune thyroid disease. In contrast, Carmel and Spencer [30] showed that 24% of 162 patients with pernicious anaemia had clinical thyroid disease, and 48% had abnormal TSH values. Hypoparathyroidism, diabetes mellitus, Sjögren's syndrome, and vitiligo are all found more often. The systemic connective tissue diseases are probably encountered more commonly [31], and there are reports of dermatomyositis [32] and polymyalgia rheumatica [33] plus autoimmune thyroiditis. Marks *et al.* (34) found mitral valve prolapse in 31 out of 75 patients with chronic lymphocytic thyroiditis, compared with 4 of 50 controls ($P<0.0005$), and they give evidence that mitral valve prolapse is an autoimmune disorder. It is not cost effective to screen for all of these conditions, but clinical awareness during follow-up is necessary.

Systemic complications of Hashimoto's thyroiditis are rare, provided that associated autoimmune disease are not included. There are a few reports of immune complex nephritis, most probably due to thyroglobulin-antithyroglobulin complexes [35–39].

9.2.5 INVESTIGATIONS

The aim of investigations is to (1) define the thyroid status of the patient, (2) demonstrate that there is thyroid autoimmunity, and (3) define the nature of any other abnormality, such as a nodule in the gland. There are a number of other tests which demonstrate abnormalities in physiology, but they have little role in clinical practice.

For the first, FT_4 and TSH are sufficient. These will show normality if present and subtle deviations, whether on the high or low side. Thyroid autoimmunity is tested for by measuring antithyroglobulin and antimicrosomal antibodies. In my experience, using radioimmunoassays for thyroid antibodies, more than 95% of those with Hashimoto's thyroiditis have positive results (sensitivity 95%) [40]. The explanation why not all patients have circulating antibodies has recently been attributed to local production of these by lymphocytes in the gland [41]. These tests are also positive in most patients with Graves' disease, and primary hypothyroidism, and about 10% of apparently normal people have these antibodies in their circulation (specificity about 85–90%). None of the tests for cellular immunity are of clinical value, and it does not help to determine the HLA type of the patient.

Thyroid scintigraphy is seldom required. However, in those patients with a dominant nodule, it might help to know if the nodule is functional. ^{123}I is the preferred radionuclide. Ramtoola *et al.* [42] have reported that the scan can mimic normality and other thyroid diseases, especially Graves' disease, which was the case in 25% of their study population. The uptake of radioiodine can be low, suggesting progression to hypothyroidism, or normal or high. The last is paradoxical, but is explained by a reduced number of follicular cells trapping iodine as avidly as possible in an effort to make sufficient thyroid hormone. As will be discussed below, all of the iodine is not organified. The pyramidal lobe is seen on scintigram frequently [Figure 9.1]. If a solitary nodule is non-functional, needle aspiration is advised; but if the clinical impression of the nodule is suspicious, the patient should be referred for surgery [26], although knowledge of the pathology on needle aspirate can be valuable

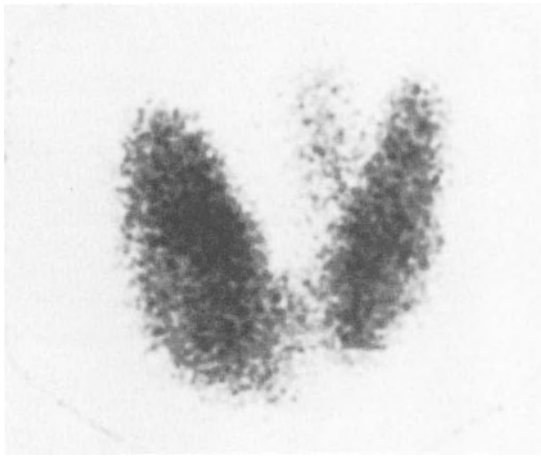


Figure 9.1 The appearance of Hashimoto's thyroiditis on ^{123}I scintigram is very variable. In general, the gland is enlarged, the distribution of radionuclide is inhomogeneous and the pyramidal lobe is apparent.

in planning the extent of the operation. The differential diagnosis in this situation lies between focal thyroiditis, lymphoma, thyroid cancer and other benign lesions. The aspirate will separate out most who have benign pathology and most with cancer. It will not differentiate lymphoid infiltrate of Hashimoto's thyroiditis from lymphoma unless there is enough tissue to prove whether the cells are monoclonal, which is typical of lymphoma (Chapter 8).

One of the characteristic abnormalities in the follicular cell in autoimmune thyroiditis is a defect in organification of iodine, and this can be demonstrated by a positive perchlorate discharge test [43]. This defect occurs in about 40–50% of patients, and is exaggerated by an excess of inorganic iodine given orally or intravenously [44]. This test plays no role in the routine diagnosis of Hashimoto's disease. Investigators have done TRH stimulation tests to determine which patients have limited thyroid reserve. This also is not necessary. If the TSH is normal, the patient can be seen annually, and have the measurement repeated. If TSH rises above the normal range, the patient is at risk of becoming hypothyroid and treatment would be advised.

The sedimentation rate is usually normal, but can be increased. Serum gammaglobulin levels can also be high. These tests are too non-specific to be of diagnostic value.

9.2.6 TREATMENT

Thyroid replacement/suppression is justified to treat hypothyroidism, or to attempt to shrink the goitre. Some patients who are euthyroid and are not bothered by the enlarged thyroid need no treatment, but should be evaluated annually. In some cases of well-established nodular goitre the response to therapy can be disappointing, and in most patients with this finding, thyroid tissue remains palpable even with treatment with thyroxine. Some patients have non-suppressible thyroid, and a full replacement dose produces hyperthyroidism. Therefore, if the patient is older, or has cardiovascular disease, it is wise to start with a small dose of thyroxine, such as 0.025 mg daily for 2 weeks, increasing with similar small increments until the patient is euthyroid and thyroid function tests normal. Younger, fitter patients can be started on 0.1 mg per day for 4 weeks, and the dose titrated to the optimal level (see below). It is generally accepted that once thyroxine is started to treat this condition, it will be required for life. Papapetrou *et al.* [45] studied 12 patients who had been on replacement therapy for 10 years. When thyroxine was stopped for 6 weeks, there was a progression of thyroid dysfunction and the patients became hypothyroid. Although it could be argued the investigators did not stop the medication long enough to ensure the thyroid had time to recover fully from the effects of the suppression *per se*, the general conclusion of progression of thyroid dysfunction is prob-

ably correct. Therefore, patients should recognize that treatment is for life. The number of cases where intrinsic thyroid function goes from low to high is very small, but clinicians should be alert to this possibility; when a patient who previously has been well on thyroxine develops symptoms of hyperthyroidism, the dose should be tapered and if symptoms persist, therapy should be stopped. If there is still clinical and biochemical evidence of hyperthyroidism, treatment will be required as discussed in Chapter 5.

Should the aim of replacement L thyroxine therapy be to produce a euthyroid patient with normal thyroid function? There is no debate about the former, but if the aim of treatment is to shrink a goitre, it is probably better to suppress TSH yet keep FT_4 within the normal range. A normal FT_4 and TSH would be more desirable if the goal of therapy is to correct hypothyroidism. However, many of the patients will have coexisting goitres. Thus replacement with resulting normal TSH, or suppression of TSH, are both appropriate, depending on the circumstances.

In view of the large number of patients with Hashimoto's thyroididitis, surgery is required very infrequently. There are a number of indications, including a solitary nodule which is not unequivocally benign, pressure symptoms, intrathoracic extension, rapidly enlarging goitre, large, cosmetically displeasing goitre which does not decrease in size with adequate suppression, and hyperthyroidism [26], although the last can also be treated by drugs or radioiodine. There can be little disagreement about these indications, but there is considerable debate about how much surgery is necessary. Perzik [25] recommends total thyroidectomy because the disease usually involves the entire gland, and since nodular growth in any residual thyroid can require a second operation with increased risk of damage to normal structures. Other surgeons advise a lesser procedure, such as lobectomy and isthmusectomy for those patients with a nodule, and isthmusectomy for pressure symptoms. Each patient should be evaluated individually and the operative procedure planned to deal with the specific clinical problem with the smallest surgical risk.

Glucocorticosteroids are seldom required to treat Hashimoto's thyroiditis. In pharmacological doses, they produce a dramatic reduction in goitre size, but the response is dose related and the therapy has to be continued for weeks to months, so side-effects are to be expected. In contrast, a recent report described painful Hashimoto's thyroiditis in 8 patients, which did not respond to steroids [46], and in 2 patients the symptoms eventually necessitated surgery to remove the thyroid. Steroids are not recommended except for exceptional circumstances where thyroxine has been ineffective and surgery contraindicated.

There is no role for external radiation.

9.3 SUBACUTE THYROIDITIS (GRANULOMATOUS OR DE QUERVAIN'S THYROIDITIS)

9.3.1 INTRODUCTION

Subacute thyroiditis is a syndrome in which there is a rapid, painful enlargement of the thyroid, systemic symptoms, such as malaise and muscle aches, plus sequential changes in thyroid function, starting with euthyroidism, followed by hyperthyroidism, then normality, then hypothyroidism and, finally, euthyroidism once more. De Quervain [47] was the first to describe this in print. It is also called granulomatous thyroiditis since this is typical on pathological examination.

9.3.2 AETIOLOGY AND PATHOGENESIS

Subacute thyroiditis appears to be caused by viruses, in particular Coxsackie, or mumps

[48]. The evidence for this is based on several facts. Firstly, the condition presents in mini-epidemics. Secondly, it frequently has a close temporal relationship to upper respiratory infections. Thirdly, when they are looked for, rising viral antibody titres are found in the convalescent phase. Other viruses thought to be causal include influenza, adenovirus and mononucleosis; this topic is reviewed in depth by Volpé [49]. A recent report notes the association with *Chlamydia* [50]. It is likely that the gland responds in a similar and limited fashion to invasion by these infective agents. In some patients, no history of antecedent viral infection can be elicited. Therefore, we should keep an open mind about aetiology. There is an increased frequency of tissue type HLA-BW35 in patients who get subacute thyroiditis. However, the condition is not considered to be an autoimmune disease [51], and other autoimmune diseases are not found more frequently.

The disease process (viral or other) causes the destruction of thyroid follicles and the release of colloid and stored thyroid hormones into the circulation. This causes the paradox of hyperthyroidism, both biochemical and clinical, with a low radioiodine uptake because the gland is temporarily destroyed and incapable of trapping (Chapter 5).

9.3.3 PATHOLOGY

Firstly, there is acute inflammation with polymorphonuclear infiltration and, somewhat later, macrophages are present. There is marked destruction of follicles and follicular cells, which are desquamated. The architecture of the gland is totally disrupted. At a later point, giant cells and granulomas are characteristic, and their presence has been attributed to a reaction to the exposed colloid. Thus the acute phase is followed by a subacute phase and, finally, recovery.

Table 9.2 Causes of painful neck

Origin of pain	*Pathology*	*Comments*
Neck	Abscess of soft tissue	Rare
Veins	Phlebitis	Rare
Trachea	Tracheitis	Common
Pharynx	Pharyngitis	Common
Branchial cyst	Abscess	Rare
Thyroid	Thyroiditis subacute	Common
	Thyroiditis acute	Rare
	Thyroiditis Hashimoto's	Pain rare
	Invasive cancer	Rare
	Lymphoma	Rare
	Haemorrhage into cyst	Pain rare
	Thyroglossal cyst abscess	Rare
	Trauma (martial arts)	Rare

9.3.4 CLINICAL PRESENTATION

Most patients have a painful, enlarged, tender thyroid. Table 9.2 lists conditions which can cause pain in the anterior neck and thyroid. Occasionally, the thyroiditis is focal and presents as a painful nodule which requires needle aspiration to clarify the diagnosis. This latter presentation can continue with the thyroiditis creeping, or marching, through the remainder of the gland. Coincidentally, or even preceding the thyroid symptoms, there are systemic symptoms, which are described below. The acute, painful part of the syndrome lasts from about 2 weeks to 2 months; protraction of symptoms well beyond that can be encountered, albeit rarely.

The thyroid pain is often referred to the ear, or the angle of the jaw and teeth, and can be misinterpreted as due to disease in these sites, but palpation of the thyroid should resolve the diagnosis. Movement of the inflamed thyroid with swallowing causes dysphagia. Hoarseness was present in 8 of 56 patients reported by Volpe and Johnston [52]. This is thought to be due to the swollen, inflamed gland stretching the recurrent laryngeal nerve. Recently, two separate case reports describe permanent vocal cord para-

lysis, which can probable best be explained by the inflammation extending out of the thyroid and causing fibrosis round the nerve, or thrombosis of the nerve's blood supply [53, 54]. The thyroid is enlarged, often more than twice normal, and it is firm to hard and exquisitely tender. The patient reflexly shies away from the examining fingers and the clinician should be very gentle and explain prior to palpation that will be the case. Occasionally, there is redness of the skin overlying the gland. This is the common presentation, but there is a spectrum from mild, which is identical clinically to silent thyroiditis, to cases which can be confused with acute suppurative thyroiditis.

Most patients have severe malaise, headache, muscle aches, lethargy and low-grade fever. When the constitutional symptoms are predominant, the correct diagnosis might well be overlooked. Rottenberg *et al.* [55] described 13 patients in whom subacute thyroiditis was eventually diagnosed. The thyroid complaints were relatively mild, and the salient symptoms pointed to a systemic or neoplastic disease. Needle biopsy of the thyroid in 10 patients showed classic pathology of subacute thyroiditis, and one-half of the patients responded to salicylates, the remainder to steroids. Subacute thyroiditis should be remembered as a cause of fever of unknown origin (FUO). Table 9.3 lists the frequency of symptoms and signs in two publications [49, 60].

Table 9.3 Symptoms and signs in subacute thyroiditis

	Reference 49	*Reference 60*
Number of patients	51	62
Percentage with:		
neck pain	89	65
ear/jaw pain	64	16
migrating pain	38	13
weight loss	11	35
palpitation	18	32
heat intolerance	30	31
malaise	84	29
Examination of thyroid:		
firm/hard	100	90
tenderness	57	77
diffuse enlargement	45	55
unilateral	55	24
nodule, single	8	
nodule, multiple	6	

The release of excessive amounts of hormones into the circulation produces clinical hyperthyroidism in 50–70% of patients. However, it is a rare cause of hyperthyroidism, and in one series accounted for only 1% of cases [56], but in another series 9.9% of all hyperthyroidism [57]. Not all patients with subacute thyroiditis will be seen by thyroidologists, and hence these statistics might be imprecise. The hyperthyroidism is usually mild to moderate in severity, but can be sufficiently prolonged to cause thyrotoxic myopathy [57]. After this phase, there is a return to normality coincidental with the metabolism of the released hormones: then about 25% of patients become hypothyroid. Figure 9.2 shows the sequence diagrammatically. Hypothyroidism occurs because the gland has not yet recovered its ability to produce hormones. Complete recovery is anticipated, and very few patients become permanently hypothyroid [58, 59]. This is remarkable in view of the extensive destruction of the gland. Some patients who become permanently hypothyroid might have had silent thyroiditis, which is known to progress to this more frequently (this is probable in 3 of 62 of the patients described by Hamburger [60]). Recurrence or relapse after complete recovery is much less common than in silent thyroiditis, but does occur rarely [61, 62].

In every large series, there is an greater number of women (3–5 to 1). It is very rare in young children [63]. The differential diagnosis includes pharyngitis and laryngitis,

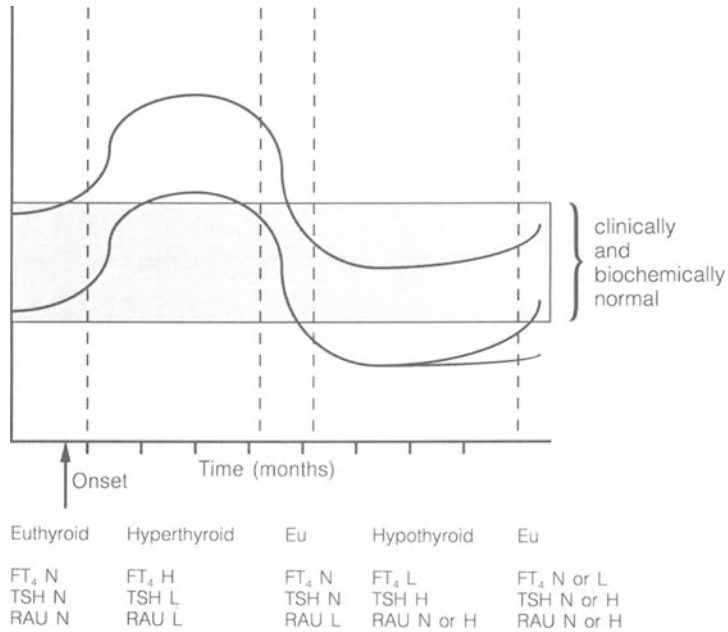


Figure 9.2 Time activity graph of subacute or silent thyroiditis. H = high; L = low; N = normal; RAU = radioactive uptake.

and some experts state that the diagnosis of subacute thyroiditis is overlooked and mislabelled as pharyngitis [52, 60]. As discussed above, the mild and severe cases of subacute thyroiditis can overlap with silent thyroiditis and acute thyroiditis respectively. The latter is the more important, since it is due to a treatable infective cause and is dangerous if not treated. Therefore, when there is doubt, needle aspiration with cytological examination and culture is advised. The differentiation of 'silent' subacute thyroiditis from silent thyroiditis depends on cytological differences, and I am not convinced that the differentiation is sufficiently important to warrant needle aspiration.

A rapidly growing cancer in the thyroid can cause pain and the release of stored iodinated compounds, and can be misdiagnosed as thyroiditis [64]. In the case of an invasive cancer, the hyperthyroid phase is not transient and the painful mass does not regress spontaneously. Rarely, Hashimoto's thyroiditis is painful, but systemic symptoms are absent. Haemorrhage into a cyst or adenoma produces a painful thyroid swelling, but usually will not be confused with subacute thyroiditis. Lymphadenitis is usually not likely to be diagnosed as subacute thyroiditis, because the nodes are lateral to the thyroid. However, Endo [65] described a case of subacute thyroiditis in a lateral aberrant thyroid. Since most authorities consider lateral aberrant thyroid to be a metastatis from primary thyroid cancer, this report should be interpreted with caution. Thyroiditis due to a karate blow to the anterior neck has been described, but the history should lead to the diagnosis [66].

9.3.5 INVESTIGATIONS

Thyroid function tests should be ordered. Depending on when testing is done in relationship to the onset of the disease, FT_4 and T_3 can be normal, high, or low. Likewise,

TSH can be normal, suppressed, or high. Figure 9.2 illustrates this. The ratio of T_4 to T_3 is greater than in other hyperthyroid conditions, and this is said to be a useful diagnostic hint. However, the clinical presentation usually makes this superfluous. Thyroid antibody levels are not helpful; they are elevated in a small proportion of patients, and in one report this occurred in 3 out of 40 patients [67]. Erythrocyte sedimentation rate is increased, and usually greater than 30 mm/h as was the case in 39 out of 42 values reported by Hamburger [60]. Very high values up to 100 mm/h are consistent with the diagnosis, and a white cell count greater than 10 000 mm^3 can be found occasionally. During the acute phase, radioiodine uptake is low and a normal result excludes the diagnosis. Values of 1–2% at 24 hours are common. Thyroid scintigraphy at 3–6 hours after ^{123}I, or minutes after intravenous ^{99m}Tc, show reduced or absent uptake in the region of the thyroid (Figure 9.3). This test is not always necessary but can be helpful when there is doubt about the diagnosis. It is not necessary to do a TSH stimulation test, but old reports show no increase in radioioiodine uptake. Weeks or months later, the uptake returns to normal and in the recovery period can be transiently elevated. However, it is not necessary to obtain serial studies.

In the setting of a typical history and examination: a high FT_4, low TSH and a low radioiodine uptake, it is not necessary to embark on additional testing.

When there is diagnostic uncertainty, a needle aspirate showing acute inflammation and giant cells clinches the diagnosis [67, 68]. The anterior neck should be anaethetized since an injection into the tender gland is not relished by any patient. In those patients in whom constitutional symptoms predominate, a ^{67}Ga (gallium citrate) scintigram showing intense focal uptake in the thyroid helps to establish the diagnosis [69, 70]. Viral antibody studies are not relevant for management of the patient, but can be of interest when epidemiological information is sought. Thyroglobulin levels are high early in the course of the disease. Madeddu *et al.* [71] found high values in 35 out of 38 patients (92%). Thyroglobulin levels remain high for some time after the patient has recovered, indicating continued leakage of colloid. This measurement is not usually necessary clinically.

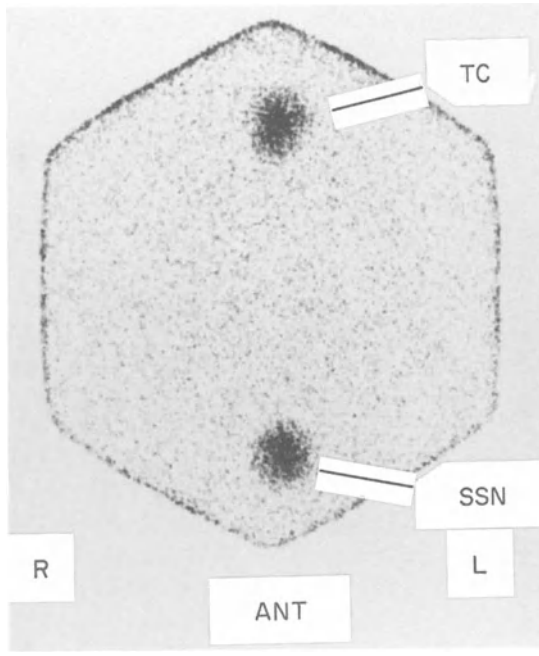


Figure 9.3 Thyroid scintiscan with markers over the thyroid cartilage and sternal notch in a patient with subacute thyroiditis. There is no uptake in the thyroid. In many patients a scan would not necessary as a low uptake would give the same information.

9.3.6 TREATMENT

Treatment starts with indicating to the patient that the diagnosis is established; secondly, relieving neck pain and thirdly, treating abnormal thyroid function when it

is symptomatic. Neck pain, which is mild to moderate, responds to adequate doses of salicylates, such as 1 g 3 or 4 times a day. This, plus reassurance and discussion about the expected sequence, suffice in many patients. Non-steroidal anti-inflammatory drugs like ibuprofen and propoxyphene can be used in place of aspirin and in preference for those who cannot take salicylates. Glucocorticosteroids are very successful in rapidly improving the the symptoms and reducing the swelling [52, 72]. Prednisone 40 mg per day is a reasonable starting dose, which can be titrated upwards after a few days if the expected response is not achieved. Steroids should be prescribed only after thoughtful consideration, because in many cases non-steroidal anti-inflammatory medications will suffice. Secondly, the patient might require a fairly large dose for months and side-effects are, therefore, more likely to occur. It is recognized that as the dose is reduced below a critical level, there can be an exacerbation of the symptoms and the dose has to be increased. Thirdly, the response is non-specific and Hashimoto's thyroiditis and lymphoma will improve substantially. Neither steroids nor anti-inflammatory drugs alter the natural history of subacute thyroiditis.

External radiation was used in the past (1000–2000 rad), but this is not advised because of concern of it causing thyroid cancer. Occasionally, surgery is advised to exclude a diagnosis such as cancer. This should not be common if needle aspiration is done first. If the diagnosis of subacute thyroiditis is made during the operation, a minimal procedure is advised because long-term problems from subacute thyroiditis are very rare.

During the hyperthyroid period, symptoms can be controlled with beta-blockers, such as propranolol, in doses ranging from 20–40 mg every 6–8 hours. This is purely symptomatic – it will slow the pulse, reduce tremor and help fatigue. There have been recommendations to prescribe T_4 or T_3 to suppress the thyroid, but if this is done during the hyperthyroid phase, it will simply add fuel to the fire and make the patient worse. The gland has already released stored hormone and it cannot be suppressed. Likewise, antithyroid drugs are of no value – the horse has already left the barn. During the transient hypothyroid phase, if there are symptoms thyroxine should be prescribed. Most patients do not require this, and in those who do, the therapy will usually be temporary. Because this is not a bacterial infection, there is no rationale to prescribe antibiotics.

9.3.7 PROGNOSIS

The long-term prognosis is good. Some unfortunate patients have ill health for several months, and they are the ones who are more likely to be referred to a specialist and more likely to be remembered because of the severity of their symptoms. Very few patients with true subacute thyroiditis develop permanent hypothyroidism [69] or hyperthyroidism [73]. Because the thyroid status fluctuates and local and systemic features can be of an unpredictable length, several office visits are usually necessary. The number and timing will depend on the individual case. Once the disease has run its full course and the patient is finally euthyroid, long-term follow-up is not necessary.

9.4 SILENT THYROIDITIS INCLUDING POSTPARTUM THYROIDITIS

9.4.1 INTRODUCTION

Silent thyroiditis is a syndrome which runs a course similar to subacute thyroiditis with a hyperthyroid phase passing through normality to hypothyroid, and finally returning to normal. Unlike subacute thyroiditis, there is no anterior neck pain and no tenderness of the thyroid. This disorder has been given various names, including silent thyroiditis

[74], hyperthyroiditis [75] spontaneously resolving lymphocytic thyroiditis [76, 77] transient painless thyroiditis [78], and painless thyroiditis with transient hyperthyroidism [79, 80]. The first report of this syndrome was in 1975 by Papapetrou and Jackson [74], and this was followed almost immediately by the publication by Gluck *et al.* [81]. The sudden discovery of a new syndrome in several geographically discrete areas is puzzling and raises the question, was it part of a spectrum of another known disease, or whether it was a new discrete syndrome? This is dicussed further below. I use the term silent thyroiditis synonymously with the other names. Postpartum thyroiditis runs an identical clinical course, investigations show similar results [82–86] and it is considered to be identical to silent thyroiditis in this text.

Table 9.4 Comparison of symptoms, signs and laboratory investigation in silent and subacute thyroiditis

	Silent	*Subacute*
Neck pain	–	+++
Fatigue/malaise	+	++
ESR >30 mm	+	+++
FT_4 high	++	++
Low RAIU	+++	+++
Permanent hypothyroidism	+	–
Thyroid antibodies	++	–
Subsequent goitre	+	–
Clinical course	Similar	Similar
Thyroid biopsy	Different	Different

9.4.2 AETIOLOGY

The major body of evidence, including pathology and immunology studies, indicate that this is an autoimmune disease. The association with other autoimmune diseases has been used to support this thesis [49, 87]. Some authorities have argued that this is simply a mild form of subacute thyroiditis [88], and a review of the patient characteristics from published series of subacute thyroiditis shows a small number of patients who could well fall into this category [60, 88, 89]. Those who believe that this is a separate disease point to the fact that the histology is different, and that the association with thyroid antibodies is much higher. Nevertheless, there are unequivocal reports of asymptomatic patients who clinically look as if they have silent thyroiditis, but a thyroid biopsy shows the feature of subacute thyroiditis with giant cells and a relatively acute inflammatory reaction. I take a pragmatic point of view. Because asymptomatic subacute thyroiditis and silent thyroiditis run a similar course and have an almost similar outcome, it does not matter what they are thought to be due to. Without question a patient with classic subacute thyroiditis has many differences from one with classic silent thyroiditis, as shown in Table 9.4. But those cases at the interface are impossible to differentiate without pathology, and biopsy of the gland is not easy to justify in an asymptomatic patient. Arguments favouring that silent thyroiditis and postpartum thyroiditis are the same condition are found in reference 90.

9.4.3 PATHOLOGY

The prominent feature in silent thyroiditis is lymphocytic infiltration with disruption of follicles. Giant cells and granulomas are not seen. Likewise those findings which are characteristic of Hashimoto's thyroiditis, including germinal centres and Hurthle cells, are not found. When the follicles lose their integrity, thyroid hormones are released into the circulation.

9.4.4 CLINICAL PRESENTATION

The usual clinical presentation is of mild hyperthyroidism with anxiety, weight loss, tremor, palpitations, etc. The onset is rapid in comparison with Graves' disease. Some

Table 9.5 Symptoms and signs in silent thyroiditis

	Reference 79 presenting features (52 patients) %	*Reference 103 features present (112 patients)* %
Nervousness	44	84
Weight loss	33	67
Sweating	25	70
Fatigue	21	83
Tremor	4	71
Goitre	4	54
diffuse		52

patients have non-specific symptoms, and just do not feel well and thyroid function tests ordered serendipitously are high. The thyroid when it can be felt is firm [76], and it is unusual for it to be more than twice normal in size. The common symptoms and signs from two series are listed in Table 9.5. In the first, the percentage of *presenting* features are given [79], in the second, the frequency of the symptoms [103]. There is no evidence of infiltrative ophthalmopathy, although stare and lid retraction can be found.

In the experience of some thyroid experts, silent thyroiditis accounts for 10–20% of cases of hyperthyroidism. This, however, is not my experience. There might be differences in referrals, but there is also a geographical variation with fewer cases seen on the west coast of the USA [91]. The highest frequency is in the mid-West and in Japan [92]. Figure 9.2 shows the expected time course for silent thyroiditis. Thyrotoxicosis lasts an average of 2–4 months, but some patients are never clinically thyrotoxic, and in others the symptoms can last as long as 8–10 months. Nikolai *et al.* [93] found that 46% of the patients they followed had peristent problems including 23 out of 54 with goitre, and 3 out of 54 with hypothyroidism. In most patients, the disease is self-limiting and return to normal thyroid function is anticipated. Therefore, it is important to make the correct diagnosis early. Clinically, it can be difficult to differentiate silent thyroiditis from a mild case of Graves' hyperthyroidism, but this is resolved by measurement of radioiodine uptake. The most difficult differential diagnosis is factitious hyperthyroidism, and this is discussed in the next section. Postpartum thyroiditis is identical to silent thyroiditis, but it occurs from 3–12 months after deliver; it is also more likely to recur with a similar presentation after subsequent pregnancies. Walfish and Farid [94] report that in their experience 50% of the women in childbearing age with a diagnosis of silent thyroiditis have, in fact, postpartum thyroiditis. This is an important diagnosis to make, since tiredness, malaise, and depression in the postpartum period are usually attributed to postpartum blues or depression. In two large series, postpartum thyroid abnormalities associated with this syndrome were found in 5.5% and 6.5% of patients respectively [95, 96]. Reference 97 provides a comprehensive review.

9.4.5 INVESTIGATIONS

The classic findings early in the disease are high thyroid hormone levels (FT_4 and T_3), suppressed TSH and low radioiodine uptake (1–2%). Surreptitious ingestion of T_4 produces similar results, and if there is any doubt, thyroglobulin can be measured. It is high in silent thyroiditis and absent in factitious hyperthyroidism [98]. Hyperthyroid states with low radioiodine uptake are discussed in more detail in Chapter 5. A variable proportion of patients have antithyroid antibodies in the circulation. Antimicrosomal antibodies are found more often than antithyroglobulin antibodies. Different authorities have published quite disparate results, and this is explained by different assay techniques [87]. When sensitive radioimmunoassays are used, almost all patients have antibodies. It is usually not necessary to

obtain antibody measurements, but in the case of factitious hyperthyroidism they are usually absent (unless the patient has autoimmune thyroid disease in addition). The course of the disorder can be followed clinically and with judicious use of FT_4 and TSH measurements.

As the disease remits, the thyroid's ability to trap iodine returns to normal and can rebound above normal. It is not necessary, however, to do serial uptake measurements. When ^{123}I uptake is ordered in a postpartum patient, breastfeeding must be stopped for at least 2 days. In this regard, Duong *et al.* [99] describe a lactating patient with postpartum thyroiditis in whom there was no thyroid uptake of ^{123}I, but there was significant breast uptake. After recovery, there was no breast uptake, but the thyroid was imaged normally.

The white blood count is normal and the ESR normal, or minimally increased. The latter contrasts with the values found in subacute thyroiditis. These measurements do not help to establish the diagnosis.

9.4.6 TREATMENT

Since the hyperthyroidism is mild and usually not protracted, treatment might not be required. Discussion with the patient that the nature of the problem is defined and the clinical course which it will take might be sufficient [100]. If the symptoms are severe enought to require treatment, beta-blockers, such as propranolol 20–40 mg 2 to 4 times a day, will provide relief. Subsequently, about 25–50% will become hypothyroid for weeks to months, and about one-half of these patients will need replacement therapy which, in a small number, will be permanent. Propylthiouracil has a minor peripheral effect by reducing the conversion of T_4 to T_3, but its major action is to inhibit synthesis of thyroid hormones. That action is not present in thyroid cells which are incapable of trapping iodine. Nikolai *et al.* [77] showed that propylthiouracil did not shorten the course of the hyperthyroid phase, whereas 4 weeks of prednisone did. They prescribed prednisone in a dose of 50 mg daily for the first week, and decreased the dose by 10 mg increments at weekly intervals. In spite of this evidence, because silent thyroiditis is generally of short duration and can be controlled symptomatically with beta-blockers, the use of steroids is not recommended [101], except in an unusually severe case. Thyroid suppression does not prevent repeated episodes. In exceptional cases where recurrences are frequent and troublesome, surgical removal of the gland is recommended [102, 103]. Alternatively, if the thyroid can trap sufficient iodine, radioiodine ablation will achieve the same goal. Obviously, this cannot be done during the hyperthyroid phase.

Because of the cyclical swings in thyroid function plus the possibility of permanent hypothyroidism, periodic clinical evaluation over the first several months will be necessary and a review at 1 year is advised.

9.5 ACUTE (SUPPURATIVE) THYROIDITIS AND THYROID ABSCESS

9.5.1 INTRODUCTION

Acute suppurative thyroiditis is extremely rare. One hypothesis why infective organisms seldom invade the thyroid is that the high iodine concentration acts as an antiseptic. Alternatively, the rich blood and lymph drainage prevent bacteria and other organisms remaining in the gland long enough to colonize it. Berger *et al.* [104] in an extensive review found 224 cases in the literature from 1900. Each of these patients had either abscess formation, or an infectious cause.

The onset of the disease is rapid and the local and constitutional features so severe that the patient is usually managed as an emergency, and may not see a thyroid specialist.

Table 9.6 Symptoms and signs of bacterial thyroiditis*

Symptom/sign	*% patients*
Pain	100
Tenderness	94
Fever	92
Dysphagia	91
Dysphonia	82
Erythema	82

* Adapted from reference 104.

9.5.2 AETIOLOGY

Acute thyroiditis is usually caused by bacteria, in particular staphylococcus, streptococcus, or pneumococcus, and there are isolated reports of salmonella [105], pseudomonas [106], *Escherichia coli* [107], mycobacteria [108, 109] and treponema [110] as causes. Fungal disease including actinomycosis [111, 112], coccidioidomycosis [113] and cryptococcus [114] are reported, and recent publications indicate that AIDS is an underlying factor in some of these patients. *Pneumocystis carinii* thyroiditis has been described in such a patient [115]. The infectious agent gains access to the gland by the blood, lymphatics, direct implantation, or through internal fistulae, such as a patent thyroglossal duct [116]. Occasionally, an upper respiratory infection, or infection elsewhere (prostatitis, pyelonephritis), precedes the thyroiditis by a few days. In some cases no good source is found.

9.5.3 CLINICAL PRESENTATION

There is rapid onset of severe pain in the neck, and the thyroid is tense and extremely tender. The pain can radiate to the jaw or ear. The skin of the anterior neck is hot and, in cases of true abscess formation, there is a fluctuant mass. As the abscess enlarges, it can cause stridor and dysphagia, the latter due to pain produced by movement of the thyroid while swallowing. Table 9.6 adapted from Berger *et al.* [104] lists the frequency of symptoms and signs. The patient is fevered and diaphoretic, has a tachycardia and chills and looks sick. Characteristically, the neck is flexed to prevent stretching of the strap muscles over the inflamed gland, and great care should be taken during examination of the neck to be gentle and not to extend the neck. A significant proportion of patients are children (approximately 40%) [117, 118], and pre-existing thyroid disease is said to be more frequent than expected [104].

Thrombophlebitis, septic emboli and septicaemia are serious complications. An enlarging abscess can track and rupture externally or internally into the trachea or mediastinum.

9.5.4 INVESTIGATIONS

The diagnosis is made clinically. The white cell count is elevated, (usually in the range of 15–20 000/mm^3) with a polymorphonuclear leukocytosis. The erythrocyte sedimentation rate is high. Thyroid function tests are usually normal, although there are reports of hyperthyroxinaemia [108]. Diagnosis and treatment should not await these results. A thyroid scintiscan is usually not necessary, but if done shows the abscess to be cold. This is one of the few settings in which I would use ^{99m}Tc pertechnetate because it will provide an image within minutes, and the ability of the thyroid to organify trapped iodine is moot. Kleinmann *et al.* [119] used scintigraphy to differentiate two patients who had neck abscesses not involving the thyroid by demonstrating normal thyroids on scintigrams. Real-time ultrasound has a role in determining whether there is true abscess formation [120], and it allows non-invasive evaluation of the neck veins for thrombophlebitis. A CT scan will seldom be required. Culture of pus obtained by needle aspiration will help to determine the most appropriate antibiotic(s).

Because the local and systemic features are

so pronounced, this disease is unlikely to be confused with other thyroid diseases, with the exception of subacute thyroiditis. The reader is referred to Table 9.2, which lists painful anterior neck and thyroid conditions. An abscess of the anterior neck has already been discussed as a potential differential diagnosis.

9.5.5 TREATMENT

The correct treatment is aspiration and/or surgical excision and drainage with microscopic examination and culture of the pus and parenteral antibiotics. Most cases do not recur. If there is a recurrence, it suggests an anatomical access to the thyroid, such as a patent thyroglossal duct. This should be defined and treated surgically. Rarely, resolution of the acute disease is followed by hypothyroidism [120], or hyperthyroidism [121]. The prognosis depends on correct, early diagnosis, drainage of the lesion and appropriate antibiotics.

9.6 RIEDEL'S THYROIDITIS (INVASIVE FIBROUS THYROIDITIS)

9.6.1 INTRODUCTION

Riedel's thyroiditis [122] is a very rare disease and many experienced thyroidologists have never seen a case. In two large surgical series, the condition was found in 37 out of 56 700 thyroidectomy specimens at the Mayo Clinic between 1920 and 1984 [92], and 2 out of 6571 thyroids examined pathologically by Lindsay *et al.* [123]. For some time there was debate whether this was a separate entity or a variant of Hashimoto's or De quervain's thyroiditis. There is no clinical, pathological, or immunological evidence that these diseases are in any way related. One exception to this sweeping statement is a single report of a patient who had subacute (de Quervain's) thyroiditis followed by Riedel's thyroiditis [124]. That patient also developed transient hypoparathyroidism. There is no clue to the aetiology of invasive fibrous thyroiditis and Levine states in 1983, 'Our knowledge has not advanced much further than that of Riedel' [125]. Although the drug methysergide has been associated with sclerosing fibrosis, especially retroperitoneal fibrosis [126], there appear to be no reports of it causing Riedel's thyroiditis.

9.6.2 PATHOLOGY

Woolner *et al.* [127] have defined three pathological hallmarks of this condition.

Firstly there is fibrosis, with the affected zone being tough, fibrous and woody. Secondly is an inflammatory fibrous process which extends beyond the gland into surrounding structures, including the strap muscles, trachea, oesophagus, veins and recurrent laryngeal nerves. Thirdly, microscopically the inflammatory fibrotic process causes almost complete destruction of the involved portion of the thyroid and there is no giant-cell reaction. To these Meijer and Hausman [128] have added a fourth, occlusive phlebitis. In some reports, only one lobe is involved and the other shows normal architecture.

9.6.3 CLINICAL PRESENTATION

The patient, usually middle-aged and female, most often seeks medical attention for a painless anterior neck mass which has grown rapidly. In some cases, it has been present for months. The mass causes pressure or a heaviness in the neck, and the invasive fibrosis can produce dyspnoea, a feeling of suffocation, or dysphagia by invasion of structures adjacent to the thyroid. On occasion, there is mild discomfort. There are no constitutional symptoms. The mass is rock hard and most frequently diagnosed clinically as cancer. Fixation to deep structures strengthen this impression. Less frequently, the clinician will make a diagnosis of subacute thyroiditis. However, the lack of pain

and tenderness and systemic manifestations are against that diagnosis. The thyroid, in the fibrous variant of Hashimoto's thyroiditis, is quite firm, but seldom has the hardness of Riedel's thyroiditis, and it almost always has discrete, well-defined edges. The majority of patients are euthyroid, but very rarely hyperthyroidism is present [136].

Riedel's thyroiditis is, on occasion, associated with fibrosis in other sites, including the mediastinum [129, 130] retroperitoneum, liver and biliary tract [131], and orbits [131–135]. I have seen a woman who presented at age 38 with a stony hard, somewhat painful swelling of the thyroid, which was causing local pressure effects. Open biopsy proved the lesion was Riedel's thyroiditis. Later she developed proptosis with palpable masses above and below the right eye which, on biopsy, were the fibrous variant of orbital pseudotumour.

The increased incidence in women is found in many publications: 5 to 1 [125], 6 to 1 [126], 3 to 1 [127], 3.1 to 1 [92].

9.6.4 INVESTIGATIONS

The diagnosis is established by surgical biopsy, which is usually necessary to exclude a diagnosis of cancer, and may be necessary to relieve pressure on the trachea. Hamburger [138] has cautioned against relying on a needle biopsy to make this diagnosis, because the fibrous tissue obtained can be found as a desmoplastic reaction in some cancers, or in the fibrous variant of Hashimoto's thyroiditis. Other investigations are not specific. Thyroid function tests are usually normal, although if there is sufficient destruction of the gland, hypothyroidism is to be expected. In a report from the Mayo Clinic 5 out of 20 patients were hypothyroid, but all with unilateral disease were euthyroid and remained so on follow-up [127]. Thyroid tests should be ordered to define the status of the patient. Raised levels of thyroid antibodies are not found, the sedimentation rate is usually normal, and thyroid scintigram shows no uptake in diseased areas. None of these tests helps establish or exclude the diagnosis.

9.6.5 TREATMENT AND OUTCOME

Although the gland is impressively hard and clinically ominous, the disease does not have a bad prognosis and is usually self-limiting, although a hard goitre persists. A surgical biopsy to establish the diagnosis can be coupled with an isthmusectomy to relieve pressure on the trachea. High doses of glucocorticosteroids have been recommended because of their apparent efficacy in treating fibrosis in other sites. Because Riedel's thyroiditis extremely rare, there are no controlled studies, but 2 out of 4 patients treated by Katsikas *et al.* [137] were dramatically improved by steroids. Therefore, if the diagnosis has been established and symptoms progressive, it is justifiable to prescribe high-dose steroids, such as prednisone 60–80 mg daily, the dose being tapered if a response is achieved. Not all clinicians have found steroids to be of value [139]. There is no role for external radiation or radioiodine. Thyroid replacement does not influence the course of the disease, but is required if the patient is hypothyroid.

9.7 RADIATION THYROIDITIS

Several days after radioiodine therapy, radiation thyroiditis can occur. The condition is similar to subacute thyroiditis with neck pain, which can be referred to the ear, jaw, or teeth [140]. The thyroid is tender on palpation and it is often swollen [141]. This complication is not common when the therapy is given to treat Graves' hyperthyroidism, and it is more likely to occur when a cancerocidal dose is prescribed to ablate a remnant of residual normal thyroid after surgery [142]. For example, a hyperthyroid patient treated to deliver 120, μCi/g tissue (9.6 mCi (361 MBq) to a 40 g gland with 50%

uptake) will get one-tenth of the thyroidal radiation compared to the patient who receives 100 mCi (3700 MBq) to ablate a 4 g remnant with 5% uptake. When radiation thyroiditis occurs, it usually results in permanent hypothyroidism [143]; and when the treatment is for thyroid cancer, thyroiditis predicts fairly reliably that thyroid tissue is ablated. Radiation thyroiditis probably only occurs when 20 000 rad (200 Gy) or more have been delivered to the thyroid. I have only seen it in relation to treatment of thyroid cancer, and the pain is controlled with aspirin, or non-steroidal anti-inflammatory drugs. If there is release of enough stored hormone to cause hyperthyroidism, beta-blockers should be prescribed. The problem is transient and recovery in 1–4 weeks is anticipated.

External radiation over the thyroid, prescribed to treat conditions such as Hodgkin's disease, produces a significant incidence of hypothyroidism [144], and this topic is discussed in detail in Chapter 13. Painful thyroiditis has not been described in this setting and would not be expected because the standard doses are 3500–4500 rad. Recently, Blitzer *et al.* [145] described two patients with a syndrome like silent thyroiditis with thyrotoxicosis and low uptake of radioiodine occurring shortly after anterior neck irradiation. Our group have confirmed this finding in three patients who were hyperthyroid clinically and biochemically, and had a low radioiodine uptake [146]. Two went on to become permanently hypothyroid, the third was transiently hypothyroid and returned to normal, but 18 months later developed classic Graves' hyperthyroidism with a high uptake of radioiodine. This type of radiation thyroiditis occurs 3–9 months after external radiation, and its incidence is not known because it is not common for thyroid function to be measured routinely at that time. Symptoms due to mild hyperthyroidism could easily be attributed to the underlying cancer, or to the radiotherapy *per se*. The cause is not known, but could be due to the radiation inducing an immunological thyroiditis.

KEY FACTS

- There are six discrete syndromes given the name thyroiditis.
- These diseases are not related genetically, aetiologically or clinically.
- **Hashimoto's thyroiditis** is also called chronic lymphocytic thyroiditis.
- Hashimoto's thyroiditis is very common, and there are more women with the disease than men (9 to 1).
- Antithyroid antibodies, both antithyroglobulin and antomicrosomal (antithyroperoxidase), are found in the serum.
- Goitre is considered by most to be a *sine qua non*.
- Hypothyroidism occurs in a proportion of patients with the passage of time.
- In mild cases, no treatment is necessary.
- When a goitre is large and/or when hypothyroidism is developing, treatment is with L thyroxine.
- There is an increased risk of other autoimmune diseases.
- There is a slight increase in lymphoma of the thyroid.
- **Subacute thyroiditis** is also called granulomatous and de Quervain's thyroiditis.
- It is presumed to be caused by viral infection.
- The disease is characterized by general ill health, severe pain over the thyroid and thyroid dysfunction.
- Thyroid dysfunction usually starts with thyrotoxicosis, followed by a normal period, then hypothyroidism with, finally, a return to normal.
- The diagnosis is clinical plus evidence of high FT_4 low TSH, low RAIU and high ESR.
- The treatment for pain is anti-inflammatory drugs, sometimes prednisone.

- The treatment of thyrotoxicosis is with beta-blockers.
- Treatment of hypothyroidism is with L thyroxine.
- **Silent thyroiditis** and **postpartum thyroiditis** appear to be identical clinically; only the setting differs.
- Most probably this is (these are) autoimmune.
- There is a sequence of thyrotoxicosis, normality, hypothyroidism and, finally, euthyroidism over a 3–6-month cycle.
- Sometimes thyroid dysfunction, especially hypothyroidism is permanent.
- It is important to consider this diagnosis, especially in the 3–6-months period after delivery.
- The diagnosis is by finding high FT_4, low TSH and low RAIU.
- Treatment of thyrotoxicosis is with beta-blockers, and hypothyroidism with L thyroxine.
- Recurrent episodes can occur in particular after subsequent pregnancies.
- **Acute thyroiditis** (thyroid abscess) is very rare.
- It is usually caused by bacteria, but fungi and protozoa can also be a cause.
- There is abrupt onset of thyroid pain, and severe constitutional symptoms.
- The diagnosis is made clinically.
- Aspiration of the lesion or surgical drainage is important.
- The organism is identified by culture. Intravenous antibiotics are given based on the best clinical judgement of the cause.
- In a recurrent episode, look for the portal of entry.
- In non-bacterial cases, consider dysfunction of the immunological system.
- **Riedel's thyroiditis** is also called invasive fibrous thyroiditis.
- Its cause is not known.
- It is extremely rare.
- It is sometimes found with other fibrosing conditions, such as mediastinitis and retroperitoneal fibrosis.
- Usually it is misdiagnosed as cancer.
- The diagnosis is clinical and by biopsy.
- There is no good treatment; prednisone can be tried and surgery may be necessary to relieve pressure.
- **Radiation thyroiditis** consists of two separate syndromes.
- One is similar to subacute thyroiditis, and occurs days to weeks after radioactive iodine.
- This is uncommon.
- The temporal relationship makes diagnosis easy.
- Treatment is with anti-inflammatory medications and, if necessary, prednisone.
- If thyrotoxicosis is present give beta-blockers.
- The second occurs after external neck irradiation.
- This is not common.
- It has a course similar to silent thyroiditis.
- Permanent hypothyroidism appears to be the common outcome.

REFERENCES

1 Hashimoto, H. (1912) Zur kenntniss der lymphomatosen veranderung der schildruse. *Arch. F. Klin. Chir.*, **97**, 219–48.
2 Volpe, R., Clarke, P.V. and Row, V.V. (1973) Relationship of age-specific incidence rates to immunological aspects of Hashimoto's thyroiditis. *Can. Med. Assoc. J.*, **109**, 898–901.
3 Fursyfer, J., Kurland, L.T., McConahey, W.M. *et al.* (1972) Epidemiological aspects of Hashimoto's thyroiditis and Graves' disease in Rochester, Minnesota (1935–67), with special reference to temporal trends. *Metabolism*, **21**, 197–204.
4 Witebsky, E., Rose, N.R., Terplan, K. *et al.* (1957) Chronic thyroiditis and autoimmunization. *JAMA*, **164**, 1439–47.
5 Roitt, I.M., Doniach, D., Campbell, P.N. *et al.* (1956) Autoantibodies in Hashimoto's disease (lymphadenoid goitre). *Lancet*, **2**, 820–1.
6 Khangure, M.S., Dingle, P.R., Stephenson, J.

et al. (1977) A long-term follow-up on patients with autoimmune thyroid disease. *Clin. Endocrinol.*, **6**, 41–8.
7 Fisher, D.A., Oddie, T.H., Johnson, D.E. *et al.* (1975) The diagnosis of Hashimoto's thyroiditis. *J. Clin. Endocrinol. Metab.*, **40**, 795–801.
8 Fatourechi, V., McConahey, W.M. and Woolner, L.B. (1971) Hyperthyroidism associated with histologic Hashimoto's thyroiditis. *Mayo Clin. Proc.*, **46**, 682–9.
9 Wyse, E.P., McConahey, W.M., Woolner, L.B. *et al.* (1968) Ophthalmopathy without hyperthyroidism in patients with histologic Hashimoto's thyroiditis. *J. Clin. Endocrinol. Metab.*, **28**, 1623–9.
10 Volpe, R. (1985) Autoimmunity in thyroid disease, in *Autoimmunity In Endocrine disease*, (ed. R. Volpe) Dekker, New York, pp. 109–286.
11 Volpe, R. (1986) Autoimmune thyroiditis, in *Werner's The Thyroid*, 5th edn, (eds, S.H. Ingbar and L.E. Braverman), J.B. Lippincott Company, Philadelphia, pp. 1266–91.
12 Wasnich, R.D., Grumet, F.C., Payne, R.D. *et al.* (1973) Graves' ophthalmopathy following external neck irradiation for nonthyroidal neoplastic disease. *J. Clin. Endocrinol. Metab.*, **37**, 703–13.
13 Moens, H. and Farid, N.R. (1978) Hashimoto's thyroiditis is associated with HLA-DRw3. *N. Engl. J. Med.*, **299**, 133–4.
14 Farid, N.R., Sampson, L., Moens, H. *et al.* (1981) The association of goitrous autoimmune thyroiditis with HLA-DR5. *Tissue Antigens*, **17**, 265–8.
15 Beierwaltes, W.H. (1969) Iodine and lymphocytic thyroiditis. *Bull. All. Ind. Inst. Med. Sci.*, **3**, 145–52.
16 Evans, T.C., Beierwaltes, W.H. and Nishiyama, R.H. (1969) Experimental canine Hashimoto's thyroiditis. *Endocrinol.*, **84**, 641–6.
17 Allen, E.M., Appel, M.C. and Braverman, L.E. (1986) The effect of iodide ingestion on the development of spontaneous lymphocytic thyroiditis in the diabetes-prone BB/W rat. *Endocrinol.*, **118**, 1977–81.
18 Woolner, L.B., McConahey, W.M. and Beahrs, O.H. (1959) Struma lymphomatosa (Hashimoto's thyroiditis) and related thyroid disorders. *J. Clin. Endocrinol. Metab.*, **19**, 53–83.
19 Tunbridge, W.M.G., Brewis, M., French, J.M. *et al.* (1981) Natural history of autoimmune thyroiditis. *Br. Med. J.*, **282**, 258–62.
20 Gordin, A. and Lamberg, B-A. (1975) Natural course of symptomless thyroiditis. *Lancet*, **2**, 1234–8.
21 Gordin, A. and Lamberg, B-A. (1981) Spontaneous hypothyroidism in symptomless autoimmune thyroiditis. A long-term follow-up study. *Clin. Endocrinol.*, **15**, 537–43.
22 Yamamoto, T. and Sakamoto, H. (1978) Spontaneous remission from primary hypothyroidism. *Ann. Intern. Med.*, **88**, 808–9.
23 Sung, L.C. and McDougall, I.R. (1978) Graves' hyperthyroidism: spontaneous occurrence after autoimmune hypothyroidism with persistent infiltrative ophthalmopathy *Arch. Intern. Med.*, **138**, 1009–10.
24 McDougall, I.R. and Bayer, M.F. (1980) Follow-up of patients with differentiated thyroid cancer using serum thyroglobulin measured by an immunoradiometric assay. Comparison with I–131 total body scans. *J. Nucl. Med.*, **21**, 741–4.
25 Perzik, S.L. (1976) *Surgery in Thyroid Disease: The Place for Total Thyroidectomy*, Stratton Intercontinental Book Corporation, New York.
26 Clark, O.H., Greenspan, F.S. and Dunphy, J.E. (1980) Hashimoto's thyroiditis and thyroid cancer: indications for operation. *Am. J. Surg.*, **140**, 65 –71.
27 Burke, J.S., Butler, J.J. and Fuller, L.M. (1977) Malignant lymphomas of the thyroid. A clinical pathologic study of 35 patients including ultrastructural observations *Cancer*, **39**, 1587–602.
28 Chak, L.Y., Hoppe, R.T., Burke, J.S. *et al.* (1981) Non-Hodgkin's lymphoma presenting as thyroid enlargement. *Cancer*, **48**, 2712–16.
29 Doniach, D., Roitt, I.M. and Taylor, K.B. (1963) Autoimmune phenomena in pernicious anaemia: serological overlap with thyroiditis, thyrotoxicosis, and systemic lupus erythematosus. *Br. Med. J.*, **1**, 1374–9.
30 Carmel, R. and Spencer, C.A. (1982) Clinical and subclinical thyroid disorders associated with pernicious anemia, *Arch. Intern. Med.*, **142**, 1465–9.
31 Becker, K.L., Ferguson, R.H. and McConahey, W.M. (1963) The connective tissue diseases and symptoms associated with Hashimoto's thyroiditis. *N. Engl. J. Med.*, **268**, 277–80.
32 Gamsky, T.E. and Chan, M.K. (1988) Coexistent dermatomyositis and autoimmune thyroiditis. *West. J. Med.*, **148**, 213–14.
33 Dent, R.G. and Edwards, O.M. (1978) Autoimmune thyroid disease and the polymyalgia

rheumatica–giant cell arteritis syndrome. *Clin. Endocrinol*, **9**, 215–19.
34 Marks, A.D., Channick, B.J., Adlin, V.A. *et al.* (1985) Chronic thyroiditis and mitral valve prolapse. *Ann. Intern. Med.*, **102**, 479–83.
35 Jordan, S.C., Johnston, W.H. and Bergstein, J.M. (1978) Immune complex glomerulonephritis mediated by thyroid antigens. *Arch. Pathol. Lab. Med.*, **102**, 530–3.
36 Jordan, S.C. Buckingham, B., Sakai, R. *et al.* (1981) Studies of immune complex glomerulonephritis mediated by human thyroglobulin. *N. Engl. J. Med.*, **304**, 1212–15.
37 O'Regan, S., Fong, J.S.C. Kaplan, B.S. *et al.* (1976) Thyroid antigen–antibody nephritis. *Clin. Immunol. Immunopathol.*, **6**, 341–6.
38 Hovarth, T., Teague, P., Gaffney, E.F. *et al.* (1979) Thyroid antigen associated immune complex glomerulonephritis in Graves' disease. *Am. J. Med.*, **67**, 901–4.
39 Churchill, D.N. and Farid, N. (1981) Proteinuria in Hashimoto's thyroiditis. *N. Engl. J. Med.*, **305**, 1286.
40 Mori, T., Fisher, J. and Kriss, J.P. (1970) Studies of an *in vitro* binding reaction between thyroid microsomes and long acting thyroid stimulator globulin (LATS): 1. Development of solid-state competitive binding radioassay methods for measurement of antimicrosomal and antithyroglobulin antibodies. *J. Clin. Endocrinol. Metab.*, **31**, 119–33.
41 Baker, J.R., Saunders, N.B., Wartofsky, L., Tseng, Y-Cl. and Burman, K.D. (1988) Seronegative Hashimoto thyroiditis with thyroid autoantibody production localized to the thyroid. *Ann. Intern. Med.*, **108**, 26–30.
42 Ramtoola, S. Maisey, M.N., Clarke, S.E.M. *et al.* (1988) The thyroid scan in Hashimoto's thyroiditis: the great mimic. *Nucl. Med. Comm.*, **9**, 639–45.
43 Gray, H.W., Thomson, J.A. Greig, W.R. *et al.* (1974) Intravenous perchlorate test in the diagnosis of Hashimoto's disease. *Lancet*, **1**, 335–8.
44 Braverman, L.E., Ingbar, S.H., Vagenakis, A.G. *et al.* (1971) Enhanced susceptibility to iodine myxedema in patients with Hashimoto's disease. *J. Clin. Endocrinol. Metab.*, **32**, 515–21.
45 Papapetrou, P.D., Lazarus, J.H., McSween, R.N.M. *et al.* (1972) Long-term treatment of Hashimoto's thyroiditis with thyroxine. *Lancet*, **2**, 1045–8.
46 Zimmerman, R.S., Brennan, M.D., McConahey, W.M. *et al.* (1986) Hashimoto's thyroiditis. An uncommon cause of a painful thyroid unresponsive to corticosteroid therapy. *Ann. Intern. Med.*, **104**, 355–7.
47 De Quervain, F. (1904) Die akute, nicht eiterige thyreoiditis und die beteiligung der schilddruse an akuten intoxikationen und infectionen uberhaupt. *Mitt. Grenzg. Med. u. Chir.*, **13**, (Suppl 2), 1–80.
48 Eylan, E., Zmucky, R. and Sheba, C. (1957) Mumps virus and subacute thyroiditis: evidence for a causal association. *Lancet*, **1**, 1062–3.
49 Volpe, R. (1986) Subacute thyroiditis, in *Werner's the Thyroid*, 5th edn, (eds S.H. Ingbar and L.E. Braverman), J.B. Lippincott Company, Philadelphia, pp. 1106–11.
50 Schonfield, P.M. and Keal, E.E. (1986) Subacute thyroiditis associated with *Chlamydia psittaci* infection. *Postgrad. Med. J.*, **62**, 33–4.
51 Strakosch, C.R. (1986) Thyroiditis. *Aust. NZ. Med.*, **16**, 91–100.
52 Volpe, R. and Johnston, M.W. (1957) Subacute thyroiditis: a disease commonly mistaken for pharyngitis. *Can. Med. Ass. J.*, **77**, 297–307.
53 Langevitz, P. and Cabili, S. (1983) Persistent vocal cord paralysis in subacute thyroiditis. *Postgrad. Med. J.*, **59**, 726–7.
54 Kallmeyer, J.C. and Hackmann, R. (1985) Vocal cord paralysis associated with subacute thyroiditis. *South Afr. Med. J.*, **67**, 1064.
55 Rottenberg, Z., Weinberger, I., Fuchs, J. *et al.* (1986) Euthyroid atypical subacute thyroiditis simulating systemic or malignant disease. *Arch. Intern. Med.*, **146**, 105–7.
56 Farrell, A. and McKenna, J. (1987) Thyrotoxicosis, subacute thyroiditis and thyroid pain in Ireland. *Ir. Med. J.*, **80**, 55–7.
57 Kitchener, M.I. and Chapman, I.A. (1989) Subacute thyroiditis: a review of 105 cases. *Clin. Nucl. Med.*, **14**, 439–42.
58 Tajima, K., Mashita, K., Yamane, T. *et al.* (1984) Thyrotoxic myopathy associated with subacute thyroiditis. *Clin. Endocrinol.*, **20**, 307–12.
59 Tikkaenen, M.J. and Lamberg, B-A. (1982) Hypothyroidism following subacute thyroiditis. *Acta Endocrinol.*, **101**, 348–53.
60 Hamburger, J.I. (1984) Subacute thyroiditis: diagnostic difficulties and simple treatment. *J. Nucl. Med.*, **15**, 81–9.
61 Bauman, A. and Friedman, A. (1983) Recurrent subacute thyroiditis: a report of three cases. *N.Y. State J. Med.*, **83**, 987–8.
62 Cutler, M. (1954) Treatment of subacute thyroiditis with corticotropin. *JAMA*, **155**, 650–1.
63 Geva, T. and Theodor, R. (1988) Atypical

presentation of subacute thyroiditis. *Arch. Dis. Child.*, **63**, 845–6.
64 Tibaldi, J.M., Shapiro, L.E. and Mahadevia, P.S. (1986) Thyroiditis mimicked by metastatic carcinoma to the thyroid. *Mayo Clin. Proc.*, **61**, 399–400.
65 Endo, Y. (1981) Subacute thyroiditis of aberrant thyroid gland. *JAMA*, **245**, 1632.
66 Blum, M. and Schloss, M.F. (1984) Martial-arts thyroiditis. *N. Engl. J. Med.*, **311**, 199–200.
67 Guarda, L.A. and Baskin, H.J. (1987) Inflammatory and lymphoid lesions of the thyroid: cytopathology by fine-needle aspiration. *Am. J. Clin. Path.*, **87**, 14–22.
68 Sanders, L.R., Moreno, A.J., Pittman, D.L. *et al.* (1986) Painless giant cell thyroiditis diagnosed by fine needle aspiration and associated with intense thyroidal uptake of gallium. *Am. J. Med.*, **80**, 971–5.
69 Seder, J., Shimshak, R. and Williams, R. (1979) Reversible 67 gallium citrate uptake in the thyroid with subacute thyroiditis. *Clin. Nucl. Med.*, **4**, 158–60.
70 White, W.B., Spencer, R.P., Szlikas, J.J. *et al.* (1984) Incidental finding of intense thyroid radiogallium activity during febrile illness. *Clin. Nucl. Med.*, **10**, 710–14.
71 Madeddu, G., Casu, A.R., Costanza, C. *et al.* (1985) Serum thyroglobulin levels in the diagnosis and follow-up of subacute 'painful' thyroiditis. *Arch. Intern. Med.*, **145**, 243–7.
72 Clark, D.E., Nelsen, T.S. and Raiman, R.J. (1953) Subacute nonsuppurative thyroiditis treated with cortisone. *JAMA*, **151**, 551–2.
73 Wartofsky, L. and Schaaf, M. (1987) Graves' disease with thyrotoxicosis following subacute thyroiditis. *Am. J. Med.*, **83**, 761–4.
74 Papapetrou, P.D. and Jackson, I.M.D. (1975) Thyrotoxicosis due to 'silent' thyroiditis. *Lancet*, **1**, 361–3.
75 Jackson, I.M.D. (1975) 'Hyperthyroiditis' a diagnostic pitfall. *N. Engl. J. Med.*, **293**, 661–2.
76 Nikolai, T.F., Brousseau, J., Kettrick, M.A. *et al.* (1980) Lymphocytic thyroiditis with spontaneously resolving hyperthyroidism (silent thyroiditis). *Arch. Intern. Med.*, **140**, 478–82.
77 Nikolai, T.F., Coombs, G.J., Mckenzie, A.K. *et al.* (1982) Treatment of lymphocytic thyroiditis with spontaneously resolving hyperthyroidism (silent thyroiditis). *Arch. Intern. Med.*, **142**, 2281–3.
78 Woolf, P.D. and Daly, R. (1977) Thyrotoxicosis with painless thyroiditis. *Am. J. Med.*, **60**, 73–9.
79 Woolf, P.D. (1980) Transient painless thyroiditis with hyperthyroidism: a variant of lymphocytic thyroiditis? *Endocr. Rev.*, **1**, 411–20.
80 Dorfman, S.G., Cooperman, M.T., Nelson, R.L. *et al.* (1977) Painless thyroiditis and transient hyperthyroidism without goiter. *Ann. Intern. Med.*, **86**, 24–8.
81 Gluck, F.B., Nusynowitz, M.L. and Plymate, S. (1975) Chronic lymphocytic thyroiditis, thyrotoxicosis, and low radioactive iodine uptake. *N. Engl. J. Med.*, **293**, 624–8.
82 Amino, N., Miyai, K., Yamamoto, T. *et al.* (1977) Transient recurrence of hyperthyroidism after delivery in autoimmune thyroiditis. *J. Clin. Endocrinol. Metab.*, **44**, 130–6.
83 Ginsberg, J. and Walfish, P.G. (1977) Postpartum transient thyrotoxicosis with painless thyroiditis. *Lancet*, **1**, 1125–8.
84 Hoffbrand, B.I. and Webb, S.C. (1978) Postpartum thyroiditis. *Postgrad. Med. J.*, **54**, 793–5.
85 Singer, P.A. and Gorsky, J.E. (1985) Familial postpartum transient hyperthyroidism. *Arch. Intern. Med.*, **145**, 240–2.
86 Goldman, J.M. (1986) Postpartum thyroid dysfunction. *Arch. Intern. Med.*, **146**, 1296–9.
87 Parker, M., Klein, I., Fishman, L.M. *et al.* (1987) Silent thyrotoxic thyroiditis in association with chronic adrenocortical insufficiency. *Arch. Intern. Med.*, **140**, 1108–9.
88 Volpe, R. and Johnston, M.W. (1957) Subacute thyroiditis: a disease commonly mistaken for pharyngitis. *Can. Med. Ass. J.*, **77**, 297–307.
89 Hamburger, J.I. (1986) The various presentations of thyroiditis. *Ann. Intern. Med.*, **104**, 219–24.
90 Hamburger, J.I. (1981) Are silent thyroiditis and postpartum silent thyroiditis forms of chronic thyroiditis, or different (new) forms of viral thyroiditis? in *Controversies in Clinical Thyroidology*, (eds J.I. Hamburger and J.M. Miller), Springer-Verlag, New York, pp. 21–30.
91 Vitug, A.C. and Goldman, J.M. (1985) Silent (painless) thyroiditis: evidence of a geographic variation in frequency. *Arch. Intern. Med.*, **145**, 473–5.
92 Hay, I.D. (1985) Thyroiditis: a clinical update. *Mayo Clin. Proc.*, **60**, 836–43.
93 Nikolai, T.F., Coombs G.J. and McKenzie, A.K. (1981) Lymphocytic thyroiditis with spontaneously resolving hyperthyroidism

and subacute thyroiditis. *Arch. Intern. Med.*, **141**, 1455–8.
94 Walfish, P.G. and Farid, N.R. (1982) Postpartum thyroid dysfunction. *N. Engl. J. Med.*, **307**, 1024–5.
95 Amino, N., Mori, H., Iwatani, Y. *et al.* (1982) High prevalence of transient thyrotoxicosis and hypothyroidism. *N. Engl. J. Med.*, **306**, 849–52.
96 Jansson, R., Bernander, S., Karlsson, A. *et al.* (1984) Autoimmune thyroid dysfunction in the postpartum period. *J. Clin. Endocrinol. Metab.*, **58**, 681–7.
97 Walfish, P.G. and Chan, J.Y.C. (1985) Postpartum hyperthyroidism. *Clin. Endocrinol. Metab.*, **14**, 417–47.
98 Mariotti, S., Martino, E., Cupini, C. *et al.* (1982) Low serum thyroglobulin as a clue to the diagnosis of thyrotoxicosis factitia. *N. Engl. J. Med.*, **307**, 410–12.
99 Duong, R.B., Fernandez-Ulloa, M. and Planitz, M.K. (1983) I-123 breast uptake in a young primipara with postpartum transient thyrotoxicosis. *Clin. Nucl. Med.*, **8**, 35.
100 Levine, S.N. (1983) Current concepts of thyroiditis. *Arch. Intern. Med.*, **143**, 1952–6.
101 Dorfman, S., Sachson, R. and Feld, S. (1982) The rationale for treatment of lymphocytic thyroiditis with spontaneously resolving hyperthyroidism: prednisone therapy v. chicken soup. *Arch. Intern. Med.*, **142**, 2261–2.
102 Gorman, C.A., Duick, D.S., Woolner, L.B. *et al.* (1978) Transient hyperthyroidism in patients with lymphocytic thyroiditis. *Mayo Clin. Proc.*, **53**, 359–65.
103 Nikolai, T.F. (1986) Silent thyroiditis, in *Werner's The Thyroid*, 5th edn, (eds S.H. Ingbar and L.E. Braverman), J.B. Lippincott Company, Philadelphia pp. 1098–106.
104 Berger, S.A., Zonszein, J., Villamena, P. *et al.* (1983) Infectious diseases of the thyroid gland. *Rev. Infect. Dis.*, **5**, 108–22.
105 Brenizer, A.G. (1951) Suppurative strumitis caused by *Salmonella typhosa*. *Ann. Surg.*, **133**, 247–52.
106 Weissel, M., Wolf, A. and Linkesch, W. (1977) Acute suppurative thyroiditis caused by *Pseudomonas aeruginosa*. *Br. Med. J.*, **2**, 580.
107 Saksouk, F. and Salti, I.S. (1977) Acute suppurative thyroiditis caused by *Escherichia coli*. *Br. Med. J.*, **2**, 23–4.
108 Kapoor, V.K., Subramani, K., Das, S.K. *et al.* (1985) Tuberculosis of the thyroid gland associated with thyrotoxicosis. *Postgrad. Med. J.*, **61**, 339–40.
109 Farrer, P.A. (1980) Caseating tuberculous granuloma of the neck presenting as an avascular 'cold' thyroid nodule. *Clin. Nucl. Med.*, **5**, 519.
110 Thomson, L. (1917) Syphilis of the thyroid. *Am. J. Syph.*, **1**, 179–91.
111 Leers, W.D., Dussault, J., Mullens, J.E. *et al.* (1969) Suppurative thyroiditis: unusual case caused by *Actinomyces naeslundi*. *Can. Med. Assoc. J.*, **101**, 714–18.
112 Arfeen, S., Boast, M.T. and Large, D.M. (1986) Unilateral thyroid swelling due to actinomycosis. *Postgrad. Med. J.*, **62**, 847–8.
113 Loeb, J.M., Livermore, B.M. and Wofsy, D. (1979) Coccidioidomycosis of the thyroid. *Ann. Intern. Med.*, **91**, 409–12.
114 Machac, J., Nejatheim, M. and Goldsmith, S.J. (1985) Gallium-167 citrate uptake in Cryptococcal thyroiditis in a homosexual male. *J. Nucl. Med. All. Sci.*, **29**, 283–5.
115 Gallant, J.E., Enriquez, R.E., Cohen, K.L. *et al.* (1988) *Pneumocystis carinii* thyroiditis. *Am. J. Med.*, **84**, 303–6.
116 Takai, S., Miyauchi, A., Matsuzuka, F. *et al.* (1979) Internal fistula as a route of infection in acute suppurative thyroiditis. *Lancet*, **1**, 751–2.
117 Schweitzer, V.G. and Olson, N.R. (1981) Thyroid abscess. *Otolaryngol. Head Neck Surg.*, **89**, 226–9.
118 Taylor, W.E., Myer, C.M., Hays, L.L. *et al.* (1982) Acute suppurative thyroiditis in children. *Laryngoscope*, **92**, 1269–73.
119 Kleinmann, R.E., Vagenakis, A.G., Abreau, C. *et al.* (1979) Anterior neck mass masquerading as acute suppurative thyroiditis, *J. Nucl. Med.*, **20**, 1051–2.
120 Elias, A.N., Kyan, T., Winikoff, J. *et al.* (1985) Acute suppurative thyroiditis. *J. Otolaryngol.*, **14**, 17–19.
121 Perloff, W.H. (1956) Thyrotoxicosis following acute thyroiditis: a report of five cases. *J. Clin. Endocrinol. Metab.*, **16**, 542–6.
122 Riedel, B.M.K.L. (1986) Die chronische, zur Bildung eisenharter Tumoren fuhrende Entzundung der Schilddruse. *Verh. Dtsch. Ges. Chir.*, **25**, 101–5.
123 Lindsay, S., Dailey, M.E., Friedlander J. *et al.* (1952) Chronic thyroiditis: a clinical and pathological study in 354 patients. *J. Clin. Endocrinol. Metab.*, **12**, 1578–99.
124 Chopra, D., Wool, M.S., Crosson, A. *et al.* (1978) Riedel's struma associated with subacute thyroiditis, hypothyroidism, and hypoparathyroidism. *J. Clin. Endocrinol. Metab.*, **46**, 869–71.
125 Levine, S.N. (1983) Current concepts of thyroiditis. *Arch. Intern. Med.*, **143**, 1952–6.
126 Kunkle, S. (1971) Fibrotic syndromes with

chronic use of methysergide. *Headache*, **2**, 1–5.

127 Woolner, L.B., McConahey, W.M. and Beahrs, O.H. (1957) Invasive fibrous thyroiditis (Riedel's struma). *J. Clin. Endocrinol. Metab.*, **17**, 201–20.

128 Meijer, S. and Hausman, R. (1978) Occlusive phlebitis, a diagnostic feature in Riedel's thyroiditis *Virch. Arch. A. Path. Anat. Histol.*, **377**, 339–49.

129 Raphael, H.A., Beahrs, O.H., Woolner, L.B. *et al.* (1966) Riedel's struma associated with fibrosing mediastinitis: report of a case. *Mayo Clin. Proc.*, **41**, 375–82.

130 Comings, D.E., Skubi, K.B., Van Eyes, J. *et al.* (1967) Familial multifocal fibrosclerosis. *Ann. Intern. Med.*, **66**, 884–92.

131 Bartholomew, L.G., Cain, J.C., Woolner, L.B. *et al.* (1967) Sclerosing cholangitis. Its possible association with Riedel's struma and fibrous retroperitonitis – report of two cases. *N. Engl. J. Med.*, **269**, 8–12.

132 Arnott, E.J. and Greaves, D.P. (1965) Orbital involvement in Riedel's thyroiditis. *Br. J. Ophthal.*, **49**, 1–6.

133 Amorosa, L.F., Shear, K. and Spiera, H. (1976) Multifocal fibrosis involving the thyroid, face and orbits. *Arch. Intern. Med.*, **136**, 221–3.

134 Sclare, G. and Luxton, R.W. (1967) Fibrosis of the thyroid and lacrimal glands. *Br. J. Ophthal.*, **51**, 173–7.

135 Schneider, R.J. (1976) Orbital involvement in Riedel's struma. *Canad. J. Ophthal.*, **11**, 87–90.

136 Greene, R. (1969) Riedel's disease. *Br. J. Clin. Prac.*, **23**, 261–3.

137 Katsikas, D., Shorthouse, A.J. and Taylor, S. (1976) Riedel's thyroiditis. *Br. J. Surg.*, **63**, 929–31.

138 Hamburger, J.I. (1980) The clinical spectrum of thyroiditis. *Thyroid Today* **3** (**4**), (ed. J.H. Oppenheimer).

139 Thomson, J.A., Jackson, I.D. and Duguid, W.P. (1968) The effects of steroid therapy on Riedel's thyroiditis. *Scot. Med. J.*, **13**, 13–16.

140 Chapman, E.M. (1971) Treatment of hyperthyroidism with radioactive iodine, in *Nuclear Medicine*, 2nd edn, (ed. W.H. Blahd), McGraw-Hill, New York, pp. 711–34.

141 Volpe, R., Schatz, D.L., Scott, A. *et al* (1960) Radioactive iodine in the treatment of hyperthyroidism. *Can. Med. Ass. J.*, **83**, 1407–13. *Idem* (1961) **84**, 37–42. *Idem* (1961) **84**, 84–7.

142 Freeman, M., Giuliiani, M., Schwartz, F. *et al.* (1969) Acute thyroiditis, thyroid crisis and hypocalcemia following radiactive iodine therapy. *N.Y. State J. Med.*, **69**, 2036–41.

143 Schwartz, T.B. (1970) Editorial comment, *Year Book of Endocrinology*, Year Book Medical Publishers Inc., Chicago, p. 160.

144 Constine, L.S., Donaldson, S.S., McDougall, I.R. *et al.* (1984) Thyroid dysfunction after radiotherapy in children with Hodgkin's disease. *Cancer*, **28**, 878–83.

145 Blitzer, J.B., Palozzi, F.P., Gottlieb, A.J. *et al.* (1985) Thyrotoxic thyroiditis after radiotherapy for Hodgkin's disease. *Arch. Intern. Med.*, **145**, 1734–5.

146 Petersen, M., Keeling, C.A. and McDougall, I.R. (1989) Hyperthyroidism with low radioiodine uptake after head and neck irradiation for Hodgkin's disease. *J. Nucl. Med.*, **30**, 255–7.

CHAPTER TEN

Simple goitre (non-endemic, non-toxic goitre) and multinodular goitre

10.1 INTRODUCTION

Simple goitre is one of the least simple thyroid disorders with particular regard to its pathogenesis. Henneman's [1] clinical definition of simple goitre as 'a benign, diffuse or multinodular enlargement of the thyroid of unknown etiology with normal hormone production occurring sporadically' is difficult to improve. Studer and Ramelli [2] have defined the condition 'as a slowly developing diffuse or nodular enlargement of the thyroid gland resulting from excessive replication of epithelial cells with subsequent generation of new follicles of widely differing structure and function'. By convention, goitres whose causes are known are not included under the term simple goitre. Therefore, Hashimoto's thyroiditis, euthyroid Graves' disease, iodine deficiency, and goitrogen induced goitre are excluded. Since differentiation of autoimmune thyroid disease with goitre from simple goitre depends on the presence, or absence, of antithyroid antibodies, the sensitivity of the assay will dictate how patients are classified.

The space allotted to this condition does no credit to its frequency. In the USA up to 5% of the population have this, and the prevalence varies from country to country. The cause is not clear and there may be multiple aetiologies which act in consort, or in different degrees, in different populations.

10.2 AETIOLOGY AND PATHOGENESIS

In Chapter 11, the role of iodine deficiency as a cause of endemic goitre is described. However, iodine lack cannot be implicated as a causal factor in simple goitre since the condition occurs in iodine-replete areas. Any theory about cause must be capable of explaining the following pathological findings in simple goitre. Firstly, there is an increase in the number of follicular cells and follicles [2, 3]. Secondly, the appearance of both the cells and the follicles are disparate from one area to another within the thyroid. This contrasts with the situation in Graves' disease where all cells are hypertrophied and follicles uniform in appearance and depleted of colloid. The changes in Graves's disease and other hyperplastic goitres are the result of strong stimulators of follicular cell function. Studer alone and with coinvestigators [4–6] hypothesize that the stimulatory factors in simple goitre are subtle and of long duration, so that populations of cells which are more sensitive to positive stimuli undergo hyperplastic changes and form outbuds and subsequently new follicles made up of progeny of these more active cells. As some follicles bud and grow more rapidly, others slowly increase in size and accumulate colloid. Therefore, an additional factor has to be implied, namely, disassociation of formation of colloid (and hormone) from its degradation and release. With the growth of some follicles and formation of new follicles at random sites, the blood supply which

starts by supplying all follicles uniformly becomes distorted. Some regions atrophy because of reduced blood supply, and haemorrhagic necrosis occurs in others. Bleeding can occur inside follicles and in extrafollicular connective tissue. These changes result in the development of fibrous tissue and scarring, which is also a characteristic finding. The laying down of fibrous bands then dictates how and where follicles can grow, thus changing the configuration from diffuse enlargement to nodular, and forming a multinodular goitre. In a series of experimental studies, Studer *et al.* [4, 5] has demonstrated that some follicular cells are more active then their neighbours and form new active follicles.

What causes the slow, subtle stimulus to growth? The first culprit could be TSH. Slightly increased levels could conceivably produce the changes described above. Why is there a raised TSH? The presence of mild goitrogens could interfere with normal thyroid hormone production and cause this, but the ubiquity of the simple goitre makes this hypothesis less probable. There is no evidence of slightly raised TSH values at the time the patient is seen with a nodular goitre, but it could be argued that high levels in the past started the sequence. The preponderance of women involved suggests a role of oestrogen and/or progesterone. Familial goitre points to an inherited defect, perhaps in one of the enzymes responsible for hormone synthesis. Complete absence of an enzyme causes goitrous hypothyroidism; incomplete deficiency could cause euthyroid goitre [7]. A somewhat related explanation has been promoted by Stanbury and Wang [8]. They point out that thyroglobulin is the largest protein molecule in the body, and its structure both intrinsically and three dimensionally is critical for the formation and subsequent release of thyroid hormone. Changes in the composition or tertiary structure of thyroglobulin could result in the production of thyroglobulin which does not contain thyroid hormones and might be formed in excess to that released. The potential for deranged amino acid sequence is great, and could be considered analogous to alterations in haemoglobin structure and their effects on red cell structure and function.

In the last decade, a body of data has been developed demonstrating growth stimulating factors which can cause hyperplasia of follicles without increase in function. Most prominent of these factors are immunoglobulins. Therefore, some simple goitres are immunologically mediated diseases, and should be considered as autoimmune in nature [9, 10]. Gaag *et al.* [11] found growth-stimulating immunoglobulins in 43 out of 62 patients with non-endemic goitre. The antibodies were found more often in patients with diffuse goitres and in those whose goitres recurred after surgery. The antibodies were not inhibited *in vitro* by TSH. Therefore, these antibodies, unlike TSI, are not directed against the TSH receptor. The methods for measurement vary, and this probably accounts for differences in sensitivity in reports. There are other growth factors, such as epidermal growth factor, but their roles are not defined in this situation.

In summary, the basic problem in simple goitre is the continued increase in the number of both follicular cells and follicles, which is not accompanied by an increase in function. Several possible ways for this to occur have been presented; they are not exclusive of one another, and one or any combination could play a role.

10.3 PATHOLOGY

The thyroid is enlarged and can be huge, weighing several hundred grams. Microscopically, there are combinations of small hyperplastic follicles and large ones with abundant colloid. There is an increase in fibrous tissue and evidence of recent and old haemorrhage.

10.4 CLINICAL PRESENTATION

Frequently, the goitre is noted in the course of a physical examination for some unrelated reason. The goitre can be diffuse or nodular. By convention, thyroids less than 40 g have been termed small and those greater than 40 g large [12]. Some small goitres are nodular, which is difficult to understand based on the explanation of pathogenesis given above. However, in general, as the thyroid enlarges the incidence of nodularity increases. Is a palpable thyroid enlarged? In a linebacker (in Europe read prop forward) it most probably is, but in a 95 lb ballerina it can be normal. Extensive experience of palpating thyroids in patients with known thyroid disorders, as well as in normal people, will help the clinician to differentiate between them, but in some patients it is impossible to determine with certainty whether a palpable gland is normal or not. As the gland enlarges it can be noted by the patient or seen by friends and relatives. As the goitre enlarges, symptoms are noted with increasing frequency. Very large goitres cause a feeling of pressure, tightness, and difficulty in breathing or swallowing. In nodular goitre a prominent nodule raises concern of malignancy by both patient and physician. The reported incidence of malignancy in multinodular glands varies, but the most widely quoted figure, 1%, is probably accurate [13]. A single nodule on clinical examination should be evaluated as discussed in Chapter 7, but imaging techniques with high resolution often show other nodules, and the pathologist will confirm this in cases referred for surgery. The cosmetic effect of the goitre can be the presenting complaint.

10.5 DIAGNOSIS AND INVESTIGATIONS

The diagnosis of non-endemic simple goitre is usually apparent from a clinical examination. The patient, usually a woman, has an enlarged thyroid, with or without nodules, and appears euthyroid. Included in the differential would be Hashimoto's thyroiditis, Graves' disease with near normal thyroid status and other painless thyroiditides. In the case of simple nodular goitre, where one nodule is particularly prominent, the differential diagnosis of a single nodule has to be considered (Chapter 7). The clinician should try and resolve three facts: what is the thyroid function, is there a cause of the goitre and, in nodular cases, what is the potential for malignancy? The first is achieved easily by FT_4 and TSH. If these are normal, the patient is euthyroid. In cases where TSH is suppressed, the patients have subclinical hyperthyroidism and can progress to toxic nodular goitre. In the situation of normal FT_4 and suppressed TSH, I measure T_3 since a high T_3 explains the low TSH. The second question usually cannot be answered. I usually measure standard antithyroid antibodies (anti-Tg and antimicrosomal) by sensitive radioimmunoassay to establish, or exclude, Hashimoto's thyroiditis. Thyroid growth antibodies are not universally available, and even in the best research laboratories, the sensitivity of the test is in the range 60–70%. As a result I do not use the test. I believe it is not justifiable to embark on an expensive and elaborate work-up unless treatment will be altered. Therefore, in most cases where the patient has a small goitre and is euthyroid, I seldom order ultrasound, radionuclide scintigraphy, or do a fine-needle aspirate. To defend this approach we must ask what could be gained by doing these tests? Ultrasound shows the size and shape of the gland and will demonstrate nodules well. It cannot differentiate benign from malignant tissue, and seldom produces data that changes the clinical diagnosis. A radionuclide scan shows an enlarged gland and demonstrates than some of the nodules are functioning and some not. This usually does not extend what is already known. In nodular goitres, the demonstra-

tion of functioning nodules is of value. In multinodular goitre where the incidence of cancer is low, is it possible to justify biopsy of all palpable nodules? What about the nodules that are not palpable? Biopsy should be reserved for patients with a dominant or suspicious nodule. Therefore, the third question is answered by clinical judgement and in selected cases FNA of dominant nodules.

In patients with pressure symptoms, a plain roentgenogram of the trachea and thoracic inlet, and a barium swallow and, in selected cases, a CT scan and ENT opinion can be useful. The tests help to determine whether goitre and symptoms are cause and effect. In some patients, it is difficult to accept that a small goitre is the cause of symptoms, such as tightness of the neck, and the clinician must ask, is the size, consistency and position of the goitre unequivocally capable of producing the symptoms? If not, the additional studies help to clarify whether the thyroid, or some other factor, is causal. Trotter [14] states that simple goitre does not cause dysphagia, and although this is not 100% true, it does make an important clinical point that other causes of this symptom should be exduded.

10.6 TREATMENT

Most patients with simple goitre do not seek medical attention and do not appear to come to much harm as a result. If a small, diffuse goitre is found serendipitously and the patient is euthyroid and there is no concern of thyroid malignancy, it is reasonable to prescribe no therapy. By contrast, Burrow [15] believes that thyroxine should be prescribed in most cases. Certainly, in patients who are euthyroid and have diffuse goitre, this is acceptable and, in some cases, the goitre regresses. In contrast, by the time the gland is nodular it is unlikely that suppression of TSH will help, since some of the nodules are autonomous and others so scarred that shrinkage would not be expected. This therapy should not be prescribed if there is clinical or biochemical evidence of hyperthyroidism, including a suppressed TSH. Therefore, thyroid testing should be done first. In cases of very large goitre which cause pressure symptoms, the best treatment is surgery. After operation it is reasonable to prescribe enough thyroxine to suppress TSH in the hope that if TSH was the growth stimulus, this will prevent recurrence. I am not aware of a trial proving this point.

Should non-toxic goitre be treated with radioiodine? I have not done so, but there is a report of its benefit [16]. The problems with this include the small but real risk of missing a thyroid cancer, and the more important problem of delivering enough radiation to cause shrinkage. For example, if the goitre is 200 g and the 24 hour uptake is 15%, and the therapist wishes to deliver 200 μCi/g, the prescribed dose would be about 250 mCi! In this example, I have taken a fairly large gland with a fairly low uptake to illustrate the problem of dosimetry, but the numbers are realistic. In selected patients, in whom operative risk is considered to be significant and in whom there is good uptake of a tracer dose of iodine, this approach could be considered.

10.7 SUBSTERNAL GOITRE

Goitres with their lower poles inferior to the thoracic inlet are called substernal. If the gland lies in its entirety below the thoracic inlet, it is termed intrathoracic. Higgins [17] subdivided the latter into complete intrathoracic and partial intrathoracic. The former describes glands completely in the thorax, the latter those where 50% or more of the volume is intrathoracic. This description is somewhat artificial since the relationship of the thyroid to the thoracic inlet can be altered greatly by extension and flexion of the neck. Substernal goitres are usually

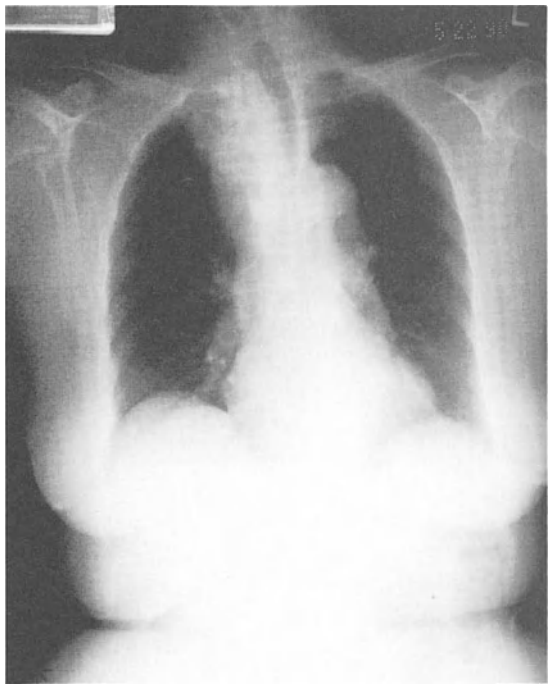


Figure 10.1 Chest roentgenogram showing a superior mediastinal mass deviating the trachea to the left. The appearance is characteristic of substernal goitre, but is not specific for that diagnosis.

non-toxic multinodular goitres, although other causes of goitre, including fetal adenoma and Hashimoto's thyroiditis, can produce the same result. The patient can be asymptomatic and the diagnosis made on clinical examination where the physician cannot palpate the inferior edge of an enlarged thyroid. More often, the abnormality is detected on a chest roentgenogram as a superior mediastinal mass (Figure 10.1). Some patients are symptomatic due to the size and pressure effects of the goitre and have dysphagia or dysphonia.

How does the thyroid reach the mediastinum? Almost every case shows communication with cervical thyroid. A minority of cases appear to be ectopic thyroid in the thorax, a topic covered in Chapter 1. The explanation for downward movement of goitre into the thorax include the following. The inferior border of the thyroid has no structures to inhibit expansion, and growth takes the path of least resistance. Once extension starts downward, it is helped by stretching of the gland by swallowing, and when the inferior border is in the thoracic inlet it is subjected to reduced intrathoracic pressure with inspiration. In addition, gravity could play a role. The writer is only partially convinced by these theories. In most patients, there is total continuity of the cervical thyroid with the substernal component, but in some the thoracic part is separate, but at operation can be seen to be connected by a band of fibrous tissue.

Substernal goitre is more common in women (3 or 4 to 1), and occurs most often in patients in the 50–70 age range [18–20]. When symptoms occur, they include difficulty in breathing, wheezing, difficulty in swallowing, a change in voice and hoarseness. On examination, the spectrum ranges from asymptomatic to patients in respiratory distress. The enlargement can be sufficient to obstruct venous return, and cause superior vena cava syndrome. In most series, the patients are euthyroid, e.g. 51 out of 52 evaluated by Katlic *et al.* [19] and 17 out of 18 of studied by lrwin *et al.* [21]. Although hyperthyroidism can occur with substernal toxic multinodular goitre, the frequency in early reports is based on clinical features without laboratory confirmation. It is not easy to determine thyroid status by examination of a patient distressed by stridor. In most large series, one or two of the patients were hypothyroid. It is sensible to measure thyroid function (FT_4 and TSH) to ensure that no patient is referred for operation with undiagnosed hyperthyroidism.

There are a variety of diagnostic tests which have been recommended to prove that the superior mediastinal mass is thyroid. In some patients, the clinical features

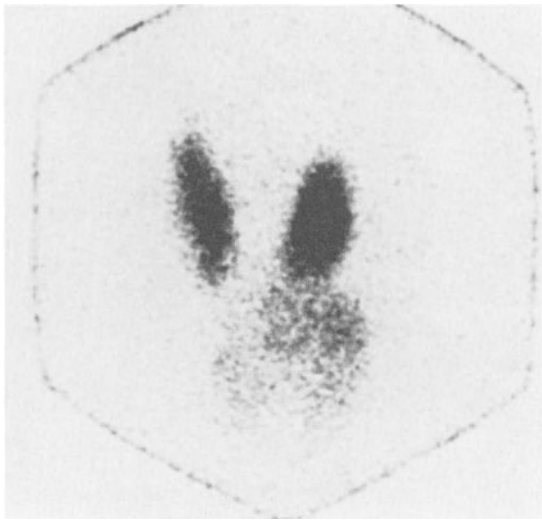


Figure 10.2 Iodine-123 scintigram made 3 hours after oral ingestion of 200 μCi ^{123}I. Scintiscan shows an irregular area extending from the inferior pole of the left lobe of the thyroid. This was substernal on clinical examination. The patient refused further work-up or therapy.

are so compelling that tests are not necessary, e.g. if there is a large cervical goitre that can be seen and felt to pass through the thoracic inlet. If there is uptake of radioiodine in a lesion seen on roentgenogram, it confirms the abnormality is thyroid tissue. Therefore, in cases where uncertainty exists, a radioiodine ^{123}I scintiscan is advised as the first test (Figure 10.2). Radioiodine scans have been successful in most investigators' experience. Irwin *et al.* [21] correctly diagnosed 20 out of 21 cases. These investigators used ^{131}I but, nowadays,^{123}I is preferred, because of the substantially lower radiation to the patient. In contrast, Sand *et al.* [22] found the scan was correct in only 58% of their patients. They provide no details of the technique. Technetium, which is used widely for thyroid scintigraphy, should *not* be used for radioisotopic imaging of this area, since background activity in vascular structures make delineation of thyroid tissue difficult. Computed tomography is very valuable and widely used to diagnose mediastinal and thoracic abnormalities, and it has been used with success in establishing that a mass was an intrathoracic goitre [23] (Figure 10.3). The clinician should be thoughtful about the sequence of testing. Computed tomography is not complete without contrast-enhanced images. Therefore, radioiodine scintigraphy must precede CT scanning, and if the former provides the correct diagnosis, the latter is superfluous.

Other tests, such as nuclear magnetic resonance imaging, barium swallow and ultrasound, may help in isolated cases but are usually not essential. Fine-needle aspiration is not advised because of the risk of bleeding in a clinically silent area, of collapse of the lung, and concern that the sample will not be representative since in most operative series the average size of the goitre has been 100–200 g.

Once the diagnosis is established, most authorities recommend surgery to remove the lesion. This is based on the following facts. The lesion usually continues to grow and if asymptomatic at presentation, it could well produce serious pressure effects in the future. Although the patients are usually about 60 years, this implies on average 10–20 years of life which could be jeapardized by non-operation. The surgery carries a low mortality and morbidity. Several series of 30–80 patients have no perioperative deaths, and complications were not troublesome. The beningnity of the lesion is not guaranteed, even when it has been present for many years. The incidence of carcinoma ranges from 2–10%. Some of these are occult carcinomas, but because of the clinically silent area they could grow unnoticed. The main reason for operation is to relieve pressure effects on the trachea and oesophagus.

An operation can usually be undertaken by a standard cervical approach. In one series, 78 out of 80 were successfully treated

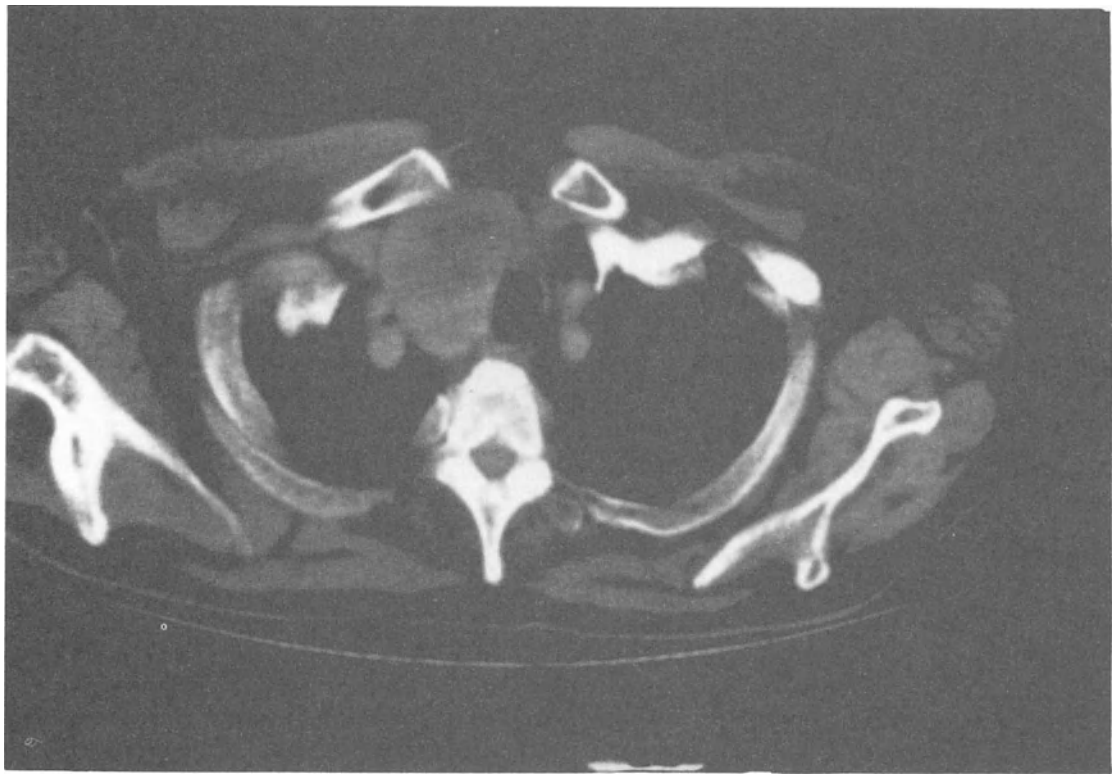


Figure 10.3 CT scan of the upper mediastinum showing the trachea deviated to the left by the right-sided substernal thyroid.

in this way, one required a partial upper sternotomy, and one a complete sternotomy [20]. The procedure is described in more detail by Katlic *et al.* [20].

Non-operative therapy with thyroid suppression is usually not valuable, because multinodular goitres seldom suppress. This treatment is certainly not advised when there are pressure symptoms. Thyroid should be prescribed for life after thyroidectomy in an effort to prevent recurrence, even although its efficacy has not been determined in a controlled study.

There are anecdotal reports of radioiodine therapy worsening symptoms, presumably by causing swelling of the goitre in an enclosed space. In contrast, Kay *et al.* [16] in their series of 14 patients treated with ^{131}I for non-toxic multinodular goitre had 8 with 'moderate degree of retrosternal extension but no patient studied had a predominantly retrosternal goiter'. These authors did not see any acute thyroid swelling after ^{131}I but advised careful observation in cases of retrosternal goitre and state 'high-dose corticosteroids could be used to reduce any chance of acute swelling'. This therapy should be reserved for patients who are considered to be poor operative risks. However, in most patients surgery is the recommended approach. There is no role for external radiotherapy.

KEY FACTS

- Simple goitre and non-toxic goitre are synonymous.
- A single cause of the condition is not clearly defined.
- By definition, goitre caused by diseases such as Graves' disease and Hashimoto's thyroiditis are not covered by this term.
- Iodine deficiency, goitrogens, TSH, autoimmune stimulators and genetic disposition have all been suggested as causal.
- Many cases might have several a etiological factors.
- One hypothesis states that some follicular cells grow and divide too rapidly, leading to formation of follicles whose cells have this characteristic.
- Diffuse goitre is the first sign.
- The patient is clinically and biochemically euthyroid.
- With time the thyroid becomes more enlarged and develops nodules.
- Some of the nodules function autonomously.
- Haemorrhage into the gland causes fibrosis and scarring.
- The end result is a multinodular goitre. In some cases, where there is significant autonomous tissue, the patient is thyrotoxic and the condition is called toxic multinodular goitre.
- FT_4 and TSH define thyroid status.
- Scintigraphy with ^{123}I shows nodularity and functional characteristics.
- Significant hypofunctioning nodules can be biopsied using fine-needle aspiration.
- In diffuse goitre, treatment with L thyroxine sometimes halts growth and can shrink the gland.
- Nodular goitre usually does not shrink with L thyroxine treatment.
- Large goitres causing pressure symptoms have to be removed.
- In older patients, there is a tendency for a nodular goitre to migrate inferiorly, and a proportion of the gland, or the entire gland, becomes substernal.
- ^{123}I scintigraphy is the best test for diagnosing substernal goitre.
- Treatment of substernal goitre is usually surgical.

REFERENCES

1 Henneman, G. (1979) Non-toxic goitre. *Clin. Endocrinol. Metab.*, **8**, 167–79.

2 Studer, H. and Ramelli, F. (1982) Simple goitre and its variants: euthyroid and hyperthyroid multinodular goitres. *Endocr. Rev.*, **3**, 40–61.

3 Studer, H. (1982) A fresh look at an old disease: euthyroid and hyperthyroid nodular goitre. *J. Endocri. Invest*, **5**, 57–68.

4 Studer, H., Peter, H.J. and Gerber, H. (1989) Natural heterogeneity of thyroid cells: the basis for understanding thyroid function and nodular goitre growth. *Endocr. Rev.*, **10**, 125–35.

5 Peter, H.J., Studer, H. and Groscurth, P. (1988) Autonomous growth, but not autonomous function, in embryonic thyroids: a clue to understanding autonomous goiter growth? *J. Clin. Endocrinol. Metab.*, **66**, 968–73.

6 Peters, H.J., Studer, H., Forster, R., *et al.* (1982) The pathogenesis of 'hot' and 'cold' follicles in multinodular goitres. *J. Clin. Endocrinol. Metabol.*, **55**, 941–6.

7 Lever, E.G., Medeiros-Neto, G.A. and De Groot, L.J. (1983) Inherited disorders of thyroid metabolism. *Endocr. Rev.*, **4**, 213–39.

8 Stanbury, J.B. and Wang, C-A. (1981) Nontoxic goiter, in *Thyroid Today*, (ed. J.H. Oppenheimer) **4**, 1–5.

9 Drexhage, H.A., Bottazzo, G.F., Doniach, D. *et al.* (1980) Evidence for growth stimulating immunoglobulins in some goitrous thyroid diseases. *Lancet*, **2**, 287–92.

10 Drexhage, H.A., Doniach, D., Bottazzo, G.F. *et al.* (1982) Detection and clinical significance of antibodies stimulating or blocking thyroid growth in disorders of the thyroid gland, in *Current Endocrine Concepts*, (ed. E.D. Williams), Praeger Publishers, London pp. 37–55.

11 van der Gaag, R.D., Drexhage, H.A. Wiersinga, W.M. *et al.* (1985) Further studies on growth-stimulating immunoglobulins in euthyroid nonendemic goiter, *J.Clin. Endocrinol. Metab.*, **60**, 972–9.

12 Kilpatrick, R., Milne, J.S., Rushbrooke, M. *et*

al (1963) A survey on thyroid enlargement in two general practices in Great Britain. *Br. Med. J.*, **1**, 29–34.
13 Sokal, J.E. (1960) The incidence of thyroid cancer and the problem of malignancy in nodular goiter, in *Clinical Endocrinology*, (ed. E.B. Astwood), Grune and Stratton, New York, p. 168.
14 Trotter, W.R. (1962) *Diseases of the Thyroid*, FA Davis Company, Philadelphia, pp. 133–43.
15 Burrow, G.N. (1989) Nontoxic goiter – diffuse and nodular, in *Thyroid Function and Disease*, (eds G.N. Burrow, J.H. Oppenheimer and R. Volpe), WB Saunders Co, Philadelphia, London, Toronto, Montreal, Sydney and Tokyo, pp. 141–51.
16 Kay, T.W.H., d'Emden, M.C., Andrews, J.T. *et al.* (1988) Treatment of non-toxic multinodular goiter with radioactive iodine. *Am. J. Med.*, **84**, 19–22.
17 Higgins, C.C. (1927) Intrathoracic goiter. *Arch. Surg*, **15**, 895–901.
18 Allo, M.D. and Thompson, N.W. (1983) Rationale for the operative management of substernal goiters. *Surgery*, **94**, 969–77.
19 Katlic, M.R., Wang, C-A and Grillo, H.C. (1985) Substernal goiter. *Ann. Thorac. Surg*, **39**, 391–9.
20 Katlic, M.R., Grillo, H.C. and Wang, C-A. (1985) Substernal goiter: analysis of 80 patients from Massachusetts General Hospital. *Am. J. Surg*, **149**, 283–7.
21 Irwin, R.S., Braman, S.S., Arvanitidis, A.N. *et al.* (1978) ^{131}I thyroid scanning in preoperative diagnosis of mediastinal goiter. *Ann. Intern. Med.*, **89**, 73–4.
22 Sand, M.E., Laws, H.L., McElvein, R.B. (1983) Substernal and intrathoracic goiter. Reconsideration of surgical approach. *Am. Surg.*, **49**, 196–202.
23 Glazer, G.M., Axel, L. and Moss, A.A. (1982) CT diagnosis of mediastinal thyroid. *A.J.R.*, **138**, 495–8.

CHAPTER ELEVEN

Iodine deficiency disorders, endemic goitre and endemic cretinism

11.1 INTRODUCTION

This chapter deals with conditions caused directly by dietary deficiency of iodine, and because the writer has worked in the west coasts of Scotland and California, both areas where iodine deficiency is rare, the text is based on published data, rather than personal experience. Iodine deficiency is a serious international health problem affecting about 400 000 000 people in Asia alone. It may cause only goitre, and the term endemic goitre is used when more than 10% of the population have enlargement of the thyroid. In many regions, a considerably higher percentage have this finding. Goitre alone is not a major health hazard, but local complications from goitre are problematic, and become more common as the size of the thyroid increases. In addition, thyroid dysfunction, in particular hypothyroidism in the population and in newborns, is a serious result of iodine deficiency. Hetzel [1] has recommended the use of the term iodine deficiency disorders (IDD) rather than endemic goitre, because the latter fails to impart the seriousness of the problem. Also, the term endemic goitre does not indicate the cause of the disease or its treatment [2].

11.2 AETIOLOGY

Iodine deficiency is the most important and common cause of endemic goitre. In some regions, local factors, such as goitrogens in water or food, inborn errors of hormone synthesis, or immunological factors, might play a role, but are relatively insignificant compared with iodine deficiency. Matovinovic [3] has provided a list of goitrogens which can aggravate the severity of iodine deficiency. Differences in the prevalence of goitre within a region are best explained by the addition of goitrogens. They include cassava, cabbage, kale, soybean, peanut, walnut and mustard. In spite of the additive role of goitrogens, evidence that iodine deficiency is *the most important factor* include the following. In all endemic goitre regions, dietary iodine is low. Normal thyroid function requires about 100 μg iodine daily, and the incidence of goitre increases directly as the daily iodine intake falls below 50 μg. In areas of greatly reduced intake (10–20 μg), goitre is universal and cretinism occurs. Direct measurement of iodine content in water and foodstuffs show low values. Patients have low plasma inorganic iodine levels, thyroid uptake is high, and urinary iodine low. All of these are reversed by adding iodine to the diet.

When the amount of dietary iodine falls below a critical level, the thyroid produces insufficient thyroid hormones, and the usual compensatory mechanisms try to correct this. TSH rises, and in virtually every series, the mean TSH value is higher than in control populations. The high TSH plus low plasma inorganic iodide lead to increased trapping of iodide and high thyroid uptake. Also as a

result of lower intrathyroidal iodine plus high TSH, there is increased formation of MIT and an increased ratio of MIT/DIT. This, in turn, results in an increased ratio of T_3 to T_4 in both thyroglobulin and the circulation. Since T_3 is metabolically more active than T_4, and since it contains less iodine, the arrangement is sensible. However, it results in the somewhat paradoxical finding of low, or low–normal T_4, elevated TSH and normal or high–normal T_3. Intuitively, a normal T_3 would be expected to produce a normal TSH. Evidence was presented in Chapter 2 that FT_4 was more important in dictating feedback at the pituitary because of its very active 5′ deiodinase. There are no good analyses of free hormone values in iodine deficiency, but by inference FT_4 should be low. TBG values are normal or high. Thyroglobulin values are high.

11.3 CLINICAL PRESENTATION

The commonest clinical finding is goitre. This finding *per se* need not be considered a major problem, and in some regions is considered by the native population to be normal. The fact that goitre is prevalent indicates that at some point thyroid hormone production was deficient in that proportion of the population to a degree that TSH secretion caused enlargement of the thyroid. Implicit with this is that biochemical hypothyroidism existed and, in some patients, clinical hypothyroidism could also exist or have been present. In population studies, all grades of thyroid function from normality to severe hypothyroidism are found. The goitre can reach considerable dimensions, and large ones tend to be nodular. Pressure effects on the trachea and oesophagus can result. Predominant nodules, some of which can be hard and cause local effects, have to be differentiated from thyroid cancer. There has been disagreement whether iodine deficiency causes, or is associated with, an increase in thyroid cancer. The body of opinion now supports an association: cancer is said to be about six times as common as in non-goitrous areas, and follicular and anaplastic cancers account for a higher proportion of the lesions compared with USA. Haemorrhage into a nodule causes sudden enlargement of the area, pain and pressure on adjacent structures.

The major clinical problem in iodine-deficient areas is cretinism, which is discussed below.

11.4 PROPHYLAXIS AND TREATMENT OF ENDEMIC GOITRE AND CRETINISM

Despite clear evidence that iodine deficiency is the major cause of endemic goitre and cretinism and that both can be eliminated by iodization, it is not possible to state that prevention has been achieved. Historically, iodine 'supplements' were used successfully 150 years ago, and there are anecdotal reports of the value of (iodized) salt in preventing goitre in the Inca population 500 years ago. The active ingredient of salt was not known, but its beneficial effects were. For an iodination programme to be successful, the affected community must recognize that there is a significant health problem and that the problem can be defined and treated. There must be political and financial willingness to embark on the project, and there has to be sufficient health practitioners to implement it. Positive feedback of the beneficial results are important to ensure enthusiastic continuation of the programme. Unfortunately, the very countries that are most in need of a programme are those where there is a lack of communication, and few medical practitioners or stable and willing legislators. Involved communities are isolated and there are no methods of disseminating information to the population. Thus implementation of an important public health measure is fraught with problems. There is convincing proof from all prophylactic trials in a wide variety of countries and regions that iodine supplements reduce the proportion of goit-

rous patients, and if given prior to pregnancy will eliminate cretinism [4, 5]. In addition, there is a general improvement of the intellect of schoolchildren and improved productivity in the community in general. There are three approaches to replenishing iodine. Firstly, to supplement salt with iodine, secondly, to give iodized oil by mouth, and thirdy, to give iodized oil by intramuscular injection. If the daily intake of salt is 10 g, 0.001% iodine provides 100 μg iodine. The major impediments to providing this to underdeveloped communities are cost, and ensuring that there is not a large competing industry supplying non-iodized salt. Lu and Ma [6] have shown that oral iodized oil is simpler, safer and cheaper than injected iodized oil. However, it is effective for a shorter time (6–30 months).

Injections of iodized oil, such as contrast agents like lipiodol or iodized poppyseed oil, provide patients with a prolonged supply of iodine. Four millilitres solution containing 2.15 g of iodine is adequate for 3–4 years as judged by urinary excretion of iodine. The material is absorbed slowly from the injection site and disappears with a half-life of 5–6 months. If any of these preparations are given before conception, cretinism in the offspring is prevented. It has been calculated that a programme of intramuscular injections costs a few pence per person per year – a small price to pay.

It could be argued that treatment should be with thyroxine. This would reverse the biochemical and clinical problems. However, the cost of this approach, plus the necessity to take medication regularly (daily or at least weekly), would limit the success of such a programme.

11.5 PROBLEMS OF IODIZATION PROGRAMMES

The major problems relate to planning, implementation and follow-up as discussed above. In addition, there are side-effects of the iodine which have to be recognized. The most important is iodine-induced hyperthyroidism (Jod Basedow hyperthyroidism). This is most likely to occur in patients having autonomous function, either nodular goitres or, less likely, Graves' disease. Prior to prescription of iodine there was insufficient iodine for the thyroid to produce enough hormone to cause hyperthyroidism. The complication is not commonly described in communities given prophylactic iodine, but it has to be kept in mind that these areas do not have ready access to skilled clinicians and cases may go unrecognized. In contrast to the enormous problem of hypothyroidism and cretinism, this potential problem should not be used as an arguement against an iodization policy.

11.6 WHO CLASSIFICATION FOR ENDEMIC GOITRE

- **Grade 0** Thyroid not palpable or, if palpable, not larger than normal.
- **Grade 1a** Thyroid distinctly palpable but usually not visible in a raised position; the thyroid is larger than normal, i.e. at least as large as the distal phalanx of the subject's thumb.
- **Grade 1b** Thyroid easily palpable and visible with the head in a raised position; the grade includes all patients with a discrete nodule.
- **Grade 2** Thyroid easily visible with the head in a normal position.
- **Grade 3** Goitre visible at a distance.
- **Grade 4** Monstrous goitre.

Such a classification is open to subjective interpretation, but it does allow for comparison of populations and evaluation of response to therapy.

Hetzel [4] has defined three groups of severity of iodine-deficiency diseases: Mild, in which 5–20% of schoolchildren have goitre; moderate, where up to 30% have goitre; and severe, where 30% or more have goitre. In these groups respectively, the urinary iodine in μg/g creatinine are more than 50, 25–50, and less than 25. The first is

improved by economic development and iodized salt, the last two require treatment with iodized oil as discussed above.

11.7 ENDEMIC CRETINISM

The derivation of the word cretin is not clear [7]. Hetzel [8] traced its definition to *Diderot's Encyclopedia* (1754) as 'an imbecile who is deaf, dumb, with a goitre hanging down to the waist'. A current definition formulated by the Pan American Health Organization is:

> an individual with irreversible changes in mental development, born in an endemic goiter area and exhibiting a combination of some of the following characteristics not explained by other causes.
>
> 1. Irreversible neuromuscular disorders.
> 2. Irreversible abnormalities in hearing, speech and leading in certain cases to deaf-mutism
> 3. Impairment of somatic development.
> 4. Hypothyroidism.

There are two distinct types of endemic cretinism, and both occur in regions where endemic goitre is prevalent. Although the prototype of each is characteristic, there is an overlap and it is more correct to consider a spectrum. One form of cretinism is the hypothyroid, or myxoedematous cretin. This is the type I learned about in medical school, and which comes to my mind when cretinism is discussed. However, it is less common in most series, except in reports from Zaïre. It has clinical similarities to sporadic cretinism of economically advanced countries. This form of endemic cretinism is thought to be due directly to deficiency of thyroid hormone in the fetus, which persists after birth. The other form has predominantly neurological deficits, and was well described by McCarrison [9] in India in 1908. Prominent features are severe mental deficiency, deafness, spastic diplegia, and squint. The infants are not very hypothyroid and probably were not hypothyroid *in utero*. Table 11.1 contrasts the clinical and laboratory findings in these forms of cretinism. Although both disorders are found in regions of iodine deficiency, their pathogeneses are different. The hypothyroid variety is associated with low levels of thyroid hormone and a high TSH. The baby or child looks hypothyroid and has dry skin, puffy features, periorbital oedema and markedly delayed somatic development. As stated above, this is less common [10]. In regions where controlled trials of correction of iodine deficiency have been undertaken, adequate replacement of iodine in the mother in the first 20 weeks of gestation almost entirely abolishes the hypothyroid variety. In contrast, thyroid function in those infants with neurological disease is near normal, and certainly different from those of the hypothyroid cretins. This syndrome is not abolished by treating the mother with iodine unless the iodine is given before conception or, at the latest, in the earliest weeks of pregnancy [11, 12]. The cause of this appears to be directly the result of iodine lack, not thyroid hormone lack on the developing brain. Animal models in rats and sheep support this hypothesis [10]. The mothers of babies with neurological features have large goitres, which trap iodine avidly and this strengthens the thesis that the fetus is starved of iodine and iodine deficiency *per*

Table 11.1 Comparison and contrast of myxoedematous and neurological cretins

Feature	*Myxoedematous*	*Neurological*
Hypothyroidism	Classic appearance	Normal
Stature	Small	Normal
Deaf mutism	Absent	Present
Cerbral diplegia	Absent	Present
Effect of thyroid	Improvement	None
Thyroid gland	Normal/large	Very large
Tests: T_4	Very low	Normal/low
TSH	Very high	Normal/high

se causes the disorder. Thyroid hormone replacement corrects the somatic abnormalities in the hypothyroid variety. However, intelligence is permanently impaired if the treatment is delayed for any length of time after birth. In addition, iodine replacement of these children reverses the biochemical and clinical features of hypothyroidism [13]. In contrast, the neurological features are irreversible and are not influenced by either thyroid hormone or iodine. Endemic cretinism is still found in New Guinea, Zaïre, Brazil, India, Pakistan, China and Mexico. For those interested in reviewing the topic in depth, there are excellent reviews [14–16], and monographs [17–19].

KEY FACTS

- Iodine-deficiency disorders are very common.
- Several hundred million people are affected.
- The main aetiological factor is iodine deficiency in the diet.
- In some regions goitrogens play a role.
- Iodine-deficient regions are usually far from the sea, often in the mountains or highlands, and frequently in areas where glaciers have stripped iodine-containing topsoil.
- Prevalence of goitre increases proportionally as the intake of iodine drops below 50 μg daily.
- Goitre can become nodular and can cause pressure effects.
- Hypothyroidism occurs and is also proportional to the decrease in iodine in the diet.
- Follicular cancer is more common.
- Cretinism is the major health hazard.
- There are two forms of cretinism, hypothyroid and neurological, although there is usually an overlap.
- The hypothyroid cretin looks myxoedematous, is small, often has a goitre, and has a low T_4 and high TSH.
- Hypothyroid cretinism is due to thyroid hormone deficiency.
- The neurological cretin is not myxoedematous, is of normal stature, has deaf mutism and cerebral diplegia, but thyroid tests are normal or borderline low.
- Neurological cretinism is due to iodine deficiency *in utero*.
- Iodine-deficiency disorders are preventable by providing sufficient dietary iodine (prophylaxis).
- In many situations, iodine deficiency persists because of social, political and economic factors.
- Treatment with depot iodine by injection or by mouth prevents goitre and reverses hypothyroidism, but not neurological problems.
- Iodine deficiency disorders are *major* international health problems.

REFERENCES

1 Hetzel, B.S. (1983) Iodine deficiency disorders (IDD) and their eradication. *Lancet*, **2**, 1126–9.
2 Editorial (1983) From endemic goiter to iodine deficiency disorders. *Lancet*, **2**, 1121–2.
3 Matovinovic, J. (1983) Endemic goiter and cretinism at the dawn of the third millenium, *Ann. Rev. Nutr.*, **3**, 341–412.
4 Hetzel, B.S. (1986) The concept of iodine deficiency disorders (IDD), in *Iodine Deficiency Disorders and Congenital Hypothyroidism*, (eds G. Medeiros-Neto, R.M.B. Muciel and A. Halpern), Ache, Sao Paulo, pp. 1–6.
5 Stanbury, J.B. (1986) Aspects of the clinical findings in endemic goiter, in *Iodine Deficiency Disorders and Congenital Hypothyroidism*, (eds S.G. Medeiros-Neto, R.M.B. Muciel and A. Halpern), Ache, Sao Paulo, pp. 7–14.
6 Lu, T.Z. and Ma, T. (1986) A clinical investigation in China on the use of oral versus intramuscular iodized oil in the treatment of endemic goiter, in *Iodine Deficiency Disorders and Congenital Hypothyroidism*, (eds G. Medeiros-Neto, R.M.B. Muciel and A. Halpern), Ache, Sao Paulo, pp. 103–9.
7 Pharaoh, P., Delange, F., Fierro-Benitez, R. *et al.* (1980) Endemic cretinism, in *Endemic Goiter and Endemic Cretinism. Iodine Nutrition in Health and Disease*, (eds J.B. Stanbury and B.S. Het-

zel), John Wiley and Sons Inc, New York, pp. 395–421.
8 Hetzel, B.S. (1971) The history of endemic cretinism. *Instit. Hum. Biol. Papua New Guinea Monograph Series*, **2**, 5.
9 McCarrison, R. (1908) Observations on endemic cretinism in the Chitral and Gilgit valleys. *Lancet*, **2**, 1275–80.
10 Hetzel, B.S. and Hay, I.D. (1979) Thyroid function, iodine nutrition and fetal brain development. *Clin. Endocrinol.*, **11**, 445–60.
11 Pharaoh, P.O.D., Buttfield, I.H. and Hetzel, B.S. (1971) Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. *Lancet*, **1**, 308–10.
12 Pharaoh, P.O.D., Buttfield, I.H. and Hetzel, B.S. (1972) The effect of iodine prophylaxis on the incidence of endemic cretinism. *Adv. Exp. Med. Biol.*, **30**, 201–21.
13 Vanderpas, J.B., Rivera-Vanderpas, M.T., Bourdoux, P. *et al.* (1986) Reversibility of severe hypothyroidism with supplemental iodine in patients with endemic cretinism. *N. Engl. J. Med.*, **315**, 791–5.
14 Pan American Health Organization (1974) *Endemic Goiter and Cretinism: Continuing Threats to World Health*, (eds J.T. Dunn and G.A. Madeiros-Neto), (PAHO Scientific Publication 292) Pan American Health Organization, Washington DC.
15 Stanbury, J.B. (1984) The pathogenesis of endemic cretinism. *J. Endocrinol. Invest.*, **7**, 409–19.
16 Medeiros-Neto, G. (1989) Endemic goiter and endemic cretinism, in *Endocrinology*, (ed. L.J. De Groot), Saunders, Philadelphia, pp. 746–57.
17 WHO (1979) *The Control of Endemic Goiter*, (eds E.M. De Maeyer, F.W. Lowenstein and C.H. Thilly), World Health Organization, Geneva.
18 Stanbury J.B. and Hetzel B.S. (eds) *Endemic Goiter and Endemic Cretinism. Iodine nutrition in Health and Disease*, John Wiley and Sons Inc, New York.
19 Medeiros-Neto, G., Muciel R.M.B. and Halpern A. (1986) *Iodine Deficiency Disorders and Congenital Hypothyroidism*, Ache, Sao Paulo.

CHAPTER TWELVE

Changes in thyroid function tests in physical and psychiatric diseases

12.1 INTRODUCTION

It has been recognized for some time that thyroid function abnormalities accompany non-thyroidal illness. When a test is abnormal, it generally implies abnormal function of the system tested. However, in the case of thyroid function tests, the abnormal results appear to be unrelated to altered thyroid function. One of the problems in being dogmatic about whether the tests alone are at fault as a result of ill health, is that there is no single, easily measured gold standard of thyroid function at the cellular level. In addition, clinical evaluation of sick patients does not always allow thyroid disease to be diagnosed, or excluded with certainty. The single best test of thyroid function as far as tissues are concerned is serum TSH, but even this is modulated by other factors apart from serum FT_4 and T_3 levels. The 5′ deiodinase in the thyrotrophe, which metabolizes T_4 to T_3, is not the same as the enzyme which has the same action and function in peripheral tissues. The former is not responsive to ill-health, whereas the latter is. As a result, the pituitary can react differently to other tissues in the course of non-thyroidal illness. In theory, measurement of TSH should be a reliable index of thyroid function, but factors such as dopamine and steroids lower the value. Whenever thyroid test result are found to be abnormal, the clinician first suspects thyroid dysfunction and responds by prescribing therapy. If the test are misleading and thyroid function normal, treatment is at best unnecessary, and at worst dangerous.

I have discussed the result under two major headings, organic illnesses and psychiatric illnesses, because the abnormal thyroid test results are somewhat disparate. The type and degree of abnormal tests are discussed and then suggestions as to the best tests which give the least inappropriate results. It is important for clinicians to determine from the patient's history and examination whether thyroid disease could be responsible for the degree of ill-health. Although thyroid disease is common, the vast majority of patients admitted as an emergency to hospital are euthyroid (probably more than 99%). Of those who actually have thyroid dysfunction, the thyroid problem is seldom the cause of the hospitalization, although it may contribute to the patient's ill health. Therefore, the physician should be selective about which patient should be tested, as well as about which tests are used.

12.2 ORGANIC NON-THYROIDAL ILLNESS

Any severe organic illness can affect the thyroid function test [1]. Abnormalities have been documented in patients with myocardial infarction, renal failure [2, 3], nephrotic syndrome [4], liver disease [5], diabetes [6], cancer, starvation [7, 8], endotoxin-induced fever [9], etc. The most frequent test

abnormality is a low T_3 [1, 10–13]. A low T_3 with a normal T_4 and TSH is called the low T_3 syndrome, but rather than being a distinct syndrome it is the mild end of a spectrum of findings in ill health [13]. This has been shown to be due to impaired action of 5′ deiodinase in peripheral cells. Therefore, T_4 is not converted to T_3. Concurrently, rT_3 values are high due to the reduced metabolism of rT_3 by the same enzyme, 5′ deiodinase. Free T_3 values are also low. It is almost guaranteed that T_3 is low and rT_3 high in sick, hospitalized patients. Do the test results help in diagnosis? It has been suggested that the ratio of rT_3 to T_3 can be used as an index of severity of ill-health. This is one setting where clinical examination is simpler and better. It is my perception that the tests do not help to prove a patient is sick, and they can only mislead clinicians into thinking that the patient is hypothyroid. To add further confusion, truly hyperthyroid sick patients have normal or low T_3 values. The degree of sickness is best determined by clinical examination, and T_3 and FT_3 should not be ordered in sick patients.

Futher along the spectrum of sickness, T_4 results can be low [13]. This is found when the illness is worse or more prolonged. As would be expected, the prognosis in patients with a low T_4 is poor, because of the underlying illness [14]. In our experience, about 50% of patients with a low T_3 have a low T_4, and most have normal TSH values. Therefore, they are not hypothyroid [15]. Many other investigators have found this combination of results [16–20]. A low T_3 and T_4 and normal TSH has been called the sick euthyroid syndrome but, again, it is stressed that this is not a disease, but part of the spectrum of abnormal test findings. There is no single explanation for the low T_4. Partly this is due to a fall in prealbumin. However, prealbumin only carries 10–20% of T_4 and little, if any, T_3. In addition, calculated FT_4I, which corrects for a degree of binding abnormalty, is also low in many sick patients [15, 16, 18]. Therefore, there must be another explanation for the finding, which is also noted in patients who take exogenous L thyroxine; thus reduced secretion of endogenous T_4 is not the explanation. Chopra *et al.* [21, 22] have promoted the theory that ill health produces an inhibitor which interferes with the binding of T_4 to the carrier proteins. The nature of the inhibitor has not been defined, but the concept is attractive. We know that free fatty acids interfere with T_4 binding to transport proteins, and this might be one of the factors. Reduced binding would cause a transient rise in FT_4 and loss of FT_4 in the urine. Some, but not all investigators, have found a rise in FT_4 which is consistent with the theory. Since T_4 and FT_4I are low in a significant proportion of sick patients who are euthyroid, it does not make sense to order these tests during the acute phase of non-thyroidal illness.

We have found that FT_4 measured by the *two-step assay* **usually** gives appropriate results as judged by clinical evaluation of the patient, prior history and subsequent course [15]. That is to say, in sick patients with no good evidence of thyroid dysfuction who on recovery are euthyroid have a normal FT_4 when they are sick. This is not true when one-step assays are done [23–28]. The one-step assays give low results which are no different from T_4 and FT_4I.

To confluse matters even more, high levels of T_4 have been found in euthyroid sick patients by some investigators [29]. This is a much less frequent occurrence than low levels as described above. One possible explanation is that the illness, especially if it involves damage to the liver, could release transiently excess binding proteins, which are synthesized in the liver, into the circulation and cause a rise in T_4 [30, 31].

Sick patients are likely to be given medications and to have radiological studies with iodine contrast agents. Many medications alter thyroid test results, and some actually alter thyroid function. Some alter the con-

centration of binding proteins, others the binding of hormones to the carrier proteins; some reduce the conversion of T_4 to T_3 and others interfere with the secretion of TSH. These have been discussed in Chapters 2 and 3. These only add more confusion and emphasize the need for selectivity in testing.

Wehman *et al.* [32] were the first to show that severe illness could produce low TSH values. We have confirmed this, but the finding is not consistent and much less common than low T_3 and T_4 [33]. In 22 brain-dead cardiac donors, serum TSH values were low (<0.3 μU/ml) in 5 patients. Since T_4 was below 5 μg/dl in 19 patients and T_3 below 90 ng/dl in 20, the low thyroid hormone values could not be attributed to depressed pituitary function. Paradoxically, elevated TSH values have been found in sick patients. Wong *et al.* [34] found that 13 out of 95 hospitalized patients had values of 10 μU/ml, or greater. The patients were elderly, (mean age 74 years) and that could have been a factor. We have found both suppressed and high TSH results in sick, apparently euthyroid, patients [35]. Heart transplant recipients and patients undergoing coronary artery bypass surgery were selected because of the severity of their illness. None had clinical evidence of thyroid dysfunction. In the latter group, the non-thyroidal illness was less severe and of shorter duration. Low TSH values were found in 21% and 7% of patients, and high values in 10% and 13% respectively. These findings were not due to the nature of the underlying problem because in 158 hospitalized patients, TSH was subnormal in 11% and above normal in 10% of patients who had no evidence of thyroid disease and had a normal FT_4. Again it is difficult to separate the role of the illness *per se*, from the effects of therapy on TSH values. It is easier to explain the changes in TSH due to exogenous factors than to serious illness. High doses of steroids suppress TSH, as does dopamine, and since these are commonly used in extremely ill patients, suppressed TSH would be expected. Perhaps high levels of endogenous steroids brought about by the illness suppress the pituitary. In some cases, the low TSH is probably an index of total body malfunction.

Many hospitalized patients have radiological studies with contrast agents, which have been shown to produce changes in thyroid function from subtle but statistically significant drops in T_4 and rises in TSH, to dramatic changes and clinically relevant disease.

In our investigations, we did not find a single patient with suppressed TSH and a high FT_4 due to sickness alone, and so this combination of tests can establish a diagnosis of hyperthyroidism. Likewise, we did not find a high TSH and low FT_4 due to sickness, and so this combination can be used to diagnose hypothyroidism. This is not to say that these combinations will never be found in euthyroid sick patients. TSH alone should not be used to establish whether a sick patient is euthyroid, or not. Likewise, total thyroid hormone measurements, in particular T_3 values, are frequently low in these settings and are of no use in defining thyroid status. In carefully determined clinical situations, if it is important to diagnose thyroid disease in a sick patient, FT_4 and TSH values interpreted together give the best index of thyroid function.

As a corollary, if FT_4 and TSH are normal, there is no reason to treat low T_3 and T_4 results. Even if FT_4 is low but TSH normal, there appears to be no evidence that replacement therapy is required; the appropriate therapy should be directed at the underlying non-thyroidal illness, although at this juncture the prognosis is poor.

12.3 PSYCHIATRIC ILLNESSES

Both hyperthyroidism and hypothyroidism can cause psychiatric problems. Original and later descriptions of toxic diffuse goitre

associated the onset of hyperthyroidism with psychological trauma [36, 37]. The typical psychiatric symptoms found in hyper- and hypothyroidism have been described in Chapters 5 and 6. In addition, some of the features of thyroid dysfunction can appear similar to those of psychiatric illness and vice versa. A tense, agitated, tremulous patient who has tachycardia and sweating should be considered to be hyperthyroid. The same symptoms and signs could be due to severe anxiety, substance abuse, or withdrawal from alcohol or drugs. It is fundamental in the management of patients with psychiatric complaints to ensure that there is no treatable organic cause. Therefore, it would seem that testing thyroid function in patients with acute psychiatric illness would be important clinically. Unfortunately, because the test results are often abnormal when no thyroid disorder exists, this is not the case. Many large series have shown a significant proportion of abnormal test results. However, on recovery from the psychiatric illness, the tests return to normal without treatment for thyroid dysfunction. Cohen and Swigar [38] found that FT_4I was high in 9% and low in 9% of 480 patients with a variety of psychiatric ilnesses. T_4 was increased in 13%. These investigators repeated testing in 31 patients and, of these, 27 showed a return to normality in approximately 2 weeks. The authors attribute the high FT_4 levels to a 'stress syndrome' with reduced binding capacity, and therefore high calculated free hormone levels. This does not explain the increased incidence of high total T_4 values.

We conducted a similar study in 645 patients hospitalized with acute psychiatric illnesses [39]. T_4 was high in 33% and FT_4I in 18% of patients FT_4I was high in 21% of patients with schizophrenia and major affective disorders, 25% of phencyclidine abusers (PCP) and 31% with miscellaneous functional psychoses. Dementia and major personality disorders were not associated with these findings. Twenty-two patients with a high FT_4I were studied on admission and on follow-up in more detail. Test results returned to normal without antithyroid therapy. T_4 fell from 13.95 ± 1.93 μg/dl to 9.33 ± 2.4 μg/dl, FT_4I from 6.15 ± 0.83 to 3.79 ± 1.1, and FT_4 from 2.43 ± 0.65 ng/dl to 1.38 ± 0.35 ng/dl. All of these changes are statistically highly significant. Serum T_3 was normal in 20 out of the 22 patients and low in 2. On follow-up, the T_3 results were lower in 17 and higher in 5. TSH values were normal, (0–6 μU/ml) but at the time of the study, sensitive TSH measurements were not available. Therefore, it is not possible to be certain if some values were truly low. Morley *et al.* [40] found 'hyperthyroid' values in amphetamine addicts.

Based on the results of these studies, it would appear that routine tests of thyroid function are misleading in patients with acute psychiatric diseases. There is no test which has high sensitivity and specificity. It would appear that the best approach is to examine the patient carefully, and if there is no goitre it is unlikely that hyperthyroidism is present. If hyperthyroidism is strongly suspected, at that juncture T_3 and radioiodine uptake are probably the most reliable tests. This differs from almost all other clinical situations. This combination of tests would not be justified for routine screening of all acute psychiatric patients. There is not enough data on sensitive TSH measurements at present to comment on their use. If the clinical suspicion is modest, it is prudent to wait until the psychiatric illness has improved, or 2–4 weeks before testing. We were surprised to find that not a single patient out of 645 had bona fide thyroid dysfunction, but this conclusion could only be reached by sequential studies.

I have left TRH testing for separate discussion. There is no doubt that some patients with psychiatric illnesses have a flat or blunted respone to TRH. This has led to the concept that the test can be used diagnosti-

cally to differentiate psychiatric disorders. However, flat responses have been described in endogenous depression [41, 42], alcoholism [43], schizophrenia [44, 45], and cocaine and heroin addicts [45]. In our series described above, the TSH response to TRH bore no relation to the type of psychiatric condition, or to the level of thyroid hormones. In the latter regard, it is different from the results in thyroid dysfunction. Baumgartner *et al.* [44, 45] conducted TRH tests on normal controls, and on depressed and schizophrenic patients. In patients the tests were done on admission and on recovery and in controls at approximately the same times. The increase in TSH from basal to peak value was used for analysis. The pre- and post-values in depression, schizophrenia and controls were 7.5 ± 4.9 to 7.9 ± 4.1, 6.9 ± 3.7 to 7.0 ± 1.6 and 9.5 ± 4.7 to 9.6 ± 5.9 respectively. These are not statistically different. The authors stress the importance of comparing patients with controls of the same age and sex. The rise in TSH normally decreases with age and normal elderly men can have flat responses. They also found that the test had no specific diagnostic value. A small proportion of patients had flat result but their underlying illnesses differed. TRH testing should not be used to diagnose psychiatric disorders because the sensitivity, specificity and positive predictive value are all low [46]. A high T_4 should not be a reason to treat a patient with an acute psychiatric disorder with antithyroid medications.

Discussion of the cause, or causes, of these changes has been left to last because they are not well defined. If the high T_4 and FT_4I values are due to increased pituitary function, TSH should be high. If the cause is autonomous excess function of the thyroid, TSH should be suppressed. Neither is correct; TSH values are mostly within normal. If the thyroid spontaneously released thyroid hormones, serum thyroglobulin would be elevated, but this was not found in a small number of patients we studied. Reduced conversion of T_4 to T_3 should result in low T_3 values as described above under physical illnesses, but this was not found. It appears that further investigations into the cause of these laboratory findings and whether they play any role in the cause of the psychiatric illness, or simply result from the illness, would be rewarding. Readers interested in reviewing the literature in more detail should proceed to the references of Baumgartner *et al.* [45] and Loosen [46], both articles having extensive bibliographies.

KEY FACTS

- Thyroid function tests can be altered by organic and psychiatric illnesses.
- In organic disease, the commonest finding is an inappropriately low T_3 level.
- T_3 is low in euthyroid sick and normal in hyperthyroid sick patients.
- In very ill patients, both T_3 and T_4 can be low in euthyroid patients.
- In extremely ill patients, FT_4 can be low.
- In extremely ill patients, TSH can be low.
- In most euthyroid sick patients, FT_4 by the two-step assay and TSH in combination are helpful.
- In most euthyroid sick patients, T_3 and T_4 give misleading results.
- In sick patients, thyroid tests should only be ordered if there is good reason to believe thyroid dysfunction is present, and that failure to diagnose and treat it would be harmful to the patient.
- In some illnesses, such as hepatitis and porphyria, T_4 can be inappropriately high.
- In acute psychiatric illness, T_4 FT_4I and even FT_4 can be elevated.
- In contrast to standard teaching, which states the one should rule out organic causes of psychiatric illness, this can be very difficult in the case of suspected hyperthyroidism.

- The best tests to prove euthyroidism in this setting are T_3 and TSH.
- If the suspicion of thyroid disease is low, the best strategy is to await treatment of the psychiatric disease and do thyroid tests (FT_4 and TSH) at that time.
- Lithium can cause hypothyroidism and goitre, in particular, in patients with thyroid antibodies. This is common.
- Lithium has been reported to cause Graves' disease and ophthalmopathy, but this is rare.

REFERENCES

1 Chopra, I.J., Hershman, J.M., Pardridge, W.M. *et al.* (1983) Thyroid function in nonthyroidal illness. *Ann. Intern. Med.*, **98**, 946–57.

2 Spector, D.A., Davis, P.J., Helderman J.H., *et al.* (1976) Thyroid function and metabolic state in chronic renal failure. *Ann. Intern. Med.*, **85**, 724–30.

3 Wassner, S.J., Buckingham, B.A., Kershnar, A.J. *et al.* (1977) Thyroid function in children with chronic renal failure. *Nephron*, **19**, 236–41.

4 Afrasiabi, M.A., Vaziri, N.D., Gwinup, G., *et al.* (1979) Thyroid function studies in the nephrotic syndrome. *Ann. Intern. Med.*, **90**, 335–8.

5 Walfish, P.G., Orrego, H., Israel, Y. *et al.* (1979) Serum triiodithyronine and other clinical and laborarory indices of alcoholic liver disease. *Ann. Intern. Med.*, **91**, 13–16.

6 Pittman, C.S. (1981) The effects of diabetes mellitus on thyroid physiology, in *Thyroid Today*, vol 4, no. 4,

7 Merimee, T.J. and Feinberg, E.S. (1976) Starvation-induced alterations of circulating thyroid hormone concentrations in man. *Metabolism*, **25**, 79–83.

8 Portnay, G.E., O'Brien, J.J., Bush, J. *et al.* (1974) The effect of starvation on the concentration and binding of thyroxine and triiodothyronine in serum and the response to TRH. *J. Clin. Endocrinol. Metab.*, **39**, 191–4.

9 Shafer, R.B., Oken, M.M. and Elson, M.K. (1980) Effects of fever and hyperthermia on thyroid function. *J. Nucl. Med.*, **21**, 1158–61.

10 Bermudez, F., Surks, M.I. and Oppenheimer, J.H. (1975) High incidence of decreased serum triiodothyronine concentrations in patients with nonthyroidal disease. *J. Clin. Endocrinol. Metab.*, **41**, 27–40.

11 Cavalieri, R.R. and Rapaport, B. (1977) Impaired peripheral conversion of thyroxine to triiodothyronine. *Ann. Rev. Med.*, **28**, 57–65.

12 Chopra, I.J., Solomon, D.H., Chopra, U. *et al.* (1978) Pathways of metabolism of thyroid hormones. *Recent Progr. Horm. Res.*, **34**, 521–67.

13 Nicoloff, J.T. (1989) Thyroid function in nonthyroidal disease, in *Endocrinology*, 2nd edn, (eds L.J. De Groot *et al.*), W.B. Saunders Company, Philadelphia, pp. 640–5.

14 Slag, M.F., Morley, J.E., Elson, M.K. *et al.* (1981) Hypothyroxinemia in critically ill patients as a predictor of high mortality. *JAMA*, **245**, 43–5.

15 Bayer, M.F. and McDougall, I.R. (1982) Free thyroxine by solid phase radioimmunoassay: improvement in the laboratory diagnosis of thyroid status in severly ill patients. Clin. *Chim. Acta*, **118**, 209–18.

16 Chopra, I.J., Solomon, D.H., Hepner, G.W. *et al.* (1979) Misleading low free thyroxine index and usefulness of reverse triiodothyronine measurement in nonthyroidal illness. *Ann. Intern. Med.*, **90**, 905–12.

17 Kaptein, E.M., Grieb, D., Spencer, C.A. *et al.* (1981) Thyroxine metabolism in the low T_4 state of critical nonthyroidal illness. *J. Clin. Endocrinol. Metab.*, **53**, 764–71.

18 Wood, D.G., Cyrus, J. and Samols, E. (1980) Low T_4 and low FT_4I in seriously ill patients: concise communication. *J. Nucl. Med.*, **21**, 432–5.

19 Vermack, W.J.H., Kalk, W.J. and Zakolski, W.J. (1983) Frequency of euthyroid sick syndrome as assessed by free thyroxine index and a direct free thyroxine assay. *Lancet*, **1**, 1373–5.

20 Kaplan, M.M., Larsen, P.R., Cranz, F.R. *et al.* (1982) Prevalence of abnormal thyroid function test results in patients with acute medical illnesses. *Am. J. Med.*, **72**, 9–16.

21 Chopra, I.J., Chua Teco, G.N., Nguyen, A.H. *et al.* (1979) In search of an inhibitor of thyroid hormone binding to serum proteins in nonthyroidal illnesses. *J. Clin. Endocrinol. Metab.*, **49**, 63–9.

22 Chopra, I.J., Solomon, D.H., Chua Teco, G.N. *et al.* (1982) An inhibitor of the binding of thyroid hormones to serum proteins is present in extrathyroidal tissues. *Science*, **215**, 407–9.

23 Kaptein, E.M., Macintyre, S.S., Weiner, J.M. *et al.* (1981) Free thyroxine estimates in nonthyroidal illness: comparison of eight methods. *J. Clin. Endocrinol. Metab.*, **52**, 1073–7.

24 Braverman, L.E., Abreau, C.M., Brock, P. *et al.* (1980) Measurement of serum free thyroxine by RIA in various clinical states. *J. Nucl. Med.*, **21**, 233–9.
25 Melmed, S., Geola, F.L., Reed, A.W. *et al.* (1982) A comparison of methods for assessing thyroid function in nonthyroidal illness. *J. Clin. Endocrinol. Metab.*, **54**, 300–6.
26 Chopra, I.J., Van Herle, A.J., Chua Teco, G.N. *et al.* (1980) Serum free thyroxine in thyroidal and nonthyroidal illnesses: a comparison of measurements by radioimmunoassay, equilibrium dialysis, and free thyroxine index. *J. Clin. Endocrinol. Metab.*, **51**, 135–43.
27 Slag, M.F., Morley, J.E., Elson, M.K. *et al.* (1981) Free thyroxine levels in critically ill patients: a comparison of currently available assays. *JAMA*, **246**, 2702–6.
28 McDougall, I.R. (1982) Limitations of free T_4 measurement, in *Free Hormones in the Blood*, (eds A. Albertini and R.P. Ekins), Elsevier Biomedical Press, Amsterdam, pp. 171–8.
29 Gavin, L.A., Rosenthall, M. and Cavalieri, R.R. (1979) The diagnostic dilemma of isolated hyperthyroxinemia in acute illness. *JAMA*, **242**, 251–3.
30 Stuart, D.D. and Schultz, A.L. (1978) Thyroid function tests simulating Graves' disease in alcoholic hepatitis. *Ann. Intern. Med.*, **89**, 514–15.
31 Schussler, G.C., Schaffner, F. and Korn, F. (1978) Increased serum thyroid binding and decreased free hormone in chronic active liver disease. *N. Engl. J. Med.*, **299**, 510–15.
32 Wehmann, R.E., Gregerman, R.I., Burns, W.H. *et al.* (1985) Suppression of thyrotropin in the low thyroxine state of severe nonthyroidal illness. *N. Engl. J. Med.*, **312**, 546–52.
33 Macoviak, J.A., McDougall, I.R., Bayer, M.F. *et al.* (1987) Significance of thyroid dysfunction in cardiac allograft procurement. *Transplantation*, **43**, 824–6.
34 Wong, E.T., Bradley, S.G. and Schultz, A.L. (1981) Elevations of thyroid-stimulating hormone during acute nonthyroidal illness. *Arch. Intern. Med.*, **141**, 873–5.
35 Bayer, M.F., Macoviac, J.A. and McDougall, I.R. (1987) Diagnostic performance of sensitive measurements of serum thyrotropin during severe nonthroidal illness: their role in the diagnosis of hyperthyroidism. *Clin. Chem.*, **33**, 2178–84.
36 Parry, C.H. (1825) *Elements of Pathology and Therapeutics*, vol 2, Crutwell, Bath, pp. 111–28.
37 Whybrow, P.C. (1986) Behavioural and psychiatric aspects, in *Werner's The Thyroid*, 5th edn, (eds S.H. Ingbar and L.E. Braverman), The Lippincott Company, Philadelphia, pp. 967–73.
38 Cohen, K.L. and Swigar, M.E. (1979) Thyroid function screening in psychiatric patients. *JAMA*, **242**, 254–7.
39 Spratt, D.I., Pont, A., Miller, M.B. *et al.* (1982) Hyperthyroxinemia in patients with acute psychiatric disorders. *Am. J. Med.*, **73**, 41–8.
40 Morley, J.E., Shafer, R.B., Elson, M.K. *et al.* (1980) Amphetamine-induced hyperthyroidism. *Ann. Intern. Med.*, **93**, 707–9.
41 Loosen, P.T. and Prange, A.J. (1980) Thyrotropin releasing hormone (TRH): a useful tool for psychoneuroendocrine investigation. *Psychoneuroendocrinol.*, **5**, 63–80.
42 Loosen, P.T. and Prange, A.J. (1982) Serum thyrotropin response to thyrotropin releasing hormone in psychiatric patients: a review. *Am. J. Psychiatry*, **139**, 405–16.
43 Loosen, P.T., Wilson, I.C., Dew, B.W. *et al.* (1983) Thyrotropin releasing hormone (TRH) in abstinent alcoholic men. *Am. J. Psychiatry*, **140**, 1145–9.
44 Baumgartner, A., Hahnenkamp, L. and Meinhold, H. (1986) The effect of age and diagnosis on thyrotropin response to thyrotropin releasing hormone (TRH) in psychiatric patients. *Psychiatry Res.*, **17**, 285–94.
45 Baumgartner, A., Graf, K-J., Kurten, I. *et al.* (1988) The hypothalamic-pituitary-thyroid axis in psychiatric patients and healthy subjects: parts 1–4. *Psychiatry Res.*, **24**, 271–332.
46 Loosen, P.T. (1988) Thyroid function in affective disorders and alcoholism. *Neurol. Clin.*, **6**, 55–82.

CHAPTER THIRTEEN

Radiation and the thyroid

13.1 INTRODUCTION

The thyroid is frequently investigated using a radionuclide of iodine and in some patients with hyperthyroidism or thyroid cancer, therapy involves radioiodine. In both of these situations, the gland is exposed to internal radiation. In the past, the thyroid was exposed to external radiation when head neck and chest lesions were treated (the range of doses was usually 500–1000 rad, 5–10 Gy) for reasons which are now not considered legitimate. There is unequivocal evidence that such doses of external radiation to the thyroid are responsible for producing an increase in the incidence of both benign thyroid nodules and thyroid cancer. Both internal and external radiation, if the dose is great enough, can cause hypothyroidism. The former includes patients treated with ^{131}I, the latter patients with cancers treated with 4000–5000 rad (40–50 Gy) in a field that includes the thyroid. This chapter reviews briefly the interaction of radiation with tissues, radioactive decay, radiobiology and dosimetry in a simple manner. Then published reports and personal clinical experience of the effects of various absorbed doses of external and internal radiation in producing thyroid disease are described.

13.2 RADIATION PHYSICS

Radiation can be divided into two categories, **electromagnetic and particulate**. There are two important forms of electromagnetic radiation, X-rays and gamma rays. Together these are also called photons. The only difference between these is that X-rays arise from electrons outside the nucleus, whereas, gamma rays are intranuclear in origin. X-rays can be man-made by accelerating a stream of electrons against a medium such as tungsten. When the charged electrons enter the electric field of the tungsten nuclei they decelerate rapidly and energy is given off as X-rays. This is also called **Bremsstrahlung** (breaking radiation) and this is the basis for the production of diagnostic X-rays. X-rays can also occur as a result of radioactive decay (see below). Gamma rays are given off by radioactive nuclides. The excess energy of the nucleus reaches the ground state by emmitting a gamma ray which carries off the energy. Photons have no mass, they have a waveform and travel at the speed of light, 3×10^{10} cm/s. The energy of a photon increases as the wavelength decreases.

From the point of view of the thyroidologist, the most important particulate radiation is the electron, which has a negative charge and is designated e^-. Another type of particulate radiation is the positron, or positive electron, e^+ which is of importance as radiation source in positron emission tomography (PET scanning). Others forms of particulate radiation are neutrons, alpha particles and pions, but these last three have little role in thyroidology. Subsequent discussion is limited to photons and e^-.

Photons produce their effects on tissues indirectly. They interact with molecules, most frequently water, since that is the main

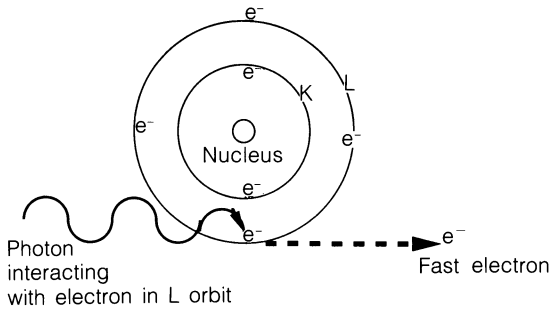


Figure 13.1 Photoelectron. Incident photon is totally absorbed and disappears. All of the energy is transmitted to the electron which has the energy of the photon – the energy of the L shell electron.

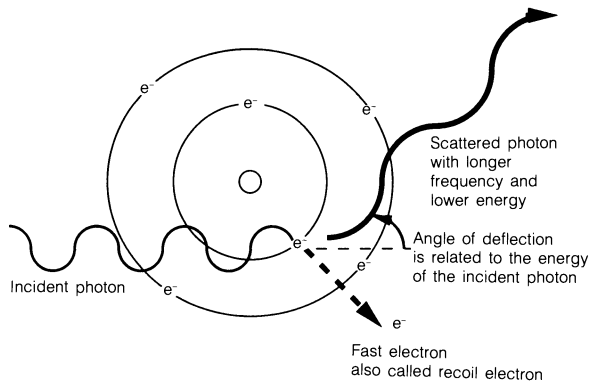


Figure 13.2 Compton electron.

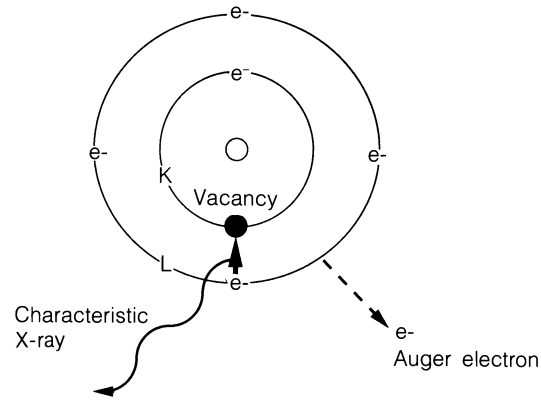


Figure 13.3 Auger electron or characteristic X-ray. As the electron moves from the L shell into the vacancy in the K shell, the excess energy is given off either as an Auger electron or as a characteristic X-ray.

constituent of the body. The photons can interact in several ways, but the three most common and important are photoelectric, Compton scatter and pair production. Of these, the first two are most important in biology, and they both result in the release of e^- from an atom. In the case of the photoelectron, the photon transfers all of its energy to an orbital electron and ejects that electron with an energy equal to the difference between the energy of the photon and the binding energy of the electron (Figure 13.1). The original photon disappears. In the second situation, Compton scatter, a Compton electron occurs when the incident photon imparts some, but not all of its energy, to an orbital electron. The electron is ejected and the photon is deviated from its original path and, since it loses energy, its wave frequency increases (Figure 13.2). Although the analogy of these interactions with billiard balls is helpful, the photon does not actually strike the electron in either case. The ejected e^- is called a fast electron and it, in turn, can produce effects which are described below. In addition, if the electron which is ejected is from an inner orbit, as is frequently the case, the vacancy has to be filled by an e^- from an outer orbit. Because the binding energy of the outer e^- is higher than the inner e^- the difference is dissipated either as an X-ray, or as a low-energy electron called an **Auger electron** (Figure 13.3). One other way that an electron can be ejected from its orbit is by a gamma ray imparting its energy to an electron of the same atom, so that the electron, not the photon, is emitted. This is called a conversion electron and is discussed below under radioactive decay.

The last common interaction of photons is pair production. This can only occur if the

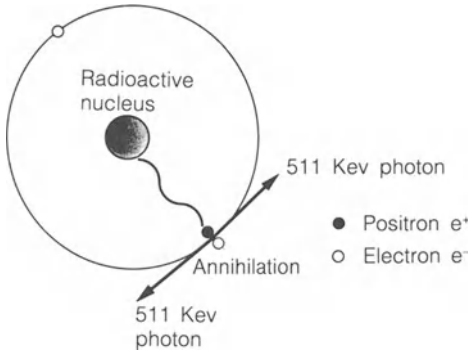


Figure 13.4 Pair production.

energy of the photon is greater than 1.022 Mev. None of the commonly used radionuclides emit photons with so high an energy. In this situation, the photon on entering the electric field of a nucleus disappears and the energy is converted into e^- and e^+. An electron has a mass equivalent of 0.511 Mev from the relationship of energy to mass

$$E = mc^2 \qquad \text{(equation 1)}$$

Mass is defined in relation to the carbon atom and 1 atomic mass unit (amu) is one-twelfth of a carbon atom. One amu is equivalent to 931 Mev of energy, and the mass of an electron 0.000549 substituted in equation 1 has an energy equivalence of 0.511 Mev. If the energy of the incident photon is greater than 1.022 Mev, the residual energy is divided between the photons as kinetic energy (Figure 13.4).

The interaction of photons with tissues is complex, e.g. a photon might produce a Compton electron by displacing a K shell electron. The electron will produce ionization. The incident photon is deflected and has less energy, and might now produce a photoelectron which, in turn, causes ionization. The vacancy in the K shell is filled by an L shell electron which can result in the production and release of an Auger electron, which produces further ionization.

When electrons interact with atoms or molecules, they produce ionization, or excitation. The latter is rare with the energy of electrons from radionuclides used in thyroidology, so we shall focus on the former. The incident electron, provided it has enough energy, displaces an orbital electron resulting in ionization (Figure 13.5(*a*)). The original electron is deflected and has its energy reduced by the binding energy of the displaced electron, which is termed a secondary electron. Both electrons are capable of producing similar events until their energies are lost. Electrons can produce Bremsstrahlung radiation in tissues (Figure 13.5(*b*)), but this is uncommon because of the low density of the medium. Charged particles travel less than photons and the distance travelled depends on their energy, mass and charge, and the medium through which the particles are travelling. The greater the energy, the further the charged particles travel. In contrast, as the mass or charge of the particle increases, the distance the particle travels decreases. Similarly, as the density of the medium increases, the distance penetrated decreases. Therefore, it can be deduced that an electron will penetrate further than a neutron on the basis of weight differential, and further than an alpha particle on the basis of weight and charge differential. Electrons in tissue have an irregular path due to their being deflected time and again by orbital electrons. As a result, their range is less than their path length. Since the range is dependent on energy, knowledge of the latter helps determine the former. However, few electrons are emitted with the maximum energy E^{max}, and the average energy E is about one-third of E^{max}. Electrons with energy of 100 Kev travel up to 200 micrometres in tissues.

It is necessary to discuss briefly types of radioactive decay, since this is relevant to the radionuclides used. There are three forms of radioactive decay: alpha, beta and gamma. Alpha emission is not important in thyroidology. It involves the emission of a

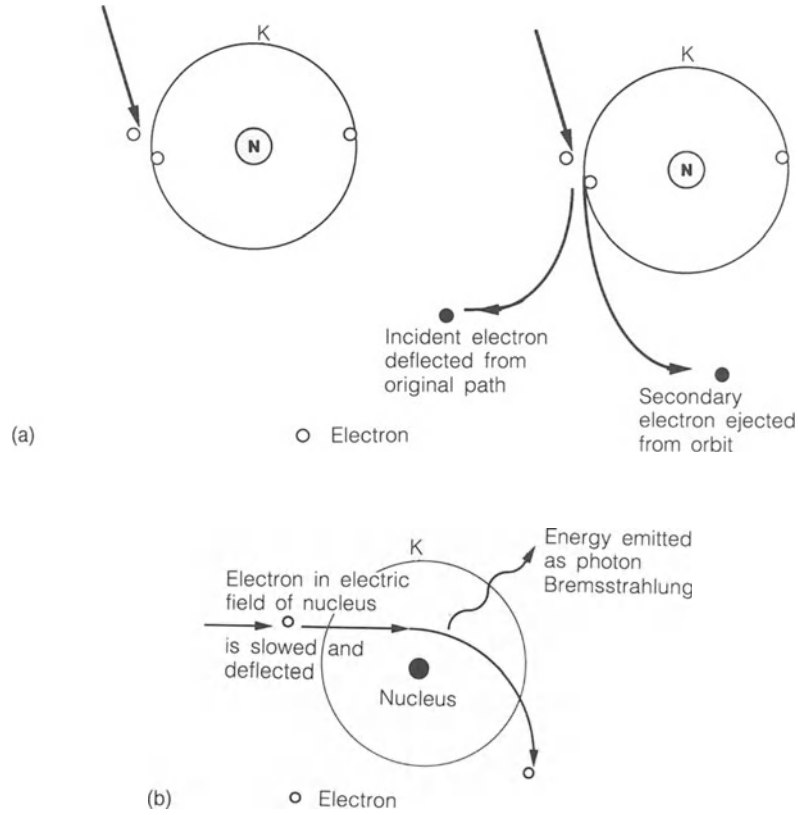


Figure 13.5 (*a*) Interaction of electron with atom; (*b*) Bremsstrahlung radiation.

helium nucleus (2 neutrons and 2 protons) from the radionuclide. Since a neutron and a proton each has a mass of 1, the parent nucleus loses 4 units of mass number. Neutrons have no charge, whereas protons have a charge of +1. Therefore, the daughter product has an atomic number of 2 less than the mother. This form of decay is found in radionuclides of a high mass number, such as radium.

$$\underset{88}{^{226}\text{Ra}} \rightarrow \underset{86}{^{222}\text{Rn}} \rightarrow \underset{84}{^{218}\text{Po}} \rightarrow \text{etc} \rightarrow \underset{82}{^{210}\text{Pb}}$$

Alpha particles because of their mass and charge travel extremely short distances in tissues, usually only a few micrometres.

There are three forms of beta decay: beta$^-$, beta$^+$, and electron capture. The last is sometimes called **inverse beta emission**.

In beta$^-$ decay, a nuclear neutron is converted into a proton, electron and antineutrino. The last is weightless and chargeless, and of no biological consequence. The electron is released from the nucleus. The daughter atom has the same mass as the radioactive mother, but its atomic number is increased by 1, since there is an additional proton present. Some radionuclides, after emitting a beta particle, still have a higher energy than the ground state and they emit the excess energy as gamma rays. This is called **beta-gamma decay**. Iodine-131 decays in this fashion.

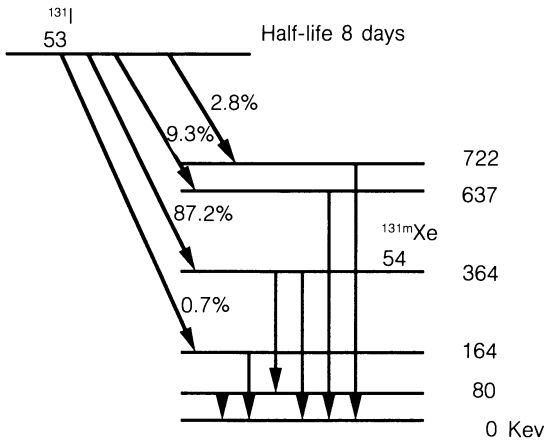


Figure 13.6 Decay of ^{131}I and an explanation of schematics. The straight horizontal line on top represents the parent radionuclide. The lower horizontal lines are daughters and the lowest is the final ground state. Arrows indicate radioactive incidents. The length of arrow (also the distance between horizontal lines) is proportional to the energy of emission. If the daughter has a higher atomic number, as in beta-decay, the arrow points down and to the right. If the daughter has a lower atomic number the arrow points down to the left. When there is no change in atomic number, as in isomeric transition, the arrow is vertical.

$$\begin{array}{ccccccc} 131 & & 131 & & & 131 & \\ & I\rightarrow & & Xe^{m} & & & Xe \\ 53 & e^{-} & 54 & & gamma & 54 & \end{array}$$

The offical way of showing this decay scheme is shown in Figure 13.6. Table 13.1 lists the type and number of radioactive emissions from ^{131}I and their energies. It can be seen that there are beta$^-$, gamma, internal conversion electrons, X-rays and Auger electrons, all of which produce interactions in tissues.

Beta$^+$ decay is also called decay by positron emission. A nuclear proton is converted into a neutron, positron (e^+) and neutrino. The positron is emitted with the neutrino which, like the antineutrino, is of no biological consequence. The positron, very rapidly and over a short distance, loses energy and eventually interacts with an electron (e^-). When e^+ and e^- interact, they annihilate one another and their mass equivalent is replaced by energy in the form of two photons, each with 511 Kev energy. These are emitted at an angle of 180 degrees. This is pair production as shown in Figure 13.4. Detection of these high-energy photons by coincidence counting, a technique by which only those incidents occurring simultaneously in detectors exactly opposite one another are registered, forms the basis of positron tomographic imaging. Several radionuclides of iodine are positron emitters, including ^{120}I, ^{121}I, ^{122}I, ^{124}I and ^{126}I. Since a positive electron is lost, the atomic number of the daughter decreases by 1 and the mass number remains constant.

In electron capture, the nucleus captures an orbital electron, which combines with a proton to form a neutron and neutrino. Because a proton is lost, the atomic number decreases by 1, but the mass number remains constant since a neutron is produced. In this regard, the end result is similar to

Table 13.1 Complete list of electrons and photons emitted by ^{131}I

Radiation i	*Energy Mev Ei*	*Mean number disintegrations ni*
Beta	0.192	0.904
Beta	0.096	0.069
Beta	0.070	0.016
Beta	0.286	0.006
Beta	0.143	0.005
Gamma	0.723	0.016
Gamma	0.637	0.069
Gamma	0.365	0.833
Gamma	0.284	0.048
Gamma	0.080	0.017
Intern conv	0.330	0.017
Intern conv	0.046	0.029
K a X-rays	0.030	0.038

There are other gamma and conversion electrons, but they give very little additional absorbed radiation.

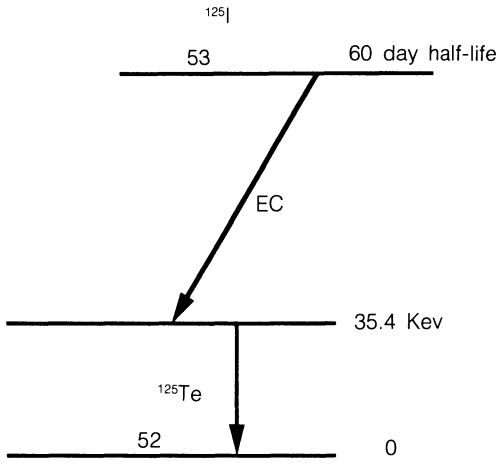


Figure 13.7 Decay scheme of ^{125}I.

Table 13.2 Electron and photon emissions of ^{125}I

Radiation	*Energy Mev*	*Number of disintegrations*
Gamma	0.036	0.068
Intern conv	0.035	0.080
Intern conv	0.031	0.110
Intern conv	0.004	0.750
X-ray	0.032	0.041
X-ray	0.031	0.199
X-ray	0.028	0.738
X-ray	0.027	0.378
X-ray	0.004	0.215
Auger e^-	0.030	0.009
Auger e^-	0.026	0.058
Auger e^-	0.023	0.137
Auger e^-	0.003	0.149
Auger e^-	0.001	0.359

decay by positron emission. Iodine-125 decays by electron capture.

$$^{125}_{53}I \longrightarrow {}^{125}_{52}Te$$

The captured electron is usually from the inner (K) shell. The vacancy created there is filled by an outer shell electron and as discussed above, the energy differential is lost as an Auger electron, or as an X-ray which is characteristic for the daughter. The complete decay of ^{125}I is shown in Figure 13.7, and the number and energies of emitted electrons, and photons in Table 13.2. Iodine-123 also decays by electron capture and its decay scheme is shown in Figure 13.8.

Decay by gamma emission occurs in radionuclides which are metastable. These radionuclides have energy above the ground state and they release the energy in the form of a gamma ray (a photon arising in the nucleus). Because the photon has no charge and no mass, the mother and daughter have the same mass number and the same atomic number. The mother product is said to be an isomer, and the form of decay is called isomeric transition. Technetium decays by isomeric transition.

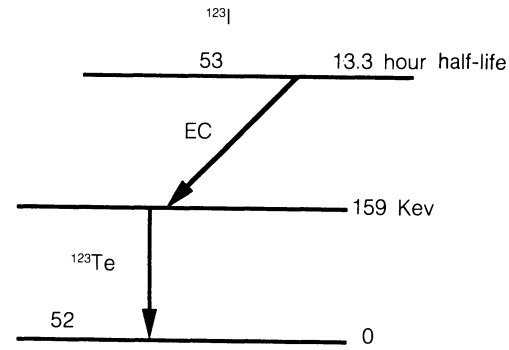


Figure 13.8 Decay of ^{123}I.

$$^{99m}_{43}Tc \longrightarrow {}^{99}_{43}Tc$$

In this case the daughter product is also radioactive, but its half-life is so long that it is of no consequence. Figure 13.9 shows the complete decay of ^{99m}Tc.

As an alternative, an excited nucleus can decay by emitting what is called a **conversion electron** (Figure 13.10). The best way of thinking about this is to imagine that the energy which would be lost with emission of a gamma ray is given to an orbital electron,

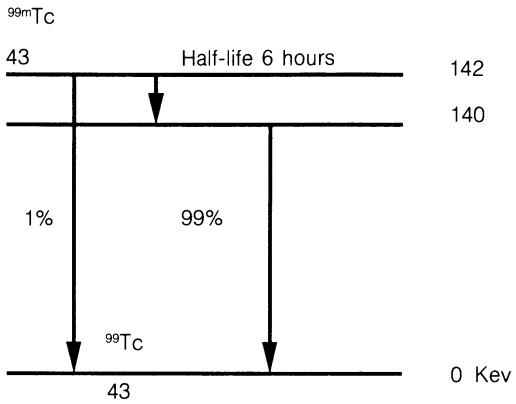


Figure 13.9 Decay of technetium-99m. Technetium-99m is obtained from molybdenum-99 which decays by beta-, with a half-life of 67 hours. Because technetium is obtained from a molybdenum generator, it is important to ensure that there is no molybdenum breakthrough in the technetium preparation, since this would give significant radiation to the patient. NRC regulations allow for 1 μCi Mo-99 per 1 mCi Tc-99m (1/1000) Bq/Bq) or a maximum of 5 μCi Mo-99 per dose (185-KBq). Tc-99 is radioactive and decays by beta-, with a half-life of 21 000 years, to ruthenium-99.

and the electron is ejected. This electron comes from a different source from the electrons in beta decay, which are nuclear. In general, the conversion electron comes from either the K or the L shell. As in previous situations, when an orbital electron is lost, its vacancy is filled by an outer electron, and either an Auger electron, or X-ray is given off. Figure 13.3 shows these two mechanisms. Two textbooks are referenced [1, 2] which will help interested readers pursue the topic of physics in relation to nuclear medicine.

Whether the radiation to the thyroid is internal, as with radionuclides of iodine, or external, as in the case of external radiation, the major effect on tissues is due to ionization. Therefore, these forms of radiation are also called **ionizing radiation**. The radiation can have a direct effect on tissues. This occurs when the radiation *per se* damages a structure such as DNA. However, this is unlikely simply on the basis of the size and number of molecules of DNA available. Most often the damage is indirect and usually related to free radicals, which have unpaired elecrons in the outer shells. These atoms, or molecules, are very active and can cause damage to adjacent molecules. Since H_2O is the most prevalent molecule, it is most likely to be ionized and form free radicals.

$$H_2O \longrightarrow H_20^+ + e^-$$

$$H_2O^+ + H_2O = H_3O^+ + OH^*$$

Hall [3] states that 75% of damage to CNA from radiation is due to OH^*. The nucleus is the most sensitive part of the molecule and severe damage results in cell death. Less severe damage produces a cell which is unable to reproduce. Therefore at the end of its life-span, it dies and is not replaced. The radiation can shorten the life of the cell and cause premature death of a cell, which is also incapable of replacing itself. This type of damage in the thyroid results in hypothyroidism, and is desirable when thyroid cancer is ablated, but less desirable when radioiodine is used to treat a non-malignant condition.

Smaller quantities of radiation produce subtle abnormalities in DNA. There are sophisticated mechanisms in the nucleus capable of repairing these defects. A full description of these is outside the scope of this text, but interested readers are referred to Friedberg [4]. Failure to repair these lesions can result in mutations, which can cause the normal regulatory mechanisms to be lost and tumours, both benign and malignant, to result. Although the DNA is the most radiosensitive part of the cell, it is not the only part which can be damaged. The nuclear membrane and the cell membrane are radiosensitive, but to a lesser degree. The clinical results of treating Graves' disease

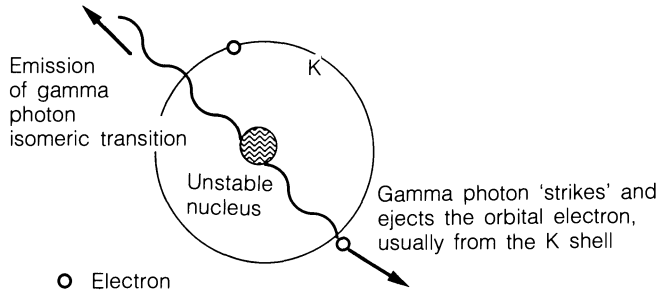


Figure 13.10 Internal conversion, isomeric transition.

with ^{125}I resulted in the same incidence of hypothyroidism as ^{131}I [5], yet the former produces intense radiation of the apical membrane of the follicular cell, and less than 10% of the dose to the nucleus. By contrast, ^{131}I produces uniform radiation across the cell, including the nucleus. Nevertheless, the final outcome is the same, namely, cell death. The implication is that the dose to the cell membrane from ^{125}I is great enough to kill the cell. Radiation may alter the cell membrane, either directly or by damaging DNA, and altering the expression of genes responsible for making membrane proteins. The altered membrane could be the basis for immunological disease after radiation.

13.3 DOSIMETRY

It is necessary to define a number of terms. There are two systems of terminology, the traditional and the Système International. In the tradition system, the rad is the unit of absorbed radiation. One rad gives 100 ergs per g absorbing tissue. In the Système International, the unit is the gray. One gray (Gy) is equal to 1 joule per go One gray is equal to 100 rad, therefore, conversion from one unit to the other is straightforward. The curie (Ci) is the amount of radiation which has 3.7×10^{10} disintegrations per second (dps). Therefore one mCi has 3.7×10^7 dps and one μCi, 3.7×10^4 dps. In the Système International, the unit of activity is the becquerel (Bq), which is defined as having 1 dps. One megabequerel (MBq) is equal to 10^6 dps. One MBq equals 27.03 μCi, and 1 gigabequerel equals 27.03 mCi. One μCi is equal to 37 Bq. To calculate the dose to an organ, it is necessary to know how much radioactivity is given and what proportion is taken into the organ. In the thyroid, these are usually well known, because the dose given is measured beforehand, and the percentage uptake can be measured with accuracy.

The half-life of the radionuclide in the thyroid has to be known. Since iodine has a biological half-life (T_b) and radioiodine, a physical half-life (T_p), these both have to be incorporated into the effective half-life (T_e). The effective half-life cannot be longer than either the biological or physical half-lives. The formula to calculate T_e is:

$$\frac{1}{T_e} = \frac{1}{T_b} + \frac{1}{T_p} \text{ or, } T_e = \frac{T_b \times T_p}{T_b + T_p}$$

The effective half-life has to be multiplied by 1.44 to obtain the average lifetime of the radionuclide, which is used to determine cumulative activity. For example, what is the cumulated activity when 5 mCi (185 mBq) are administered to a thyroid with 50% uptake given the biological half-life of iodine is 16 days, and the physical half-life of ^{131}I is 8 days? Effective half life is $(8 \times 16)/(8 + 16) = 5.33$ days = 128 hours. Cumulative activity is $5000 \times 50/100 \times 128 \times 1.44 = 460\,080$

Table 13.3 Dosimetry from ^{131}I

Radiation i	*Energy Mev* Ei	*Mean number disintegrations* ni	$\triangle i$ $2.13 \times E \times n$	$\varnothing$
Beta	0.192	0.904	0.370	1
Beta	0.096	0.069	0.014	1
Beta	0.070	0.016	0.002	1
Beta	0.286	0.006	0.004	1
Beta	0.143	0.005	0.001	1
Gamma	0.723	0.016	0.025	0.03
Gamma	0.637	0.069	0.093	0.03
Gamma	0.365	0.833	0.646	0.03
Gamma	0.284	0.048	0.029	0.03
Gamma	0.080	0.017	0.003	0.035
Intern conv	0.330	0.017	0.012	1
Intern conv	0.046	0.029	0.003	0.03
K a X-rays	0.030	0.038	0.002	0.15

Sum of $\triangle$ i $\times \varnothing = 0.433$

μCi. This assumes that the uptake of radioiodine is instantaneous. The next step is to determine the absorbed radiation dose, and this depends on the type of radioactive emissions, their energy and frequency. The number (n) and energy (E) are used to determine the equilibrium absorbed dose constant:

$$= 2.13 \times n \times E$$

(The rate of energy emission of 1 μCi is 213 E ergs/hour/μCi.h and by definition 1 rad is 100 erg/g; therefore 1 g.rad is 100 erg.) Because there can be many emissions, each has to be taken individually, and each equilibrium absorbed dose ($\triangle$), $2.13 \times n \times E$, calculated. In the case of ^{131}I, there are 5 beta emissions, 8 gamma, 5 conversion electrons and an X-ray. The next step is to calculate how much of the radiation is absorbed by the target organ, this is called the **absorbed fraction** ($\varnothing$). In the case of the thyroid, where the source volume and target organ are the same, this is 1 for electrons. It is less for photons, since their energy is not entirely deposited in the gland. The equilibrium absorbed dose is multiplied by the absorbed fraction for each emission, and the sum of these obtained. The data about number of emissions and their energy, as well as the absorbed fractions, are given in MIRD tables [6]. Therefore, by simple arithmetic the sum of absorbed doses can be determined.

To calculate the dose in rad the formula is:

[Activity in organ $\times$ T_e $\times$ 1.44 $\times$ sum of $\triangle$ $\times$ $\varnothing$]/weight of organ

The sum of $\triangle \times \varnothing$ for ^{131}I is 0.433 (Table 13.3).

For example, what is the absorbed dose to the thyroid of 40 g when 10 mCi are administered and the uptake is 50%? Assume effective half-life is 100 hours.

[10 000 $\times$ 50/100 $\times$ 100 $\times$ 1.44 $\times$ 0.433]/40 = 7794 rad (77.9 Gy)

The sum of absorbed radiations from ^{99m}Tc results in a dose of 0.078 rad/μCi/h. Therefore a dose of 1.0 mCi given intravenously with immediate trapping of 2% and an effective half-life fo 6 hours in a thyroid of 20 g would give a dose of:

[1000 $\times$ 2/100 $\times$ 6 $\times$ 1.44 $\times$ 0.078]/20 = 0.67 rad (0.0067 Gy)

13.4 THYROID DISEASE DUE TO EXTERNAL RADIATION

I have divided this somewhat arbitrarily into three sections dependent on the absorbed dose, firstly, low doses up to 100 rad (1 Gy), secondly, intermediate doses between 101 and 2000 rad (1–20 Gy), and thirdly, high doses greater than 2000 rad (>20 Gy). In practice, it is very unusual for the thyroid to receive more the 6000 rad from external radiation.

13.4.1 LOW-DOSE EXTERNAL RADIATION

A long-term investigation in Israel has demonstrated that thyroid cancer is associated with much lower radiation doses than most investigators thought possible. The 'patient group' in this study was a large group of children who were treated for ringworm of the scalp using external radiation between 1949–60 [7]. The investigators compared the incidence of thyroid and other cancers in the irradiated patients with matched controls, and with a second smaller control group of sibs who were not irradiated and not matched exactly for age and sex. The first report in 1974 showed an increase in thyroid tumours and also brain and parotid lesions [7]. The investigators, using a phantom and knowledge of the radiation technique, were able to determine dosimetry with accuracy and the mean dose to the thyroid was 9 rad (0.09 Gy). In 1977, they calculated that the risk of thyroid cancer was 6.3/rad/10^6 people/year [8]. An updated analysis in 1984 showed that 29 of the treatment group of 10 842 had thyroid cancer, compared to 6 in the control group of 10 842, and 2 of the 5400 sibs. The relative risk was × 5.4 (× 2.7 – 10.8, 95% confidence limits) [9].

Two brothers were found to have thyroid cancer at ages 33 and 38 respectively. There was no family history of thyroid cancer, but both had been investigated for congenital heart disease with cardiac catheterization, and calculations made in retrospect indicated radiation doses to their thyroids of 20–30 rad (0.2–0.3 Gy) at ages 11 and 9 respectively [10].

Parker *et al.* [11] analysed the incidence of thyroid cancer in Japanese who had been exposed to radiation from atomic bombs. The population studied had received direct radiation with neutrons and gamma rays, but no radioactive fallout. In regard to the last, they differ from the Marshallese islanders who are discussed below. The investigators found that there was a cut-off at a dose of 50 rad (0.5 Gy), above which the risk of thyroid cancer increased considerably. The relative risk in women was × 5 and in men × 9.4, both being statistically significant. The authors of the study take pains to indicate that they do not imply there is no risk at doses less than 50 rad (0.5 Gy).

Therefore, there is data which associates an increase in frequency of thyroid cancer in patients who received external radiation (usually X-rays) in doses from 9–99 rad (0.09–0.99 Gy).

13.4.2 INTERMEDIATE-DOSE EXTERNAL RADIATION

The largest body of information incriminating external radiation as a cause of thyroid cancer relates to patients who received doses of 101–2000 rad (1–20 Gy). There are also data from experiments in animals indicating this dose range is associated with a greater frequency of cancer and benign nodules.

The first report of this association indicated that of 28 patients younger than 18 years with thyroid cancer, 10 had prior radiation to the thymus [12]. The authors, although universally recognized for this association, are seldom quoted to have written, 'To propose a cause-and-effect relationship between thymic irradiation and the development of cancer would seem quite unjustified'. There followed a report by

Clark [13] who found that all 13 children with thyroid cancer that he treated had a history of radiation. The dose range was 200–725 rad (2–7.25 Gy), and the time between radiation and discovery of the cancer was 6.9 years. In contrast, Uhlmann [14] stated that in his experience the statistics, 'Did not justify the acceptance of a correlation'. Nevertheless, he found that 4 of 25 children with thyroid cancer had indeed been irradiated, and the 4 cases came from a population of 480 patients who had been irradiated and recalled for examination. One thyroid cancer per 120 irradiated children certainly justifies association. Hempelmann *et al.* [15, 16], in a series of papers, strengthened the association by finding 19 cancers and 22 benign nodules in 2878 children who received radiation in infancy. They determined the risk of thyroid cancer to be 1.7 cases/rad (0.01 Gy)/10^6 people/year. Using this data, if we review the paper of Uhlmann [14] and assume a dose of 750 rad (7.5 Gy) was absorbed by the thyroid and the 480 patients were followed for 7 years (these can be inferred from the paper), the number of thyroid cancers expected would be 4, which happened to be the case.

Favus *et al.* [17] examined 1056 patients with a history of neck irradiation, and palpated a nodule in 16.5%. Using ^{99m}Tc scintigrams they found lesions in an additional 10.7%. In total, 287 patients (27.2%) had an abnormal thyroid, and of these 182 underwent surgery and 60 had thyroid cancer. There are several ways of looking at the data. From the most pessimistic but also realistic, 33% of surgically removed thyroids contained cancer. Alternatively, 5.7% of the patients who were examined had thyroid cancer. However, the 1056 were from a larger population of 5266 who were irradiated, and since there is no data on the remaining 4210 it is difficult to draw firm conclusions of the overall risk. If none of the unexamined patients had cancer, which is unlikely, the true risk would be 60/5266 or 1.1%. These investigators calculated the risk as 1.5 cases/rad (0.01 Gy)/10^6/year, which is almost identical to the number developed by Hempelmann *et al.* [15]. The data of Favus *et al.* [17] needs further scrutiny. Many of the lesions were impalpable and discovered by scintigraphy. Pathologically many of the cancers were not at the palpably, or scintigraphically, abnormal site and they were minimal or occult cancers. This raises the question whether tests should be done to find impalpable lesions which, even if they are carcinomatous, have an outstanding prognosis. Other investigators have demonstrated that thyroids which have been irradiated have more scintigraphic abnormalities than non-irradiated glands. In one study, after patients with palpable nodules were excluded, 16 out of 150 irradiated glands were scintigraphically abnormal, compared to 1 out of 97 controls [18]. The authors of this paper advise scintigraphy as part of the initial work-up of patients who received more than 700 rad (7 Gy) before the age of 10. This conflicts with the advice of the American Thyroid Association, who advise palpation of the gland (this should be done by a physician with training and experience) [19]. Hofenberg [20] in a discussion paper also opposes regular scanning and favours clinical examination. The patients should not be lost to follow-up, since additional cancers are found with the passage of time.

Proof that the findings are not isolated is found in publications from other centres. De Groot and Paloyan [21] found that of 50 consecutive patients with thyroid cancer, 20 had neck irradiation. In a period of 18 months, Hamburger and Stoffer [22] found 16 cancers in 814 patients (2%) with a history of radiation. Twenty-one cancers were found from 530 patients (4%) by Murphy *et al.* [23]. They referred 30 patients to surgery immediately, and 9 had cancer (30%); several months later a further 30 were advised to have surgery and 7 had cancer (23%). Maxon *et al.* [24] compared 1266 patients who were radiated,

with 958 well-matched controls. In the former group, 16 were found to have thyroid cancers and 15 had benign thyroid nodules, which contrasted with 1 cancer and 2 benign lesions in the control group. Depending on the reason for therapy and the number of courses, the radiation dose to those who developed cancer varied considerably, from 210–1130 rad (2.1–11.3 Gy) with a mean of 524 rad (5.24 Gy). The mean time from radiation to finding the cancer was 16 years (6–28 years). The risk was approximately 1.5 cases/rad (0.01 Gy)/10^6/year.

The radiation was given for a variety of reasons most, if not all of which, would now be considered unjustified. The original patients had thymic irradiation for the syndrome of status thymicus, a non-existent syndrome. It was recognized on chest radiograph of children with 'failure to thrive', bronchitis, sniffles, etc. that the thymus was large. Therefore, this was accepted as the cause of the symptoms. Since the thymus was known to be very sensitive to radiation, this form of therapy was prescribed. Of course, the thymus is proportionally much larger in infants, and if chest radiographs had been obtained in normal children, there would have been no difference in its size compared to abnormals. Other indications for radiation were pertussis, enlarged cervical lymph nodes, including tuberculous nodes, enlarged tonsils and adenoids, otitis, mastoiditis, furunculosis and acne.

In summary, the data supports that approximately 2% of children who received 700 rad (7 Gy) to the thyroid develop thyroid cancer. The usual latent period is 10–20 years. However, patients are found with cancer outside these dose and temporal ranges. In addition to cancers, there is also an increase in benign thyroid tumours. Using published results, Maxon *et al.* [25] calculated that the risk of cancer was greater by more than a factor of 2 than previously stated. Their analysis indicated a figure of 4.2 cancers/rad (0.01 Gy)/10^6/year. The risk for developing a benign nodule was 3 times as great, 12.3 cases/rad/10^6/year. The risk of developing either a benign or malignant nodule was linear up to 1500 rad (15 Gy).

What should be done when a patient presents with a history of prior neck irradiation? Firstly, it is important to determine that the radiation was ionizing. Sometimes it is a relief to find that ultraviolet radiation was given, and this is not associated with thyroid cancer. Also, local radium to the tonsillar bed does not produce distant radiation since the alpha particles only penetrate a few micrometres. If the radiation was ionizing, it is helpful to know the dose and the port, although this information has often been lost. The thyroid should be examined carefully. When no nodule is felt, a repeat examination after a year is sufficient. When a nodule is felt, there is a difference of opinion about its management. Some argue that the risk of cancer in the thyroid is at least 30%, therefore surgery is advised. Others argue about 60–70% of nodules are benign, therefore they advise fine-needle aspiration and base the decision to operate, or not, on the result. I tend to use the former approach unless the patient is opposed to operation. There is controversy about the extent of surgery, a topic covered in Chapter 8. Since the entire gland was irradiated, the need for total thyroidectomy is advocated. However, the same arguments which were presented in Chapter 8 hold true, and ipsilateral lobectomy on the side of the clinical abnormality plus subtotal contralateral lobectomy is recommended. Schneider *et al.* [26] found that the course of radiation-induced thyroid cancer was similar to spontaneously occurring cancers. They have followed 318 patients and found the factors associated with recurrence were histology, angioinvasion, size, and lymph node metastases. Three patients died (1%) and 40 had a recurrence (12.6%). Neither the extent of operation nor the 'prophylactic' use of radioiodine lowered the recurrence rate. After operation, patients

should be given a suppressive dose of thyroxine. An earlier report of Roudebush *et al.* [27] suggested that radiation-induced cancers were more aggressive but, on balance, any difference is marginal. Because radiation causes an increase in tumours of the parotid [28] and parathyroid, the former should be palpated and the latter tested by measuring serum calcium. If calcium is high, the clinician should complete the work-up for hyperparathyroidism.

13.4.3 HIGH-DOSE EXTERNAL RADIATION

Based on a careful analysis of the literature, Maxon *et al.* [25] stated 'it would appear, then, that external radiation of the thyroid at doses higher than 2000 rem is not clearly associated with the induction of thyroid cancer'. However, we have found 6 patients with thyroid cancer in a group of 1791 patients who received external radiation for the treatment of Hodgkin's disease [29 *a*, *b*] and there are additional reports in the literature [30–33]. In general, the cancers are papillary, but adenosquamous and anaplastic cancers have been described [34, 35]. If we use the formula 1.5 cases/10^6/rad/year, the number of thyroid cancers expected would be significantly more than in actuality. In the Stanford experience, 1791 patients received 4000 rad (40 Gy) and were followed for 10 years. Therefore, approximately 107 cases should have been found, whereas, we found 6. Nevertheless, clinicians should examine the thyroids of these patients at follow-up; I recommend this annually for life. Eighteen patients have had surgery for benign nodules, almost all had multiple nodules, and several others have received thyroxine for nodular goitre; therefore the true incidence of benign nodules has not been determined at the time of writing. When a nodule is found, it is not clear what is the best approach for its management. It is correct to obtain a fine-needle aspirate, but since these patients have already been treated for a life-threatening disease, and since they frequently are very concerned about new abnormal clinical findings, and because thyroid cancer has been described in this situation, it is also correct to advise a subtotal thyroidectomy. If the nodule is malignant, the correct procedure has been done, and if benign, concerns are put to rest and the patient greatly relieved.

External radiation in doses greater than 2000 rad (20 Gy) can cause hypothyroidism. This was first described by Markson and Flatman [36] in 1965. There is abundant literature to document this, and it has been found largely in patients with lymphoma treated with 3000–5000 rad (30–50 Gy) [37–44], although it has also been described in patients with head and neck cancer (Shafer *et al.*) [45]. There is considerable variation in the incidence of postradiation hypothyroidism from 4% [37] to greater than 80% [40], but this is largely related to the method of defining hypothyroidism. In most reports, the definition is biochemical and based on a high TSH, and in others an abnormal response to TRH is used [37, 42]. We routinely measure TSH and FT_4 in these patients when they are seen for review of their Hodgkin's disease [46]. We do not advise TRH testing. The reasons for the apparent increased frequency in patients with lymphoma are that as a group their survival is superior to that of other cancers, and they frequently have diagnostic tests such as lymphangiogram or CT with contrast, that give a large iodine load which can cause hypothyroidism [47]. Our studies did not allow us to separate completely the effect of radiation from lymphangiogram, although in children with treated Hodgkin's disease, the frequency of hypothyroidism was 78% (74 out of 95 children) in those who received more than 2600 rad and 17% (4 out of 24) who received less than that dose [44]. All

patients had a lymphangiogram; therefore radiation is the more important factor. In our total group of 1791 patients of all ages, 498 have an elevated TSH (28%).

It would appear from animal studies that an elevated TSH plus radiation to the thyroid is important in the production of thyroid cancers. These studies usually involved lower doses of radiation. Doniach [48] showed convincingly in rats, that 500 rad plus an antithyroid drug to raise TSH, produced malignant thyroid tumours in 5 out of 10 animals and benign tumours in all 10. By contrast, radiation plus thyroxine resulted in none of 17 rats developing cancer, and only 1 had a benign tumour. If the animal experiments can be extended to the human, a strong argument can be made for prescribing thyroxine to irradiated patients who have a high TSH. However, it should be remembered that thyroxine was given to animals immediately after radiation, not when biochemical hypothyroidism was detected. Should all patients receive thyroxine, and should the dose be sufficient to suppress TSH? These questions are not resolved, but since at the time of writing the risk of cancer is small, it would also appear better to screen, rather than treat, and it would appear satisfactory to have TSH in the low normal range. Since other thyroid conditions, including hyperthyroidism, can occur after external radiation, it is important to measure thyroid function (TSH and FT_4) annually.

Wasnich *et al.* [49] were the first to describe Graves' hyperthyroidism and euthyroid Graves' ophthalmopathy after mantle radiation for Graves' disease. We continue to see patients with these diseases (30 out of 1791), and other investigators confirm the finding [50]. There is no doubt that the incidence is increased. The cause is thought to be due to radiation producing an alteration in the follicular cell antigens that is recognized as foreign by the immune system. Since not all patients are affected, it is likely that there is a genetic factor. In addition, since many patients also receive iodine contrast, that could play a role. Physicians managing these patients should be aware of this possibility and when there is weight loss, malaise, nervousness, etc., they should order tests for TSH and FT_4. If these tests confirm hyperthyroidism, ^{123}I uptake should be obtained. If high, it is likely that the patient has Graves' disease and treatment with ^{131}I should be prescribed. I have treated one such patient for more than 10 years with propylthiouracil since he was extremely concerned about additional radiation. There is not enough data to know whether antithyroid drugs are more likely to be toxic in a patient who has had extensive radiation and chemotherapy. Nevertheless, in this setting, an ablative dose of ^{131}I would appear to be better.

Some patients are found to have a diffusely enlarged granular thyroid and elevated levels of antithyroid antibodies. I have not biopsied the thyroid, but felt that the clinical diagnosis was Hashimoto's thyroiditis. The response to thyroid has been satisfactory. We have encountered patients who went from definitive hypothyroidism to classic Graves' hyperthyroidism after mantle radiation [51]. We have also found a syndrome like silent hyperthyroidism in 6 patients, 4 of whom are permanently hypothyroid. Since silent hyperthyroidism is generally accepted to be an immunological disease, we believe this should be included as one of the immunological diseases which can be found after external radiation to the thyroid [52, 53].

In summary, a wide spectrum of thyroid diseases occurs after external doses of greater than 2000 rad to the thyroid. The most common is biochemical hypothyroidism. Hypothyroidism is usually permanent, but can be transient. Immunological diseases include classic Graves' hyperthyroidism, with

or without ophthalmopathy, euthyroid Graves ophthalmopathy, Hashimoto's and silent thyroiditis. Thyroid nodules and thyroid cancer are found, but to date their frequency does not support a linear relationship to the administered dose.

13.5 THYROID DISEASE DUE TO INTERNAL RADIATION

13.5.1 LOW AND INTERMEDIATE DOSES

The optimal radionuclide for diagnostic thyroid tests is ^{123}I. This radionuclide in a dose of 200 μCi (7.4 MBq) gives about 2 rad (0.02 Gy) to a normal thyroid. There are two methods of making ^{123}I and, of these, cyclotron production results in considerably less ^{124}I contamination and a lower absorbed radiation. This preparation is more expensive. Even smaller thyroidal absorbed doses are obtained with ^{99m}Tc. There is no data showing any association of thyroid cancer with internally deposited radiation of this amount. It is only fairly recently that these radionuclides have replaced ^{131}I, although we made a plea in favour of ^{123}I in 1977 [54]. Iodine-131 in a dose of 100 μCi (3.7 MBq) gives an absorbed dose to a normal sized thyroid with uptake of 20% of about 100 rad (1 Gy). This is in the dose range which is of considerable concern with external photon radiation, although with ^{131}I almost 90% of the radiation is due to electrons. There is very little data pointing to a risk from this dose causing either nodules or cancers.

A single report by Pilch *et al.* [55] described a patient who at age 4 and 12 had ^{131}I scintigraphy and a calculated dose of 240 rad (2.4 Gy) to the thyroid. At age 20 she was found to have metastatic papillary cancer. The reason for the investigations was suspected hyperthyroidism, and there was no description of a nodule which could have been a pre-existing cancer. Recently the results of a multi-institute review of thyroid disease in children who had had procedures with ^{131}I in comparison with well-matched controls showed no statistical risk of thyroid cancer from a mean dose of about 100 rad (1 Gy). However, there were 5 cancers in 3503 exposed and only 1 cancer in 2594 controls, and one wonders, if the groups had been larger, if the conclusion would have been the same [56].

In 1954, islanders on the Rongelap islands (Marshallese) were accidentally exposed to an atomic explosion. They received both external gamma radiation of 175 rad (1.75 Gy) and internally absorbed radiation from ^{131}I, ^{132}I, ^{133}I, and ^{135}I. The dose to the thyroid varied depending on the age of the patient (actually size of thyroid), and the closeness to the explosion. Children less than 10 years on the nearest island received 175 rad direct radiation plus 500–1400 rad from radionuclides of iodine (6.75–15.75 Gy). One of 19 developed thyroid cancer and 17 developed benign thyroid nodules. In 34 older people who received smaller internal doses, there were 2 cancers and 3 benign nodules. Therefore, a total of 3 cancers and 20 benign nodules were found in 53 patients after a follow-up of 15 years [57]. It appears that the combination of radiations produces significantly more lesions than would be calculated from the external dose alone. Doses in the range 100–1500 rad (1–15 Gy) would not be expected to cause an increased incidence of hypothyroidism.

13.5.2 HIGH DOSES OF INTERNAL RADIATION

Radioiodine-131 therapy is the most common form of therapy for Graves' hyperthyroidism in the USA, and its use in Europe is extensive, although there children and young adults are more likely to be treated by alternative methods. If this treatment is to be prescribed, when there are alternatives, and if patients are expected to have a long ex-

pected survival, we should evaluate critically the data about unwanted effects on the thyroid.

Under this heading, the dose to the thyroid is in the range 2500–15 000 rad, and I shall accept that the most common doses to the thyroid are about 10 000 rad (100 Gy). The major theoretical concern is that cancers of the thyroid would be found with increased frequency after ^{131}I. The data do not support this.

Thyroid cancer can coexist with Graves' hyperthyroidism. The frequency from pathological series varies considerably. Sokal [58] reported 0.15%, Olen and Klinck [59] 2.5% and Kilpatrick *et al.* [60] 7%. In two clinical series, 17 out of 576 (3%) patients with cancer [61], and 10 out of 502 (2%) [62] had Graves' disease. These cases of hyperthyroidism were not due to the cancer secreting excessive amounts of hormones, but the cancers were incidental findings at operation, or after work-up of a nodule. The corollary of 9 cases of cancer found in 720 patients (1.25%) with hyperthyroidism [62] shows that there is a small but definitive correlation between these two conditions. Therefore, in patients treated for hyperthyroidism, it is expected that a small proportion already have cancer. What is the true incidence? This is hard to determine since there may be a bias in those patients sent to surgery and the numbers could be too high. Alternatively, cancers arising in patients not treated by operation could well be attributed to whatever treatment was prescribed. If we assume that the incidence of thyroid cancer in patients with hyperthyroidism is in the range of 0.1–1.0%, and that 1 000 000 patients have received ^{131}I treatment, there should be 1000–10 000 associated cancers. In the Cooperative Thyrotoxicosis Therapy Follow-Up Study there were 50 cancers in 11 732 patients who had thyroidectomy (0.4%), and 19 arose more than 1 year after radioiodine in 21 714 patients (0.08%) [63]. This does not indicate a risk from radioiodine. Holm *et al.* [64, 65] found 4 cases of thyroid cancer in 3000 radioiodine-treated patients, and this was not different from the expected incidence. The total follow-up was 39 066 patient-years, and the mean follow-up 9.5 years. All 4 patients who developed cancer had nodular goitres; in 1 it is probable that thyroid cancer pre-existed the treatment with radioiodine, and in another there was an alternative source of radiation. By contrast, Hoffman [66] found 3 thyroid cancers in 1005 radioiodine-treated patients, which was 3.8 times the expected frequency. The number is small and the percentage 0.3% within the broad limits defined above.

I have treated 3 patients with thyroid cancers which were diagnosed 4, 7 and 13 years respectively after ^{131}I therapy for Graves' disease. In the last 2, the original ^{131}I therapy was prescribed elsewhere, so it was impossible to determine the true incidence of this finding. On two occasions I reviewed the literature and in 1971 could find 8 similar patients [67] and in 1981, 25 reports [68]. Of these 25 cases, 7 arose less than 5 years after therapy and are unlikely to be associated. Even if there are cases which have not been reported, this small number, taken along with the follow-up studies discussed above, indicates that there is not an increased risk of thyroid cancer after therapeutic doses of ^{131}I in patients. How is this the case, when external radiation is clearly implicated?

It is very unlikely that the explanation is insufficient data for analysis, since there have been sufficient patients studied and the length of follow-up is long enough, because most of the cases reported have occurred within 15 years and all within 20 years. There is a difference in the carcinogenic effects of ^{131}I and external radiation with X-rays based on experimental and clinical data. The former is considerably less carcinogenic. The most likely explanation is that ^{131}I in therapeutic doses sterilizes the population of

follicular cells, and if the cells are dead, or unable to reproduce, they will not produce cancers. Therefore, there is an inverse relationship of hypothyroidism and potential for thyroid cancer. The topic of post- ^{131}I hypothyroidism was reviewed and referenced in detail in relation to treatment of hyperthyroidism (Chapter 5), and only a few references are listed here [69–75]. This is by far the most common thyroid disorder related to high doses of internal radiation. Iodine-125 was used by several groups of investigators as an alternative to ^{131}I, and there is one report of a patient developing laryngeal cancer which could have been associated with this radionuclide [76]. Iodine-125 emits low-energy conversion and Auger electrons, which are very destructive over distances of about 1 micrometre. This contrasts with ^{131}I whose β emissions travel tens to hundreds of micrometre. In addition, ^{125}I emits low-energy photons, and it has a long physical half-life of 60 days, so the radiation is of a different type, over a different path-length and different length of time. It is too early to be certain that this radionuclide is the same as ^{131}I with regard to lack of association with subsequent thyroid cancer. As discussed previously, ^{125}I in doses which cure hyperthyroidism also causes hypothyroidism.

In summary, the major thyroid abnormality caused by internal radiation from high doses of ^{131}I is hypothyroidism.

13.5.3 VERY HIGH INTERNAL RADIATION DOSES

Very high radiation doses cause thyroiditis. Clinically this is similar to subacute thyroiditis, with pain and tenderness over the thyroid, plus referred pain to the jaw and ears. Fever with these symptoms add to the similarity with subacute thyroiditis [77]. Maxon *et al.* [25] in their review of the literature and their personal experience in treating patients with thyroid cancer indicate that this complication is rare with absorbed doses less than 20 000 rad, and it is seen in 90% with doses greater than 200 000 rad. These numbers demonstrate the intense radiation that can be delivered using ^{131}I. In very rare circumstances, the radiation causes disruption of follicles and releases stored hormones into the circulation, which can cause hyperthyroidism [78, 79]. Permanent hypothyroidism is the usual sequel to radiation thyroiditis [80].

Table 13.4 Absorbed doses from radionuclides of iodine rad/mCi or mrad/μCi

Radionuclide	*Absorbed dose*
^{123}I	7.5
^{124}I	530.0
^{125}I	450.0
^{130}I	68.0
^{131}I	800.0
^{132}I	7.4

The following cases give examples of the dosimetry.

1. A hyperthyroid patient has a thyroid of 50 g and the 24-hour uptake is 50%. Assuming the effective half-life of ^{131}I is 100 hours, how many rad are delivered from a dose of 10 mCi?

1μCi ^{131}I in 1 g tissue for 1 hour gives 0.433 rad. Therefore rad = [10 000 × 50/100 × 100 × 1.44 × 0.433]/50
= 6235 rad (therefore no thyroiditis)

2. A patient with 2 g of residual thyroid receives an ablative dose of 100 mCi to treat thyroid cancer. The uptake is 5% and effective half-life assumed to be 100 hours.

Therefore rad = [100 000 × 5/100 × 100 × 1.44 × 0.433]/2
= 155 880 rads (thyroiditis expected)

There is some support for the concept that radiation, both internal, or external, is responsible for causing anaplastic transforma-

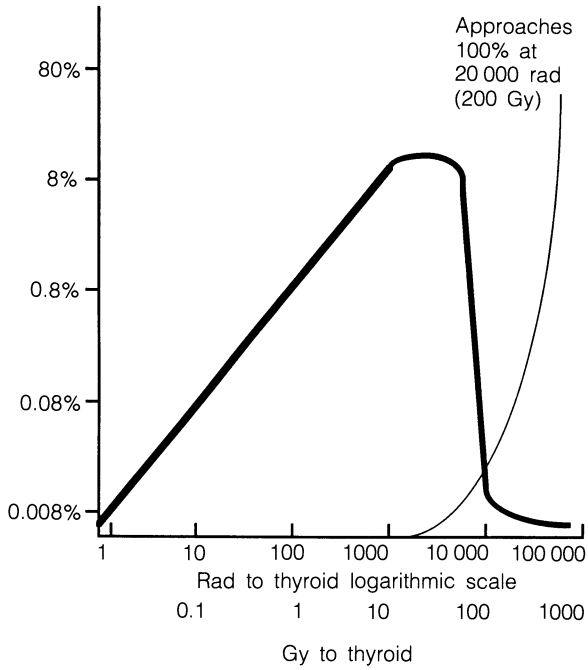


Figure 13.11 Effect of an increasing dose of radiation on the thyroid. Thick line = incidence of cancer; thin line = incidence of hypothyroidism after follow-up of 20 years.

tion of differentiated cancer. The data cannot exclude spontaneous transformation of differentiated to anaplastic cancer, since in many series this transformation is found in patients who have not received any form of radiation [81]. This is discussed in the section on anaplastic cancer in Chapter 8.

For reference, Table 13.4 gives absorbed dose estimates from 6 radionuclides of iodine. Figure 13.11 shows diagrammatically the incidence and type of thyroid disease produced by radiation in relation to the absorbed dose [82].

KEY FACTS

- Gamma radiation is less destructive than beta particles, which in turn are less destructive than alpha particles.
- For diagnostic uses, pure gamma-emitting radionuclides are preferred.
- For therapeutic uses, radionuclides that emit particles are preferred.
- Significant thyroid disease is associated with radiation to the thyroid.
- External radiation is associated with an increased risk of thyroid cancer.
- The risk of thyroid cancer is approximately 1.5–4.2 cases per rad (0.01 Gy) per year per 10^6 cases.
- Benign thyroid nodules are also found in thyroids which have been radiated externally.
- Graves' hyperthyroidism and euthyroid Graves' ophthalmopathy are found more often after neck irradiation than would be expected by chance.
- As the dose of external radiation increases above 3000–4000 rad (30–40 Gy), the relative risk of cancer falls and of hypothyroidism increases.
- In patients receiving more than 4000 rad (40 Gy) external radiation, 20–50% become hypothyroid.
- Low doses of radiation delivered internally (radionuclides of iodine) are seldom associated with an increase in any thyroid disease.
- Internal radiation in high doses (more than 7000 rad (70 Gy)) often results in hypothyroidism.
- High doses of internal radiation seldom cause thyroid cancer.
- Very high doses can cause radiation thyroiditis.

REFERENCES

1 Chandra, R. (1976) *Introductory Physics of Nuclear Medicine*, Lea and Febiger, Philadelphia.
2 Sorenson, J.A. and Phelps, M.E. (1987) *Physics in Nuclear Medicine*, 2nd edn, Grune and Stratton, Orlando.
3 Hall, E.J. (1978) *Radiobiology for the Radiologist*, 2nd edn, Harper and Row, Hagerston.
4 Friedberg, E.C. (1985) *DNA Repair*, W.H. Freeman, New York.
5 McDougall, I.R. and Greig, W.R. (1976) ^{125}I therapy in Graves' disease: long-term results in 355 patients. *Ann. Intern. Med.*, **85**, 720–3.

6 MIRD/DOSE Estimate Report No 5 (1975) *J. Nucl. Med.*, **16**, 857–60.
7 Modan, B., Baidatz, D., Mart, H. *et al.* (1974) Radiation-induced head and neck tumours. *Lancet*, **1**, 277–9.
8 Modan, B., Ron, E. and Werner, A. (1977) Thyroid cancer following scalp irradiation. *Radiol.*, **123**, 741–4.
9 Ron, E. and Modan, B. (1984) Thyroid and other neoplasms following childhood scalp irradiation, in *Radiation Carcinogenesis: Epidemiology and Biological Significance*, (eds J.D. Boice Jr, and J.F. Fraument Jr), Raven Press, New York, pp. 139–51.
10 Fisher, C. and Edmonds, C.J. (1980) Papillary carcinoma of the thyroid in two brothers after chest fluoroscopy in childhood. *Br. Med. J.*, **281**, 1600–1.
11 Parker, L.N., Belsky, J.L., Yamamoto, T. *et al.* (1974) Thyroid carcinoma after exposure to atomic radiation: a continuing survey of a fixed population, Hiroshima and Nagasaki, 1958–71. *Ann. Intern. Med.*, **80**, 600–4.
12 Duffy, B.J. Jr and Fitzgerald, P.J. (1950) Thyroid cancer in childhood and adolescence: Report on 28 cases. *Cancer*, **3**, 1018–32.
13 Clark, D.E. (1955) Association of irradiation with cancer of thyroid in children and adolescents. *JAMA*, **159**, 1007–9.
14 Uhlmann, E.M. (1955) Cancer of the thyroid and irradiation. *JAMA*, **161**, 504–7.
15 Hempelmann, L.H., Pifer, J.W., Burke, G.J. *et al.* (1967) Neoplasms in persons treated with X rays in infancy for thymic enlargement: a report of the third follow-up survey. *J. Natl. Cancer Inst.*, **38**, 317–41.
16 Hempelmann, L.H. (1968) Risk of thyroid neoplasms after irradiation in childhood. *Science*, **160**, 159–63.
17 Favus, M.J., Schneider A.B., Stachura, M.E. *et al.* (1976) Thyroid cancer occurring as a late consequence of head-and-neck irradiation: evaluation of 1056 patients. *N. Engl. J. Med.*, **294**, 1019–25.
18 Gonzalez-Villalpando, C., Frohman, L.A., Bekerman, C. *et al.* (1982) Scintigraphic thyroid abnormalities after radiation: a controlled study with ^{99m}Tc pertechnetate scanning. *Ann. Intern. Med.*, **97**, 55–8.
19 McConahey, W.M. and Hayles, A.B. (1976) Radiation and thyroid cancer. *Ann. Intern. Med.*, **84**, 749–50.
20 Hoffenberg, R. (1984) Radiation-induced thyroid tumours in man: discussion paper. *J. Roy. Soc. Med.*, **75**, 893–6.
21 De Groot, L. and Paloyan, E. (1973) Thyroid carcinoma and radiation: a Chicago endemic. *JAMA*, **225**, 487–91.
22 Hamburger, J.I. and Stoffer, S.S. (1977) Late thyroid sequelae of radiation therapy to the upper body, in *Radiation-Associated Thyroid Carcinoma*, (eds L.J. De Groot, *et al.*), Grune and Stratton, New York, pp. 17–31.
23 Murphy, E.D., Scanlon, E.F., Swelstad, J.A. *et al.* (1977) A community hospital thyroid recall clinic for irradiated patients, in *Radiation-Associated Thyroid Carcinoma*, (eds L.J. De Groot, *et al.*), Grune and Stratton, New York, pp. 35–40.
24 Maxon, H.R., Saenger, E.L., Thomas, S.R. *et al.* (1980) Clinically important radiation-associated thyroid disease: a controlled study. *JAMA*, **244**, 1802–5.
25 Maxon, H.R., Thomas S.R., Saenger, E.L. *et al.* (1977) Ionizing irradiation and the induction of clinically significant disease in the human thyroid gland. *Am. J. Med.*, **63**, 967–78.
26 Schneider A.B., Recant, W., Pinsky, S.M. *et al.* (1986) Radiation-induced thyroid carcinoma: clinical course and results of therapy in 296 patients. *Ann. Intern. Med.*, **105**, 405–12.
27 Roudebush, C.P., Asteris, G.T. and De Groot, L.J. (1978) Natural history of radiation-associated thyroid cancer. *Arch. Intern. Med.*, **138**, 1631–4.
28 Becker, F.O. and Economou, S.G. (1975) Parotid tumor and thyroid cancer: simultaneous occurrence after irradiation of the neck in childhood. *JAMA*, **232**, 512–14.
29 (*a*) McDougall, I.R., Coleman, C.N., Burke, J.S. *et al.* (1980) Thyroid carcinoma after high-dose external radiotherapy for Hodgkin's disease: report of three cases. *Cancer*, **45**, 2056–60.
29 (*b*) Hancock, S.L., Cox, R.S. and McDougall, I.R. (1991) Thyroid diseases after treatment of Hodgkin's disease. *N. Engl. J. Med.*, in press (August).
30 Rosen, I.B., Simpson, J.A., Sutcliffe, S. *et al.* (1984) High-dose radiation and the emergence of thyroid nodular disease. *Surgery*, **96**, 988–94.
31 Meyer, O.O. (1971) Carcinoma of the thyroid following ionizing radiation for Hodgkin's disease. *Wis. Med. J.*, **70**, 129–33.
32 Morris, J.H. and Hardin, C.A. (1964) Thyroid cancer in adults following external radiation. *Arch. Intern. Med.*, **113**, 97–100.
33 Weshler, Z., Krasnokuki, D., Peshin, Y. *et al.* (1978) Thyroid carcinoma induced by irradiation for Hodgkin's disease. *Acta Radiol. Oncol.*, **17**, 383–6.

34 Getaz, E.P. and Shimaoka, K. (1960) Anaplastic carcinoma of the thyroid in a population irradiated for Hodgkin's disease, 1910–60. *J. Surg. Oncol.*, **12**, 181–9.
35 Bakri, K., Shimaoka, K. and Tsukada, Y. (1983) Adenosquamous carcinoma of the thyroid after radiotherapy for Hodgkin's disease: a case report and review. *Cancer*, **52**, 465–70.
36 Markson, J.L. and Flatman, G.E. (1965) Myxoedema after deep X-ray therapy to the neck. *Br. Med. J.*, **1**, 1228–9.
37 Slalina, J., Musshoff, K., Rahner, T. *et al.* (1977) Long-term side effects in irradiated patients with Hodgkin's disease. *Int. J. Radiat. Oncol. Biol. Phys.*, **2**, 1–19.
38 Nelson, D.F., Reddy, K.V., O'Mara, R.E. *et al.* (1978) Thyroid abnormalities following neck irradiation for Hodgkin's disease. *Cancer*, **42**, 2553–62.
39 Kim, Y.H., Fayos, J.V. and Sisson, J.C. (1980) Thyroid function following neck irradiation for malignant lymphoma. *Radiol.*, **134**, 205–8.
40 Schimpff, S.C., Diggs, C.H., Wiswell, J.G. *et al.* (1980) Radiation-related thyroid dysfunction: implications for the treatment of Hodgkin's disease. *Ann. Intern. Med.*, **92**, 91–8.
41 Green, D.M., Brecher, M.L., Yaker, D. *et al.* (1980) Thyroid function in pediatric patients after neck irradiation for Hodgkin's disease. *Med. Pediat. Oncol.*, **8**, 127–36.
42 Smith, R.E., Adler, R.A., Clark, P. *et al.* (1981) Thyroid function after mantle irradiation in Hodgkin's disease. *JAMA*, **245**, 46–9.
43 Tamura, K., Shimaoka, K. and Friedman, M. (1981) Thyroid abnormalities associated with treatment of malignant lymphoma. *Cancer*, **47**, 2704–11.
44 Constine, L.S., Donaldson, S.S., McDougall, I.R. *et al.* (1984) Thyroid dysfunction after radiotherapy in children with Hodgkin's disease. *Cancer*, **53**, 46–51.
45 Shafer, R.B., Nuttall, F.Q., Pollack, K. *et al.* (1975) Thyroid function after radiation and surgery for head and neck cancer, *Arch. Intern. Med.*, **135**, 843–6.
46 Donaldson, S.S., Link, M.P., McDougall, I.R. *et al.* (1989) Clinical investigations of children with Hodgkin's disease at Stanford University Medical Center – a preliminary overview using low-dose irradiation and alternating ABVD/MOPP chemotherapy, in *Hodgkin's Disease in Children*, (ed. W.A. Kamps), Kluwer Academic Publisher, Boston, pp. 307–15.
47 Braverman, L.E., Ingbar, S.H., Vagenakis, A.G. *et al.* (1971) Enhanced susceptibility to iodide myxedema in patients with Hashimoto's disease. *J. Clin. Endocrinol. Metab.*, **32**, 515–521.
48 Doniach, I. (1974) Carcinogenic effect of 100, 250 and 500 rad X-rays on the rat thyroid gland. *Br. J. Cancer*, **30**, 487–95.
49 Wasnich, R.D., Grumet, F.C., Payne, R.O. *et al.* (1973) Graves' ophthalmopathy following external neck irradiation for nonthyroidal neoplastic disease. *J. Clin. Endocrinol. Metab.*, **37**, 703–13.
50 Loeffler, J.S., Tarbell, N.J., Garber, J.G. *et al.* (1988) The development of Graves' disease following radiation therapy in Hodgkin's disease. *Int. J. Rad. Oncol. Biol. Phys.*, **14**, 175–8.
51 Constine, L.S. and McDougall, I.R. (1982) Radiation therapy for Hodgkin's disease followed by hypothyroidism and then Graves' hyperthyroidism, *Clin. Nucl. Med.*, **7**, 69–70.
52 Petersen, M., Keeling, C.A. and McDougall, I.R. (1989) Hyperthyroidism with low radioiodine uptake after head and neck irradiation for Hodgkin's disease. *J. Nucl. Med.*, **30**, 255–7.
53 Blitzer, J.B., Paolozzi, F.P., Gottlieb, A.J. *et al.* (1985) Thyrotoxic thyroiditis after radiotherapy for Hodgkin's disease. *Arch. Intern. Med.*, **145**, 1734–5.
54 McDougall, I.R. and Kriss, J.P. (1976) Which radioisotope for diagnosis of thyroid disorders? *Clin. Nucl. Med.*, **1**, 217–18.
55 Pilch, B.Z., Kahn, R. and Ketcham, A.S. (1973) Thyroid cancer after radioactive iodine diagnostic procedures in childhood. *Pediatrics*, **51**, 898–902.
56 Hamilton, P.M., Chiacchiernini, R.P. and Kacmarek, R.G. (1989) A follow-up study of persons who had iodine-131 and other diagnostic procedures during childhood and adolescence. *Health and Human Services Publication, Food and Drug Administration*, 89–8276.
57 Conard, R.A. *et al.* (1973) *A Twenty-year Review of Medical Findings in a Marshallese Population Accidentally Exposed to Radioactive Fallout.* Brookhaven National Laboratory, Upton, New York.
58 Sokal, J.E. (1954) Incidence of malignancy in toxic and nontoxic nodular goiter. *JAMA*, **154**, 1321–5.
59 Olen, E. and Klinck, G.H. (1966) Hyperthyroidism and thyroid cancer. *Arch. Pathol.*, **81**, 531–5.
60 Kilpatrick, R., Blomfield, G.W., Neal, F.E. *et al.* (1957) Carcinoma of the thyroid. *Quart. J. Med.*, **26**, 209–33.
61 Mazzaferri, E., Young, R., Oertel, J. *et al.*

(1977) Papillary thyroid carcinoma: the impact of therapy in 576 patients. *Medicine*, **56**, 171–96.

62 Edmonds, C.J. and Tellez, M. (1988) Hyperthyroidism and thyroid cancer. *Clin. Endocrinol.*, **28**, 253–9.

63 Dobyns, B.M., Sheline, G.E., Workman, J.B. *et al.* (1974) Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the Cooperative Thyrotoxicosis Therapy Follow-up Study. *J. Clin. Endocrinol. Metab.*, **38**, 976–98.

64 Holm, L.E., Dahlqvist, I., Israelsson, A. *et al.* (1980) Malignant thyroid tumors after iodine-131 therapy. A retrospective cohort study. *N. Engl. J. Med.*, **303**, 188–91.

65 Holm, L-E. (1984) Malignant disease following iodine-131 therapy in Sweden, in *Radiation Carcinogenesis: Epidemiology and Biological Significance*, (eds J.D. Boice Jr and J.F. Fraument Jr), Raven Press, New York, pp. 263–71.

66 Hoffman, D.A. (1984) Late effects of I-131 therapy in the United States, in *Radiation Carcinogenesis: Epidemiology and Biological Significance*, (eds J.D. Boice Jr and J.F. Fraument Jr), Raven Press, New York, pp. 273–80.

67 McDougall, I.R., Kennedy, J.S. and Thomson, J.A. (1971) Thyroid carcinoma following iodine-131 therapy. Report of a case and review of the literature. *J. Clin. Endocrinol. Metab.*, **33**, 287–92.

68 (*a*) McDougall, I.R., Nelsen, T.S. and Kempson, R.L. (1981) Papillary carcinoma of the thyroid seven years after I^{131} therapy for Graves' disease. *Clin. Nucl. Med.*, **6**, 368–71.

68 (*b*) Tomlinson, C., Knowles, K.W. and McDougall, I.R. (1991) Papillary cancer in a patient treatment with radioiodine for Graves' hyperthyroidism: case report and a review of the risk. *Clin. Nucl. Med.*, **16**, in press.

69 Beling, U. and Einhorn, J. (1961) Incidence of hypothyroidism and recurrences following ^{131}I treatment of hyperthyroidism. *Acta Radiol.*, **56**, 275–88.

70 Burke, G. and Silverstein, G.E. (1969) Hypothyroidism after treatment with sodium iodide ^{131}I. *JAMA*, **210**, 1051–8.

71 Glennon, J.A., Gordon, E.S. and Sawin, C.T. (1972) Hypothyroidism after low dose ^{131}I treatment of hyperthyroidism. *Ann. Intern. Med.*, **76**, 721–3.

72 McDougall, I.R. and Greig, W.R. (1972) Combined carbimazole-^{131}I treatment of thyrotoxicosis. *Scot. Med. J.*, **17**, 57–61.

73 Smith, R.N. and Wilson, G.M. (1967) Clinical trials of different doses of ^{131}I in treatment of thyrotoxicosis. *Br. Med. J.*, **1**, 129–32.

74 Segal, R.L., Silver, S., Yohalem, S.B. *et al.* (1961) Myxedema following radioactive iodine therapy of hyperthyroidism. *Am. J. Med.*, **31**, 354–6.

75 Nofal. M.M., Beierwaltes, W.H. and Patno M.E. (1966) Treatment of hyperthyroidism with sodium iodide ^{131}I. *JAMA*, **197**, 605–10.

76 McKillop, J.H., Doig, J.A., Kennedy, J.S. *et al.* (1978) Laryngeal malignancy following iodine-125 therapy for thyrotoxicosis. *Lancet*, **2**, 1177–9.

77 Freeman, M., Giuliani, M., Schwartz, F. *et al.* (1969) Acute thyroiditis, thyroid crisis and hypocalcemia following radioactive iodine therapy. *N.Y. State J. Med.*, **69**, 2036–41.

78 Shafer, R.B. and Nuttal, F.Q. (1971) Thyroid crisis induced by radioactive iodine. *J. Nucl. Med.*, **12**, 262–4.

79 Krishnamurthy, G.T. and Blahd, W.H. (1974) Hyperthyroidism in the presence of panhypopituitarism. Thyroid crisis and hypothyroidism following radioiodine treatment. *West. J. Med.*, **120**, 491–6.

80 Schwartz, T.B. (1970) Editorial comment, in *Year Book of Endocrinol*, Year Book Medical Publishers Inc, Chicago.

81 Kapp, D.S., Li Volsi, V.A. and Sanders, M.M. (1982) Anaplastic carcinoma following well-differentiated thyroid carcinoma: etiological considerations. *Yale J. Biol. Med.*, **55**, 521–8.

82 Harbert, J.C. and Pollina, R. (1984) Absorbed dose estimates from radionuclides. *Clin. Nucl. Med.*, **9**, 210–21.

Index

The following abbreviations are used – TRH for thyrotropin releasing hormone, and TSH for thyroid stimulation hormone.