INTRODUCTION
Pre-eclamptic toxemia is one of the major problems for the obstetrician, particularly in developing countries like India where antenatal care is still beyond the reach of many. It is one of the major causes of maternal mortality. There is also a high perinatal mortality rate and a high bed occupancy by women, who have either pre-eclampsia or eclampsia. It is not surprising, therefore, that much time, thought and effort has gone in trying to determine the etiology of this condition and thus possibly devising means to prevent the disease or, at least, to develop an effective treatment against the disease. Many aspects of this disease have been studied in the hope that the etiology might be found. A hypothesis has been produced and attempts made to fit the known facts into the hypothesis in order to try to prove it. The method has been to make observations on the women with pre-eclampsia and try to determine what were the basic changes and which changes were responsible for the production of the hypertension, proteinuria and edema which occur in this condition.
Reproductive function is very directly under the control of endocrine glands. The response of endocrine glands to pregnancy and the effect of such response on the bodily functions are so very marked that the whole physiology of the woman is altered during pregnancy. Among the many alterations which take place in maternal physiology in pregnancy, hormonal changes are most significant. It is also known that in pre-eclampsia, the hormonal changes may differ from that met with, in normal pregnancy.

The automatic control of the reproductive process lies in hypothalamus and its regulation on the pituitary glands and from recent experiments it is known that there is no nervous connection between the hypothalamus and anterior pituitary. The hypophysial portal system carries humoral substances from the hypothalamus which regulate the anterior pituitary activity. The hypothalamus is in turn influenced by impulses from the higher centres in the cortex such as fear, anxiety and other emotions. The pituitary, by elaboration of its gonadotrophic hormones, stimulate the ovaries to produce the sex hormones, oestrogen and progesterone. The average life of corpus luteum is about 14 days and its function is maintained by follicle stimulating hormone and luteinising hormone. The other pituitary hormones playing a part in pregnancy are adrenocorticotropic, adrenocortical, thyrotropic.
and oxytocic hormones. In pregnancy in addition to the above mentioned sex hormones, chorionic gonadotrophic hormones and placental hormones play a major role. The maternal hormones are essential for fertilisation process and for preparing the ground for the conceptus, but this relative importance diminishes as pregnancy advances.

STEROIDS:

The sex hormones are androgens, oestrogens and progesterone. They are all chemical substances known as steroids, which act to regulate the reactions continually producing in living tissues. All the above steroids are derivatives of the tetracyclohydrocarbon (i.e. perhydrocyclopentanophenanthrene \( \text{C}_{17}\text{H}_{28} \)). Almost all hormones, which are not protein in nature are steroids and are excreted in urine conjugated with glucuronic and sulphuric acid.

From the extracts of the adrenal glands of animals, a number of steroids have been isolated (1), namely steroids solely derived from the adrenal cortex for example cortisol (2), dehydroepiandrosterone (3), testosterone (4), gonadal steroids such as progesterone (5), estrone (6) and equilenin (7) have been isolated from adrenal glands.

The sex hormones are elaborated by the different specific reproductive organs. However these steroidal sex hormones are also elaborated by the adrenal cortex which
synthesises the cortical steroids as well. In 1936, the isolation of adrenocortical hormones from the adrenal gland was effected (8, 8-11).

There is a strong belief that the presence of steroids in the urine is directly related to the production of steroidal hormones by the endocrine glands and indirectly to the stimulation of steroid producing glands by certain substances. Most of the urinary steroids are biologically inactive. The increasing knowledge on the chemistry and the metabolism of the hormones has resulted in numerous methods for the determination of these compounds or their metabolites. Great precautions have to be taken in assaying the steroids. On the basis of the chemical point of view, steroids of urine consists of compound with 18 carbon atoms (Castratriens), 19 carbon atoms (Androstanes), 21 carbon atoms (Pregnanes), which have a common nucleus composed of Phenantrene ring system and a cyclopentane ring.

On the basis of the physiological point of view, urinary steroids can be classified (a) steroid hormones secreted by the endocrine glands namely cortisol, 17-β estradiol androstendione etc. which are found in very small quantities in normal conditions, (b) catabolic pathways of steroid hormones or their intermediary end products - estriol, pregnenediol, cortolones, tetrahydrocortisone etc.,
which constitute a major portion of the steroids in normal urine, (c) through the bio-synthetic pathway, intermediary products of steroid hormones or their reduction compounds, namely pregnanetriol, tetrahydro-8 and pregnanolones, which are very important in pathological conditions. All the steroids are excreted in a water soluble form and mainly conjugated with glucosiduronic acid and sulphuric acid and the main site of their metabolism is the liver.

The steroids which have got a practical significance are as follows:

a) A relation with the reproductive function in women, namely estrogens mainly of the ovarian origin.

b) A relation with the reproductive function in women, namely metabolites of progesterone, partly derived from adrenal cortex as well as ovarian origin.

c) The 17-oxosteroids, a group of mixed origin partly derived from androgens as well as from the adrenal cortex, degradation products, the most important precursor of cortisol namely metabolites of 17-alpha-hydroxyprogesterone; metabolites of cortisol concerned with carbohydrate metabolism and the protection of the body from stress; the hormones concerned with the electrolytes namely metabolites of corticosterone.
Alterations that are observed following adrenalectomy are (1) disturbance of the sodium, potassium chloride and water balance, increased excretions of sodium, chloride and water and retention of potassium, (2) increase of the urea content of blood; (3) asthenia and disturbance of carbohydrate metabolism.

Androgens probably arise from cholesterol, since the structures of the naturally occurring androgens are closely related to that of the structure of cholesterol. The acetate of cholesterol particularly are precursors of the steroid hormones. Floch (12) has experimentally shown that cholesterol can be converted to steroid hormones namely corticosterone, corticoids and hydrocortisone (13) and the conversion of cholesterol to various androgens and related substances such as androsterone and dehydroepiandrosterone (14). Adrenal tissue contains a high concentration of cholesterol of which 80 to 85% is in the esterified form (15). A marked drop was observed when adrenocorticotropin hormone was administered to rats in the cholesterol ester fraction of the adrenal (16). It has been suggested that adrenal cholesterol esters may be involved in the biosynthesis of steroid hormone when there is an increased demand for the production of the steroid hormones, particularly during stress conditions (17). Rat adrenal cholesterol ester have been
shown to contain high proportion of essential fatty acids and play a role in the formation of steroid hormones (18, 19).

Adrenal glands and adrenal homogenates are capable of transferring one steroid into another and interconversions are being done by micro-organisms (20-25). By means of isotopic studies, it has been postulated that pregnenolone is presumably derived from acetate via progesterone (12).

The formation of all steroid hormones including progesterone has been demonstrated in the ovarian tissue by utilizing acetate of the cholesterol as precursors.

Acetate cholesterol, testosterone, progesterone all serve as precursors in the formation of estrogens (26-28).

The pathway from cholesterol to progesterone appears to be common in all steroid secreting glands. It is an established fact that adrenal androgens are produced from acetate in invitro.

The Figure I shows postulated pathway for the formation of progesterone from cholesterol. Short (29) has established the fact that there is production in invitro of the adrenal androgens from acetate by various preparations of the human adrenal glands. Figure II shows the biosynthetic pathways for adrenal androgens and estrogens. Figure III shows the origin of urinary 17-oxo steroids.
Fig. 1 Postulated Pathway for the Formation of Progesterone from Cholesterol

(A, B, C, D, E) enzymes - (A, B, 2α, 2β, 2α, 2β, 2α, 2β)
A: 2α hydroxylase; B: 22 hydroxylase; C: 2α, 22 desmolase;
D: 3β hydroxysteroid dehydrogenase; E: isomerase. Transfers double bond from carbon 5 and 6 to carbons 3 and 4.

Fig. 2. Biosynthetic Pathways for Adrenal Androgens and Oestrogens.

Aldosterone (XI) → 18-hydroxytestosterone → Testosterone (X)
Fig. 3. Origin of Urinary 17-Oxo Steroids.

Androstenolone  \rightarrow  Testosterone  \rightarrow  Dehydroepiandrosterone (DHA)

\downarrow \rightarrow \downarrow \downarrow

Androstene  \rightarrow  Adreno- \rightarrow  DHAA

\rightarrow \rightarrow \rightarrow

11-\beta-Hydroxy- \rightarrow  11-Oxo- \rightarrow  11-\beta-Hydroxy-

androstenedione  \rightarrow  adreno- \rightarrow  adreno-

androstenedione  \rightarrow  cholanolone  \rightarrow  cholanolone

Cortisol
Notwithstanding the fact that methods of investigation have grown increasingly refined, a knowledge about the actual physiological changes in pregnancy and the adaptive mechanisms made by the human body is still incomplete. Eclampsia was first used by Verandeam (30) and understood by Hamilton (31) to be due to alterations in the constituents of the blood in pregnant state. Numerous hypothesis were made by various authors to explain the condition and to discuss the etiological factors underlying the outcome of toxemias of pregnancy. Young (32) considered the causative factor as a dead substance in the shape of the interated placental tissue. The retention of water in the tissues might be a causative factor according to Zangemeister (33). Parmore (34) suggested that the alteration in the circulatory condition in the liver and kidneys might be due to the increased intra-atrial pressure of pregnancy and thereby degenerative changes occurring in parenchyma. Theobald believed that the disturbance in calcium metabolism was the most important factor. It was said (36) that the anti-diuritic factors of the posterior pituitary may be the cause of oedema and blood pressure, which were not acceptable in the light of many findings (37-39). Browne (40) emphasized the importance of adrenocortical steroids in the causation of pre-eclamptic toxemia of pregnancy. Most of the authors have accepted the hyper function of the adrenal cortex, as a phenomena.
associated with eclampsia (41-44).

The retention of water, sodium and increased excretion of adrenal corticosteroid and raised levels of anti-diuretic factors of posterior pituitary origin in pre-eclampsia have been reported (45-47).

The excretion of glycogenic corticoids, oxosteroids, pregnanediol, estrogens and the gonadotrophin were studied in pregnant women (48-52). An increased excretion of the adrenal steroids in pregnancy was uniformly reported by Venning (48-49).

Different authors have demonstrated an increase in the free and conjugated (reducing) steroids. However conflicting values have been reported on free formaldehyde-hydrogenic steroids in urine. Devis (54) studied the behaviour of reducing steroids in the urine of 17/normal pregnant women. The same conclusions were arrived at, in the cases of free 17-hydroxycorticosteroids using Porter-Silber reaction. There was no uniformity of results.

Tobias, Lloyd and coworkers (50, 51), Parvisinen and associates (52), Devis and Jayle (54, 55) observed an increase in the level of corticosteroids in urine in normal pregnancy and a further increase in toxæmia of pregnancy. Schuurmann (42) and Parvisinen and associates (53) have concluded that pre-eclamptic toxæmia and eclampsia may be
the result of continued hyper function of the adrenal cortex. Increased cortical function occurs in normal pregnancy and a greater increase in pre-eclamptic toxemia. Much work has been done to translate the physico-chemical alterations observed into the functional role of the steroids. The chemical and physiological processes have been observed in the body fluids on the onset of the disease namely, imbalance in the electrolytes of the body fluids, increase in the body weight, oedema, hypertension, proteinuria and attempts have been made to link abnormal pregnancy with abnormal functions of one or more of the glands of the internal secretion.

In recent years, the research is concerned in the etiological factors to obtain an up to date knowledge of the physiology, biochemistry and pathology of the foeto-placental unit to determine the status of foetal compartment of the foeto-placental unit.

PREGNANEDIOL:

Pregnanediol output was estimated during the 2nd and 3rd trimester of pregnancy by Russell et al (56) and concluded that the estimations are of value in cases of placental insufficiency. Shearmann (57) also studied on the same lines. Abnormal low values of sodium pregnanediol in urine were observed by some workers in cases of pre-eclamptic toxemia (58). Cope (59) observed the excretion of pregnanediol to be within normal limits in his study of
10 eclamptic patients. Smith and Smith (60) stated that low excretion of pregnanediol and estrogens precede any clinical manifestations of pre-eclampsia and eclampsia. Robertson and Maxwell (61) also carried out measurements in normal pregnancy cases in order to assess the functional status of the placenta, while they (61) found conflicting results. It was stated (62) that in certain circumstances, the assay of pregnanediol in urine reflects not only progesterone secretion, but also other metabolites. The values of pregnanediol excretion are much more variable from day to day and also from one subject to another at comparable stages of pregnancy (62). The urinary pregnanediol arrived from the amount of exogenous progesterone varies from time to time and person to person even in non pregnant subjects (64).

**ESTROGENS**

In 1912 Wellner (65) isolated the presence of estrogenic substances in the human placenta. A number of biological methods were employed for the estimation of estrogen in blood and urine. Spielman et al (66) employed the biological method for the determination of the estrogen in blood to have a knowledge of the foetal welfare. Smith and Smith (67) found diminished values of estrogens and an increased level of chorionic gonadotrophin in urine of abnormal pregnancy cases (Pre-eclampsia and eclampsia).
Ascheim and Zondek (69) discovered a large amount of estrogen originating in the placenta and the urine of pregnant women and the measurement of these hormones may provide an index of the placental function. Since the principal estrogen in the urine of pregnant women is estriol, any abnormality may be recognised by abnormal patterns of urinary excretion of estriol. Casam (69) has supported the view that foetal death is accompanied by the marked decrease in the levels of urinary estrogens. Urinary estriol values below 1 mg. per day have been recognized as suggestive of foetal death by Zondek (70), Finkelstein (71) and Taylor (72). Linters (75) found normal values in mild toxemic cases and he correlated his findings with the biological picture of the placenta besides the foetal weight and the placental weight. Keller et al (74) recorded values at different weeks of normal pregnancy and toxemic patients. They were of opinion that urinary estriol values could be taken as an index of the placental function. Frandsen and Stakemann (75) observed urinary estriol values which varied from person to person in normal pregnancy cases. The estriol excretion in foetal distress has been studied (76, 77) and it has been shown that low estriol excretion is suggestive of foetal distress although the range has not been agreed upon.
Benerjes (78) stressed the importance of the estimation of urinary estrogens in the assessment of placental function. Coyle (79) correlated his studies on estriol excretion with that of the weight of the baby. Wray and Russell (80) were of the opinion that the urinary estriol values were to be interpreted in the assessment of welfare of the foetus with great care. Low excretion of estriol has also been accounted to follow placental insufficiency. A review of the literature reveals that estriol values are low in cases of pre-eclampsia, hypertension, chronic renal disease, perinatal deaths, stillbirths, maternal and foetal death and foetal growth retardation (81-86, 74).

Recent investigations indicate that the urinary estriol determination mainly represent the status of the foetal compartment of the foeto-placental unit (87-91).

**ADRENAL STEROIDS**

It is believed that 17-oxosteroids excretion in urine arise from precursors, which are secreted by the adrenal cortex, by the testis and to a small extent by the ovaries. In women, the main source is the adrenal cortex. The excretion of total neutral 17-oxosteroids in the urine of normal individuals have been studied by a number of investigators (93-98).
17-oxosteroids excretion throughout the normal menstrual cycle were studied (99, 100, 101). No definite cyclic fluctuation and no relationship to the various phases of the cycle were observed. During pregnancy, the quantity of 17-oxo steroids in urine were reported to be more as compared to normal non-pregnant (49, 102).

Simultaneous analysis of estrogens, pregnanetriol, pregnanediol and pregnanolone in the urine as the significant test in the evaluation of the foeto-placental unit has been advocated by Acevedo et al (92). There is strong evidence (102-106) that dehydroepiandrosterone acts as a precursor in the bio-synthesis of estrogen by the foeto-placental unit and that the foetal component of the foeto-placental unit is the main source of urinary pregnanetriol.

DIET AND STEROIDS:

M-Carrison (107) studied a relationship of diet to adrenal glands on pigeons, guinea pigs and monkeys and concluded that the adrenal function can also be modified by diet. Pyridoxin and aneurine deficiency, pantothenic acid and Vitamin C are all said to modify the structural integrity of the adrenal gland to a greater or lesser extent. It has been observed (108-115) that pantotheine causes enlargement of the adrenal gland accompanied by reduction in the steroid content of the fasciculate and a decrease in the weight of the thymus. This suggests that the deficiency will
stimulate an excessive secretion of corticosterone and its homologues (116). Thus diet and physiology of the endocrine glands are closely related (117).

Hendricks (118) in studies of reproductive performance noted "the difficulty of documenting a specific aspect of human reproductive failure as being due to a specific nutritional inadequacy". It has been said that folic acid deficiency is a constant threat to pregnant women (119).

Dietary deficiencies such as protein, thiamine, niacin and under-nutrition have been observed to be potential factors leading to pre-eclampsia (120-123).

Diet and dietetic habits vary from country to country and from race to race. Socio-economic conditions play an important part in determining the diet and dietetic habits of mankind. According to Dieckmann (44), eclampsia is very rare in those regions of Africa, where the diet and habits have not been changed by the white race. Eastman (124) is of the opinion that eclampsia in the United States shows a striking relationship to the distribution of vitamin B complex deficiencies. In China, Gordon King (125) showed that there was a greater incidence of pre-eclampsia and eclampsia in those patients with Vitamin B1 deficiency.
Eclampsia is common in India and Ceylon.

Dietetics have indicated that the nutrient intake of pregnant subjects in South India is quite inadequate especially in poor income group and it has been observed that the nutritional status of pregnant women has got an influence to the birth weights of the babies and a correlation exists between the birth weights of the babies with the nutritional status of the women (126-129).

Not much work has been done on Indians regarding the steroid pattern in body fluids. The data available are scanty and especially so in the case of South Indians. The interpretation of the values obtained in normal and abnormal pregnancy cases requires a knowledge of the values obtained in health. The dietary habits of the Europeans are different from those of Indians especially so in the South India and hence it could not be possible for us to draw conclusions by comparing the abnormal values of patients in South India with those of the values obtained in European countries. The diet of the poor lower middle class (general ward patients) is found to be poor and imbalanced. The typical diets of the poor class and lower middle class are given below.
TABLE V

I. Diet sheet showing the average daily consumption of proteins, Carbohydrates and Fats by poor class South Indians.

<table>
<thead>
<tr>
<th>Article of food</th>
<th>Quantity of article of food</th>
<th>Proteins present in the article of food</th>
<th>Carbohydrates present in the article of food</th>
<th>Fats present in the article of food</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice</td>
<td>4.19</td>
<td>7.54%</td>
<td>92.018</td>
<td>0.469</td>
</tr>
<tr>
<td>Ragi</td>
<td>2.00</td>
<td>4.000</td>
<td>42.800</td>
<td>0.728</td>
</tr>
<tr>
<td>Chana</td>
<td>8.00</td>
<td>22.200</td>
<td>165.600</td>
<td>4.256</td>
</tr>
<tr>
<td>Pulses.</td>
<td>0.16</td>
<td>1.056</td>
<td>2.720</td>
<td>0.030</td>
</tr>
<tr>
<td>L.V.</td>
<td>0.07</td>
<td>0.126</td>
<td>0.356</td>
<td>0.021</td>
</tr>
<tr>
<td>Oils</td>
<td>0.01</td>
<td>..</td>
<td>..</td>
<td>0.280</td>
</tr>
<tr>
<td>Meat, fish etc</td>
<td>0.01</td>
<td>0.060</td>
<td>..</td>
<td>0.025</td>
</tr>
<tr>
<td>Condiments</td>
<td>0.06</td>
<td>0.180</td>
<td>0.540</td>
<td>0.090</td>
</tr>
</tbody>
</table>

| Total          | 36.164                      | 305.028                                | 5.949                                       |

L.V. : Leafy vegetables.

Calorific value of the diet:

1. Proteins .. 36.164 x 4  144.656 calories.
2. Carbohydrates .. 305.028 x 4  1220.112 "
3. Fats .. 5.949 x 9  53.541 "
Total  1418.309 "
Table - V (contd.).

II. Diet sheet showing the average daily consumption of Proteins, Carbohydrates and Fats by Lower Middle Class South Indians.

<table>
<thead>
<tr>
<th>Article of food</th>
<th>Quantity of article of the food (Oza.)</th>
<th>Proteins present in the article of food (Gm.)</th>
<th>Carbohydrates present in the article of food (Gm.)</th>
<th>Fats present in the article of food (Gm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice</td>
<td>6.65</td>
<td>11.970</td>
<td>147.620</td>
<td>0.744</td>
</tr>
<tr>
<td>Cholam &amp; Kaatu</td>
<td>3.00</td>
<td>23.275</td>
<td>201.225</td>
<td>5.187</td>
</tr>
<tr>
<td>Pulses</td>
<td>0.29</td>
<td>2.577</td>
<td>6.620</td>
<td>0.195</td>
</tr>
<tr>
<td>L.V.</td>
<td>0.70</td>
<td>0.540</td>
<td>1.500</td>
<td>0.080</td>
</tr>
<tr>
<td>N.L.V.</td>
<td>0.90</td>
<td>0.020</td>
<td>0.125</td>
<td>0.009</td>
</tr>
<tr>
<td>R &amp; T</td>
<td>0.14</td>
<td>0.042</td>
<td>1.050</td>
<td>0.007</td>
</tr>
<tr>
<td>Oils</td>
<td>0.7</td>
<td>--</td>
<td>--</td>
<td>1.960</td>
</tr>
<tr>
<td>Meat, Fish etc.</td>
<td>0.03</td>
<td>0.180</td>
<td>--</td>
<td>0.075</td>
</tr>
<tr>
<td>Condiments</td>
<td>0.21</td>
<td>0.620</td>
<td>1.290</td>
<td>0.315</td>
</tr>
</tbody>
</table>

44.301          360.660          7.582

L.V. : Leafy vegetables.  
N.L.V. : Non-Leafy Vegetables.  
R. & T.: Roots and Tubar.

Calorific value of the diet:

1. Proteins .. 44.301 x 4 .. 177.204 calories.
2. Carbohydrates .. 360.660 x 4 .. 1442.640 "
3. Fats .. 7.582 x 9 .. 68.238 "

Total 1688.082 "
The diet is found to be deficient in the caloric value in poor and middle class people (the same class of people in whom the studies were undertaken), as they often report to Government Hospitals for treatment of illness.

**LIVER FUNCTION IN PREGNANCY**

It is found that in most of the studies connected with pre-eclamptic conditions, the liver plays an important role. It is interesting to note that many authors have studied the function of the liver during normal pregnancy (128-137, 140).

The majority of reports suggest that some disturbance of liver function is a common manifestation of pregnancy in pre-eclamptic toxemias, namely increased serum bilirubin and urobilinuria and some degree of bromosulfalein retention (138). However, the abnormal results have been observed by many investigators occasionally with no clinical symptoms of liver disease. Liver function is normally investigated by uptake, storage and excretion studies.

There seems to be a lot of controversy over the status of the liver in normal pregnancy. Histological studies namely liver biopsy, examination with electron microscope and hepatic blood flow measurements have revealed that no abnormality has been found in the liver in normal pregnancy (139).
But some of the laboratory liver function tests in pregnancy like serum alkaline phosphatase and \textit{lucine amino peptidase} which have been found increased, was attributed to the contribution of these enzymes by the placenta (141, 142). So a study of liver function tests will be of interest in normal pregnancy as well as in pre-eclampsia and anemia.

**STEROIDS AND LIPIDS**

Much importance have been attached pertaining to the role of proteins and lipids in blood during pregnancy (143-147). It has been well established that among the factors that regulate the serum lipid level are the sex hormones. The occurrence of hyperlipidemia was observed by a number of workers in normal pregnancy (148-155). Elevated total cholesterol are found in the 3rd trimester of pregnancy (156-161). Very few reports are available regarding the disturbances in lipid metabolism in pre-eclamptic toxemia (162, 163) since cholesterol is both a precursor to hormone as well as a metabolite which serves as an index in liver function. Hence, a study of cholesterol and phospholipids will be of interest.