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# HYPERPLASTIC THYROID GLAND;

## VASCULAR AND FOLLICULAR CHANGES PRODUCED BY DEXAMETHASONE DURING INVOLUTION

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**ABSTRACT... Aim and Objective:** The study was conducted to see the vascular and follicular changes induced by dexamethasone (synthetic corticosteroid) during involution of hyperplastic thyroid gland in albino rats. **Study Design:** A comparative histological study done in Post Graduate Medical Institute Lahore in 1998 **Procedure:** 54 adult rats were taken and divided at random into two control groups having 27 rats and experimental groups containing 27 rats. Control group was given normal diet along with 2 microgram of Potassium iodide intraperitonealy for 21 days while experimental groups further subdivided into group A having 3 rats and group B and C containing 12 rats each. All the experimental groups were treated with Thiourea for 21 days. Group A was sacrificed on day 22 after withdrawal of thiourea. Group B was given Potassium iodide intraperitonealy after stoppage of TU on day 21 and were sacrificed on days 22, 26, 30 and 50 in 4 sub groups ( B1-B4) to study the involution process. Group C was injected dexamethasone from 22 to 50 days after withdrawal of TU and sacrificed on same days in 4 subgroups (C1-C4) as sub groups B. **Result**s: The results of experimental group. A showed increase in thyroid and relative tissue weight. Histologically this group exhibited significant increase in stromal congestion with tall follicular cells lining the small sized follicles having scanty colloid. The results of experimental groups B and C demonstrated increase in thyroid and relative tissue weight but microscopically subgroups B revealed early and complete involution whereas subgroups C showed significantly persistent hyperplastic changes in the form of stromal congestion, vessels wall remained well defined and tall follicular cells lining small empty follicles. **Conclusion:** It was concluded that dexamehasone did retain hyperplastic changes during involution evident by stromal congestion and small sized regular follicle lined by tall follicular cells, so it should be carefully used in thyroid diseases.

**Key words:** Thiourea and thyroid, Dexamethasone and thyroid, Hyperplasia of thyroid and dexamethasone.

## INTRODUCTION

Thyroid gland is brownish red highly vascular organ placed in the lower neck at the level of 2nd to 4$^{th}$ tracheal rings.

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It is ensheathed with pretracheal fascia and consists of right and left lobe connected in the mid line by narrow isthmus.

It is derived from endoderm of primitive pharynx posterior to tongue at foramen caecum, resides at lower larynx after descent anterior to hyoid bone[1].

Histologically thyroid gland is covered by thin fibrous capsule which extends into the glandular parenchyma which divides each lobe into irregular shaped and sized lobules. The functional units of the thyroid gland are the follicles which are spherical or cyst like of variable sizes having colloid in the centre lined by single layered epithelium resting on basal lamina. The sufficient amount of hormone is stored in the form of colloid in the follicles is present enough for body need for up to 3 months[1] The follicular cells vary from squamous to low cuboidal to coloumnar, depending on their level of activity[2]. Colloid consists of almost entirely by an iodinated glycoprotein, iodothyroglobulin. This is an inactive form of active thyroid hormone triiodothyronin (T3) and tetraiodothyronin, thyroxin (T4). Thyroid follicles are surrounded by delicate connective tissue stroma containing dense plexuses of fenestrated blood capillaries Thyroid parenchyma also contain C cells ( clear cells) located in the thyroid follicle resting on basal lamina not reaching to the lumen of the follicles and have pale looking cytoplasm, and they secrete thyrocalcitonin[1].

T3 and thyroxin are under the influence of circulating TSH, which is secreted by anterior lobe of pituitary gland. Thyroid is the gland whose secretion is stored in the form of thyroglobulin.Iodine is absorbed from the blood capillary through iodide pump, the absorbed iodine is transported by a specific transmembrane protein sodium iodide symporter[3,4,5]. Iodine transportation is directly related with TSH whereas thiocynate and perchlorate inhibit its absorption by blocking its receptor sites. Iodine is activated by peroxidase in the presence of $H_2O2$ as oxidant[6], this enzyme is located at apical region of plasmalemma[7]. The active iodine then incorporates in the tyrosyl residues of globulin, coupling of mono- iodo tyrosin and di-iodotyrosin leads to T3 and T4. This process can be blocked by Thiourea.

## HYPERPLASIA

Hyperlasia is defined as an increase in the number of cells in an organ which contributes to increase in volume. Both structural and functional activities are under the control of thyroid stimulating hormone (TSH) released by pituitary gland. TSH stimulates synthesis of inositol triphosphate and causes increase in cytosolic Ca++ in follicular cells[8,9,10], this in turns stimulates $H_2O_2$[11]. TSH stimulates adenyl cyclase which in the presence of Ca++ converts ATP into cAMP that acts as intercellular messenger, stimulates the enzyme protein kinase[12,13] responsible for hyperplastic changes. Goiter is visible swelling in the neck found in iodine deficient areas. Hyperplasia can also be produced by antithyroid drugs like Thiourea. It inactivates peroxidase enzyme necessary for iodine activation which only occur when heme is oxidized[14,15]. Histologically both stromal and parenchymal changes are visible in hyperplastic thyroid gland. Stromal changes are thick capsule having congested interfollicular tissue[16,17]. Whereas tall follicular cells lining the small empty follicles[18,19]are the parenchymal changes.

## STEROID

Steroid are naturally occurring or synthetic fat soluble organic compounds having 17 carbon atoms arranged in four rings and included in these are sterols and bile acids, adrenal and sex hormone, certain natural drugs like digitalis, and also the precursor of certain vitamins. Dexamethasone is the synthetic corticosteroid, a hormone released by zona fasciculata of adrenal gland. It is commonly used in certain autoimmune diseases and its release is enhanced in stressful condition and is mediated by mutual interaction of hypothalamic pituitary axis and immune mechanism[20]. It is absorbed both orally and parentrally with the dose of 1.25mg/kg body weight. Steroid bound globulin the blood reaches the receptors site then translocated across cell membrane and acts on target gene on DNA, which is transcribed into specific protein concerned with the actions of steroid. Some effects of it are immediate and mediated by G protein phosphate complex which activate second messenger across the cytoplasm[21].

## AIMS AND OBJECTIVES

The present study was conducted

To evaluate effects of dexamethasone on stromal blood vessels and on follicles during involution of hyperplastic thyroid gland.

## MATERIALS AND METHODS

Total 54 adult male albino rats weighing 120-300 grams were taken from National Institute of Health Islamabad. All the rats were healthy, kept in animal house of PGMI Lahore in standard cages for two weeks for acclimatization. All were given normal diet and were divided at random into two groups control and experimental each having 27 rats.

## GROUPING

### Control groups

Control group comprised of 27 rats and were randomly divided into 3 subgroups. Group 1 was sacrificed on day 22 containing 3 rats and other 2 groups containing 12 rats each and were sacrificed on days 22, 26, 30 and 50 with experimental groups B and C

## EXPERIMENTAL GROUPS

Experimental groups comprised of 27 rats and were given thiourea, an antithyroid drug in the dose of 10 mg/100 gram bodyweight orally for 21 days. This group was divided at random into A, B and C

## GROUP A

Three rats were given thiourea at the dose of 10mg/100 gram body weight orally for 21 days and were sacrificed on day 22

## GROUP B

Total 12 rats were placed in this group which were given thiourea 10mg/100 gram body weight for 21 days along with 2 microgram Potassium Iodide intrapertonealy as replacement therapy for involution study. They were sacrificed on day 22, 26, 30 and 50 in 4 subgroups B1-B4 respectively each containing 3 rats

## GROUP C

The rest of 12 were given thiourea 10mg/ 100gram bodyweight orally along with 2 microgram of potassium iodide intraperotonealy as for replacement therapy for 21 days. These were also injected 1.25 mg/kg body weight of dexamethasone intramuscular daily from day 22 to 50. They were sacrificed on day 22, 26, 30 and 50 in sub groups C1-C4 respectively, each containing 3 rats.

## DRUGS

### THIOUREA

It is the anti thyroid drug and marketed as Thiourea GPR prepared by BDH London, taken from the Lahore Scientific Store Lahore. It is white crystalline powder, soluble in water

## DOSE PREPARATION

The dose was prepared by dissolving 2 grams of thiourea in 50ml of distilled water and with the help of insulin syringe calibrated for one ml into 100 units so 0.25ml=25units=10mg thiourea

## DEXAMETHASONE

It is synthetic corticosteroid available in market. In this study dexamethasone was used in the form of ampule of 1 ml containing 4 mg prepared by Tabrose Pharmaceutical Karachi.

## DOSE PREPARATION

The dose used was 1.25 mg / kg bodyweight per day by intramuscular injection in quidriceps muscles of rats. The dose was calculated with the help of insulin syringe, according to the dose 100 grams body weight required 0.125 mg dexamethasone. As one ampule of dexamethasone contains 1ml=4mg. i.e 0.03 ml=0.125mg from the ampule. Insulin syringe is calibrated for 100 units per ml so 3 units = 0.125mg per 100 grams bodyweight

## PROCEDURE

All the rats both control and experimental were sacrificed on specified days using ether anesthesia. A parmedian incision was made in the neck extending to upper larynx to expose thyroid gland. The thyroid lobes were fixed in 10% formaldehyde for 16 hours processed and dehydrated. Tissue was cut at 5 micron meter by rotatory microtome. 10 slides of each group were prepared stained with H&E and examined by light microscopy. Students t test and Duncan Multiple Range Tests were applied for statistical analysis.

## PARAMETERS

### GROSS PARAMETERS

### BODY WEIGHT

All the animals were weighed before the experiment and at the time of sacrifice

### TISSUE WEIGHT

Tissue taken from the control as well as experimental groups were weighed.

### RELATIVE TISSUE WEIGHT %

It is calculated by the formula:

Tissue weight X 100

Body weight

### HISTOLOGICAL PARAMETER

1. **BLOOD CAPILLARIES**

   Their number and size were measured both in control and experimental groups

2. **FOLLICLES**

   They were observed for numbers, size and shape

All the measurements were carried out in three random fields of microscope. In each microscopic field, the follicles and blood vessels were calculated, from one marker point to the other. Those follicles were counted which were cut at right angle .Measurements were carried out with the help of an oculometer under 40x.

## RESULTS

### GROSS APPEARANCE

### RELATIVE TISSUE WEIGHT

The mean thyroid weight of control group was 0.027± 0.0016 grams relative tissue weight was 0.013%. The mean thyroid weight of experimental group A (treated with thiourea for 21 days) was 0.04±0.0089 grams greater as compared to control and had relative tissue weight 0.020% (Table-I). The animals of experimental group B (treated with thiourea and potassium iodide) showed thyroid that were found red congested and enlarged. The mean thyroid weight 0.03 ±0.0137 grams and Relative tissue weight was 0.019% (Table-I).

**TABLE-I. Relative Tissue Wight % of Thyroid Gland**

| GROUPS | | MEAN BODY WEIGHT (G) | MEAN THYROID WEIGHT (G) | RELATIVE TISSUE WEIGHT % |
|---|---|---|---|---|
| CONTROL | | 207 ± 37.07 | .027 ± .0016 | .013 |
| | A | 198.3 ± 14.38 | .04 ± .0089 | .020 |
| EXPERIMENTAL | B | 155.8 ± 31.96 | .03 ± .0137 | .019 |
| | C | 209 ± 38.28 | .035 ± .08 | .016 |

which was higher as compared to control and group A. Whereas experimental group C (treated with thiourea, potassium iodide and dexamethasone) had mean thyroid weight .035±.08 and relative tissue weight = 0.016% (table1) which was less compared to experimental groups A and B

## MICROSCOPIC APPEARANCE

### STROMAL CAPILLARIES

Inter-follicular stroma of the control group contained many blood capillaries their mean number per field was 23.06± 6.42 (Fig 1). The size was variable, close to the capsule these were larger, their mean size was 36.06±24.0 micrometer.

In experimental group A stroma was hyperemic numerous blood vessels were prominent. Their number was significantly higher (P=.0003) as compared to control group (Table-II).

Many blood vessels contains RBCs in the lumen and some encircling the follicles (fig.3). The mean size of capillaries was 25.31 micron meter.( Table-II).

The stromal blood capillaries in experimental group B were also numerous, their mean number per field was 28.07±2.25 and was significantly increased as compared to control (P= 0.005), (Table II). The mean size was 21.49±1.50 micrometer.

In the Experimental group C microscopic field appeared congested, having many blood vessels. The blood vessels were well demarcated the mean size was 32.36±2.53 micrometer which showed insignificant change compared to control (Table II, Fig. 4 ) whereas their number was significantly increased P= 0.04 ( Table II).

**Table-II. Comparison of experimental groups a, b and c (Variables) number & size (micro meter) of blood capillary and follicles**

| GROUPS | | MEAN | ST. DEV. | SE. MEAN | DF | P VALUE |
|---|---|---|---|---|---|---|
| EXP. A N=10 | No. of Blood capillaries | 42.1 | 10.9 | 3.4 | 14 | 0.0003* |
| | Size of Blood capillaries | 25.31 | 9.62 | 3.0 | 11 | 0.9 # |
| | No. of Follicles | 30.88 | 9.18 | 2.09 | 16 | 0.11 # |
| | Size of Follicles | 86.6 | 15.1 | 4.8 | 12 | 0.0013* |
| EXP. B N=10 | No. of Blood capillaries | 28.07 | 2.25 | 0.71 | 11 | 0.0056* |
| | Size of Blood capillaries | 21.49 | 1.50 | 0.47 | 9 | 0.07 # |
| | No. of Follicles | 29.31 | 1.45 | 0.46 | 9 | 0.066 # |
| | Size of Follicles | 102.98 | 5.30 | 1.7 | 9 | 0.01* |
| EXP. C N=10 | No. of Blood capillaries | 30.54 | 2.83 | 0.89 | 12 | 0.04* |
| | Size of Blood capillaries | 32.36 | 32.53 | 0.80 | 9 | 0.11* |
| | No. of Follicles | 32.49 | 3.58 | 1.1 | 13 | 0.007* |
| | Size of Follicles | 91.32 | 5.21 | 1.6 | 9 | 0.0028* |

** = Significant P value < 0.05 # = Insignificant P value > 0.05*
*All the values were calculated with respect to control*

Interfollicular stromal capillaries showed remarkable changes in subgroups of experimental group B and C. In group C fields appeared congested, vessels walls well defined (Fig.4),their number increased significantly with mean 28.16 compared to group B ( Mean= 27.66 ) Table 3, Fig.3. Within subgroups C on day 50 their number increased significantly compared to day 26 whereas in subgroups B this parameter coincides with control.

Regarding luminal size of the blood vessels subgroups C showed increased congestion in subgroups C and size was greater as compared to subgroup B having mean 26.59 micrometer. Within subgroups on day 50 (C4) showed significant narrowing compared to day 22(C1).

Table III). The size of the capillaries in sub group C was significantly increased on day 26 as compared to B ( Table III).

## THYROID FOLLICLES

The parenchyma of control group consisted of many follicles of irregular in shape, some one rounded and few were longitudinally cut lined by regular looking cuboidal cells. Their mean number per field was 24.63±6.94. The size showed diversity, larger at periphery smaller in the central field (Fig.1). The mean size was 132.6±31.6 micrometer.

The parenchyma of experimental group A (treated with thiourea for 21 days) showed irregular follicles, larger were located at periphery, smaller were found in the centre lined by tall cuboidal cells ( Fig. 2). The centrally

located follicles showed intercommunication and some detached cells were also found. The lining cells were visible in the form of cellular column having well defined nuclei with pink cytoplasm (Fig.1). The mean number of the follicle was 30.88±9.18, whereas the size was significantly reduced compared to control P= 0.005 ( Table II).

**Table-III. DMRT (Duncan Multiple Range Test) for experimental groups b & c variables: number & size (micron meter) of blood capillaries and follicles**

| VARIABLES | GROUPS | DAYS | | | | MEAN |
|---|---|---|---|---|---|---|
| | | 22 | 26 | 30 | 50 | |
| No. of Blood capillaries | B | 24.60 | 26.06 | 31.03 | 29.04 | 27.66 |
| | | de | cde | abcd | bdce | |
| | C | 29.210 | 23.09 | 27.55 | 32.86 | 28.16 |
| | | bcde | e | bcde | abc | |
| MEAN | | 26.19 | 24.57 | 29.29 | 29.95 | |
| | | BC | C | AB | AB | |
| Size of Blood capillaries | B | 27.56 | 33.64 | 23.00 | 18.30 | 25.6 |
| | | bc | bcd | bcd | d | |
| | C | 27.93 | 35.8 | 21.27 | 21.37 | 26.59 |
| | | b | a | cd | cd | |
| MEAN | | 27.75 | 29.74 | 22.14 | 19.83 | |
| | | A | A | B | BC | |
| No of follicles | B | 25.18 | 35.43 | 32.60 | 33.66 | 31.7 |
| | | de | b | bc | bc | |
| | C | 43.33 | 26.94 | 30.83 | 30.63 | 32.92 |
| | | a | cde | bcd | bcd | |
| MEAN | | 34.20 | 31.18 | 31.72 | 32.15 | |
| | | A | A | A | A | |
| No of follicles | B | 107.62 | 93.53 | 94.08 | 98.55 | 98.6 |
| | | abc | bcdef | bcdef | abcde | |
| | C | 79.56 | 92.40 | 83.40 | 100.30 | 88.8 |
| | | f | cdef | def | abc | |
| MEAN | | 93.60 | 92.96 | 88.66 | 99.42 | |
| | | BC | BC | C | BC | |

The parenchyma of experimental group B( treated with thiourea and potassium iodide) the follicles were irregular in shape small sized follicle (microfollicle) were also visible. Some follicles showed detached cells in the lumen( Fig.3). These cells had well defined nuclei and pink cytoplasm. The mean size was significantly lowered as compared to control (Table II).

In the experimental group C (treated with thiourea, potassium iodide and dexamethsone) parenchyma comprised of a number of follicles of variable sizes and shapes lined by tall cuboidal cells, shape was mostly round in the central field ( fig.4). Centrally located follicles contained tall cuboidal cells resting on basal lamina making the lumen narrow. The lumen appeared uniform having thick apical plasmalemma (Fig. 4). The size showed significant reduction ( P=.0028), ( table II, Fig. 4)

**Graph-I. Comparison of control with experimental groups Relative tissue weight % of thyroid gland**

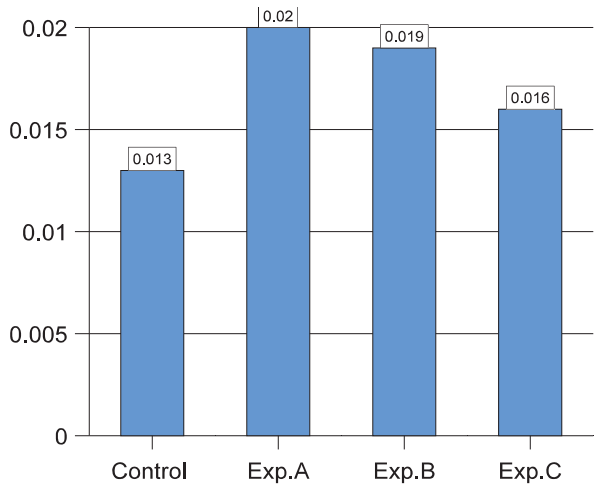
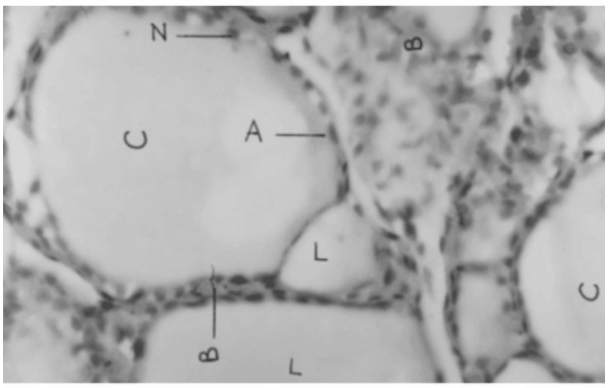



**Fig-1. Control Group**




A: Flat follicular cells
C: Colloid fully fille
Mag:2800X
B: Blood vessel
L: Large irregular follicular lumen

**Graph-3. Comparison of experimental groups B & C variables size of the follicles (micro meter)**

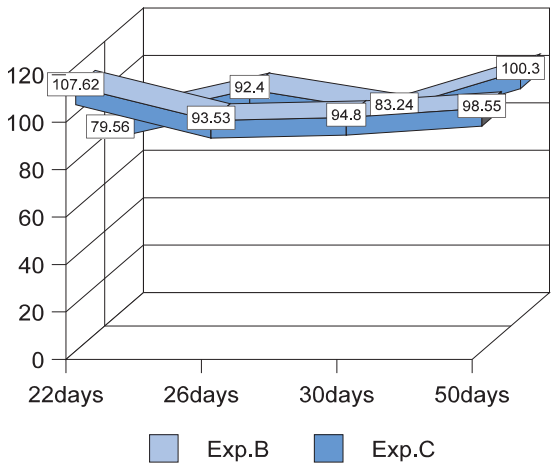
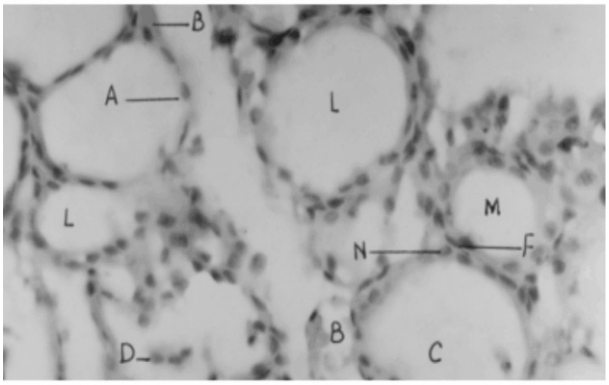



**Fig-2. Experimental Group A**

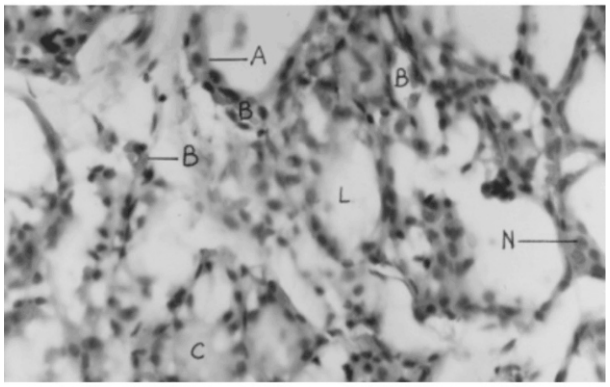



A: Tall cuboidal cells
L: lumen of small sized follicle
D: Detached cells
B: Dilated blood vessels (numerous)
C: thin marginal colloid
Mag: 2800x

In subgroups B the follicles were larger lined by stunted cells as compared to subgroups C, where they were rounded, small and lined by tall cells (Fig.3). The number of follicles were significantly increased in sub groups C as compared to subgroups B (mean= 32.92), (Table III). In comparison between subgroups B and C their number significantly increased in subgroups C on days 22 and decreased on 26 ( Table III). Within subgroups C there is significant increased in number on days 30,50 (C3,C4) compared to day 22(C1), whereas in subgroups B in all days this parameter showed insignificant change ( Table III).

The lumen profile showed remarkable changes, the mean size was 88.8 micron meter in group C compared

**Fig-3. Experimental Group B( B3)**



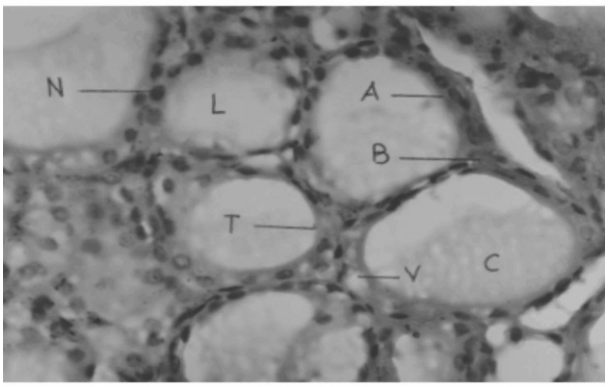

A: Flat low cuboidal cells
B: Numerous blood vessels
C: scanty colloid
L: Irregular small follicular lumen
Mag. 2800x

to group B exhibiting significant reduction in group C (Table-III). Within subgroups B & C there was significant reduction in group C on day 22. (Table III). In subgroups C the lumen size gradually increased compared to subgroups B.

## DISCUSSION

In the present study hyperplasia was produced by the administration of anti thyroid drug thiourea with the dose of 10 mg / 100 gm body weight daily for 21 days. The dose was 1/3 less than given by Schneider and Golden(1987)[22] while Mitsumuri etal., in 1994[23] used thiourea at the dose of 0.05%. The duration of 21 treatment was the same as previously given by many researcher including Wollman etal.,(1990)[24] and Tachiwaki etal., 1990.25

**Fig-4. Experimental C (C4)**




Mag:2800x

A: Tall cuboidal cells
B: well localized small sized blood vessels
C: marginal thin colloid
N: nucleus with nucleolus
T: Thick apical plasmalemma
V: vacuolated spaces

## MEAN THYROID WEIGHT

The increase in the mean thyroid weight observed in experimental group A treated with thiourea for 21 days correspond the results of Bauck etal., (1986)[26]. In both experimental groups B & C the weight and relative tissue weight of thyroid gland was increased but was less as compared to Experimental A. Experimental group C had greater relative tissue weight as compared to control due to persistent hyperplastic changes observed by the treatment of group C with dexamethasone for prolonged period up to 50 days. The reason being that dexamethasone treatment might cause increased in the number of cells and cytoplasmic organellae while stromal congestion may be the added effect.

## STROMAL CAPILLARIES

The significant increase in stromal congestion was observed in all experimental groups and is in accordance to the observation made by Wollman etal., (1990)[24]. The increase in the stromal vascularity is due to hyperplasia and was observed in experimental group C (Fig.4). In hyperplasia endothelial lining cells and pericytes of capillaries become protein synthesizing cells containing

well defined golgi complex, rough endoplasmic reticulum and apical vesicles[17]denoting hormonal influence on the vessel wall. On withdrawl of thiourea their number reduced in group B denoting normal involution.

During hyperplasia in group A and sub-groups C blood vessels appeared basket like encircling the follicles as observed by Imada 1986 (Fig 3.)[27]. Overlaping phenonmena of the capillary plexuses made them difficult to measure but in subgroups C showed gradual thickening (Fig.5) .The insignificant change in lumen size was contrary to observed by Wollman etal., (1990)[24]. The reason for this contradiction was because the capillaries were affected earlier and remodeled after stoppage of thiourea ( Imada 1986)[27].

## THYROID FOLLICLES

Significant increase in the number of follicles in all experimental groups was due to hyperplasia as observed by Wollman etal.,(1990)[22] Many etal., (1983)[28] caused by folliculogenis as result of anti thyroid drug thiourea. The shape and size of the follicles were variable. In experimental groups, the large moieties were located at peripheral region, while rounded and small in the centre (Wollman etal.,1990)[24]. The larger moieties were produced by fusion of neighboring small and rounded follicle and some were tangentially cut. In all the subgroups B and C on day 50 the reason of large sized follicles is being that epithelial cell divide once in 21 days during which thiourea was fed[12]. More over all the daughter cells were in contact with the lumen[29]. Moreover all the follicles including new follicles in groups B and C would be expected to increase in size because pre-existing daughter cells divide repeatedly under the influence of TSH after withdrawl of thiourea. Moreover smaller follicles may also arise by partial division of the existing follicles as observed by Panel etal.,(1982)[30].The follicles with narrow and empty lumen remained the characteristic feature of the group C which was treated with dexamethasone in accordance with the work done by Joseph and Ramanchandran (1993, Fig. ).[31]The absence of colloid in these microfollicles was due to rapid turnover along with increase in cell height which is contrary to the observation made by Maes etal., (1990)[32].

## CONCLUSION

It is concluded from the results that in subgroups C stromal congestion is marked and follicles are small sized lined by tall follicular cells as compared to subgroups B denoting delayed involution process by the treatment of dexamethasone. Thus its liberal use in thyroid diseases should be careful.



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