Chapter 7

Thyroid disorders, dementia and Down syndrome

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Introduction

A long-standing association between Down syndrome (DS) and thyroid disorders has been well documented in the literature.[1–27] However, because of uncertainty about what to use as normal reference levels for interpretation of test results on people with DS, the question of whether or not these individuals have an unusually high prevalence of thyroid dysfunction has recently been raised.[19] The relationship between dementia and thyroid dysfunction in Alzheimer's disease (AD) in the general population has for many years been the focus of considerable clinical and research interest.[28–72] Because people with DS are at risk of developing dementia in Alzheimer's disease (DAD) 20–30 years earlier than in the general population (*see* Chapter 1), the question of whether or not there is a relationship between thyroid dysfunction and DAD in DS has also been a focus of interest.[16,17,73–77] An understanding of thyroid disease in individuals with DS who are at high risk of developing DAD is essential in order to ensure the provision of optimum care for patients with dementia.

Before reviewing the possible association between thyroid disorders and AD, this chapter will discuss thyroid function in general, including the following topics:

1 the main functions of the thyroid gland[78–116]
2 tests for thyroid function[11,78,101,103–106,111,117]
3 abnormalities of thyroid function in the general population[24,29,78,81,83, 95–97,106–108,118–128] and in DS[1–3,5–9,11–13,15–19,21–27,129]
4 the controversial issue of subclinical hypothyroidism and whether or not to treat it in the general population[130–134] and in individuals with DS[8,9,15,19,26]
5 involvement of the thyroid in AD in the general population[15–17,28–37,39–53,55,73,74,75,135] and in DS[15,16,17,73,74,75]
6 strategies for managing thyroid dysfunction,[130,136–144] especially in people with DS,[9,11,19,145–147] including studies of oral supplementation with selenium and zinc in individuals with DS, and other approaches.[25,148–173]

The thyroid gland and its functions

Importance of thyroid function

Thyroid dysfunction is possibly the most important topic in endocrinology. Normal thyroid function is essential not only for normal physical growth and

brain development, but also for regulation of the rate of metabolic reactions in the body throughout the lifespan, and for neural activity. Thyroid hormone effects include increasing the body's overall metabolic rate, increasing heat production, increasing target-cell responsiveness to catecholamines (adrenaline and noradrenaline) and acetylcholine, increasing the heart stroke volume and heart rate, having an effect on growth hormone action, and promoting normal myelination and development of the nervous system.[98,113]

Thyroid dysfunction may occur at any age. It should be treated in the earliest possible stages, when it is reversible.[28,29,174,175] Correcting hypothyroidism, even if mild, during pregnancy is key to normal fetal development. Fetuses do not acquire the ability to synthesise thyroid hormones until 10–12 weeks of age, but during pregnancy there is substantial transfer of maternal thyroid hormones across the placenta.[82,93,116] The next opportunity for correcting thyroid dysfunction is shortly after birth.

The thyroid gland

The thyroid gland is located at the base of the throat. It is butterfly-shaped and weighs 15–25 g, the right lobe being larger than the left. It is composed of many follicles which contain colloid surrounded by a single layer of epithelium. In addition to a person's genetic make-up, a number of other factors and processes affect function of the thyroid. These include thyroid hormone production; binding of thyroid hormone and derivatives to receptors; the availability of iodine, iron, selenium and zinc; thyroid-hormone-binding proteins; thyroid hormone degradation and the hypothalamic–pituitary–thyroid (HPT) axis.[106,107]

Thyroid hormone production

The following processes are involved in the production of thyroid hormones. Ingested iodine is absorbed through the small intestine and transported in the plasma to the thyroid. There it is concentrated, oxidised and incorporated into thyroglobulin (Tg) under the action of haem-containing thyroperoxidase, which uses hydrogen peroxide as a substrate. Iodide attaches to tyrosine residues in Tg, and iodinated tyrosine residues couple to form thyroid hormone precursor, which is stored in thyroid follicles. When hormone is needed, the hormone precursor is endocytosed by the follicular epithelial cells, hydrolysed in lysosomes and the released hormones are secreted into the circulation where specific binding proteins carry them to target tissues. Thyroxine (T4) is the precursor of triiodothyronine (T3), the most active thyroid hormone (the numbers 3 and 4 indicate the number of iodinated tyrosine residues that are present in the hormone molecules). T3 is more potent than T4, but levels of T4 are about 50-fold higher than those of T3.[102,106,107]

How thyroid hormones exert their effect

T3 exerts its effect by crossing the cell membrane and binding to a receptor in the cell nucleus. The receptors then bind to DNA at sites in the 5′ untranslated regions of thyroid-hormone-responsive genes called thyroid response elements. Interaction of T3 with its receptor causes the binding of accessory protein cofactors that

either activate or repress a specific gene's transcription.[85,91,106,107,113] One example of a gene whose transcription is upregulated as a result of T3 stimulation is that for Na^+/K^+-ATPase, to increase oxidative metabolism.[176] An example of a gene whose transcription is downregulated as a result of T3 stimulation is that for amyloid precursor protein (APP).[30,72]

Non-genetic factors that affect levels and/or activity of thyroid hormones

Availability of iodine and trace elements

Thyroid function is dependent upon the availability of iodine and several other trace elements. The relationship between the iodine intake level of a population and the occurrence of thyroid diseases is U-shaped, with an increase in risk associated with both low and high iodine intake. At the low end of the spectrum, severe iodine deficiency leads to endemic goitre (swelling in the neck due to an enlarged thyroid gland), cretinism (a congenital form of thyroid hormone deficiency that retards mental and physical growth) and developmental brain disorders in young children, a spectrum of disorders sometimes referred to as fetal iodine-deficiency disorder. The features of cretinism include a puffy face, open mouth with large protruding tongue, short thick neck, narrow forehead, pug nose, short legs, distended abdomen, hoarse voice, dry yellowish skin, excessive hairiness, lethargy and intellectual disability. Less severe iodine deficiency is associated with multinodular autonomous growth and function of the thyroid gland, leading to goitre and hypothyroidism in middle-aged and elderly subjects. Extremely excessive iodine intake is associated with a high prevalence of thyroid hypofunction and goitre in children. Moderate and mild iodine excesses are associated with a more frequent occurrence of hypothyroidism, especially in elderly people. Fetal iodine-deficiency disorder is the commonest cause of intellectual disability worldwide.[95–97,177] The supplementation of salt with iodine, introduced in the 1920s, has markedly reduced the frequency of fetal iodine-deficiency disorder and thyroid disorders in older individuals resulting from iodine deficiency. Yet iodine deficiency is still a problem for at least 20% of the world's population, including people in North America who do not use iodised salt.[81,92] Although excess iodine can cause hypothyroidism, an abrupt increase in dietary iodine intake can cause hyperthyroidism. 'Epidemics' of hyperthyroidism have been seen in several countries when iodine was added to the national diet in order to correct widespread iodine deficiency.[78] Hypothyroidism and hyperthyroidism are also known to occur as a result of treatment of heart arrhythmia with amiodarone, an iodine-containing benzofuran.[178] One 100 mg tablet of amiodarone contains 250 times the daily requirement of iodine.[179]

In addition to iodine, iron, selenium and zinc are important for normal thyroid function. Iron deficiency impairs thyroid hormone synthesis by reducing the activity of haem-dependent thyroid peroxidase which iodinates tyrosine residues in Tg.[115] Whereas severe iodine deficiency leads to a neural form of cretinism associated with predominantly neuromotor defects, including strabismus, deaf mutism, spastic diplegia and other disorders of gait and coordination, combined selenium and iodine deficiency leads to a myxoedematous form associated with short stature and markedly delayed bone and sexual maturation, but rarely with deafness or thyroid enlargement.[94] The term 'myxoedema' is derived from the

Greek words *myxa,* meaning 'slime', and *oidema*, meaning 'swelling.' Myxoedema develops after birth and is associated with less severe cerebral deficiency than cretinism. Selenium plays an important role in oxidative defence and intracellular redox regulation and modulation in the body, processes that are thought to be impaired in different types of neurodegenerative diseases, including AD in DS (see below). It is a component of a number of important enzymes, including the glutathione peroxidases which detoxify peroxide, the three deiodinases (D1, D2 and D3) that remove iodide from thyroxine and T3 (thus decreasing the stimulation of oxidative metabolism promoted by thyroxine), the thioredoxine reductases and methionine-sulphoxide reductase.[180] Selenium is incorporated into all of these enzymes in the form of an amino acid to which the selenium is already bound, called selenocysteine.[84]

Thyroid dysfunction is known to influence zinc metabolism, and zinc status in the body is known to influence thyroid function, although the reasons for these effects are not well understood. Zinc may mediate the binding of thyroid hormone receptor to the thyroid hormone response element via its 'zinc fingers.'[84,90] (Zinc fingers are small protein domains in which zinc plays a structural role contributing to the stability of the domains.) Zinc is also a cofactor of cytoplasmic Cu,Zn-superoxide dismutase-1 (SOD1), the enzyme that dismutates superoxide radicals into peroxide in cells[99] (for further information on SOD1 and its possible role in AD in DS, *see* Chapter 5).

Availability of thyroxine-binding proteins

Thyroxine is mostly bound to proteins called thyroxine-binding proteins (TBP). These include thyroxine-binding globulin (TBG), prealbumin (now called transthyretin), albumin and apolipoprotein E (ApoE).[89,101] The ApoE gene has three common alleles: $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$. The $\epsilon 4$ allele is overexpressed in people with late-onset DAD, yet it is also associated with increased embryo survival.[114] In the Han Chinese, $\epsilon 4$ is significantly overexpressed in individuals affected by fetal iodine-deficiency disorder, DAD and vascular dementia.[111,112] This observation suggests an involvement of iodine deficiency and its consequences in all three of these disorders.

Inactivation processes

Once it has exerted its effect, thyroid hormone is inactivated by deiodination and other mechanisms (including glucuronidation, sulphation, oxidative deamination and ether bond cleavage). Three selenium-containing deiodinases (D1, D2 and D3) regulate the levels of T3. In humans, D1 is expressed mainly in liver, kidney and thyroid, D2 is expressed in the brain, pituitary and brown fat, and D3 is restricted to the brain, placenta and pregnant uterus. D1 and D3 deiodinate T4 and T3 and are under positive control by T3. D2 is under negative control by T4, which induces its ubiquitination (addition of ubiquitin groups), accelerating its destruction.[181]

Competition with reverse T3

One derivative of thyroid hormone is called reverse T3 (rT3). This derivative is inactive, but it will compete with T3 for its receptor. The formation of rT3 is promoted by cortisol, the levels of which are increased as a result of stress.[181]

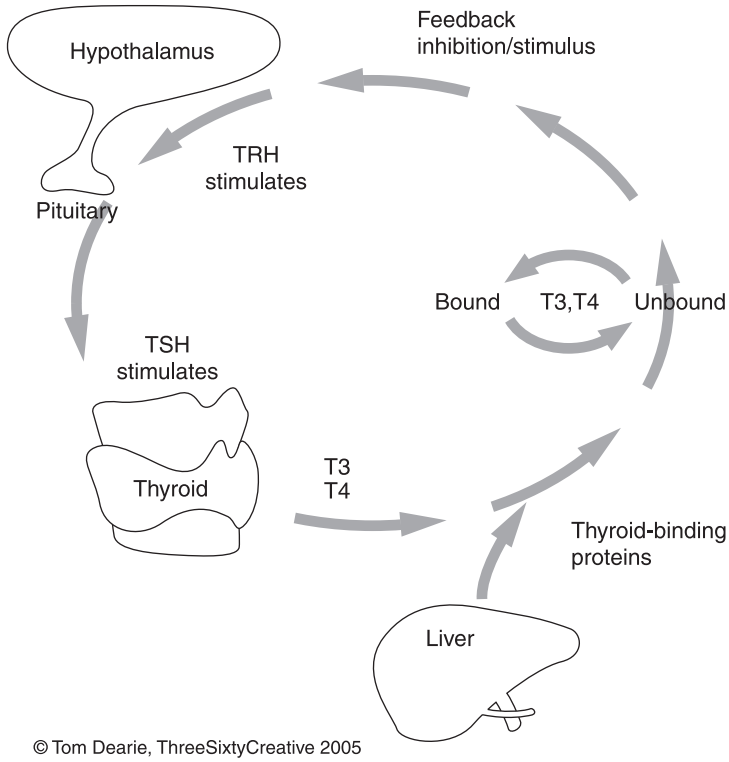

Figure 7.1 Hypothalamic–pituitary–thyroid axis. Thyroid hormones T3 and T4 are controlled by the hypothalamus through a feedback loop. TRH from the hypothalamus triggers T3 and T4 release via TSH from the pituitary. Thyroid-binding proteins then bind circulating T3 and T4. Surplus unbound T3 and T4 inhibit further TRH and TSH release by the hypothalamus and pituitary.

The hypothalamic–pituitary–thyroid axis

The thyroid gland operates in concert with the hypothalamus and the pituitary gland, an arrangement which is referred to as the 'hypothalamic–pituitary–thyroid' (HPT) axis (*see* Figure 7.1). The hypothalamus secretes thyroid-releasing hormone (TRH), which stimulates the anterior pituitary to synthesise and secrete thyrotropin or thyroid-stimulating hormone (TSH). In turn, TSH acts on the thyroid gland to upregulate production of T4 and T3.[106,182]

The HPT axis is subject to feedback inhibition by the circulating thyroid hormones. The synthesis and secretion of TSH are stimulated by TRH in response to low levels of circulating thyroid hormones. T4 and T3 downregulate TSH in a classic feedback inhibition loop. TRH production in the hypothalamus is also inhibited by these thyroid hormones, but to a lesser degree than TSH production. Recently, two other hormones that are produced in the hypothalamus have been shown to affect TSH secretion. Corticotrophin-releasing hormone (CRH), which stimulates the production of adrenocorticotropic hormone (ACTH) by the pituitary, leading to cortisol production by the adrenal glands, has been shown

to stimulate TSH secretion. Furthermore, somatostatin blunts the TSH response to TRH and CRH.[86] Primary causes of thyroid dysfunction (i.e. those that directly affect the function of the thyroid gland) are most common. Secondary causes of thyroid dysfunction result from impairment of the function of the hypothalamus or pituitary.[88,100,106,182]

Tests for thyroid function

Normal reference ranges and factors that affect them

Development of the radioimmunoassay in the 1970s revolutionised the study of thyroid hormones and the whole field of endocrinology.[104] It enabled sensitive assays to be developed that are diagnostic for thyroid malfunction. No single laboratory test is 100% accurate in diagnosing all types of thyroid disease. However, a combination of two or more tests usually can be. Table 7.1 lists the tests that are commonly used to assess thyroid function and the representative 'normal' reference ranges in serum samples from adults.

Values for children and for pregnant women are different. Normal ranges from different laboratories will vary slightly, as there is no calibration of the tests between different laboratories.

At present there is concern that normal ranges for most thyroid tests are too broad. This means that certain individuals who are near the upper or lower limits of normal may have some thyroid malfunction. There are several reasons why normal ranges for thyroid tests may be too broad. Test results are known to be affected by genetic factors, time of day and season of the year, age, gender and

Table 7.1 Typical serum reference ranges for thyroid tests in adults aged 20–80 years

Test	*Normal reference range*
TSH	0.5–5 μU/ml
Total T4 (TT4)	5.0–12.0 g/dl or 64.4–154.4 nmol/l
Free T4	0.9–2.0 ng/dl or 12–26 pmol/l
Free T4 index (T7 or FT4I) (total T4 × T3 uptake)	5–12 SI units
Total T3 (TT3)	95–200 ng/dl or 1.5–3.0 nmol/l
Free T3	0.2–0.52 ng/dl or 3–8 pmol/l
Free T3 index (FT3I)	1.3–4.2 or 16–54 SI units
T3 uptake (indirect measure of thyroid-binding globulins)	23–35% or 0.2–0.35 SI units
Thyroid antibodies (to thyroglobulin, peroxidase, thyroid receptor)	Values differ between laboratories
Other (iodine uptake scan, thyroid scans, ultrasound, needle biopsy)	

Thyroid hormone tests. Normal reference ranges; www.keratin.com/ab/ab011.shtml#03.[109]

probably fasting, but such factors are not usually taken into consideration when normal ranges are established. When people are tested on more than one occasion, inter-individual variation in serum TSH, free T4 and free T3 concentrations has been found to be much greater than intra-individual variation, which suggests that each individual may have a genetically determined thyroid function set-point.[15,79,80,104,105,183]

Thyroid function tests and interpretation

Thyroid-stimulating hormone (TSH)

Normally, low levels (less than 3–5 units) of TSH are sufficient to keep the normal thyroid gland functioning properly. Clinically, measurement of the serum TSH level is used first to assess thyroid status. An elevated TSH level is indicative of primary hypothyroidism, whereas a lowered level is indicative of primary hyperthyroidism. The first-generation TSH tests had no lower limit of normal. The second- and third-generation tests have clearly defined lower limits, and involve the use of two or more antibodies directed to different portions of TSH.[107,117]

Thyroid hormones

Measurements of T4 and T3 levels aid the diagnosis of thyroid status. Elevated T4 levels are characteristically seen in patients with primary hyperthyroidism, whereas T4 levels are generally reduced in patients with primary hypothyroidism. Normal T4 levels accompanied by high T3 values are seen in patients with *T3 thyrotoxicosis*. Thyroxine levels may be altered by physiological or pathological changes in TBP capacity. Drugs that compete for T4-binding sites in the T4 assay, such as phenylbutazone, diphenylhydantoin or salicylates, can result in a lowered T4 measurement. Serum T4 levels in neonates and infants are higher than the corresponding values in the normal adult, due to the increased concentration of TBG in neonate serum. Thyroxine values should therefore be normalised for variation in TBP capacity. The free thyroxine index (FT4I) is used to achieve this measurement.[101,103,104,106]

The following serum tests are commonly used to characterise thyroid hormone function.[104,106,108]

- **Total T4.** This represents the total amount of T4. Uncorrected T4 levels may be high not only as a result of hyperthyroidism, but also due to pregnancy, oral contraceptive pills, oestrogen replacement therapy and other factors.
- **Free T4.** This test directly measures the free T4 level in the blood.
- **Total T3.** This test is usually ordered when thyroid disease is being investigated. T3 is more potent and short-lived than T4. Some people with an overactive thyroid secrete more T3 than T4. In such cases, T4 levels can be normal, T3 levels elevated and TSH levels low. Total T3 is a measure of the total amount of T3 in the bloodstream, including the T3 bound to carrier proteins plus free and circulating T3.
- **Free T3.** This measures only the T3 that is free and not bound to carrier proteins.
- **T3 resin uptake.** This is not a thyroid test. It reflects the level of proteins that carry thyroid hormone in the bloodstream. A high T3 resin uptake level reflects a low level of these proteins.

- **Free thyroxine index.** A mathematical computation allows the laboratory to estimate the free thyroxine index from the T4 and T3 uptake tests. The result indicates how much thyroid hormone is freely available in the body.

Thyroid antibodies

Some individuals produce antibodies to thyroglobulin, thyroid peroxidase or the TSH receptor. The measurement of titres of thyroid autoantibodies should be undertaken if the TSH is mildly abnormal but T4 and T3 indicators are normal.[104,106,108]

Abnormalities of thyroid function

Thyroid dysfunction in the general population

Prevalence rates of thyroid disorders vary markedly from one country to another, but they generally show increasing frequency with age and they also occur more commonly in women. About one in 13 people (7.35%) in the USA have diagnosed thyroid disorders, and about one in 20 (4.78%) have undiagnosed thyroid disease.[128] Low-grade functional disorders are more common than cases of overt disease.

Hyperthyroidism

A laboratory diagnosis of hyperthyroidism is characterised by the following:

- decreased TSH and elevated T4 (primary)
- elevated T4/T3, FT4I and TSH (secondary and tertiary).

The prevalence of hyperthyroidism in community-based studies in the USA has been estimated to be 2% for women and 0.2% for men. As many as 15% of cases of hyperthyroidism occur in patients over 60 years of age.[184] There are several causes of hyperthyroidism. Most often the entire gland is overproducing thyroid hormone. This is called Graves' disease. Less commonly, a single nodule is responsible for the excess hormone secretion. This is referred to as a 'hot' nodule. Inflammation of the thyroid gland, known as thyroiditis, can lead to the release of excess amounts of thyroid hormones. Hyperthyroidism can also occur in patients who are taking excessive doses of any of the available forms of thyroid hormone.

Clinical manifestations of hyperthyroidism include weight loss, loss of muscle mass, dyspnoea, loss of fat stores, exercise intolerance, easy fatiguability, nervousness, irritability, insomnia, tremor, heat intolerance, excessive sweating, increased cardiac output, diarrhoea, changes in menstrual periods and warm moist skin.[123] A disorder dubbed 'apathetic hyperthyroidism' (paradoxical presentation of hyperthyroidism with fatigue, psychomotor slowing, depression and weight gain) is common in the elderly.[29] This condition can exacerbate chronic diseases, especially cardiovascular conditions.

Hypothyroidism

A laboratory diagnosis of hypothyroidism is characterised by the following:

- increased TSH and decreased T4 (primary)
- decreased T4, T3, FT4I and TSH (secondary and tertiary).

This disorder is associated with the presence of insufficient thyroid hormones to meet metabolic needs. It may be congenital (i.e. present since birth, transient or permanent) or acquired.

Congenital hypothyroidism

This disorder occurs when the thyroid gland fails to develop or function properly. In 80–85% of cases the thyroid gland is absent, abnormally located or severely reduced in size. In the remaining cases, a normal-sized or enlarged thyroid gland is present, but production of thyroid hormones is decreased or absent. Although many countries have introduced programmes to prevent iodine deficiency by providing iodised salt, fetal iodine deficiency is still the commonest cause of congenital hypothyroidism worldwide, affecting as many as 10% of individuals in an iodine-deficient area. Worldwide, the frequency of congenital hypothyroidism resulting from iodine deficiency is about 18 in 1000.[95–97] If babies with iodine deficiency are not treated, cretinism will develop (see above).

In iodine-replete areas, the incidence of congenital hypothyroidism from other causes ranges from about 1 in 3000 to 1 in 4000.[116,185] Congenital hypothyroidism with a genetic basis occurs sporadically in about 85% of cases. Mutations in the following genes are now known to cause congenital hypothyroidism that is not a result of iodine deficiency: PAX8 (essential for regulation of the thyroglobulin gene by transforming growth factor); SLC5A5 (provides instructions for synthesising a protein that facilitates the uptake of iodide in certain tissues); Tg; thyroid peroxidase (TPO); thyroid-synthesising hormone β-subunit (TSHB); thyroid-synthesising hormone receptor (TSHR). Mutations in other genes that have not yet been well characterised may also cause congenital hypothyroidism.[120] Gene mutations cause the loss of thyroid function in one of two ways. Mutations in the PAX8 gene and some mutations in the TSHR gene prevent or disrupt the development of the thyroid gland before birth. Mutations in the SLC5A5, Tg, TPO and TSHB genes prevent or reduce the production of thyroid hormones, even though the thyroid gland is present. If treatment for congenital hypothyroidism is started within a month after birth, children develop almost normally. However, because they still undergo a brief period of thyroid hormone deficiency, they are at risk for subtle selective impairments.[185] As neuropsychological tools have become more sensitive, it has become apparent that even mild thyroid hormone deficiency in humans can produce measurable deficits in very specific neuropsychological functions. Interestingly, among newborns in the general population who have been diagnosed with congenital hypothyroidism, there is evidence for an unusually high frequency of other congenital birth defects, including cardiac anomalies and gastrointestinal anomalies, raising the possibility that multiple congenital anomalies in single individuals have resulted from the same teratogenic event.[186,187]

Acquired overt hypothyroidism

The overall prevalence of overt hypothyroidism in the USA is 5–10 in 1000 in the general population. Above the age of 65 years it increases to 6–10% of women and 2–3% of men. It occurs more frequently in women than in men (female:male ratio, 5–10:1). As many as 3–5% of the population are thought to have some degree of hypothyroidism. Some of the common causes of hypothyroidism include Hashimoto's thyroiditis, lymphocytic thyroiditis, thyroid destruction,

hypothalmic or pituitary disease, pituitary injury, medications and iodine deficiency.[78,106]

Overt hypothyroidism in adults is associated with a familiar set of symptoms and signs, including fatigue, weakness, weight gain or difficulty losing weight, slowed heart rate, coarse dry hair, dry rough pale skin, hair loss, cold intolerance, muscle cramps, frequent muscle aches, constipation, irritability, memory loss or slowed mental processing, abnormal menstrual cycles and decreased libido. However, such symptoms cannot be used to reliably diagnose hypothyroidism. Once a diagnosis has been made on the basis of quantitative laboratory measurements, treatment is straightforward and the patient's prognosis is excellent.[124] A normal TSH level does not exclude central hypothyroidism involving hypothalamic or pituitary dysfunction, which may not be as rare in elderly people as was previously thought.[29]

Autoimmune thyroiditis

This disorder is characterised by elevated titres of autoantibodies produced against TSH, thyroid peroxidase or the TSH receptor. Autoimmune thyroiditis may or may not be accompanied by altered levels of TSH or the thyroid hormones. Graves' disease, Hashimoto's thyroiditis and Ord's thyroiditis are examples of autoimmune thyroid disorders termed 'autoimmune thyroiditis.' Interestingly, Hashimoto's thyroiditis is associated with goitre (enlargement of the thyroid gland), whereas Ord's thyroiditis is associated with thyroid atrophy. Hashimoto's thyroiditis is reported to be common in North America, whereas Ord's thyroiditis occurs more frequently than Hashimoto's in Europe.[188] De Quervain's thyroiditis (also called subacute or granulomatous thyroiditis) is much less common than Hashimoto's thyroiditis. The thyroid gland generally swells rapidly and is very painful and tender. The gland discharges thyroid hormone into the blood and the patient becomes hyperthyroid. However, the gland stops taking up iodine and the hyperthyroidism generally resolves over the next few weeks. Silent thyroiditis is the least common type of thyroiditis. The majority of patients with the latter disorder are young women following pregnancy. The disease usually requires no treatment, and 80% of patients show complete recovery, with the thyroid gland returning to normal after about three months.[78,107,188]

It is not known whether antithyroid antibodies cause thyroid disease, whether thyroid disease causes the antibodies, or whether the antibodies' functions are physiologically beneficial.[127] Rarely, elderly people with autoimmune hypothyroidism have a condition called Hashimoto's encephalopathy, which features cognitive abnormalities (usually a delirium state but sometimes a stroke-like syndrome).[65] Thyroid hormones are unlikely to be directly involved in this condition, which may respond to corticosteroid treatment.

Euthyroid 'sick syndrome'

This term refers to abnormalities in thyroid function that are not caused by primary thyroid or pituitary dysfunction.[87] Causes are thought to include hypothalamic and pituitary suppression, decreased conversion of T4 to T3, alterations in serum binding of thyroid hormones, and decreased TSH production and/or its effect on the thyroid. Cytokines such as tumour necrosis factor alpha, interleukin-1, interleukin-6, free fatty acids, cortisol and glucagon all have effects on thyroid function. Abnormalities of thyroid function also result from conditions

such as surgical stress and serious infection. It is not clear whether these changes reflect a protective response in the face of a serious illness, or a maladaptive process that needs to be corrected. Some patterns of abnormalities that fall into the category of euthyroid 'sick syndrome' include the following.

- **Low T3 with an increase in rT3.** This is thought to be due to a decrease in the conversion of T4 to T3 by the hepatic deiodinase system.
- **Low T3 and low T4 with normal to low TSH.** This may be due to low TBG levels or the presence of a thyroid-hormone-binding inhibitor.
- **Low TSH, low T3 and low T4.** This suggests an alteration in pituitary or hypothalamic responsiveness.
- **Elevated T4 with normal or elevated TSH and normal or elevated T3.** This may be seen in primary biliary cirrhosis and acute or chronic hepatitis in which TBG synthesis and release are increased, in acute psychiatric illnesses, and as a result of use of certain drugs.[83,106]

Thyroid dysfunction in Down syndrome

History

The first suggestion of a link between thyroid dysfunction and DS was made unintentionally over 130 years ago before the disorder of DS had been formally recognised. In 1866, a French physician, Edouard Seguin, described a condition termed 'furfuraceous' cretinism in a particular subgroup of children:

> With its milk-white, rosy, and peeling skin; with its shortcomings of all the integuments, which give an unfinished aspect to the truncated fingers and nose; with its cracked lips and tongue; with its red, ectopic conjunctiva, coming out to supply the curtailed skin at the margin of the lids.[22]

Retrospectively, some people have suspected that 'furfuraceous cretinism' was in fact the disorder now known as DS, although there is not universal agreement about this.

In 1866, John Langdon Haydon Down coined the term 'mongoloid' to denote the characteristics of a group of children with the remarkably similar abnormalities that we now associate with DS, and to distinguish such abnormalities from those in cretinism.[119] Before the genetic reason for DS was known, many people thought that the syndrome was caused by hypothyroidism. One reason for this was that, in 1896, Telford Smith reported that giving thyroid therapy improved the physical and mental condition of these children.[23] Another reason was that two autopsy studies revealed a high rate of thyroid abnormality in 'mongolism.' One study, published in 1903, reported that all thyroid glands were histopathologically abnormal in these individuals.[3] A second study, published in 1948, reported that only one out of 48 thyroid glands examined was normal, 20% having colloidal goitre with scattered areas of hyperplasia.[1,11] Although these fascinating studies suggest that the thyroid gland may be morphologically abnormal in all people with DS, they should be treated with caution because it was not until the 1970s that an objective distinction could be made between DS and cretinism.[18] A definite diagnosis of DS became possible in 1959 when Jerome Lejeune and Patricia Jacobs independently discovered that people with the

clinical phenotype of DS carried an extra chromosome, which is now called chromosome 21.[189,190] With the advent of the radioimmunoassay in the 1970s that led to accurate measurement of thyroid hormones in blood, it became possible to categorise thyroid disorders and to make an objective distinction between conditions of overt thyroid dysfunction and DS. However, clinical laboratory testing has revealed an unusually high frequency of clinically abnormal thyroid results in individuals with DS, the majority being indicative of subclinical hypothyroidism (see below).

Thyroid abnormalities occur in all age groups in DS.[4,8,9,11,15,129] Clinical forms of hypothyroidism that are found in individuals with DS include congenital hypothyroidism, transient and primary hypothyroidism, compensated hypothyroidism, pituitary–hypothalamic hypothyroidism, TBG deficiency, autoimmune thyroiditis and chronic lymphocytic thyroiditis. Hyperthyroidism also occurs. As in the general population,[187,191] babies with congenital hypothyroidism and DS are at increased risk of having other congenital abnormalities. In one study, congenital hypothyroidism in DS was found to occur significantly more frequently in individuals diagnosed with congenital gastrointestinal anomalies than in those without such a diagnosis.[192] Thyroid disease is difficult to diagnose clinically in individuals with DS because of the overlap of symptoms. This means that thyroid blood screening is a particularly important part of the annual preventive medicine screening of each person with DS.

When data from thyroid function tests are compared in newborns with or without DS, there is evidence that a high percentage of newborns with DS have abnormalities in thyroid function, in particular somewhat elevated TSH levels and somewhat reduced T4 levels.[26] Because newborns with DS are rarely treated for thyroid problems, an important question is whether some of the characteristics attributed to DS, such as impairment of development and growth, may be the result of neonatal thyroid dysfunction. Van Trotsenburg and colleagues[26] conducted a single-centre, randomised, double-blind, 24-month trial with nationwide recruitment, comparing thyroxine administration with placebo in 196 neonates with DS in order to address this issue. Compared with placebo, thyroxine treatment significantly reduced the delay in motor development and mental development in the study population. Furthermore, children who were treated with thyroxine were taller and heavier than those who were not treated. This study concluded that thyroxine treatment of neonates with DS should be considered in order to maximise their development and growth. However, the long-term consequences of thyroid hormone treatment need to be considered. Unnecessary treatment with thyroid hormone can lead to bone demineralisation and cardiac arrhythmias.[11] Furthermore, *in-vitro* and *in-vivo* studies indicate that thyroid hormones have a strong influence on oxidative stress, a state that develops when antioxidative defence mechanisms are not sufficient to cope with cellular damage resulting from oxidative processes.[163]

Thyroid dysfunction in adults with Down syndrome

A number of papers have covered the topic of thyroid dysfunction in adults with DS.[5,6,11–13,15,17–20,25–27] There is an age effect on the frequency of thyroid abnormalities in individuals with DS as well as in the general population, the frequency increasing with age. Autoimmune thyroiditis associated with mild hypothyroidism is very common, with as many as 30% of people over the age of 40 years

being affected. Males as well as females with DS are prone to developing thyroid dysfunction, although the frequency is higher in females. Overt hypothyroidism and overt hyperthyroidism are also more common in adults with DS than in the general population.[9,15]

An important issue that needs to be further investigated is whether the apparently increased prevalence of mild hypothyroidism in adults with DS results artefactually from the use of reference ranges for people without DS.[19] It has been argued that if reference ranges for healthy people with DS are used, prevalence rates for hypothyroidism would be the same as in the general population. On the other hand, the increased prevalence of thyroid dysfunction in individuals with DS may reflect accelerated ageing and/or early onset of DAD in this population.[15,19] The finding of abnormal histopathology in the thyroid glands of individuals with DS, and the striking association of autoimmune thyroiditis in older people with DS with the HLA DQA 0301 antigen[13] and with chronic hepatitis B virus infection,[12] support the hypothesis that the high frequency of thyroid disorders in DS is not entirely a result of using inappropriate reference ranges. Other reported associations with apparent thyroid dysfunction in DS include the following:

- a statistical association between elevated TSH levels and the presence of autoantibodies to gliadin (characteristic of coeliac disease)[24]
- an association between elevated TSH levels and lowered serum selenium levels[7]
- among females with DS, an association between treated hypothyroidism and the $\epsilon 4$ allele of ApoE, the $\epsilon 2$ allele appearing to be protective[16]
- a possible association between hypothyroidism and arthritic presentations in DS.[2]

Interestingly, having DS may protect against the development of malignant neoplasms of the thyroid.[21] Some key findings with regard to thyroid dysfunction in adults with DS are listed in Table 7.2.

Subclinical hypothyroidism in the general population and in individuals with Down syndrome

Subclinical hypothyroidism is defined as elevated TSH with normal thyroxine levels, or normal TSH with low thyroxine levels. Because the laboratory reference ranges are so broad, individuals whose test results fall just within the current normal limits may have mild thyroid disease. An issue that is currently controversial is whether or not people with subclinical thyroid disease, especially subclinical hypothyroidism, should be treated.[133]

On the one hand, it is possible that even slightly abnormal thyroid hormone results may affect cognitive function. For example, in a study of 628 women aged 65 years or over who were community based and physically impaired, the relationship between cognitive function and levels of thyroid hormones was assessed at entry to the study and after 1, 2 and 3 years, using the Mini Mental State Examination.[134] Although no association between T4 and TSH levels and cognitive function was noted at the start of the study, those women with the lowest levels of thyroid hormones had a twofold higher risk of cognitive decline,

Table 7.2 Some key findings with regard to thyroid dysfunction in adults with Down syndrome

Study	*Findings*
Percy *et al.* (1990)[15]	Autoimmune thyroiditis associated with mild, subclinical hypothyroidism was found to be common in older people with DS. This disorder was found to affect more people and to be milder in DS than the hypothyroidism that affects older people in the general population. Compared with healthy control individuals without DS or ID, patients with DS had, overall, lower mean total T4 and free T3, higher T3U and TSH, no difference in free T4, and higher thyroid antithyroglobulin and antimicrosomal autoantibody titres. Similar trends were apparent in males and females with DS, and in individuals with DS who were not taking any drugs
Hestnes *et al.* (1991)[6]	Clinical and laboratory endocrine variables in adult institutionalised patients with DS were compared with those for matched controls consisting of other patients with ID from the same institution. The average TSH level in DS patients was higher than in the controls. There was no clear-cut correlation between TSH and thyroid hormone levels. The data indicated a tendency towards primary thyroid dysfunction in DS. There was some evidence of a relative failure of TSH secretion
Nicholson *et al.* (1994)[13]	Susceptibility to autoimmune thyroiditis in DS was found to be associated with the major histocompatibility class II DQA 0301 allele
May and Kawanishi (1996)[12]	The frequency of thyroiditis in patients with DS who were also carriers of hepatitis B virus surface antigen (HBsAg) was threefold higher than the frequency of thyroiditis in those patients with DS who were not carriers of HBsAg (65% *vs.* 23%; $P < 0.01$). No similar association was observed in patients with ID who did not have DS
Storm (1996)[24]	A statistical correlation was found between increased TSH levels and a positive titre for gliadin antibodies, which are characteristic of coeliac disease in DS
Rooney and Walsh (1997)[20]	Abnormalities in thyroid function tests were found to occur more frequently in patients with DS who were institutionalised than in those who lived in the community
Kanavin *et al.* (2000)[7]	Increased TSH, decreased free T4 and decreased serum selenium levels were found in institutionalised adults with DS compared with people with ID matched for age, gender and behavioural function as controls. A positive correlation was observed between serum concentrations of free T4 and selenium in the patients with DS ($r = 0.393$, $P < 0.05$)

Table 7.2 (*cont.*)

Study	*Findings*
Percy *et al.* (2003)[16]	In older women with DS, there was an ApoE allele effect on thyroid status, with $\epsilon 2$ negatively ($P \leq 0.01$) and $\epsilon 4$ positively ($P \leq 0.05$) associated with treated hypothyroidism. In this case hypothyroidism was defined as having at least one elevated serum TSH level. There was no evidence for an ApoE allele effect on thyroid status in older men with DS
Bosch *et al.* (2004)[2]	Among eight patients with DS who had a slipped capital femoral epiphysis, hypothyroidism was diagnosed in 6 cases. This observation raised the possibility that hypothyroidism is a predisposing factor for this disorder, at least in DS
Prasher and Haque (2004)[19]	About one-third of a group of apparently healthy adults with DS were found to have subclinical hypothyroidism (elevated TSH with normal free T4 or low free T4 with normal TSH levels). The others were biochemically euthyroid. The authors raised the question of whether standard general population laboratory free T4 and TSH reference ranges are really applicable to the DS population. They pointed out that adults with DS are susceptible to premature ageing, and that the higher TSH values might reflect this. They also pointed out that use of the current standard laboratory reference ranges for thyroid function tests does not allow researchers or physicians to take an age effect into account
Satge *et al.* (2004)[21]	Malignant neoplasia of the thyroid were found to be rare in DS

leading the authors to conclude that low thyroid hormone levels may contribute to cognitive impairment in physically impaired women.[134] In another study of 36 older women with mild hypothyroidism, Bono and colleagues[130] found an improvement in verbal fluency and depression scores, and a positive correlation between TSH reduction and improved mood scores after treatment with L-thyroxine, supporting the treatment of asymptomatic mild hypothyroidism in order to reset hormonal levels and protect the brain against the potential risk of cognitive and affective dysfunction. Yet in population studies of the 'oldest old', subclinical hypothyroidism was not associated with adverse health effects, and was in fact associated with a survival advantage.[131–133]

This issue of whether or not to treat subclinical hypothyroidism is even more relevant in the case of people with DS. As already mentioned, hypothyroidism appears to be greatly over-represented in this disorder, affecting as many as 30–50% of DS patients in their lifetime.[9,15] In particular, in early infancy as many as 80–90% of neonates with DS appear to have mild hypothyroidism.[26] The cause(s) of subclinical disease in people with DS is not known. It may be due to a true thyroid hormone deficiency and a consequence of trisomy 21 itself, or it may be due to a micronutrient deficiency (e.g. iodine, selenium or zinc deficiency) or

other causes (see summary and discussion). Alternatively, as already discussed, subclinical hypothyroidism may be at least in part an artefact resulting from the use of reference ranges for people without DS.[19] Furthermore, it has yet to be established whether there are different causes of subclinical thyroid abnormalities in individuals with DS over their lifespan. In conclusion, well-designed clinical trials are needed to determine the advantages and/or disadvantages of treating very mild abnormalities of thyroid function in DS patients as well as in the general population.

Thyroid dysfunction and dementia in Alzheimer's disease

Rationale for a possible connection

For many years there has been considerable interest in the hypothesis that thyroid dysfunction is an integral feature of AD. If thyroid status or levels of thyroid hormones are consistently abnormal in a high percentage of patients with DAD, then such measurements might be used as diagnostic markers for DAD in the general population. Some reasons that have fuelled studies in this area include the following:

- Some cases of dementia are known to be the result of hypothyroidism caused by thyroid hormone deficiency. If the hypothyroidism is treated at an early stage, it can often be reversed.[28,29,31] When dementia is first diagnosed, efforts should be directed towards ruling out the presence of thyroid hormone deficiency, and at least nine other disorders that are potentially reversible.[29] As discussed above, even very mild hypothyroidism may have an effect on cognitive function.
- A high percentage of people worldwide suffer from iodine deficiency and are therefore prone to developing clinical thyroid dysfunction.[118] Iodine deficiency may result in hypothyroidism that is overt or subclinical,[97] and such deficiency has been implicated theoretically in AD and in Parkinson's disease.[37]
- It has been proposed that thyroid hormone deficiency in the central nervous system, resulting from a variety of causes, including insufficient blood flow to the brain, may cause or contribute to DAD.[60]
- Brain changes occur in AD that may affect thyroid function. Neuropathological studies of adults in the general population with DAD, and of adults with DS and DAD, have demonstrated that neurochemical changes occur not only in the cerebral cortex but also in the hypothalamus, which is involved in the regulation of thyroid hormone production. Characteristic neurochemical changes include a reduction in choline acetyltransferase activity.[193–197] Because the somatostatinergic system inhibits the release of TSH, a decrease in somatostatin levels would result in an increase in TSH levels.[198] Loss of brain tissue as a result of neurodegeneration may also affect the function of the HPT axis in people with DAD.

Other observations that support the involvement of thyroid function in AD are listed in Table 7.3. Of particular interest are the effects of thyroid hormone on the expression of choline acetyltransferase[59] and also on the expression of APP and its splice variants.[52,72] (Choline acetyltransferase is the enzyme that catalyses the formation of acetylcholine, levels of which are reduced in AD. Deposits of

Table 7.3 *In-vitro* studies that support the possible involvement of thyroid function in dementia or Alzheimer's disease

Study	*Findings*
Sutherland *et al.* (1992)[68]	Message levels for a thyroid hormone receptor located on chromosome 21 and highly expressed in brain (c-ERB A alpha) were reduced by 52% in CA1 and 43% in CA2 in AD hippocampus compared with Huntington controls
Benvenga *et al.* (1993)[136]	Exon 3 of ApoE was found to carry a thyroid-hormone-binding domain (the ϵ4 allele of ApoE is a major risk factor for DAD; the binding of thyroid hormone to different ApoE isoforms may vary)
Quirin-Stricker *et al.* (1994)[59]	Thyroid hormone activates the human choline acetyltransferase gene via binding of thyroid hormone receptor to its 5′ untranslated region
Schmitt *et al.* (1995)[62]	Thyroid epithelial cells were found to produce large amounts of the Alzheimer β-APP and potentially amyloidogenic APP fragments
Schmitt *et al.* (1996)[63]	The production of an amyloidogenic metabolite of APP in thyroid cells was found to be stimulated by interleukin-1-β, but inhibited by interferon-γ
Belandia *et al.* (1998)[30]	Thyroid hormone was found to negatively regulate the transcriptional activity of the β-APP gene
Latasa *et al.* (1998)[52]	Thyroid hormones were found to regulate β-amyloid gene splicing and protein secretion in neuroblastoma cells
Labudova *et al.* (1999)[51]	TSH receptor was found to be overexpressed in the brains of patients with DS and DAD
Luo *et al.* (2002)[57]	Decreased thyrotropin-releasing hormone levels were found in the hippocampus of patients with DAD compared with normal controls
Villa *et al.* (2004)[72]	A response unit in the first exon of the β-APP gene containing thyroid hormone receptor and Sp1 binding sites was found to mediate negative regulation by T3

amyloid β-peptide (Aβ), a breakdown product of APP, are a characteristic hallmark of AD; *see* Chapter 1.)

Association between thyroid disease and Alzheimer's disease in the general population

For the general population, a considerable number of clinical studies have investigated an association between thyroid disease and DAD (*see* Table 7.4). The first such studies were reported by Heyman and colleagues, who investigated genetic aspects and a number of possible associated clinical disorders in 68 adults in whom dementia appeared before the age of 70 years.[45,46] Although the studies primarily focused on DAD presenting in the relatives of individuals with familial DAD, they did show that of the 68 probands, 14 individuals (one man and 13

Table 7.4 Studies that have investigated a clinical association between thyroid disease and Alzheimer's disease in the general population

Study	*Findings*
Heyman *et al.* (1983, 1984)[45,46]	History of thyroid disease was found to be significantly more frequent in DAD probands than in non-DAD controls
Small *et al.* (1985)[64]	No significant association between DAD and thyroid dysfunction was found in individuals with DAD
Tappy *et al.* (1987)[69]	Hypothyroidism was not found to be significantly associated with cognitive disorders
Lawlor *et al.* (1988)[53]	No significant difference in history of thyroid disease was found between DAD and non-DAD subjects
Katzman *et al.* (1989)[50]	Risk factors for DAD were investigated, and thyroid disease was not found to be a significant risk factor
Lopez *et al.* (1989)[55]	Findings did not support an association between thyroid disorders and DAD
Yoshimasu *et al.* (1991)[77]	For myxoedema, there was a positive non-significant association with DAD. For Graves' disease, there was a statistically significant negative association with DAD
Edwards *et al.* (1991)[34]	The frequency of thyroid dysfunction was found to be similar in individuals with familial and non-familial DAD
Lopez *et al.* (2000)[56]	The authors examined the clinical characteristics of 267 patients diagnosed with possible DAD. They identified six categories of patients: possible DAD with cerebrovascular disease (69%), with history of alcohol abuse (15%), with history of depression (7%), with thyroid disease (4%), with history of head trauma (6%), with vitamin B_{12} deficiency (6%), and with other disease processes that may have affected the clinical presentation of DAD (4%). Thus thyroid disease is not a major factor in DAD

women) had a history of thyroid disease or were receiving thyroid hormone replacement therapy. This number was significantly more than expected. A significantly higher frequency of previous thyroid disease was found in female patients than in female control subjects (25% and 7.1%, respectively), and a possible association between DAD and thyroid dysfunction was highlighted.

Although thyroid dysfunction can occur concurrently with DAD, most population studies conducted subsequent to the reports of Heyman and colleagues have failed to confirm a significant excess of thyroid disease in patients with DAD compared with a non-DAD control group.[34,64,69] However, Yoshimasu and colleagues found a trend towards a positive association of myxoedema with DAD and a statistically significant negative association of Graves' disease with DAD.[77] In conclusion, the above data indicate that comorbid overt thyroid disease does exist in a relatively small percentage of patients with DAD, but that it is not a major factor in AD.

Association between thyroid dysfunction and dementia in Alzheimer's disease in the general population

Rather than investigating the association between thyroid dysfunction and DAD, a number of researchers have investigated the possibility that abnormalities in the levels of thyroid hormone in serum, plasma or cerebrospinal fluid could be used as markers for DAD (*see* Table 7.5). Although some studies have reported negative or non-significant results, others have reported positive findings. Furthermore, in studies of individuals with DAD, hypothyroidism and hyperthyroidism have been observed. Although the published data document thyroid dysfunction in DAD, it is unclear whether abnormalities of thyroid function are useful markers for DAD.

Association between thyroid hormone dysfunction and dementia in Alzheimer's disease in Down syndrome

A limited number of studies on the association between thyroid hormone dysfunction, cognitive dysfunction and/or DAD have been reported for the DS population.[15–17,73,74,75] As in the general population, conflicting results have been found. Percy and colleagues investigated thyroid disorder in adults with DS and DAD.[15] A total of 46 individuals with DS (community and institution based) were recruited, of mean age 45.3 years (range 31–70 years), as well as 36 age-matched healthy controls. The individuals with DS were divided into those with probable dementia and those without the condition, using the guidelines of MacKhann and colleagues.[76] Compared with healthy controls, the DS group as a whole had lower mean total T4 and T3 levels. In this study it was not possible to age-match individuals with DS and dementia to those without dementia, as individuals who showed manifestations of dementia were significantly older than those who did not. When corrections were applied for age and gender, individuals with DS and DAD had significantly lower T3 levels compared with individuals with DS without manifestations of DAD. The authors concluded that there was an association between mild 'subclinical' hypothyroidism and DAD in the DS population.

Bhaumik and colleagues[73] published evidence that mild hypothyroidism might be protective in DS and that more severe hypothyroidism might be harmful. They demonstrated in a group of 26 institutionalised DS patients with normal thyroid function that global scores of ability (assessed by using Part 1 of the Adaptive Behavior Scale (ABS)) were higher than those in a group of patients with elevated TSH levels in the presence of normal T3 and T4 levels. The actual concentration of TSH was shown to be significantly and inversely related to the score for global abilities. The authors suggested that estimation of TSH levels might provide confirmatory evidence of clinical dementia in people with DS.

Prasher[17] investigated the association between thyroid dysfunction (as indicated by T4 and TSH levels) and DAD in 201 adults with DS, of whom 27 subjects fulfilled the *ICD–10* criteria for DAD.[199] Nine out of 26 demented individuals (34.5%) for whom data on thyroid status were available had thyroid dysfunction, compared with 41 out of 116 non-demented subjects (35.3%). No statistically significant difference was found between the two groups.

Devenny and colleagues[74] monitored groups of adults with or without DS and mild or moderate mental retardation over a six-year period on yearly measures of

Table 7.5 Clinical studies investigating a biochemical association between thyroid dysfunction and dementia, including Alzheimer's disease, in the general population

Study	*Findings*
Sunderland *et al.* (1985)[67]	Baseline TSH, total T4 and free T4 levels were higher in DAD than in non-DAD subjects. DAD subjects showed a blunting of the TSH response to the TRH stimulation test
Christie *et al.* (1987)[32]	Statistically significantly higher plasma levels of TSH were found in patients with DAD than in controls
Thomas *et al.* (1987)[70]	Compared with controls, the DAD group had significantly lower plasma T3 levels but showed no difference in T4 and T3 levels
Ichibangase *et al.* (1990)[47]	Cognitive function was found to be closely related to serum free T3 levels and cardiac function in subjects with cerebrovascular dementia. It was concluded that serum free T3 concentrations may be a good indicator of health and cognitive status
Molchan *et al.* (1991)[58]	DAD patients with a blunted TSH response had significantly higher mean free T4 levels ($P < 0.03$) and tended to be more severely demented than those with a non-blunted response
Faldt *et al.* (1996)[36]	No significant association was found between thyroid dysfunction and DAD
Ganguli *et al.* (1996)[39]	A significant association was found between elevated TSH levels and definite dementia, as well as possible and/or definite dementia, in a community-based sample. The findings are consistent with the hypothesis that subclinical hypothyroidism is associated with cognitive impairment and that thyroid state may influence cerebral metabolism
Kalmijn *et al.* (2000)[48]	Subclinical hyperthyroidism in the elderly was found to be associated with an increased risk of DAD. Individuals with reduced TSH levels at baseline had a more than threefold increased risk of dementia, after adjustment for age and gender. Among individuals with reduced TSH levels, T4 levels appeared to be positively related to the risk of dementia, although none of those who became demented had a T4 level above the normal range. The risk of dementia was markedly increased in subjects with low TSH levels who were positive for TPO-Abs (relative risk = 23.7)
Kapaki *et al.* (2003)[49]	Cholinesterase inhibitors used to treat DAD were found to produce significant changes in free T3 levels as a function of duration of treatment. Free T3 levels were significantly higher in patients who received cholinesterase treatment for 6–12 months, but then decreased
Dobert *et al.* (2003)[33]	Decreased or borderline TSH values were found to be associated with an increased probability of having dementia, especially vascular dementia

Table 7.5 (*cont.*)

Study	*Findings*
Spiegel *et al.* (2004)[65]	Two patients with a syndrome consisting of rapidly progressive dementia with myoclonus were found to have Hashimoto's encephalopathy
Van Osch *et al.* (2004)[71]	In a study of DAD patients and cognitively screened control subjects who were all euthyroid, lowered TSH levels within the normal range were found to be a risk factor for DAD, independent of several cerebrovascular risk factors and confounding variables
Sampaolo *et al.* (2005)[61]	In a study of the cerebrospinal fluid of euthyroid patients with overt DAD and matched healthy controls, DAD subjects showed significantly increased rT(3) levels and an increased ratio of rT(3) to T(4) in the face of unchanged cerebrospinal fluid total T(4) and transthyretin levels. These results suggest that there is abnormal intracerebral thyroid hormone metabolism and possibly brain hypothyroidism, either as a secondary consequence of the ongoing process or as a cofactor in the progression of the disease

mental status, short- and long-term memory, speed of psychomotor function and visuospatial organisation. Only four out of the 91 individuals with DS in their current sample showed changes in functioning that led to a diagnosis of possible DAD, and in these individuals causes of decline in performance other than DAD were concurrently present (e.g. thyroid dysfunction). These findings indicate that some age-associated changes in functioning are related to 'normal' but probably precocious ageing in adults with DS. Furthermore, these results suggest that adults with DS and mild or moderate mental retardation may be at relatively low risk for dementia during their fourth and fifth decades.

As described above, Percy and colleagues[16] noted effects of the $\epsilon 4$ and $\epsilon 2$ alleles on apparent hypothyroidism in older women with DS, but not in men of similar age with DS. Because $\epsilon 4$ is a risk factor for AD in the general population and possibly also for DAD in DS, and $\epsilon 2$ is protective, it was proposed that hypothyroidism may be contributing to DAD at least in women with DS. In an 11-year longitudinal study of one woman with DS who developed DAD, Devenny and colleagues[75] highlighted the difficulties in distinguishing clinical manifestations of DAD from those of depression and hypothyroidism.

Association between thyroid autoimmunity and dementia in Alzheimer's disease in the general population and Down syndrome

The possibility that thyroid autoimmunity may be a peripheral marker for AD has been investigated both in the general population and in people with DS. In the general population there is support for an association between thyroid autoimmunity and DAD. However, statistical data on the sensitivity and specificity of

thyroid autoimmunity as a marker for AD are unavailable. Data on the relationship between thyroid autoimmunity and DAD in DS are limited.

Thyroid autoimmunity and dementia in Alzheimer's disease in the general population

Ewins and colleagues[35] investigated the prevalence of autoimmune thyroid disease in familial DAD kindreds without intellectual disability in order to determine whether there was any evidence for genetic linkage between the two disorders. The research involved a large retrospective study of 70 affected and unaffected family members from 12 kindreds. Antithyroglobulin and antimicrosomal autoantibody status was determined. The authors found that 41.1% of the family members showed evidence of autoimmune disease, with significant co-segregation between the presence of thyroid autoantibodies and the development of DAD. The study demonstrated a very high prevalence of autoimmune thyroid disease in familial DAD kindreds, and suggested that a gene for the development of autoimmune thyroid disease may be located on chromosome 21 with close proximity to the familial AD gene. The possibility that thyroid autoimmunity might be a marker for DAD was raised.

Support for an association between thyroid autoimmunity and DAD was subsequently provided by Frecker and colleagues,[38] who found an increase in thyroid autoimmunity in familial DAD cases compared with non-familial DAD cases, and by Genovesi and colleagues,[40] who reported significantly higher levels of both antithyroglobulin and antimicrosomal autoantibody in 34 DAD patients (mean age, 65.17 years; range, 58–75 years) compared with 30 non-demented controls. More recently, Kalmijn and colleagues[48] found that having low TSH levels and autoantibodies to thyroid peroxidase was associated with an especially high risk of DAD. Interestingly, Creutzfeldt–Jacob disease, a neurodegenerative disease associated with altered expression of the prion gene on chromosome 20, is also reported to be associated with a high titre of antithyroid antibodies.[200]

Thyroid autoimmunity and dementia in Alzheimer's disease in Down syndrome

Two studies have been reported for the DS population, with conflicting results. Percy and colleagues[15] investigated thyroid autoimmunity in a study of 46 older people with DS and a group of healthy normal individuals without DS, as already described above. In the latter study it was not possible to age- and gender-match individuals with DS and DAD to those without DAD. However, when corrections for age and gender were applied to individuals with or without DS, individuals with DS and dementia were found to have higher antimicrosomal autoantibody titres than controls without DS, and individuals with DS without dementia had significantly higher antithyroglobulin titres than controls without DS. This study therefore found an association between autoimmune thyroiditis in DS adults with dementia, compared with those without. Prasher,[17] in his study of 201 adults with DS, of whom 27 individuals fulfilled the *ICD–10* criteria for DAD,[199] found no association between the presence of thyroid autoimmunity and DAD. The results from these two studies should be compared with caution because of the

differences in methodology. In the former study, antibody titres were compared in cases and controls, whereas in the latter study, frequencies of antibody titres that were above the upper limit of normal were compared. Furthermore, one population was from Canada and the other was from the UK.

Screening and management of thyroid disorders

Screening

It is important to screen for thyroid disorder in people with DS over their entire age range. Some children with DS and hypothyroidism may exhibit decreased growth and development. Symptoms such as obesity, reduced muscle tone, delayed deep tendon reflexes, 'puffy' face, dry skin, constipation, cold intolerance, brittle hair and delayed pubertal development also support the diagnosis of thyroid hormone deficiency. Physical examination of the neck is variable, revealing a thyroid gland that may be normal in size, barely palpable or a diffusely enlarged goitre. Many of these symptoms may be difficult to evaluate, especially in infants. The signs and symptoms of hypothyroidism can develop slowly over time, and may be difficult to discriminate from those of DS itself. Due to increased synthesis and release of thyroid hormone, serum T4 and T3 levels rise, leading to low or suppressed serum TSH. In contrast to the symptoms of hypothyroidism, some children with DS and hyperthyroidism may exhibit tachycardia, tremor, nervousness, sweating, heat intolerance, frequent stools, weight loss, goitre and decreased attention span. However, in contrast to the general population, clinical history and examination are known to be unreliable indicators of thyroid dysfunction in DS. Therefore this population should be regularly screened for thyroid abnormalities. The venous blood test for TSH is used as the gold standard. The capillary blood spot on filter paper to test for TSH is a less costly and more convenient alternative. A filter paper T4 test has also been developed, but is not very sensitive.[9,11,137,138]

Guidelines on best practice for screening vary from one country to another, and some countries do not have them.[201] Most guidelines recommend yearly screening for thyroid disease, as the frequency increases with age. In the USA, screening for thyroid disease at birth, at 6 months of age and yearly thereafter with tests for T4 and TSH is the standard of care.[146] In the UK, the Down Syndrome Medical Interest Group (DSMIG) has recommended screening every two years after the first year of life.[145] A survey of current patterns of screening in the UK was published recently. It was concluded that physicians who completed this survey were complying with the recommended guidelines and that 83% of them were using the venous blood TSH test.[147]

Management

Treatments for thyroid disorders are associated with benefits and risks. The benefits include the restoration of thyroid function if this is abnormal. If thyroid function is not kept within the normal range, the therapy can actually induce disease that is opposite in nature. Both thyroid and antithyroid medications can have harmful effects independently of their effects on thyroid function, and they sometimes have adverse side-effects. Overt hypothyroidism and hyperthyroidism

and other thyroid disorders in DS should be treated in the same way as they are in the general population.

Hyperthyroidism

This is treated by one of three modalities, namely antithyroid medications, subtotal or total thyroidectomy, or radioactive iodine ablation.[135,137,184] In many cases these treatments can render the patient euthyroid, but they all have potential adverse effects. Drug treatment may not eliminate recurrences. Pregnant women with hyperthyroidism should be treated with drugs or surgery and not with radioactive iodine, as the latter may have adverse effects on the neonate, such as prematurity, intrauterine growth retardation and fetal or neonatal thyrotoxicosis. Antithyroid medications include the thionamide drugs thiamazole and propylthiouracil. Rare side-effects include rash, itching, fever, liver inflammation or white-blood-cell deficiency. When these drugs are discontinued the problem usually recurs. Radioactive iodine treatment for hyperthyroidism can be administered by mouth without the need for hospitalisation. The majority of patients are cured, but they may end up hypothyroid. Surgical removal of all or part of the thyroid gland as warranted is a permanent cure. This is highly suitable for removing nodules, but not for treating Graves' disease, which affects the whole thyroid. With removal of much or all of the gland comes the need for permanent hypothyroid medication. Surgery also carries the risk of injury to the recurrent laryngeal nerve (the nerve to the voice box).

Hypothyroidism

The treatment of choice for hypothyroidism that is due to insufficient thyroid hormone is levothyroxine sodium (thyroxine). This is a synthetic version of T4, which is converted in the body to T3. This is effective in many cases, although some cases do not respond. An alternative to the commonly used pharmaceuticals is Armour thyroid, a pharmaceutical preparation of purified desiccated pork thyroid tissue that contains significant levels of both T3 and T4. It may be useful in patients suffering from disorders of T4 to T3 conversion. However, excessive use of this preparation has been anecdotally reported to trigger autoimmune-type thyroid disorders, and some people have been reported to develop allergies to it.[137,144]

Subclinical hyperthyroidism and hypothyroidism

The question of whether or not subclinical thyroid abnormalities should be treated is currently controversial. It has been argued by many that it is desirable to be able to prevent overt disease by treating abnormalities at a mild stage of development, or to prevent thyroid disorders and irreversible damage by addressing the primary cause.[130,139–143] On the other hand, treatment that is not necessary may actually cause iatrogenic thyroid disease of the opposite type. Moreover, excess thyroid hormone has harmful effects on the skeletal and cardiovascular systems.

Treatment guidelines

May has published the following guidelines for thyroid screening and treatment in DS.[11]

1 Thyroid function in individuals with DS should be tested annually by measuring T4 and T3 uptake, TSH and T3 levels, and the presence of thyroid autoantibodies.
2 If the T4 value is low (corrected for binding with T3 uptake) and is associated with an elevated TSH level, treat with synthetic thyroid hormone, starting at 25 μg per day after a baseline echocardiogram and electrocardiogram have been obtained. If heart disease is present, baseline Holter monitoring should be undertaken. Increase the thyroid hormone dose by 25 μg every 6 weeks or until the TSH level is normal. Monitor cardiac function carefully.
3 If the TSH level is elevated but the 'corrected' T4 value is normal, repeat the thyroid tests every 6 months, as the natural history of thyroid dysfunction in DS is not well understood and there is always a danger of subclinical medication toxicity.
4 If the autoantibody titres are elevated but the TSH level is normal, continue to monitor annually.
5 If the 'corrected' T4 or T3 value is elevated (i.e. hyperthyroidism), obtain a complete blood cell count and begin treatment with Tapazole 10 mg every 12 hours. Monitor the complete blood cell count frequently initially.

Research studies involving oral supplementation with selenium or zinc

In the introductory section of this chapter we explained how body levels of selenium, zinc and iron can affect thyroid function. The importance of selenium for brain function in the general population is increasingly being recognised.[180] The suggestion that selenium might affect brain function in individuals with DS arose from a literature indicating a direct correlation between cognitive function in people with DS and the activity of red-cell glutathione peroxidase, a selenocysteine-containing enzyme. Individuals with DS tend to have lower than normal serum levels of zinc and selenium and higher than normal copper levels.[158] These findings have led to the idea that people with DS might benefit from selective mineral supplementation to improve their thyroid function and cognitive status. However, supplementation studies have not considered the fact that such aberrations in metal ion levels are also characteristic of the acute-phase response.[202] This response consists of a group of physiological changes that occur shortly after the onset of an infection or other inflammatory process, including an increase in the blood level of various proteins (especially C-reactive protein), fever and other metabolic changes. Thus in some instances low serum levels of selenium and/or zinc may be physiologically protective. Observations from published studies on selenium and zinc supplementation in DS are summarised below.

Selenium supplementation

Published effects of selenium supplementation in DS include the following:

- increased plasma and erythrocyte selenium concentrations but decreased red-cell glutathione peroxidase activity after selenium supplementation in children. Children were reported to have fewer infections while taking the selenium[149]
- increased serum concentrations of immunoglobulin G2 and G4 after selenium supplementation in children[203]
- increased red-cell glutathione peroxidase activity.[150]

Zinc supplementation: positive reports
These include the following:

- normalisation of thyroid function tests and white blood cell function[160]
- a significant increase in DNA synthesis; normalisation of the lymphocyte response to phytohaemagglutinin (PHA) up to 6 months after the end of zinc treatment, and lowered response to PHA in half of the patients 22 months after therapy[170]
- normalisation of plasmic zinc, thymulin and TSH levels after 4 months of therapy; decreased incidence of infectious diseases and improved school attendance[204]
- improvement in DNA repair after irradiation[155]
- promotion of increased growth in a proportion of treated children[164]
- reduction in FT3 levels in 17 of 523 patients, and improvement in thyroid function in 9 of 52 patients with low zinc levels[165]
- induction of death of immature white blood cells[172]
- reduction in the number of white blood cells undergoing apoptosis[151]
- correction of abnormally high blood TSH levels in children with low blood zinc levels.[205]

Zinc supplementation: negative and/or adverse reports
These include the following:

- no effect on serum immunoglobulin levels or complement or lymphocyte function. Zinc supplementation may have decreased the frequency and/or severity of infection, as a trend towards fewer sick days was noted anecdotally by parents of participants[162]
- of five patients who presented with recurrent infection and low thymulin levels, three had low cellular zinc levels that normalised after zinc treatment. However, low thymulin levels persisted in four of five patients[152]
- lower T4 and higher TSH levels[25]
- adverse effects on cognitive function in people with AD in the general population. Because people with DS are at high risk of developing dementia at an early age, zinc supplementation in DS may also have adverse consequences.[173] Further studies of this topic are possibly warranted.[154]

Iron supplementation
There have been no reports of iron supplementation to improve thyroid function in DS. It should be noted that too much body iron may result in iron deposition and damage in soft tissues, including the thyroid gland. Interestingly, unusually high levels of iron have been described in adults with DS, particularly those with documented DAD.[206]

Summary and discussion

Causes of thyroid dysfunction

Thyroid dysfunction can result from a number of different causes, either individually or in combination. These include iodine deficiency or excess, defects in the structure or function of the thyroid gland, micronutrient imbalances (includ-

ing iron, selenium and zinc), genetic causes, structural abnormalities in the hypothalamus and/or pituitary that affect the function of the HPT axis, autoimmune disease associated with the production of antibodies to thyroglobulin, thyroid peroxidase and/or thyroid hormone, and thyroiditis. Thyroid dysfunction can occur at any age. If present, it should be corrected as early as possible to prevent irreversible changes. Treatment is especially important in the neonate in order to promote normal development and function of the brain and the rest of the body. Iodine deficiency is an enormous problem globally. Because it is still the main cause of intellectual and developmental disability worldwide, efforts to eliminate this problem need to be escalated.

Is thyroid function really abnormal in Down syndrome?

There is a large body of evidence indicating that hypothyroidism, both subclinical and overt, is increased in frequency in people with DS, including the newborn.[9,25] In support of the hypothesis that such observations are physiologically meaningful, there are a number of observations which indicate that thyroid dysfunction in DS has some unique features – for example, the widespread abnormal histopathology of the thyroid gland in DS, and the fact that autoimmune thyroiditis in adults with DS is associated with the HLA DQA 0301 allele. We speculate that because APP is apparently expressed in the thyroid, and because the gene for this protein is present in triplicate in individuals with DS due to trisomy 21, overexpression of APP may well be a fundamental cause of histopathology of the thyroid gland in DS. On the other hand, it has been suggested that thyroid abnormalities may be no more frequent in DS than they are in the general population, and that published reports contain much false-positive data.[19] The putative false-positive data are due to the fact that the reference ranges used for the diagnosis of thyroid dysfunction in DS are derived from measurements for people without DS. More research needs to be done on this topic.

Reference ranges should be established specifically for people with DS. Longitudinal studies of thyroid function in individuals with DS, in which each person serves as their own control, should be particularly informative. Furthermore, attention should be paid to age and gender as well as to diurnal and seasonal variation in measures of tests for thyroid function.

The issue of subclinical hypothyroidism

Because the laboratory reference ranges used to interpret tests of thyroid function are too broad, subclinical hypothyroidism is underdiagnosed in the general population. Because laboratory reference ranges for individuals without DS are used to interpret test results for individuals with DS, subclinical hypothyroidism is likely to be overdiagnosed in DS. The issue of whether or not to treat this disorder in the general population or in individuals with DS has not been resolved. On the one hand, adjustment of thyroid hormone status in the case of mild hypothyroidism may be cognitively beneficial for the intellect. On the other hand, long-term use of synthetic thyroid hormone may have adverse effects on the skeletal and cardiovascular systems. New laboratory reference ranges are warranted for the general population as well as for individuals with DS.

Furthermore, well-designed clinical trials are needed to determine the advantages and/or disadvantages of treating very mild abnormalities of thyroid function in the general population and in individuals with DS.

Association between thyroid dysfunction and Alzheimer's disease in the general population

Although there is a strong rationale for the involvement of thyroid dysfunction, especially hypothyroidism, in AD, our review of studies in this area has not revealed consistent trends. A diagnosis of thyroid dysfunction or changes in the results of biochemical tests of thyroid function are not valid ante-mortem measures of DAD, nor do they have any potentially significant value as a diagnostic marker.

The findings of studies of the involvement of thyroid autoimmunity in DAD appear to be more consistent, raising the possibility that the presence of thyroid autoimmunity might be a peripheral measure for AD. However, researchers have not controlled for subject age or gender as variables. Increasing age and being female are risk factors for both thyroid autoimmunity and DAD. It is therefore unlikely that thyroid autoantibody titres can be used as diagnostic markers for AD.

The possibility cannot be excluded that thyroid dysfunction is involved in some cases of dementia and/or DAD. There are a number of different ways in which this could occur. Certainly long-standing hypothyroidism that is not treated can result in irreversible dementia. In any case of DAD, screening for thyroid dysfunction and several other potentially reversible disorders should be undertaken. Thyroid dysfunction in DAD could also be a result of neuropathological changes in the degenerating brain. Decreased levels of CRH and somatostatin are both characteristic of AD. The former change would lead to decreased TSH secretion, and the latter to increased TSH secretion. It has been reported that somatostatin regulates brain Aβ42 through modulation of proteolytic degradation.[207] Changes in thyroid status also could be effected by the stress response, which may be altered in AD as in some other psychiatric illnesses. In the stress response, excessive CRH would stimulate TSH secretion and increase levels of free T4. A raised plasma free T4 level with a normal TSH level is a not uncommon finding in psychiatric illnesses.[208,209] In this case, lowered levels of thyroid-hormone-binding proteins are thought to result in the high levels of free T4. Theoretically, thyroid anomalies in DAD in individuals with DS may result in, or be caused by, the excessive oxidative stress that is characteristic of AD.[10,153,166] Both hypothyroidism and hyperthyroidism are reported to lead to oxidative stress,[158,168,210] which consists of an imbalance between oxidative and antioxidative processes in the body which results in oxidative damage to lipids, nucleic acids and proteins. Oxidative stress can cause cell damage either directly or by altering signalling pathways.[156] Other topics of potential relevance to thyroid dysfunction and DAD are folate deficiency and elevated levels of the amino acid homocysteine, both of which are involved in cognitive decline in ageing.[211] Folate deficiency and high levels of homocysteine are also characteristic of dementia.[211–213] Associations between folate deficiency and hypothyroidism[209] as well as high levels of homocysteine and hypothyroidism[214] have been established. (Folate is a generic term for one of the B vitamins (B_9) that occurs in many different chemical forms

and is essential for the synthesis of nucleic acids, the production of methionine from homocysteine, haem synthesis and the production of tyrosine from phenylalanine.[215]) Last but not least, the possibility should be considered that some cases of subclinical thyroid disease among people with DAD reflect physiological defence mechanisms. For example, studies in animals as well as studies of cells and tissues in culture have shown that TSH will counteract cell death resulting from apoptosis (programmed cell death).[216]

As in other disciplines, when controversies arise there are always explanations. We suggest that the failure of subsequent studies to confirm the original findings of Heyman and colleagues[45,46] may be a result of inter-centre differences in one or more of the following factors: criteria used to diagnose DAD; study inclusion/exclusion criteria, including gender, age and stage of dementia; ethnic/genetic background of participants; differences in iodine, selenium, zinc and/or iron status; medications being taken by study participants, such as acetylcholinesterase inhibitors, which may affect thyroid function; and changes in the frequency of untreated hypothyroidism since the 1920s. It is known that hypothyroidism can be masked as DAD, and that if this is not treated at an early stage, the effects can become irreversible. Given that the incidence of hypothyroidism due to iodine deficiency has been gradually decreasing since supplementation of salt with iodine became standard practice in the 1920s, that screening and treatment for hypothyroidism have become increasingly effective, with the development of sensitive methods for measuring thyroid hormone levels since the 1970s, and that screening dementia patients for thyroid abnormality is now standard practice, it would not be surprising to find that the frequency of hypothyroidism (particularly irreversible hypothyroidism) has decreased since Heyman and colleagues conducted their studies in the 1980s, and that currently very few cases of DAD are associated with previous or current thyroid dysfunction.

Association between thyroid dysfunction and dementia of Alzheimer's disease in Down syndrome

More studies are required to determine whether or not there is a connection between thyroid dysfunction and DAD in DS. Although some studies have found no association between thyroid dysfunction and DAD in DS,[16] this possibility has not been excluded.[15,16] Such studies are difficult because, in practice, it is not possible to select groups of people with or without clinical manifestations of AD who are closely matched with regard to age.[15] Furthermore, it is important to keep an open mind as to whether there are differences in the causes of thyroid dysfunction in DS in different countries.

In theory, micronutrient deficiencies of iron, selenium and zinc could result in thyroid dysfunction. The role of imbalances of these nutrients in thyroid disease and in dementia requires further research. One concern is that at least in some cases of apparent zinc and selenium deficiency the micronutrient anomalies may reflect a response to inflammation, and attempts to normalise them might be harmful rather than beneficial. Furthermore, studies of selenium supplementation in geographical areas that are selenium deficient have cautioned that such supplementation should only be undertaken after normalisation of iodine intake, due to the likely upregulation of the selenocysteine deiodinases. Because a literature review indicated that specific vitamin and mineral deficiencies were

associated with DS,[148] a placebo-controlled double-blind clinical trial is now under way in the UK to study the effects of supplementation with selenium, zinc and vitamins A, C and E, with or without folinic acid, in babies with DS. The trial outcomes are height, weight, general development, speech and health, and various markers in blood. It will be very interesting to see whether such interventions also affect thyroid status and cognitive status, at least in the short term, and protect against cognitive decline in later years. It could be argued that early treatment of thyroid dysfunction protects one's 'cognitive reserve' later in life. The term 'cognitive reserve' is used to reflect the density of synapses in the brain and also the ability of individuals to function normally despite the presence of histopathological brain features of AD.[217,218]

The topic of folate supplementation and its relationship to thyroid function is of particular interest in the DS population as well as in the general population. People with DS have an unusually high rate of metabolism of folate, due at least in part to their having three copies of the cystathionine β-synthase gene.[167,219,220] In a recent study, serum folate levels were reported to be inversely associated with the level of intellectual disability in people with DS.[221] It would be of great interest to determine whether folate supplementation affects not only the level of intellectual disability, but also thyroid function in DS. Because excess folate is neurotoxic when there is a deficiency of vitamin B_{12}, a balanced B vitamin supplement should be considered instead of folate supplementation on its own.

Management of thyroid disorders

Screening for thyroid dysfunction should be performed in all individuals, including those with DS, over their entire age range. Because thyroid disease appears to be unusually common in people with DS, yearly screening is recommended for this population. As in the general population, if dementia is suspected in older individuals with DS, tests for TSH and vitamin B_{12} levels should be performed, together with tests for other conditions that can mask as DAD, to determine whether there is a reversible cause of the dementia.[29,222] Structural neuroimaging with non-contrast computed tomography or magnetic resonance imaging is also recommended. Other testing should be guided by the history and physical examination. Neuropsychological testing can help to determine the extent of cognitive impairment. When screening for a thyroid disorder, the single best test of thyroid dysfunction is plasma TSH. Measurement of T4 and T3 uptake, T3 levels and the presence of thyroid autoantibodies is also recommended.

Individuals with or without dementia who have overtly abnormal TSH levels and abnormal thyroid hormone test results should be treated. Treatment of individuals with subclinical thyroid disease, with or without dementia, is controversial. The importance of conducting well-designed clinical trials to determine whether treatment has a positive outcome in terms of neurocognitive and/or neurobehavioural functions cannot be overemphasised.

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