# CHAPTER I

## INTRODUCTION

Graves 'disease is just one type of thyrotoxicosis. Thyrotoxicosis is a general term used for clinical manifestations caused by excessive circulating thyroid hormones in the blood, be it from excessive production by the thyroid gland itself, from excessive ectopic production of thyroid hormone, or from excessive administration of exogenous thyroid hormones. Hyperthyroidism and thyrotoxicosis have been used interchangeably but specifically hyperthyroidism refers to thyrotoxicosis which results from overproduction of thyroid hormones by the thyroid gland and excludes those resulting from ectopic production and exogenous administration. Most cases of thyrotoxicosis are caused by hyperthyroidism. These two words have been used synonymously. Graves' disease is the most common cause of hyperthyroidism. It was first recognized by Parry in 1825. It was Graves (1940) who popularized the triad of hyperthyroidism, goiter and exophthalmos and the eponym was given to this disease under his name.

At present Graves' disease is universally defined as a multisystemic disease of unknown etiology, characterized by one or more of three pathognomonic entities:

1. hyperthyroidism associated with diffuse hyperplasia of the thyroid gland,
2. infiltrative ophthalmopathy, and
3. infiltrative dermopathy (localized pretibial myxedema)

(Solomon and Chopra, 1972)

In clinical practice however the presence of diffuse hyperplasia of the thyroid gland with thyrotoxicosis is the most common manifestation diagnostic of Graves' disease. The presence of exophthalmos and dermopathy only helps to confirm the diagnosis. The so-called euthyroid Graves' disease (Liddle et al., 1965) with the presence of exophthalmos or dermopathy in the absence of thyrotoxicosis can be diagnosed only when the thyroid gland can be demonstrated to be non-suppressible. That is it is functioning autonomously independent of the control by TSH.

One biochemical entity pathognomonic of Graves' disease is the long acting thyroid stimulator (LATS). LATS is an IgG immunoglobulin found in about 70% of patients with Graves' disease (Chopra et al., 1970). It differs from TSH in that its peak action in mouse bioassay is at 9 hours instead of 2 hours as for TSH. The discovery of LATS (Adams and Purves, 1956; 1958) stirred the enthusiasm and belief that it was the cause of hyperthyroidism in Graves' disease. However this theory is now greatly disputed since LATS has not been found in all patients with Graves' disease despite highly sensitive method used in the assay (Chopra et al., 1970). Moreover, the presence of LATS does not correlate with degree of hyperthyroidism but rather correlates more with the presence of exophthalmos and localized pretibial myxedema (Wyse et al., 1968) and last but strongest evidence against LATS being etiologic factor in Graves'disease is the findings of suppressible thyroid function in some patients despite very high levels of long acting thyroid stimulator (Wong and Doe, 1972). Despite all these evidences LATS seems to be clearly the cause of hyperthyroidism in at least one entity, neonatal hyperthyrodism (McKenzie, 1964). In neonatal hyperthyroidism the

level of LATS in neonatal cord blood correlates well with clinical hyperthyroidism and the subsidence of symptoms also approximates the expected rate of clearance of IgG and LATS from the neonates.

Since LATS is an immunoglobulin, an antibody, the question naturally arises——what antigen is LATS directed against. There is major evidence that it is an antibody to a component of the thyroid gland, the antigen possibly resides in the plasma membrane of the follicular cell (McKenzie, 1972). LATS can be shown to be neutralized by incubation with thyroid gland preparations (Kriss et al., 1964). It was later found that there is another thyroid autoantibody which will compete with LATS in the neutralization reaction (Adams and Kennedy, 1967). These LATS protector does not stimulate the mouse thyroid nor interfere with the action of LATS in the mouse. LATS protector however has thyroid stimulating action in human (Adams et al., 1974) and was found in 90% of patients with Graves' disease (Adams et al., 1974). The finding of the autoantibodies together with other antithyroid antibodies commonly found in both Graves' disease and Hashimoto's disease (Doniach and Roitt, 1963) led to the concept that Graves' disease is an autoimmune disease. Since Graves' disease and Hashimoto's disease are found frequently in association with autoimmune disease such as pernicious anemia, Volpe (1972) advanced the hypothesis that all these diseases arise from genetic defect in delayed hypersensitivity and immuno-surveillance allowing forbidden clone of thymic dependent lymphocytes to infiltrate and initiate diseases of the thyroid gland. This hypothesis of Volpe is compatible with Weinstein and Kitchen's (1971) theory of polygenic or multifactorial causes of thyroid disease. They

pointed out that the genetic component of common thyroid disorders can be thought of as the degree to which variation and individual risk of acquiring the disease are conditioned by the genetic endowment. The risk of acquiring the disease may be modified further by environment such as stress (Skillern, 1972). The effect of environment is suggested by the great increase in the incidence of Graves' disease in Denmark during the occupation by the German Army in World War II.

Graves' disease is a disease found most frequently in young female with a ratio of female to male about 7 to 1. The most frequent presenting symptoms are fatiguability and palpitation. Weight loss despite good appetite, excessive sweating and nervousness are common accompanying symptoms though occasionally may be the presenting symptoms. Hyperdefecation is commonly present but is usually not the main complaint. The most common presenting sign is thyroid enlargement. Bruit over the thyroid gland is very common sign and is quite diagnostic of hyperthyroid condition. Rarely, particularly in older patients above 60 years old, thyroid gland may not be palpable. Exophthalmos is not found as frequently as would be expected. It is found less frequently than lid edema which when seen is quite pathognomonic of Graves' disease. Tachycardia is almost universally found but diagnosis of Graves' disease is still possible in its absence. Hand tremor may be the main complaint and occasionally may be the only sign found.

The two active hormones of the thyroid glands are thyroxine ($T_4$) and triiodothyronine ($T_3$). Both hormones are found to be elevated in Graves' disease. In about 5% of patients with Graves' disease $T_4$ is found to be normal while $T_3$ is elevated. This is the so-called $T_3$ thyrotoxi-

cosis (Hollander et al., 1971; Wahner, 1972). These patients, however, still have elevated radioactive iodine uptake which is not suppressed by administration of thyroid hormones.

Triiodothyronine found in the blood exists in the form of 3,5, 3'-triiodothyronine with only one iodide atom attached to the terminal benzene ring. This is the active hormone found in adult. However in fetus there exists in amniotic fluid a large amount of 3,3',5'-triiodothyronine or the so-called "reverse $T_3$" (Chopra and Crandall, 1975; Nicod et al., 1976) with two iodide molecules attached to the terminal benzene ring but only one attached to the amino terminal ring. The function of reverse $T_3$ in the fetus is not yet known.

$T_3$ was suggested since its discovery in 1952 by Gross & Pitt-Rivers to be the active hormone. However his suggestion fell out of favor when Standbury reported that there was no transformation of $T_4$ to $T_3$ (1972). A new interest in the peripheral deiodination of $T_4$ to $T_3$ was restimulated by the finding of Braverman that the athyreotic individuals who are given thyroxine have significant level of triiodothyronine in their blood (Braverman, 1970). This can only be interpreted that there is a peripheral deiodination of $T_4$ to $T_3$. The question remains whether both $T_3$ and $T_4$ are active peripherally or $T_3$ alone is active and $T_4$ has to be transformed into $T_3$ to be active. This question was clarified partially by Oppenheimer (1974) who studied specific nuclear binding of $T_3$ and $T_4$ in various tissues. He found specific nuclear binding site for $T_3$ but not $T_4$. Moreover the number of nuclear binding sites varies with different tissues depending on

that tissue responsiveness to thyroid hormone. Therefore spleen and testis which respond little to thyroid hormone have least numbers of nuclear binding sites for $T_3$ and pituitary gland, liver and kidney which are very responsive to thyroid stimulation have large numbers of $T_3$ nuclear binding sites. Furthermore to substantiate the assumption that nuclear binding of $T_3$ is a step in the process of thyroid hormone action it was found that thyroid hormone action is inhibited by chemicals which inbibit protein synthesis such as cycloheximide and actinomycin D. The current thought therefore is that $T_4$ must be transformed to $T_3$ to be active and peripheral action of $T_3$ involves specific binding to nuclear binding sites where it influences RNA template and protein synthesis.

Becker (1972) arbitrarily divided patients with Graves' disease clinically into three subsets. Subset A are those who are at high risk of developing Graves' disease, namely, those with positive family history of Graves' disease but who have no clinical manifestation nor biochemical evidence of the disease. Subset B are those who are asymptomatic but who have abnormally elevated circulating thyroid hormone. Subset C are those whose circulating thyroid hormone has reached the level and duration such that symptoms and signs of Graves' disease appear. Patients in Subset C may be detected easily by history and physical examination. Laboratory tests only help to confirm the diagnosis. Laboratory tests are the only means to detect patients in subset B and early therapy may be instituted. Moreover recent data (Hollander, 1971) suggest that some patients may have elevated serum $T_3$ level before $T_4$ become elevated and before any signs and symptoms of Graves' disease

appear. This makes the laboratory measurement of $T_3$ and $T_4$ very important in the management of Graves' disease.

Prior to 1964 the only blood test for thyroid function was protein bound iodide (PBI). PBI is simply a measurement of iodide content of the circulating iodide containing organic compound in the blood. This serves a very useful purpose so long as most of the circulating iodide containing compound are thyroid hormone. However with some diseases which destroy thyroid gland such as various kinds of thyroiditis other iodide containing compounds such as DIT, MIT and thyroglobulin may be released into the circulation in large amount and will be measured as PBI as well. Moreover with an increasing use of iodide containing x-ray dyes which last in circulation for a long time PBI measurement becomes useless in these circumtances. With the discovery of radioimmunoassay by Yalow and Berson in 1960, and application of the principle by Murphy and Pattee (1964) for measurement of thyroxine in the blood by using the specific binding property of thyroid-binding-globulin, the circulating thyroid hormone could be measured directly for the first time in clinical laboratory. It was only recently that radioimmunoassay of $T_3$ was developed (Gharib et al., 1970; Gharib et al., 1971; Chopra et al., 1971) enabling a detection of a new entity called $T_3$ thyrotoxicosis. It was found further that the ratio of $T_4/T_3$ varies in different regions depending on the level of iodide intake in different areas (Gharib, 1972). The lower the iodide intake the lower the $T_4/T_3$ ratio will be since the synthesis of $T_3$ utilizes less iodide molecules.

There are many antithyroid compounds that can inhibit the synthe-

sis of thyroid hormones at various steps of synthesis. The first pure chemical compound that was found to cause goiter and thus inhibit thyroid hormone synthesis was sulfaguanidine. MacKenzie, MacKenzie and McCollum, (1941) observed this while they were using this compound to inhibit nutritional flora for nutritional studies. Another related compound was phenylthiourea which was found by Richter and Clisby (1942) to cause goiter in rats. These are the forerunners of the currently used antithyroid drugs, all of which belong to the thionamide group. The three most widely used antithyroid drugs are propylthiouracil (PTU), methimazole and carbimazole. These antithyroid drugs were found to inhibit thyroid hormone synthesis at the step of organic iodination and coupling although it is not known which step of the two is more important. The understanding of the mechanism of action of these antithyroid drugs is tampered by the incomplete understanding of the iodide-oxidizing system of the thyroid gland. Aside from the direct action on the thyroid gland propylthiouracil but not methimazole and carbimazole was shown in rats to have peripheral action (Stasilli et al., 1960) probably by reducing the rate of deiodination of thyroxine (Jones and Van Middlesworth, 1960). With the recently developed radioimmunoassay of triiodothyronine, propylthiouracil was shown to interfere with the peripheral conversion of $T_4$ to $T_3$ (Oppenheimer et al., 1972 and Frumess and Larsen, 1975). Moreover PTU was also shown to inhibit pituitary release of TSH (Jagiello and McKenzie, 1960; Escolbar del Rey, F, et al., 1961; 1962; Balfour, 1969). In man however this peripheral effect of PTU has not been documented. Abuid and Larsen (1974) found $T_4/T_3$ ratio to increase in the first five days after initiation

of PTU therapy in man. This was interpreted as a result of inhibition of the peripheral conversion of $T_4$ to $T_3$ by PTU.

The purpose of the present study is to find the long term effect of antithyroid drug, particularly methimazole, on the levels of $T_4$ and $T_3$. This study will also document the incidence of side effects of this drug during treatment. Methimazole is selected for this study because it is popularly used to treat hyperthyroidism in this country.