An attempt has been made in the present study to understand the pattern of thyroidal lipids, trace elements and some enzymes involved in membrane transport and thyroid hormone synthesis under pathological conditions associated with multinodular goiter, follicular adenoma and papillary carcinoma. Information on these aspects of thyroidal metabolism are expected to enlighten the knowledge on the pathogenesis of these disorders. At present, imaging studies and histopathological reports are considered mainly with supportive data on serum thyroid hormones and TSH to understand the pathogenesis of thyroid goiter and cancer. Only very little information is available on human thyroidal biochemistry, particularly under pathological conditions.

Pathological thyroid samples from 31 women with multinodular goiter, 38 women with follicular adenoma and 25 women with papillary carcinoma were investigated in the present study. Presurgical blood samples from the patients were also used. Blood samples from 20 myxedematous women were included to have a comparative picture of blood parameters.

Control thyroid tissues from accident victims without known history of nonthyroidal and other clinical illness and normal paranodular thyroid tissues were used for statistical comparison of the data. Blood samples from normal age matched control subjects were used for comparison of blood parameters.
Serum free and total thyroxine (T₄) and triiodothyronine (T₃) and thyroid stimulating hormone (TSH) were assayed to understand the thyroid hormone status of these subjects.

Serum follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol (E₂) and progesterone (P) were assayed to know the reproductive function of women with different thyroid disorders.

Various classes of neutral and phospholipids were investigated in the pathological thyroid tissues and blood serum.

Important trace elements like Zinc (Zn), Copper (Cu), Manganese (Mn), Cadmium (Cd), Iron (Fe), Calcium (Ca) and Magnesium (Mg) were also analysed in thyroid tissues and blood serum of selected subjects.

Thyroid membrane enzymes involved in membrane transport and hormone synthesis like Na⁺-K⁺, Ca²⁺ and Mg²⁺ ATPases, 5’nucleotidase, thyroperoxidase (TPO), monoamine oxidase (MAO) and phosphomonoesterases were also investigated in the pathological thyroid tissues.

On the basis of serum total and free T₄ and T₃ and serum TSH, most of the women with multinodular goiter were found to be non-toxic. Six of these were found to be hypothyroid and most of the remaining subjects were euthyroid. 27 women with follicular adenoma were with hypothyroid status and 11 were euthyroid. Among the 25 women with papillary
carcinoma, 13 were hypothyroid and others were euthyroid. All myxedematous subjects were found to be hypothyroid.

The present study suggests that serum free T₄ and TSH as good indices to diagnose marginal hypothyroid subjects. Decreased serum total T₄ and total T₃ with elevated TSH appears to be a good index of true clinical hypothyroid conditions seen in myxedema.

Serum FSH, LH and E₂ in follicular phase showed a general trend of decrease or no change in women with multinodular goiter, follicular adenoma, papillary carcinoma and myxedema. However, serum LH in women with myxedema showed the opposite trend. On the other hand serum P exhibited the trends of either elevated or unaltered levels, in women from all four groups at follicular phase. Comparatively less number of myxedematous women at follicular phase had increased serum P.

Serum FSH, E₂ and P at luteal phase suggest decreasing trend in a number of women with multinodular goiter, follicular adenoma, papillary carcinoma and myxedema. Nevertheless, serum FSH in most of the myxedematous women at luteal phase was unaltered. Luteal phase serum LH revealed enhancement or decrease in women with multinodular goiter and follicular adenoma. While it was elevated in women with myxedema, it was diminished in women with papillary carcinoma. While serum E₂ in
most of the women with papillary carcinoma was uniformly decreased, serum P exhibited the opposite trend in all women with papillary carcinoma.

The data on serum gonadotrophins and sex steroids in postmenopausal women suggest reversal of the normal trend in a number of women with multinodular goiter, follicular adenoma, and myxedema. However, serum FSH in postmenopausal women with multinodular goiter was predominantly unaffected.

The data on serum PRL indicate hyperprolactinemia in almost all women with myxedema. Either hypoprolactinemia or normal prolactin were evident in women with multinodular goiter, follicular adenoma and papillary carcinoma.

The present study suggests altered feed back regulation of FSH by E₂ at follicular and luteal phases. Feed back regulation of LH by P appears to be intact at follicular phase but is likely to be modified in some women at luteal phase.

Modified E₂ : P ratio, altered sensitivity of pituitary sex steroid receptors and ovarian gonadotrophin receptors are proposed as factors responsible for the observed changes in pituitary-ovarian hormone axis in women with thyroid disorders. Apart from these, changes in the MCR of gonadotrophins and sex steroids, overlapping of TSH and gonadotrophin
secretion and hyperprolactinemia may also contribute for the changes in serum gonadotrophins and sex steroids.

The reversal of normal pattern of gonadotrophins and sex steroids in postmenopausal women with thyroid disorders did not affect the negative feed back system. Enhanced supply of sex steroids from adrenal gland and peripheral conversion of adrenal androgens are suggested as the reason for increased sex steroids in thyroid disorders.

The data on serum PRL suggests hyperprolactinemia in almost all women with myxedema. On the other hand, hypoprolactinemia and normoprolactinemia are likely to be present in women with multinodular goiter, follicular adenoma and papillary carcinoma. The study reveal differential response of PRL in clinical hypothyroidism and subclinical hypothyroidism. While TRH induced secretion of PRL appears to be responsible for hyperprolactinemia in myxedematous women, reduced E$_2$ stimulation seems to be the reason for hypoprolactinemia in most of the women with multinodular goiter, follicular adenoma and papillary carcinoma. An inhibitory effect of elevated serum Zn on PRL secretion is also proposed as the reason for hypoprolactinemia.

Serum total, free and esterified cholesterols were diminished in women with multinodular goiter, follicular adenoma and papillary carcinoma. An opposite trend was seen in women with myxedema.
Serum glyceride glycerols showed inconsistent changes in women with different thyroid disorders. While serum total glyceride glycerol was elevated in myxedema and follicular adenoma, an opposite trend was seen in other two groups. Monoacyl glycerol concentration was diminished in women with multinodular goiter and papillary carcinoma with an opposite trend in myxedema. Diacylglycerol was elevated in all four groups. Serum triacyl glycerol exhibited more or less the same trend as that of serum cholesterol with increase in myxedema and decrease in other groups. In women with follicular adenoma, both monoacyl and triacyl glycerols were either decreased or increased.

Serum total phospholipid and various classes of phospholipid were markedly elevated in all women with multinodular goiter, follicular adenoma and papillary carcinoma. No discernible change in serum phospholipid classes could be seen in myxedematous women, even though total phospholipid was elevated.

Thyroidal total, free and esterified cholesterol were elevated in women with follicular adenoma, while an opposite trend was seen in women with papillary carcinoma. No clear pattern was seen in thyroidal cholesterol of multinodular goiter. Thyroidal total, mono, di- and triacyl glycerols were elevated in most of the women with follicular adenoma and papillary carcinoma. However, women with multinodular goiter showed increased or unaltered pattern of thyroidal mono- and triacyl glycerol.
An uniform trend of increase in thyroidal total phospholipids and its fractions was evident in women with multinodular goiter, follicular adenoma and papillary carcinoma.

Serum Zn, Cu and Mn showed a tendency to increase due to thyroid disorders. However, serum Zn in women with multinodular goiter and serum Cu in myxedema subjects did not show any appreciable change. Serum Cd was increased in myxedematous women alone and was decreased in women with papillary carcinoma.

Serum Fe, Ca and Mg were uniformly decreased in all subjects with multinodular goiter, follicular adenoma and papillary carcinoma. In myxedematous women, while serum Fe was decreased, Ca was elevated and Mg was unaltered.

Thyroidal Zn was elevated in women with multinodular goiter and papillary carcinoma and was unaffected in women with follicular adenoma. On the other hand, only follicular adenomatous thyroid had diminished Cu in most of the subjects. Such a trend was seen only in a few multinodular goiter and papillary carcinoma thyroids. While thyroidal Mn was elevated in all three groups, thyroidal Cd was diminished. However, few papillary carcinoma thyroids had elevated Cd.

Thyroidal Fe and Ca were diminished uniformly in all women with multinodular goiter, follicular adenoma and papillary carcinoma. On the
other hand, thyroidal Mg was increased in only few papillary carcinomas and was unaffected in others.

Thyroid membrane Na⁺-K⁺, Ca²⁺ and Mg²⁺ ATPases registered significant increase in women with multinodular goiter, follicular adenoma and papillary carcinoma, irrespective of serum TSH status. A similar trend was seen in membrane bound 5' nucleotidase.

Thyroidal TPO activity was also found to be enhanced in majority of the subjects with multinodular goiter, follicular adenoma and papillary carcinoma, irrespective of serum TSH status.

The specific activity of MAO was also stimulated in most of the multinodular goiter, all papillary carcinomas and in about 50% of women with follicular adenoma, irrespective of TSH status.

While thyroidal acid phosphatase was unaffected, alkaline phosphatase showed increased activity in all multinodular goiters and in a number of women with follicular adenoma and papillary carcinoma. As in other enzymes, no clear correlation was seen between serum TSH and alkaline phosphatase.

The data on serum cholesterol suggest hypercholesterolemia in myxedematous hypothyroidism and hypocholesterolemia in hypothyroid and euthyroid subjects with multinodular goiter, follicular adenoma and papillary carcinoma. Diminished levels of serum thyroid hormones appear to be the
main factor responsible for hypercholesterolemia in women with myxedema. On the other hand, enhanced serum Cu and reduced bioavailability of T, to peripheral organs from serum T, pool seems to be the reason for hypocholesterolemia seen in non-myxedematous thyroid disorders.

The data on serum glyceride glycerol suggests accumulation of diacyl glycerol which may be either due to increased rate of synthesis or disproportionate utilization for the synthesis of triacyl glycerol and phospholipids. Dietary intake and serum Cu status may be responsible for decreased triacyl glycerol in women with multinodular goiter and papillary carcinoma as well as in those adenoma subjects with reduced triacyl glycerol.

Variation in the bioavailability of thyroid hormones at peripheral organs involved in lipid metabolism and Cu-dependent serum lipoprotein lipase may be responsible for the difference seen in serum cholesterol and triacyl glycerol in myxedematous and non-myxedematous women.

Increased synthesis of phospholipids from diacyl glycerol may be responsible for elevated serum phospholipids in all four groups. Mn induced fatty acid synthesis may also contribute for the increased serum phospholipids in women with multinodular goiter, follicular adenoma and papillary carcinoma.

The observed changes in thyroidal lipids appears to be the inherent property of goitrous and neoplastic thyroids. Since thyroidal lipids were
elevated in subjects with increased and normal levels of serum TSH, modified TSH receptor adenyl cyclase activity may be attributed for increased thyroidal lipids.

Increased thyroidal cholesterol is suggested to be the result of enhanced synthesis. Increased thyroidal Mn content might have facilitated enzymes involved in cholesterol synthesis.

Enhanced conversion of phospholipids from glyceride glycerols is implied as a possible reason for the uniform increase in all classes of thyroidal phospholipids. Increased thyroidal Mn might also have facilitated phospholipid synthesis.

Altered intestinal absorption, excretion and dietary intake may be responsible for the changes in serum Zn, Cu, Mn, Cd, Mg and Ca. Modified deposition and resorption of bone Ca may also contribute for the increase in serum Ca.

Thyroidal uptake of Zn, Cu appears to be affected due to multinodular goiter, follicular adenoma and papillary carcinoma. While the thyroidal uptake of Cd seem to be adversely affected in all the groups, an opposite trend is likely to exist with regard to Mn.

Serum Zn showed a positive correlation to TSH, suggesting the stimulatory effect of Zn on TSH secretion. An inverse relationship exists between elevated serum Zn and PRL status in non-myxedematous
hypothyroid and euthyroid women and positive correlation was seen in myxedematous women.

Impaired T₁ action may be implied due to increased serum Zn, Cu and Cd. This appears to be the reason for the observed uniform changes in serum lipids, particularly phospholipids and cholesterol, irrespective of thyroid hormone status in women with multinodular goiter, follicular adenoma and papillary carcinoma. The diminished thyroidal Ca may modify TSH action on thyroid glandular function.

The significance of altered thyroidal Cd is not known at present due to lack of information on its importance in thyroid function. Similarly, the reason for the opposite trend seen in thyroidal Fe content and TPO activity is not clear at present. However, the present study opens new vistas of research on these lines.

Enhanced activities of ATPases, particularly Na⁺-K⁺ ATPase may suggest increased thyroidal iodide transport in most of the multinodular goiter, follicular adenoma and papillary carcinoma subjects. Increased activity of 5' nucleotidase provides supportive evidence for enhanced membrane transport and TSH action.

Increased thyroidal phospholipids is correlated to enhanced iodide transport by stimulated activity of Na⁺-K⁺ ATPase. Increased ethanolamine plasmalogen, choline plasmalogen, phosphatidyl serine and phosphatidyl
choline may be specifically linked to enhanced iodide transport. The modified membrane fluidity due to altered phospholipid : cholesterol ratio may also influence iodide transport.

Multinodular goitrous, follicular adenomatous and papillary carcinomatous thyroids with stimulated TPO and MAO activities may indicate increased iodide oxidation.

Increased iodide transport and oxidation may suggest high rate of hormone production. Defective hormone synthesis at post iodide oxidation steps is proposed as the causative factor of the hypothyroidism or euthyroidism observed in these women. Increased MAO activity may affect efflux of I⁻ from follicle into lumen by decreasing the availability of norepinephrine. Therefore, the euthyroid and hypothyroid status of most of the selected women with multinodular goiters, follicular adenomas and papillary carcinomas suggest illproportionate hormone secretion to iodide transport and oxidation. The illproportionate iodide transport and hormone secretion may lead to colloid accumulation and nodular formation.

The increased enzyme activities in multinodular goiters appears to be mainly due to increased sensitivity of TSH receptor adenyl cyclase activity. In follicular adenomas and papillary carcinomas, both modified TSH receptors and increased TSH titres appear to have stimulated these thyroidal enzymes.
In conclusion, the data obtained in the present study suggests that clinical hypothyroidism in myxedema and sub-clinical hypothyroidism associated with multinodular goiter, follicular adenoma and papillary carcinoma may be delineated on the basis of serum free T₄ and TSH.

Modified Zn and Cu metabolism in thyroid disorders are implicated in altered pituitary-ovarian hormone axis. Hypo- or normal secretion of PRL may occur in women with multinodular goiter, follicular adenoma and papillary carcinoma, depending upon the serum Zn status.

An inverse relationship is found between serum Cu and cholesterol. Cu plays an important role in the development of juxtaposed pattern of serum cholesterol in women with myxedema and those with multinodular goiter, follicular adenoma and papillary carcinoma.

Altered Zn, Cu and Cd metabolism in subjects with multinodular goiter, follicular adenoma and papillary carcinoma may interfere with T₄ action.

Enhanced iodide transport and oxidation with normal or reduced secretion of thyroid hormones may be the causative factor of colloid accumulation and thus pathogenesis of nodular goiter or adenoma.

Thus, modified thyroidal trace elements, lipid metabolism and membrane transport mechanism associated with multinodular goiter, follicular adenoma and papillary carcinoma appears to have marked influence on the
functional status of the gland and thyroid hormone action. Information on the trace element status of subjects with multinodular goiter, follicular adenoma and papillary carcinoma may help in better management of subjects with varied degrees of modified thyroid hormone status.