INTRODUCTION
SURVEY OF LITERATURE

Eversince Galen described the secretory nature of the thyroid gland in 1822, our knowledge on the chemistry, physiology and pathophysiology of thyroid hormones has immensely grown, yet it is incomplete (see Ramalingaswami, 1964; see Morreale de Escobar and Escobar del Rey, 1983; see Morreale de Escobar, et al 1987; see Hoch, 1988; see Mendelsohn, 1988; see Visser, 1988; see Gaitan et al, 1990).

Experimental thyroidectomy in animals by Cooper (1836) proved the relationship between thyroid and various body organs. Kocher (1883) as well as Reverdin and Reverdin (1883) reported the similarity between the clinical symptoms of spontaneous myxedema and post thyroidectomy. Thyroid disease represents one of the major and most common endocrine disorders, next only to diabetes mellitus (see Hay and Klee, 1988).

ETIOLOGY AND PATHOLOGY OF THYROID SWELLING

There has been a significant improvement in the diagnostic tools of various thyroid disorders, particularly immunocytochemistry and fine needle aspiration cytology during the past 15 years. These helped in better diagnosis and understanding of thyroid neoplasia and Graves’ disease (see Mendelsohn, 1988). Nevertheless, there is dearth of knowledge and we have to make great strides, particularly in understanding the biochemistry of goitrous and neoplastic thyroids.
GOITER

In general, the swelling of the neck due to thyroid enlargement is referred as goiter. The term goiter may be applicable for the swelling of the gland due to its hypo-or hyperfunction as well as tumorous and infectious conditions (see Oertel and Livolsi, 1986).

Endemic goiter

The occurrence of goiter in a particular geographical area due to iodine deficiency in the environment is termed as endemic. It may also be due to factors which affect the availability of dietary iodine or which impose an abnormal demand on the thyroid or interfere in the utilization of iodine by the thyroid (see Ramalingaswami, 1964).

Endemic goiter or iodine deficiency disorder (IDD) still remains as one of the world’s most serious public health problems (Stanbury and Hatzel, 1980; see Ingbar, 1985; see Hetzel, 1990; Thilly et al, 1990). The prevalence of goiter increases considerably after the age of three and attains the peak during puberty and is more common in girls than boys, when they are above 10 years (Delange, 1974). When iodine is supplemented with food to the affected people, the incidence of goiter is markedly reduced, in the absence of goitrogens in the environment (see Ramalingaswami, 1964; see Ingbar, 1985).
Endemic goiter results in morphological changes of the thyroid with striking macroscopic and microscopic heterogeneity. Epithelial hyperplasia, involution and nodule formation are the three fundamental components of endemic goiter pathogenesis (see Ramalingaswami, 1964). Increased thyroid stimulating hormone (TSH) secretion, secondary to iodine deficiency and decreased thyroid hormone synthesis, is responsible for hyperplasia of the gland. The initial temporary phase of hyperplasia is followed by involution and colloid storage. Irregular involution and resorption of stored colloid lead to nodule formation (see Mendelsohn, 1988). Diffuse enlargement is rarely found in young subjects. Histochemical studies showed the presence of abundant parenchyma, elongated follicular epithelium with papillary infolding and little colloid. Some nodules may undergo degenerative processes leading to fibrosis and become calcified or ossified (see Ramalingaswamy, 1964; see Ingbar, 1985).

Sporadic goiter

While endemic goiter is due to an inherent population-wide iodine deficiency, sporadic goiter reflects a relative dietary deficiency of iodine in individual patients and interference in iodine metabolism by environmental and immunogenetic factors (see Ingbar, 1986; see Gaitan et al., 1990).

Defective hormone synthesis due to subnormal iodide transport, organification, coupling reaction, dehalogenase activity or secretion of hormones may lead to goitrous hypothyroidism. Chronic administration of
large doses of iodine, either organic or inorganic form as in the case of treatment for chronic respiratory disease also leads to goitrogenesis with or without hypothyroidism (see Ingbar, 1988; see Gaitan et al, 1990).

Sporadic goiter is more frequent in adult females than in males (10:1) and it may not be predisposed to thyroid cancer. However, the accelerated growth of a solitary nodule with a sporadic goiter is a single, most alarming sign (see Mendelsohn, 1988). The malignancy rate of cold nodules occurring in young patients is higher than in adults (Belfiore et al, 1989). The simple non-toxic goiter was thought to be the result of impaired hormone synthesis leading to excess TSH stimulation (see Kilpatrick and Wilson, 1964). However, recent reports do not favour the participation of TSH, as its level does not increase in majority of the cases. Since the gland is non-functional, it has been suggested that some growth promoting immunoglobulins may be involved (see Ingbar, 1988; see Mendelsohn, 1988). TSH is the main growth factor in some sporadic goiters and acts as a co-factor in others (see Studer and Ramelli, 1982; Studer, 1985).

The pathological changes of simple non-toxic goiter are hyperplasia, colloid accumulation and nodularity of the gland. The third stage is most commonly seen in surgical specimens. The epithelium becomes cuboidal or flattened and resembles that of the normal gland (see Mendelsohn, 1988).

If the gland is not nodular but diffusely enlarged and soft with glistening cut surface due to excess colloid, the disease is termed as
non-toxic colloid goiter. Toxic multinodular goiter develops from a long standing, non-toxic multinodular goiter. Thyrotoxicosis in multinodular goiter occurs whenever the number of new follicles become large enough that their joint hormone production exceeds the optimum level. The extent of hormone over production in toxic multinodular goiter is usually mild and serum thyroxine (T\textsubscript{4}) and triiodothyronine (T\textsubscript{3}) are marginally increased (see Ingbar, 1985). It predominantly affects older individuals, particularly females with long standing goiters (see Mendelsohn, 1988). Sometimes, multinodular goiter and thyrotoxicosis also appear in young individuals, irrespective of the sex, typically around the age of 30 to 40 years (see Studer and Gebel, 1986).

Thyroid hyperplasia also occurs in Graves' disease. It is characterized by diffuse toxic goiter, infiltrative ophthalmopathy, and occasionally infiltrative dermopathy. The disease occurs predominantly above 30 or 40 years with a female : male ratio of 6 :1 (see Oertel and Livolsi, 1986). Long acting thyroid stimulant (LATS), an immunoglobulin, thyroid stimulating immunoglobulins (TSI) and thyroid growth immunoglobulins (TGI) are considered as etiologic factors in Graves' disease (see Mendelsohn, 1988).

Thyroiditis

Another thyromegalic disease which is most common in women with a wide spectrum of clinical and pathologic changes is autoimmune thyroiditis
(Hashimoto's thyroiditis). It is one of the triad of autoimmune thyroid disorders, the other being Graves' disease and primary thyroid atrophy (Knecht et al, 1981; Shamsuddin and Lane, 1981; Yagi, 1981). It is the most common cause of goitrous hypothyroidism in areas of iodine sufficiency and may be familial (see Ingbar, 1986). The thyroid enlargement in Hashimoto's thyroiditis is typically diffuse and painless but may be asymmetric. Initially, the patient may be euthyroid but in chronic cases, hypothyroidism may develop (see Mendelsohn, 1988) with asymptomatic thyroid hormone deficiency. The hypertrophy of the gland may be secondary to elevated TSH. Lymphocytic infiltration of the thyroid gland, chronic inflammation and presence of antithyroid antibodies in circulation are some of the characteristic features of the disease (see Ingbar and Woeber, 1981; see Ingbar, 1985). Fibrosclerosis is also called invasive fibrosis thyroiditis and Riedel's struma. It is a rare condition with systemic collagenosis (Woolner et al, 1957).

Granulomatous thyroiditis is otherwise known as subacute thyroiditis and de Quervain's or giant cell thyroiditis. This disease is caused by viral infection and often causes upper respiratory tract infection for few months. The gland is slightly enlarged. Euthyroidism may return after few months but severe cases may develop hypothyroidism. Antithyroid antibodies, including thyroid stimulating antibodies have been reported in some patients (see Mendelsohn, 1988).
THYROID NEOPLASMS

Nearly one third of clinically suspicious thyroid nodules are formed by benign (adenoma) and malignant (carcinoma) thyroid tumors. Majority (80%) of thyroid tumors, either benign or malignant are with cold nodules (unable to accumulate iodine) and less than 20% of cold nodules are malignant. Epidemic, environmental and genetic factors have been implicated in the causation of thyroid cancer (see Matovinovic, 1986; see Mendelsohn, 1988; Samaan, 1989; Olah et al, 1990).

Adenoma of the thyroid

Generally an adenoma is defined as solitary, encapsulated benign neoplasm with uniform internal architecture, substantially different from the surrounding thyroidal parenchyma and compressing the adjacent gland (see Hazard, 1968; see Doniach, 1978). However, some adenomas differ from these characteristic features. Thus, strictly defined true adenomas are rare and the majority are benign tumors really representing nodules of the nodular goiter. Vast majority of the adenomas are non-functional cold nodules but rare toxic nodules are also encountered with hyperplastic cells secreting T3 and reverse T3 (rT3) (see Ingbar and Woeber, 1981; see Mendelsohn, 1988).

Follicular adenomas of the thyroid are benign neo-plasm of follicular epithelial cells and are the most common of all thyroid neoplasms. The
disease has a preponderance of occurrence in females between the age of 30 and 50 years (see Ingbar and Woeber, 1981; see Mendelsohn, 1988).

In people with rare and severely hyperplastic nodular goiters caused by inborn errors in metabolism, follicular adenoma and carcinoma can develop when the TSH level is chronically elevated. In the absence of spontaneous mutations or mutations due to ionizing radiation, chronic high TSH level alone may act as an initiator (mitotic errors) and promoter of follicular adenoma. Chronic elevation of TSH secretion, especially after sub-total thyroidectomy, is attributed to the high frequency of follicular adenoma and carcinoma in severe iodine deficient areas (see Matovinovic, 1986). Follicular adenomas are able to accumulate and retain iodine, a feature distinguishing it from most carcinomas. Functional adenomas may retain their ability to respond to TSH but are not dependent upon TSH for their functional maintenance (see Ingbar, 1985).

Teratoma

The most common neoplasm of the thyroid other than adenoma is teratoma. Teratomas occur predominantly in infants and are usually diagnosed at the time of birth. Microscopically, teratoma is seen to be composed of multiple elements often with a preponderance of neural components (see Oertel and Livolsi, 1986).
Carcinoma of the thyroid

Carcinogenesis may occur as a result of a somatic mutation, aberrant differentiation, virus activation and cell selection (see Matovinovic, 1986). Mutagenic factors of thyroid carcinogenesis include (i) artificial ionizing radiation due to X-rays and radioactive iodine (Doniach, 1971) (ii) chemical carcinogens like 2-acetylaminofluorene and methyl cholangrene (Doniach, 1971) (iii) inborn errors of iodine metabolism (De Groot et al, 1984) and (iv) Mendelian dominant tumor syndromes like multiple endocrine neoplasia with thyroid adenoma and medullary thyroid carcinoma, sporadic and familial, respectively (see Sipple, 1961; Williams, 1965).

Aberrant differentiation (faulty repression or derepression on genetic information leading to neoplastic growth and differentiation) related thyroid cancers are evident in simple colloid goiters with metastases or benign metastasizing goiter (Matovinovic et al, 1971). Cell selection mechanism of carcinogenesis occurs in some cells previously exposed to some "cancer initiating agents". For example, ionising irradiation may be followed by a latent period of several years and increased or normal TSH may promote carcinogenesis during this latent period (see Upton, 1982). The factors mentioned above in combination or individually can cause thyroid carcinogenesis in human. The most important being endemic goiter, ionizing radiation, autoimmune thyroiditis, Graves' disease, endogenous
thyroid stimulators, genetic abnormalities and excessive nutritional iodine consumption (see Matovinovic, 1988; Samaan, 1989; Olah et al., 1990).

Increased prevalence of thyroid follicular carcinoma was suggested in endemic goiter areas (Wahner et al., 1966; see Phillips et al., 1988), due to continuous stimulation of the gland by TSH in the absence of effective thyroid hormone synthesis and secretion. Experimental evidences also proved that iodine deficiency and subsequent increased TSH stimulation may favour the development of thyroid neoplasia (see Matovinovic et al., 1968). If the pituitary stimulation is marked and prolonged, the thyroid becomes large and nodular with enlarged follicular cells having large bizarre, hyperchromatic nuclei (Hazard, 1964; Kennedy, 1969; see Rosai, 1981). The incidence of major sub types of thyroid carcinoma in the United States is as follows: papillary, 60-70% ; follicular 15-20% ; medullary 5-10% and anaplastic 5-10% (see Mendelsohn, 1988).

Papillary carcinoma is the most common primary type of thyroid cancers, predominant among young people and accounts for, atleast 80% of all thyroid cancers occurring before the age of 40 years. Two thirds to three quarters among affected people in the United States are children (Nemec and Silink, 1975; Zimmerman and Hayles, 1980). The incidence is more common in women than in men and rarely familial (Lote et al., 1980; Yashiro et al., 1987; Samaan, 1989). In adolescents and young women, many of the hot or toxic nodules contain numerous papillae, suggesting a
Papillary carcinoma occurs most frequently in those parts of the world where ample iodine is present in the diet and environment (Williams et al., 1977; Hofstadter, 1980; see Phillips et al., 1988). The higher relative incidence of papillary carcinoma in Iceland (with high iodine consumption) than that of North East Scotland (with normal iodine consumption) was attributed to a secondary decrease in the incidence of follicular carcinoma because of low serum TSH in this population (Williams et al., 1977). TSH secretion may have a permissive role in the development of papillary carcinoma (Yashiro et al., 1987). Inborn errors of metabolism in thyroid hormone synthesis resulting in dyshormonogenetic goiters also lead to the development of papillary carcinoma as a result of continued increased secretion of TSH (De Groot et al., 1984; Yashiro et al., 1987). A patient with metastatic pure papillary carcinoma may remain euthyroid but there may be greater growth rate and function of the gland under TSH stimulation (see Matovinovic, 1986).

Papillary carcinomas possess characteristic cytologic features with papillary and follicular growth patterns (Williams, 1979; Vickery, 1981; Cooper et al., 1981; see Mendelsohn, 1988). It may have a trabecular pattern (rarely) or entirely papillary with small cysts lined by a single layer of neoplastic cells. In some cases, a distinct cyst may be evident but one
or more cystic spaces may occupy most of the neoplasm (Woolner et al., 1961; Hawk and Hazard, 1976). Fibrosis is common in papillary carcinoma and is distributed in an extremely irregular fashion (see Lindsay, 1969; Tscholl — Ducommun and Hedinger, 1982). Sclerosis also occurs in papillary carcinoma, more densely in small carcinomas than in large bulky tumours (Vickery et al., 1985).

Papillary carcinoma is a least aggressive disorder (Hawk and Hazard, 1976; see Doniach, 1978). However, papillary thyroid carcinomas can give rise to metastases with a partially or entirely follicular pattern (see Mendelsohn, 1988). About one third papillary carcinomas have laminated calcific spherules known as psammoma bodies, measuring about 5 μm to 100 μm in diameter, probably it begins in damaged or dying cells (Johannessen and Sobrinho-Simoes, 1980). Psammoma bodies are so rare in follicular carcinomas and medullary carcinomas, if they are found in or near such a neoplasm, they presumably originate from a small papillary carcinoma (see Mendelsohn, 1988).

Follicular carcinoma is the second most common thyroid cancer occurring in older age group than papillary carcinoma, after 40 years of age (see Ingbar and Woeber, 1981). Previous history of radiotherapy to the neck region during childhood or infancy may be evident. Follicular carcinomas are typically encapsulated. Invasion of adjacent thyroid parenchyma and vascular invasion distinguishes these tumours from
follicular adenoma (see Ingbar and Woeber, 1981; see Mendelsohn, 1988). Ultrastructurally, the follicular carcinomas have no specific characteristics and may resemble papillary carcinoma. It's capacity to accumulate iodine as that of surrounding normal tissues distinguishes it from other malignancies (see Ingbar and Woeber, 1981; see Mendelsohn, 1988).

Medullary carcinoma, the least common form of thyroid carcinomas, is from the thyroid C-cells (parafollicular cells) and is predominantly sporadic and rarely familial (Cushman, 1962; Jackson et al, 1973; see Ingbar and Woeber, 1981). It is usually uncapsulated with progressive C-cell proliferation; the thyroid follicles are filled with calcitonin-positive C-cells, leading to nodular C-cell hyperplasia (see Mendelsohn, 1988).

THYROID FUNCTIONAL STATUS

Measurement of serum total $T_3$ and $T_4$ have been considered as parameters to assess hypo or hyper function of the thyroid. However, there may be varied degree of thyroid hormone deficiencies in hypothyroid conditions. Neither total nor free $T_3$ is a good parameter to assess primary hypothyroidism (see Hay and Klee, 1988). Demonstrable decrease in serum total $T_3$ and increased TSH may be considered as good biochemical diagnosis of primary hypothyroidism (see Hoffenberg, 1986). Bigos et al (1978) suggested several categories of biochemical hypothyroidism. In the mildest form of hypothyroidism there will be low normal serum $T_3$ and normal $T_4$ with a slight increase in TSH; in severe cases of hypothyroidism $T_3$ may
be subnormal with normal $T_1$, but the elevation of TSH will be high and in the most severe case both $T_1$ and $T_3$ will be reduced with marked increase in TSH. Nevertheless, there will be exaggerated TSH response to thyrotrophin releasing hormone (TRH) in all cases of biochemical hypothyroidism. Hypothyroidism with normal or elevated serum $T_1$ and low $T_3$ and elevated TSH are referred as $T_3$ compensated or latent hypothyroidism (see Hoffenberg, 1986) and this may be seen in hyperthyroid patients treated with $^{131}$I or surgery or anti-thyroid drugs and in iodine deficiency.

Euthyroid patients with simple goiter have low thyroidal contents of $T_4$, $T_3$, and $T_3/T_4$ ratio and the euthyroid status may be the result of compensatory function of paranodular normal tissues (Solter et al, 1987). In mild hypothyroidism with or without goiter, increased secretion of TSH is associated with relatively elevated proportion of thyroidal $T_3$ (Larsen, 1972; Schimmel and Utiger, 1977).

Patients with severe hypothyroidism show higher initial serum TSH concentrations because they have more thyrotroph hyperplasia (Aizawa et al, 1978). Besides, elevated serum TSH concentrations can be found in many patients whose serum $T_1$ and $T_3$ concentrations are within the normal range in states of resistance to thyroid hormones; TSH may also be below normal in some patients with normal range of serum $T_4$ (Ehramann and Sarne, 1989). Most euthyroid patients with diffuse goiter or
multinodular goiter or thyroid carcinoma have serum TSH concentrations within the normal range (Toft et al, 1976).

Most of the patients with multinodular goiter are clinically euthyroid but basal TSH may be elevated in some suggesting borderline or subclinical hypothyroidism (see Mendelsohn, 1988). TRH unresponsive suppressed TSH secretion in the presence of normal serum T₃ and T₄ is a common finding in multinodular goiter (Gemsenjager et al, 1976; Blichert-Toft et al, 1978; Hamburger, 1980). Consequently, TSH secretion shunts off and the follicular function is reset at a low level (Studer et al, 1976; Trost et al, 1980).

Thyroid hyperfunction leads to an overall increase in thyroid hormone synthesis and secretion with a disproportionate overproduction of T₃ than T₄ resulting in the increased T₃/T₄ ratio and T₃ toxicosis (see Woeber, 1986; see Hay and Klee, 1988). Serum TSH concentration is usually undetectable or very low in hyperthyroid patients (Pekary et al, 1975; see Hay and Klee, 1988). However, in some cases, hyperthyroidism may develop due to excessive TSH secretion (Weintraub et al, 1981; Smallridge and Smith, 1983).

Hyperthyroidism in uni- and multinodular goiters may be the result of new follicles with high iodine metabolism (Studer et al, 1985). Marsden et al (1975) reported elevated T₃ levels in 8/8 subjects with autonomous thyroid nodules but only 3/8 subjects had increased T₄. Hamburger (1980)
reported T₄ toxicosis in 46% (16/35) subjects with toxic autonomous nodules, elevated T₄ and T₃ in another 46% and increased T₃ alone in 8% of the subjects. Recently, Martins et al (1989) concluded from their study in the endemic areas of North Brazil that iodine induced thyrotoxicosis is common in patients with multinodular goiters which may be transient or persistent and tending to resolve spontaneously by 60 months.

T₄/T₃ ratio in paranodular tissues of autonomously functioning adenomas is increased when TSH is suppressed by enhanced secretion of thyroid hormones from hyperfunctioning adenomatous tissues (Solter et al, 1985a). High thyroid T₄/T₃ ratio with low T₃ in some non-toxic goiters may be attributed to decreased TSH-5'-monodeiodinase activity (Solter et al, 1985b). Recently, these authors reported similar results without any significant increase in thyroid tissue T₄, following the administration of T₄ to nodular goiter subjects and attributed the same to suppressed TSH secretion (Solter et al, 1987).


TSH secretion may be decreased in patients with toxic adenomatous benign tumour and toxic multinodular goiter with foci of functional autonomy. Suppressed TSH is a good diagnostic tool for autonomous thyroid function (Ehrmann et al, 1989). Similarly, subacute or chronic
thyroiditis with leakage of hormone may also exhibit low TSH secretory activity (see Ingbar, 1986).

Abnormalities in the TSH receptor-adenyl cyclase system in thyroid tumours may vary. Initially, the high affinity TSH binding sites are affected and with more pronounced abnormalities of the TSH receptor, the low affinity sites adenyl cyclase stimulation are also decreased. Finally, complete destruction of the TSH receptor adenyl cyclase system will occur (see Matovinovic, 1986).

Similar changes were also recorded in tissues of primary and lymph node metastases of some papillary carcinomas. Non-functional tumours have total defect in TSH receptor or may have normal receptor binding and stimulation of adenyl cyclase. Some other categories may have intact adenyl cyclase but with defective TSH binding and adenyl cyclase stimulation. Another group of non-functional tumours may have normal receptor binding with defective adenyl cyclase or ribosyl transferase activity (see Matovinovic, 1986). Lack of adenyl cyclase response to TSH in rat thyroid tumour lines was attributed to poor binding of TSH to its receptors (Mandato et al, 1975; Macchia et al, 1977).

Lee et al (1977) reported normal adenyl cyclase activity in thyroid cells of microfollicular, trabecular and toxic adenomas as well as in colloido-nodular and microfollicular goiters. However, the enzyme activity was enhanced in patients with Graves' disease. On the other hand, TSH
induced adenyl cyclase activity in Graves' disease appears to be higher than normal, goitrous or adenomatous cells, as evident from increased cyclic adenosine monophosphate (AMP) level. Unaltered adenyl cyclase activity, glucose oxidation and iodination also were reported in adenomatous human thyroid tissues (Lee et al, 1977).

Thyroid hormones have a suppressing effect on serum thyroglobulin (Tg) levels (Van Herle et al, 1975). Administration of TSH as well as TRH induced TSH increase serum concentration of Tg (Uller et al, 1973, 1977; Muraskawa et al, 1979; Unger et al, 1980). Iodine deficiency also leads to increased serum Tg levels in human and rats (Van Herle et al, 1976; Pezzino et al, 1978). However, Pezzino et al (1977) reported undetectable and very low levels of Tg in hypothyroid subjects. In Graves' disease, the elevation of serum Tg level is related to the amount of thyroid stimulating antibodies (TSAb) in circulation (Uller et al, 1973; Brown et al, 1976). Serum Tg levels are elevated not only in patients with Graves' disease but also in toxic adenomas, papillary carcinomas, follicular carcinomas and toxic multinodular goiters (Ericsson et al, 1984, see Van Herle, 1986). Serum Tg levels are well correlated with thyroidal cancer activity (Botsch et al, 1983). High serum Tg concentrations are commonly found in patients with differentiated thyroid carcinoma. Tg can leak from imperfectly malignant follicles into the lymph vessels surrounding the follicles (Gebel and Studer, 1984). Persistence of elevated serum Tg after surgical and radioactive iodine therapy may indicate the presence of thyroid
cacinoma (see Sarne, 1988). Recently, Tokmakjian et al (1989) suggested that serum Tg above 20 pmol as the predictive value for recurrence of thyroid carcinoma.

THYROID STATUS AND OTHER HORMONES

Human hypothyroid subjects have subnormal adrenocortical function with decreased metabolic clearance rate leading to unaffected plasma cortisol and aldosterone (see Ingbar, 1985). Hellman et al (1961) reported increased cortisol production rate in hyperthyroid subjects. Thyrotoxicosis is associated with increased secretion and metabolic clearance of cortisol and aldosterone resulting in normal plasma levels of these corticosteroids (see Ingbar, 1985).

Thyroid hormones are well known to induce growth hormone (GH) synthesis and secretion (see Oppenheimer et al, 1987). Primary hypothyroidism decreases the secretion of GH in prepubertal girls (Iwatsubo et al, 1967; MacGillivray et al, 1968; Buchanan et al, 1988). Pringle et al (1988) observed attenuated GH pulse amplitude in children with primary hypothyroidism and was reversed by T₄ treatment. However, GH pulse and frequency may be unaffected (Hindmarch et al, 1986).

Reproductive disorders in association with thyroid dysfunctions are known for a long time. Hypothyroidism leads to anovulation and the consequent prolonged maintenance of proliferative endometrium results in heavy irregular bleeding and these changes are reversible with T₄ therapy.
Children with primary hypothyroidism have abnormal sexual development with cystic ovarian enlargement, estrogenization of the uterus and vagina, galactorrhea and isolated breast development. Hypothyroid boys may have inappropriate testicular enlargement with tubular development but without increase in Leydig cells (Laron et al, 1970; Barnes et al, 1973; Buchanan et al, 1988; Pringle et al, 1988).

Hyperthyroid women have irregular menstrual cycles (Goldsmith et al, 1952; Barnes et al, 1973). Premenopausal women with hyperthyroidism may have hypomenorrhea or amenorrhea (Bensen and Dailey, 1955). Hyperthyroid men may have oligozoospermia or azoospermia, loss of libido and gynecomastia (Kidd et al, 1979). Reproductive dysfunction in hypo- and hyperthyroidism have been attributed to altered hypothalamo-hypophyseal-gonadal hormone axis. Even though number of reports are being published on this line, no crystal clear idea has emerged so far due to inconsistency among various reports.

Franchimont and Burger (1975) reported decreased serum levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in hypothyroid subjects. In primary hypothyroidism, the LH:FSH ratio will be modified as LH may be unaltered, while FSH is elevated. Further, the pulsatility of gonadotrophins may be absent in these subjects (Buchanan et al, 1988; Pringle et al, 1988). Buitrago and Diez (1987) found unaltered
FSH and LH with low prolactin (PRL) and slightly increased testosterone in primary hypothyroid men. Hypothyroidism, in general, is associated with increased PRL (Barnes et al., 1973; Buchanan et al., 1988; Pringle et al., 1988).

Hyperthyroidism in men and women has been reported to be accompanied with increased serum LH and FSH (Chopra and Tulchinsky, 1974; Clyde and Walsh, 1976; Tanaka et al., 1981; Valenti et al., 1984). Recently, Erfurth and Hedner (1987) reported increased plasma LH levels and enhanced response of FSH and LH to gonadotrophin releasing hormone (GnRH) in hyperthyroid women. Short term administration of T₃ to normal women increased the basal and GnRH induced LH and FSH secretion (Erfurth and Hedner, 1987).

Kidd et al (1979) found high serum FSH, LH and testosterone in men with Graves' thyrotoxicosis but LH and FSH response to GnRH was normal. Recently, Rojdmrk et al (1988) reported normal levels of serum FSH, LH, PRL, testosterone and estradiol (E₂) in men with chronic hyperthyroidism. However, these hyperthyroid men showed enhanced response to GnRH. Buitrago and Diez (1987) also reported normal FSH, LH and testosterone in hyperthyroid men. In general, the production and clearance rates of serum PRL are increased in hyperthyroidism (Cooper et al., 1979).
Spontaneous hyperthyroidism may be associated with increased plasma testosterone (Gordon et al., 1969; see Abelin, 1983). Similar increase was reported in men with induced hyperthyroidism (Ruder et al., 1971). Monson et al. (1988) showed elevated testosterone and steroid hormone binding globulin (SHBG) in men affected with Graves’ thyrotoxicosis. Hyperthyroidism is usually associated with high SHBG levels and it returns to normal levels after treatment (Vermeulen and Verdoncle, 1968; Anderson, 1974; Nisula et al., 1978). Gordon et al. (1969) reported increased metabolic clearance rate (MCR) and conversion ratio of testosterone to androstenedione in hyperthyroid subjects. However, the conversion ratio of androstenedione to testosterone was significantly increased. E2 and progesterone are predominantly unaltered in hyperthyroid subjects but may show a tendency of elevation in some subjects. The metabolic clearance rate of E2 is decreased in association with increased SHBG (Ridgway et al., 1975).

Bradlow et al. (1966) showed that the metabolic transformation pattern of progesterone is unaltered in myxedematous women. However, a shift towards the production of 5 alpha-reduced metabolites was evident in hyperthyroid subjects. Gordon et al. (1969) showed normal MCR of androstenedione and increased MCR of testosterone in hypothyroid subjects. These authors also showed decreased conversion ratio of androstenedione to testosterone.
While hypothyroid men were found to have low levels of plasma testosterone, hypothyroid women did not show any change in the same (Cavaliere et al., 1988). Basal SHBG levels in hypothyroid men and women were shown to be low and $T_4$ and $T_3$ therapy increased the same towards normalcy (Cavaliere et al., 1988; Wortsman et al., 1988).

Experimental studies on hypo- and hyperthyroid animals have also been with inconsistent changes in serum FSH, LH, PRL, $E_2$ and testosterone due to variations in experimental designs, duration and species (Bruni et al., 1975; Suzuki et al., 1978; Aruldas et al., 1982a,b; Chandrasekar et al., 1985a, b). Wu Wang et al., (1987) showed the inhibitory effect of thyroidectomy on the basal and GnRH stimulated LH release as well as on the release of GnRH in the absence of ovarian hormones in rats. $T_4$ and $E_2$ have antagonistic effect on the pituitary response of LH to GnRH, and the release of GnRH (Wang et al., 1987). Another report from the same laboratory showed reduced PRL release in thyroidectomized rats in the absence of ovarian steroids (Pu et al., 1987).

**BIOCHEMICAL STUDIES IN THE BLOOD**

Hyperthyroidism is associated with enhanced rate of oxygen consumption, leading to increased energy production, utilization and heat generation and clinically manifested with elevated basal body temperature. An opposite trend is evident in hypothyroidism (see Ingbar, 1986).
A delicate balance exists between circulatory thyroid hormones and the synthesis and breakdown of proteins. Since the rate of protein breakdown predominates, hyperthyroidism is associated with negative nitrogen balance and loss of muscle mass (Ramsay, 1974). There may be mild hyperalbuminemia and decreased level of low density lipoproteins (LDL) (Walton et al, 1965). In both experimental and clinical hypothyroidism, there is decrease in synthesis (Crispell et al, 1956) and degradation (Hoberman and Graff, 1951) of proteins.

In general, the diminished protein synthesis is mainly due to inhibition of a variety of specific mitochondrial and cytosol enzymes (Pilot and Yatvin, 1973). Plasma LDL levels increase nearly 3 fold, indicating decreased catabolism (Walton et al, 1965). Despite, decreased synthesis and degradation, there is a significant increase in plasma albumin in hypothyroidism, due to increased vascular pool of the same (Schwartz, 1955; Lewaller et al, 1959).

A wide range of abnormal carbohydrate metabolism has been reported in thyroid disorders. Glucose absorption, uptake by adipose tissue and muscle, utilisation and production are enhanced in hyperthyroidism (Emmer et al, 1971; see Loeb, 1986). Glucose intolerance and post prandial glucosuria have been reported in hyperthyroid patients (Kreines et al, 1985). Glucose uptake by both adipose tissue and muscle is increased in hyperthyroidism (see Loeb, 1986). Hypothyroid subjects may have a
decreased rate of glucose absorption and may show flattened oral glucose tolerance curves, despite concomitant reduction in peripheral glucose assimilation (see Loeb, 1986).

Thyroid hormones have marked influence on lipid metabolism. Enhanced rate of lipid mobilization, synthesis and degradation are reported in hyperthyroidism (see Loeb, 1986; See Hoch, 1988). Plasma cholesterol and phospholipid levels fall significantly in hyperthyroidism. Administration of T₃ to normal healthy men enhanced the degradation and excretion of cholesterol, resulting in hypocholesterolemia (Kritchevsky, 1960).

Increased excretion and reduction in the concentration of LDL cholesterol and phospholipid binding apolipoproteins may be attributed to reduction in serum lipids of hyperthyroid subjects (Walton et al, 1965). Abrams and Grundy (1981) reported low triacylglycerol in hyperthyroid patients and attributed it to increased lipoprotein lipase activity. Thyrotoxicosis may be associated with mild increase in plasma triacylglycerol, plausibly due to its increased synthesis without any significant alteration in the clearance rate (Nikkala and Kekki, 1972). Clinical and experimental hyperthyroidism have been associated with increased turnover rate, oxidation and plasma concentration of free fatty acids (Tibbling, 1969; see Loeb, 1986).

A variety of changes in blood lipids have been recorded in hypothyroidism. Lipolytic effect of TSH, adrenocorticotrophin (ACTH),
glucagon and catecholamines are decreased in hypothyroid rats and human (Deykin and Vaughan, 1963; Goodman and Bray, 1966; Rosenquist, 1972). While free fatty acid level in the blood may be normal (Hamburger et al., 1963) or slightly subnormal (Nikkala and Kekki, 1972), plasma cholesterol, triacylglycerol and phospholipids are significantly elevated in hypothyroid subjects (see Loeb, 1986).

Hypercholesterolemia is a common feature in over 80% of the hypothyroid subjects (Watanakunakorn et al., 1965). Decreased rate of cholesterol excretion, concomitant with marked increased LDL cholesterol may be the reason for hypothyroidic hypercholesterolemia in human (Chobanian et al., 1962; Rabinowitz et al., 1963; Walton et al., 1965; Abrams and Grundy, 1981; Hylander and Rosenquist, 1982).

While the rate of triacylglycerol synthesis appears to be normal, the fractional removal of the same is markedly reduced and this could be the reason for the increased level of this lipid class in hypothyroidism (Nikkala and Kekki, 1972). Abrams and Grundy (1981) showed normal level of plasma triacylglycerol in non-obese hypothyroid subjects and an increase in obese hypothyroids.

MINERALS AND TRACE ELEMENTS IN THE BLOOD

Apart from the metabolism of carbohydrates, proteins and lipids, trace elements and minerals metabolism also undergo marked changes.
during thyroid disorders. Hypercalcemia and fecal loss of calcium (Ca) are common and important electrolyte abnormalities in thyrotoxicosis (Bradley et al., 1974; Katz et al., 1975). Ca deposition and resorption in the bone are increased in hyperthyroid subjects (Krane et al., 1956), though intestinal absorption of Ca is decreased (Haldimann et al., 1980). However, no correlation is found between the severity of thyrotoxicosis and serum Ca (Adams et al., 1967; Gordon et al., 1974). Hyperphosphatemia is also commonly seen among hyperthyroid subjects (Parson and Anderson, 1964; Adams et al., 1967). Despite increased tubular resorption of phosphate (Parson and Anderson, 1964), there is hyperphosphaturia in hyperthyroidism (Adams et al., 1967).

Abnormality in Ca and phosphorus are rare in hypothyroidism. However, hormonal and non-hormonal homeostatic mechanisms responsible for maintaining normal serum Ca may respond slowly in hypothyroidism (Bastienne, 1946; Bouillion and Demoor, 1974; Bradley et al., 1974; Castro et al., 1975).

Changes in magnesium (Mg) metabolism under altered thyroid conditions are of clinical significance (see Kleeman and Danovitch, 1986). Plasma Mg level tends to be low in hyperthyroidism (Frizel et al., 1967), with an abnormal ultrafiltrability of plasma Mg (Soffer et al., 1939, 1941, Dine and Lavietes, 1942). Increased urinary excretion of Mg occurs in hyperthyroidism and an opposite trend in hypothyroidism (Rizek et al., 1965).
Studies on experimental animals also showed decreased plasma Mg after the administration of T, (Aikawa, 1960). The apparent exchangeable body pool of Mg was shown to be increased in hyperthyroid rats and decreased in hypothyroidism (Aikawa, 1960; Avioli et al., 1963). Plasma and serum Mg levels in hypothyroidism may be slightly greater than normal and renal clearance will be reduced in myxedematous subjects (Jones et al., 1968; Frizel et al., 1967).

Normal regulation of sodium (Na) and potassium (K) is typical features of thyrotoxicosis and the concentration of these ions remain within normal range (Schizume et al., 1966; see Bradley, 1976). However, increased total exchangeable body Na in terms of both body weight and lean body mass have been reported in thyrotoxic patients (Monro et al., 1958; Wayne, 1960; Schizume et al., 1966). Administration of thyroid extract produces transient increase in K excretion (see Kleeman and Danovitch, 1986). Experimental hypothyroidism is associated with enhanced loss of urinary Na during Na loading, restriction and dehydration, and during administration of large doses of hydrocortisone or aldosterone. T, administration quickly corrects this tubular abnormality (Bradley et al., 1974).

Apart from minerals, trace elements metabolism in thyroid disorders are also given clinical importance in recent times. Hikosaka et al. (1982) found a good relation between serum zinc (Zn) and thyroid hormones. Nada and King (1986) reported a positive correlation between Zn intake and
serum levels of \( T_1 \) and \( T_2 \) in normal healthy men. Recently, Jordon \textit{et al} (1986) suggested an inhibitory effect of Zn on the release of TSH from the pituitary. However, Morley \textit{et al} (1980) reported such an effect at the level of hypothalamus as Zn deficiency lead to decreased levels of hypothalamic TRH content. While normal level of Zn was reported in the plasma of hyperthyroid subjects (Bremmer and Fell, 1977; Nishi \textit{et al}, 1980; Morley \textit{et al}, 1981), enhanced levels in serum Zn (Wolff, 1956) and low levels in erythrocytes (Pangaro \textit{et al}, 1974; Swaminathan \textit{et al}, 1976; Bremmer and Fell, 1977. Nishi \textit{et al}, 1980) have also been reported. Aihara \textit{et al} (1984) found low and high erythrocyte Zn values in hyper- and hypothyroidisms, respectively. Recently, Dolev \textit{et al} (1988) reported low plasma and blood mononuclear cell Zn in hypothyroid subjects but these authors reported normal plasma Zn in hyperthyroid subjects. But Zn content in erythrocytes was found to be low and inversely proportional to serum \( T_1 \) (Aihara \textit{et al}, 1984). The activity of erythrocyte carbonic anhydrase, a Zn metallo enzyme is inhibited in hyperthyroidism and stimulated in hypothyroidism (Pangaro \textit{et al}, 1974). Urinary excretion of Zn is increased in hyperthyroid and decreased in hypothyroid subjects (Nishi \textit{et al}, 1980; Aihara \textit{et al}, 1984; Dolev \textit{et al}, 1988).

Copper (Cu) is another essential trace element involved in human and animal growth, differentiation and metabolic activities (Hambidge, 1976; see Underwood, 1977; Mason, 1979). Plasma and erythrocyte concentrations of Cu are significantly elevated in hyperthyroidism (Aihara \textit{et al}, 1984) and
this may be due to the increase in Plasma aminoacids and ceruloplasmin, the carrier protein for Cu (see Aspin and Sass-Kortsak, 1981; Remesar et al, 1981).

Like that of Zn and Cu, manganese (Mn) also has some relation to thyroid status. Aihara et al (1984) found a significant correlation between erythrocyte Mn concentration and T₄ and T₃ levels. Nevertheless, they could not find any appreciable change in plasma and erythrocyte Mn in hypo- and hyperthyroid subjects.

Serum T₄ and T₃ have good correlation to the level of serum ferritin, carrier protein for iron. Administration of T₄ to euthyroid subjects for one week increased serum ferritin level. Serum ferritin was also found to be elevated in hyperthyroid patients (Macron and Macron, 1982; Van de Vyver et al, 1982). Takamatsu et al (1985) reported that ferritin concentrations in euthyroid, hypothyroid or thyrotoxic subjects are not significantly different. However, most of the thyrotoxic subjects given antithyroid therapy and made euthyroid showed a decrease in ferritin level. Similarly, hypothyroid subjects with Hashimoto's disease showed increased serum ferritin when euthyroidism was achieved with T₄ therapy. Administration of 75 µg T₃, daily for one week to euthyroid subjects resulted in more than 100% increase in serum ferritin (Takamatsu et al, 1985). Modified iron metabolism in thyroid disorders may cause alteration of ferritin (Van de Vuyer et al 1982).
THYROID TISSUE BIOCHEMISTRY

The normal functional status of an endocrine or any other secretory organ is determined by the structural and functional integrity of plasma membrane, enzymes concerned with the function of the organ and related metabolic activities (see Moolenaar, 1981).

Membrane bound adenosine triphosphatases (ATPases) regulate the transport of ions, aminoacids and sugars across the plasma membrane (Wolf and Halmi, 1963; Singer and Nicolson, 1972; Jorgensen, 1975). Thyroidal ouabain sensitive Na⁺-K⁺ ATPase facilitates the active transport of iodine across the thyroid follicular membrane (Ismail Beigi and Edelman, 1971; see Taurog, 1986). TSH induced iodine transport was shown to be associated with enhanced activity of thyroid follicular ouabain sensitive Na⁺-K⁺ ATPase (Brunberg and Halmi, 1966). Na⁺ has been considered as one of the major regulators of thyroidal iodine transport (Bagchi and Fawcett, 1973) and it inhibits the efflux and increases the influx of iodine across the follicular membrane (see Taurog, 1986).

Thyroperoxidase (TPO), an integral membrane enzyme of the thyroid gland, catalyses the oxidation of iodine and tyrosine as well as coupling of ioddotyrosyl residues (Nunez and Pommier, 1982; Virion et al, 1985; see Taurog, 1986). TPO is present in the nuclear envelope, rough endoplasmic reticulum, Golgi bodies, apical plasma membrane and at the base of pseudopods of thyroid follicles (Strum and Karnovsky, 1970; Tice - Wollman,

Thyroid follicular phospholipids were reported to have specific iodine binding properties (Vilkki, 1962; Schneider and Wolff, 1965). Na⁺-K⁺ ATPase induced iodine transport is closely linked to membrane phospholipids (Braganoa and Aravindakshan, 1960). Phosphatidyl choline, lecithin and phosphatidyl ethanolamine are the major membrane phospholipids associated with thyroidal iodine transport (see Taurog, 1986).

TSH has a stimulating effect on thyroidal phospholipids, particularly phosphatidic acid, phosphatidyl serine, phosphatidyl ethanolamine (Dumont, 1971; see Field, 1986) and phosphatidyl inositol (Scott et al, 1966). Such an effect of TSH on thyroidal phospholipids was reported to be retained in
human and canine adenomas and carcinomas (Schneider and Leav, 1977). TSH was found to stimulate the incorporation of \(^{32}P\)-glycerophosphate into phosphatidyl inositol and phosphatidic acid and not into phosphatidyl choline (see Pierce, 1986).

Apart from enzymes and lipids, thyroidal trace element metabolism may also undergo modifications during thyroid disorders. Cu has been reported to be present in thyroid tissue (Carlton and Henderson, 1963; see Underwood, 1977). Thyroidal superoxide dismutase, a metalloenzyme involved in the generation of H\(_2\)O\(_2\) has Zn and Cu and its activity was found to be reduced in endemic goitrous thyroid tissues (Markland, 1982; Suguwara et al, 1988). Thyroidal monoamine oxidase (MAO) is also a Cu containing metalloenzyme. Ishida et al (1984) reported high concentration of ferritin, the iron carrier protein in benign thyroid cystic fluid.

Increased thyroid size has been seen in Mg-deficient rats (Corradino and Parker, 1962). Administration of Mg decreased the size of the thyroid gland in human beings (Neguib, 1963). Mg appears to have a stimulatory effect on T\(_3\) secretion from the thyroid (Hsu et al, 1984). Apart from these informations, there is hardly any report on the fate of various trace elements in goitrous, adenomatous or carcinomatous human thyroid tissues.
The data obtained from the present study encompassing thyroidal enzymes, lipids and trace elements in multinodular goiter, follicular adenoma and papillary carcinoma along with serum thyroid hormones and TSH may help to understand the pathogenesis of these disorders in a better manner, with histopathological and imaging studies. Additional informations on serum lipids, trace elements and hormones are expected to provide a comparative and comprehensive picture about these parameters in the selected thyroid disorders. The data on serum hormones of the pituitary ovarian axis will help to understand the reproductive dysfunctions accompanying these thyroid disorders. In general, the present study is expected to throw more light on the existing knowledge on the pathogenesis of multinodular goiter, follicular adenoma and papillary carcinoma, as information on the selected aspects are lacking.
SCOPE OF THE PRESENT INVESTIGATION

The foregoing survey of literature reveals that studies on thyroid enlargements are predominantly oriented on histology of the gland, serum thyroid hormones and TSH. The information on the biochemistry of goitrous or neoplastic thyroid tissue is sorely lacking, except for few reports. Most of the biochemical studies have been restricted to the blood of hypothyroid and hyperthyroid subjects, in general. There is not much information on blood biochemistry in specific cases of goiter or thyroid neoplasms with varying status of thyroid hormones. Data on thyroid tissue and blood biochemistry, in addition to the routine pathological reports may serve as a good tool to understand the pathogenesis of goiter, adenoma and carcinoma. Having this in mind, the present study was designed to have a comprehensive data on tissue and blood biochemistry in selected thyroid disorders associated with swelling of the gland.

Women with multinodular goiter (sporadic), follicular adenoma and carcinoma were included in the present study as the number of subjects available was comparatively more in these categories. Further, Madras being a non-endemic area, papillary carcinoma and multinodular goiter (sporadic) are more prevalent than other carcinomas or goiters. Myxedematous women were also included to have a comparative picture on blood parameters.
The following blood and thyroidal parameters were selected in view of their importance to understand the pathogenesis of these disorders.

No study on thyroid will be complete without data on serum TSH and thyroid hormones. Only on the basis of T₄, T₃, and TSH one can assess the hypo- or hyper- or euthyroid status of the subjects. The biological effects of thyroid hormones are determined by the binding of free T₄ and T₃ to specific receptors (see Mendel, 1989). Hence, in the present study serum total and free T₄ and T₃, and TSH were also included.

Eventhough a number of reports are available on gonadotrophins, PRL and sex steroids in thyroid disorders, there is no common agreement among them as evident in the survey of literature. This is mainly because of variations in severity and duration of the disease and race. Further, most of the available reports are from Graves' disease, and hypo- or hyperthyroidism. Not much information is available on goitrous and neoplastic thyroid disorders. Therefore, it is felt pertinent to have data on these hormones in each subject of study, rather than to rely on existing reports to understand the impact of the disease clearly.

Any change in metabolic and physiological status of the body will be reflected in the blood. Lipid metabolism is well known to be influenced by thyroid hormones (see Loeb, 1986). However, most of the available information on blood lipids are mainly confined to triacyl glycerol and cholesterol in hypo- and hyperthyroid conditions. Therefore, in the present
study various classes of phospholipid, cholesterol and glyceride glycerol were assessed in the blood serum of patients with multinodular goiter, follicular adenoma and papillary carcinoma of the thyroid.

Thyroidal phospholipids are well known regulators of iodine transport (Schneider and Wolf, 1965). Alterations in the ratio of phospholipid and cholesterol interfere with the activities of membrane transport enzymes like ATPases (Kimelberg and Papahadjopoulos, 1974). Since there is not much information on thyroid tissue cholesterol and phospholipids in goitrous or neoplastic conditions, various fractions of phospholipid and cholesterol were studied. As glyceride glycerols serve as energy source and precursor for phospholipids (see Abdel - Latif, 1983), different classes of glyceride glycerols were also investigated.

In recent years, trace elements and minerals have been found to influence the synthesis, secretion and action of a number of hormones (Dekker and Field, 1970). Ca has been implicated in TSH induced iodine transport (Weiss et al, 1984; Bidey and Tomlinson, 1987), H₂O₂ generation (Bjorkman and Ekholm, 1984) and thyroid hormone secretion (Zor et al, 1968; Dekker and Field, 1970). Mg may have a role in maintaining the structure and function of the thyroid gland (Neguib, 1963). Further, the activities of ATPases, alkaline phosphatase and a number of other enzymes are influenced by these ions.
Zn has an essential role in maintaining membrane structure (Bettger and O’ Dell, 1981). Zn and Cu play a vital role in regulating a number of enzymes including MAO; alkaline phosphatase and thyroid superoxide dismutase (Prasad, 1985). Iron (Fe) metabolism may undergo modification due to altered thyroid functions (see Herbert 1986a, 1986b) leading to anemic diseases. Apart from these, Cadmium (Cd), and Manganese (Mn) also have been shown to have influence on various endocrine organs. Mn is known to influence lipid metabolism (see Underwood, 1977). However, there is not much information available on these elements in blood and thyroid gland except few reports on blood. In the present study concentrations of these elements were assessed in normal and abnormal human thyroid tissues and blood.

Serum trace elements were included as they may provide a clue to thyroidal status of these elements. Further, reproductive abnormalities, growth retardation and anemia which are known to accompany thyroid dysfunctions have been found to be associated with deficiency or excess of trace elements like Zn, Cu, Mg, Fe and Cd (see Prasad, 1985).

The plasma membrane has a marked influence on ionic transport, secretory activities, cell proliferation, antigenicity, metabolic activities, cellular adhesiveness and contact inhibition (see Mollenour, 1981). The functional status of the plasma membrane of thyroid follicles may be assessed on the basis of activity of some membrane bound enzymes. Plasma
membrane bound ATPases play a vital role in regulating ion transport. Thyroidal ATPases, particularly Na^+-K^+ ATPase, are implicated in iodine transport (see Taurog, 1986). Ca^{2+} and Mg^{2+}-ATPases may influence the secretory activity of thyroid by altering intracellular ionic balance. Not much information is available on the status of human thyroidal ATPases in goiter, adenoma or carcinoma. Therefore, thyroidal ATPases were included in the present study. 5'nucleotidase, a membrane bound enzyme is also present in the follicular cells of thyroid, behaving as an ectoenzyme and may be involved in the regulation of TSH induced adenyl cyclase activity (Stanley et al, 1982; Franc et al, 1984). Therefore, this thyroidal enzyme was also investigated.

Thyroperoxidase (TPO) and monoamine oxidase (MAO) are involved in the oxidation of iodide and tyrosine and in the coupling reaction of thyronine residues in the thyroid gland (Fisher et al, 1966; Virion et al, 1985; see Taurog, 1986). In view of these vital roles played by TPO and MAO on thyroid glandular function, both these enzymes were considered.

Thyroidal acid phosphatase is shown to involve in the hydrolysis of Tg to release T₄ (Stein and Cross, 1964; see Halmi, 1986). Alkaline phosphatase may help cell proliferation by facilitating nucleoprotein synthesis as it cleaves phosphate esters (see Meyer - Sabellek, 1988). Hence, activities of these two phosphomonoesterases were assayed in the thyroid tissues.