SYNOPSIS

The discovery of anti-inflammatory action of cortisone stimulated considerable research in the field of steroids. The knowledge of steroid chemistry, their production and metabolism has made steroid therapy a vital part of medicine. Alteration of metabolic pathways of steroids in various diseased states is manifested by excretion rates which may be altered independently of glandular secretion rates. With the availability of the precise techniques it has become possible to measure directly the secretion rates of the individual steroids. The use of C\textsuperscript{14} labelled and tritiated steroids have demonstrated the importance of various biosynthetic pathways and the role of different enzymes at the cellular level. The isotope dilution or double isotope techniques have made possible the measurements of steroids in microgram quantities.

In spite of rapid progress in steroid biochemistry, there is paucity of information regarding steroid metabolism in various endocrine diseases. Studies on the mechanism of steroid hormone action are seriously handicapped by lack of knowledge as to the chemical transformation actually undergone by the steroid molecule during its physiological action. Whether the biosynthetic pathways are altered or certain enzymes are stimulated or inhibited in the metabolism of steroids in endocrine disorders is not
known. The interrelationship between the release of anterior pituitary hormones to the secretion of steroids by adrenal cortex and gonads are well established as examples of feed-back mechanism phenomenon. The failure of these mechanisms causes an abnormal production of adrenocortical or gonadal steroids, thereby resulting into a number of diseases. Our knowledge of various components of anterior pituitary hormones and the control of specific enzymes involved in the biosynthesis of steroids is limited. The absence of this information poses a challenging problem in providing suitable biochemical tests in the diagnosis of endocrine diseases such as Cushing's syndrome, adrenal insufficiency and precocious puberty. On the other hand, in diseases such as Addison's disease and Klinefelter's syndrome the pituitary function is primarily normal.

This thesis includes a detailed study of pathological conditions due to defective secretion of gonads and adrenal cortex. The diseased conditions were evaluated by repeated estimations of urinary 17-ketosteroids and 17-ketogenic steroids. Measurements of 17-hydroxy corticosteroids in plasma provide a precise method to differentiate adrenal cortical function from that of the abnormal function of liver and kidney. To test the defective biosynthesis of steroids
by adrenal cortex caused either by a partial or complete block at 11 or 21 hydroxylation in the biogenesis of cortisol, pregnanetriol and pregnanetriol-11-one were determined in the urine. Further, the performance of the adrenal cortex or the adrenal cortex–pituitary axis in patients were studied by stimulating the adrenals by a standard test dose of ACTH and determining the levels of plasma 17-hydroxycorticosteroids and urinary 17-ketosteroids, 17-ketogenic steroids, pregnanetriol and pregnanetriol-11-one. The following endocrine diseases were studied in patients referred to the Department of Endocrinology, Indian Cancer Research Centre: Idiopathic hirsutism, Cushing's syndrome, Adrenogenital syndrome, Klinefelter's syndrome and Hermaphroditism.

The investigation on "Steroid metabolism in health and endocrine diseases" carried out on human subjects suffering from rare pathological conditions. Each patient was followed up for a protracted period of time to confirm the results by repeated observations on a particular day of menstrual cycle or a certain time after surgical removal of endocrine organs.

In order to evaluate and appreciate the significance of the tests for the diagnosis and prognosis of endocrine diseases, it is important to determine the secretory and excretory rates of steroid hormones in normal human beings. This is necessitated by the fact that the
endocrine methodology has progressed rapidly making available more precise methods from time to time. Therefore, in many instances the average range for the normal values differ from laboratory to laboratory. As for the normal range for Indian population, our studies appear to be the first of its kind. Besides establishing a normal range in Indian population these studies help to formulate racial comparison of secretory and excretory steroid levels. Though the excretion of 17-ketosteroids and 17-ketogenic steroids are lower in Indian subjects than in the white population of the United States, the levels of plasma 17-hydroxycorticosteroids were similar in both races living under different environmental conditions. This finding would indicate that a difference in steroid clearance exists between Indian population and the U.S. Whites. Finally, it also appeared that normal Indian women had higher concentration of plasma 17-hydroxycorticosteroids in the post-ovulatory phase than in the pre-ovulatory phase of the menstrual cycle.

A major problem to be discussed in the present investigation is the biochemical basis for the etiological causes of the idiopathic hirsutism. A group of 22 women having a male type of hair growth were carefully selected for this study. This group did not show apparent lesion such as hyperplasia or tumour of adrenals, gonads or anterior pituitary gland. The excretion of 17-ketosteroids and
17-ketogenic steroids during the different phases of menstrual cycle was slightly higher than the excretion of these steroids in normal women. In some of the patients investigated, an abnormal ACTH response indicated presence of a mild form of adrenocortical hyperplasia. No correlation was found between the excretory levels of 17-ketosteroids and 17-ketogenic steroids and the number of abnormal regions of hair growth on the body. Furthermore, in some cases of idiopathic hirsutism higher excretion of pregnanetriol and the presence of pregnanetriol-11-one in the urine was noted indicating that the enzymes 11-hydroxylase and 21-hydroxylase may be inhibited or blocked. Another possible reason could be that some abnormality in the biosynthetic pathways leading to estrogens may be associated with ovary. The isolation and identification of steroids have been carried out in the cyst fluid obtained directly from the ovaries of normal and hirsute women to obtain more direct evidence. On laparotomy most of the patients showed sclerotic ovaries with multiple cysts. The steroids in the cyst fluid had high concentration of androstenedione which may give rise to increased formation of testosterone. This high potent androgen and high concentration of androstenedione could be responsible for the male type of the hair growth.

Attempts were also made to study the biosynthesis of estrogens by the ovaries of the patients suffering from idiopathic hirsutism. The ovarian tissues were obtained
from patients suffering from Stein-Leventhal syndrome and homogenised. It was then incubated with carbon 14 labelled progesterone, 17\alpha-hydroxyprogesterone, androstenedione and testosterone. Our observation suggests these tissues are capable of producing small amounts of estrone and estradiol indicating only a partial block of 19-hydroxylation of androstenedione rather than a complete block previously suggested by Short and London (1961) based on cyst fluid analysis of polycystic ovaries.

Cushing's syndrome has been shown to be a clinical entity with different etiological disfunctions of the adrenal cortex and the anterior pituitary gland. The hyper secretion of cortisol which causes this disease may be due to basophilic adenoma of pituitary gland causing high secretion of ACTH or hyper-responsiveness of the adrenal cortex to normal amount of ACTH independent tumour of the adrenal cortex. A detailed investigation has been carried out by studying secretory and excretory levels of corticosteroids, adrenocortical response to a standard test dose of exogenous ACTH in normal and in patients suffering from Cushing's syndrome to locate the site of the lesion from differential diagnosis. However, in addition to the test employed for the latter two diseases, response to injection of chorionic gonadotrophin, four cases of Klinefelter's syndrome with normal adrenal function were investigated on similar lines to hirsutism and Cushing's syndrome. Another interesting case of true hermaphroditism
having testis and ovary followed for a period of about seven years showed normal adrenocortical function. This patient had XX sex chromosome and after surgical removal of female gonad and uterus, the production of androgenic steroids was not stimulated by the intramuscular administration of chorionic gonadotrophin at various dose levels. This patient proved to be basically a female with an abnormal development in intrauterine life.

In conclusion, the estimations of steroids in urine and plasma before and after administration of ACTH in Indian population have provided the basis for comparison and evaluation of endocrine diseases. An investigation has been carried out on similar lines in patients suffering from various endocrine disorders. Attempts have been made to locate the defect in steroidogenesis in adrenal cortex and ovarian tissues of patients suffering from Cushing’s syndrome and idiopathic hirsutism respectively.

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