HEREDITY IN ENDOCRINOLOGY WITH SPECIAL EMPHASIS ON ABNORMAL SEXUAL DIFFERENTIATION

EILEEN SZABO

Albert Szent-Györgyi University

Szeged, Hungary

INTRODUCTION

/Historical perspective/

Endocrinology is a relatively infant science which began with the first recorded endocrine experiment published by Berthold /1849/. No other truly significant discoveries were made until about 50 years later /1889-1902/. The pace quickened after 1910 and the outlines of vertebrate and invertebrate endocrine systems were generally complete by 1950. From then on, chemistry played a most important role in the development of the science and many advances in the field were made.

The history of endocrinology progressed, as one might expect, from simple observations to complex experimentation. Early medical writings described the general symptoms of many endocrine dysfunctions long before the pathophysiology of any of the now well characterized endocrinopathies were at all understood.

Berthold in the earliest endocrinological study on record, noted that if he castrated cockerels, they failed to develop their combs and wattles and they to exhibit male behavior /Berthold 1849/. Replacement of the testes /one or both/ back into the abdominal cavity of the same or another bird resulted in normal development of the comb and wattles, and the birds exhibited male behavior. Berthold concluded that the testes secreted something that conditioned the blood. These experiments only demonstrated the need for the presence of testes to maintain male characteristics. The hormone of the testes, testosterone

was finaly obtained in pure crystalline form in 1935.

Another crucial discovery was the demonstration that the pituitary gland, the so called master gland of the body, was controlled by the brain, specially the area known as the hypothalamus. Harris, 1955, had provided data suggesting that the release of the pituitary hormones was controlled by humoral factors, probably of hypothalamic origin. A number of workers then showed that extracts of the hypothalamus contained substances that affected the release of pituitary hormones /Moss, Setalo, Vale.W/. The race to Stockholm was then on /Wade 1978/. Schally and Guillemin, working independently of each other, began purification of hypothalamic extracts from porcine and ovine sources.

Schally and his collaborators were also able to provide the chemical structure of porcine gonadotropin releasing hormones /GnRH/. Guillemin /1978/ and his collegues were the first to discover and report the structure of a peptide, somatostatin, that an inhibitor to the pituitary somatotropin /GH/ secretion.

The ability to isolate and characterize chemically the hypothalamic factors was enhanced by the development or radioimmunoassay /RIA/. By the use of RIA's, it was possible to detect the presence of hormones in the blood or tissues at a very minute concentration.

REGULATORY HORMONES

/Feedback Regulation/

The feedback regulation is the 1° mechanism for hormonal secretory control systems. If there is an elevation in serum hormone concentration that stimulates or increases the release of another hormone, this is re ferred to as a "Positive Feedback". Conversely, if increased levels of circulatory hormones suppress a second hormone, it is referred to as a "Negative Feedback". A good example of this system is the hypothalamic-pituitary-peripheral gland system, which is a prime example of feedback regulation, which has been proposed to consist of three loops.

FEEDBACK REGULATION

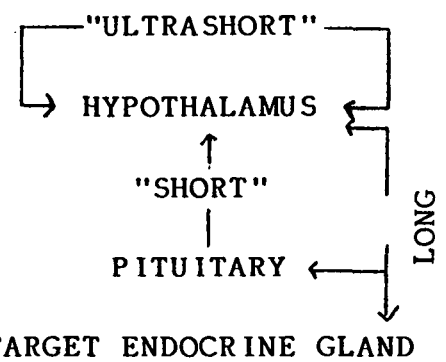

Fig. 1.
Control of endocrine systems
Motta 1969, 1968 et al.

The three loops are as follows:

a/ The long feedback loop of hormone from the target endocrine organ. which influences hypothalamic and or pituitary secretory activity

b/ The short feedback loop of which the pituitary hormone modulates hypothalamic releasing factor.

c/ The ultrashort feedback loop of the hypothalamic hormone which influences the secretion of hormones within the hypothalamus.

NON-HORMONAL CONTROL

The control of endocrine system is not only provided by hormones. For example, GH secretion is affected by a variety of non hormonal influences.

SECRETION

Many endocrine glands secrete their hormones in periodic bursts. This was considered to be previously justified for insulin, epinephrine, and GH, but later evidence suggests for ACTH, cortisol, LH, FSH and Prolactin, secretion is also pulsatile.

Diurnal rhythm which refers to a time dependent variation in hormone concentration during a 24 hour period, has been demonstrated for ACTH and cortisol.

PTH prolactin and TSH. This has been atrributed to the hypothatical CNS regulators referred to as the biological clock /Gibson/.

PRIMARY, SECONDARY TERTIARY DEFECTS

A deficiency in the concentration of circulating hormone may result from a basic defect in either the targer gland, which is producing the hormone, termed primary hypofunction, or in the pituitary, called secondary hypofunction. See Fig. 2.

LEVEL OF ENDOCRINE DEFECTS

Hypothalamus	**- "Tertiary"**
Pituitary	**- Secondary**
Target endocrine gland	**- Primary**

Fig. 2.

Primary overproduction of a pituitary hormone or a hypothalamic releasing hormone can cause the appropriate target gland to be excessively stimulated. The final result being hyperplasia and hormone overproduction. Motta 1968.

Hormones stimulate or inhibit the activity of cells directly or indierctly through modulation of the actions of other chemical messengers. Some hormones

often referred to as first messengers interact with the cell membrane to increase the production of intracellular second messenger, which are more directly responsible for activation of the cell. The second messenger is usually a cyclic nucleotide, either cyclic adenosine monophosphate /cAM// or cyclic-guanosone monophosphate /cGMP/. This first messenger second messenger model if hormone action must now be expanded to include other messengers in temporal sequence of hormone action. For example some hormones require calcium for activation of cyclic nucleotide formation. In some cells the first messenger acting through induction of an inward calcium influx may activate prostaglandin biosynthesis.

These cyclic nucleotides actually mediate their actions through stimulation of cellular enzymes.. kinases, which phosphorylate specific cell proteins. These phosphorylated proteins then function as the ultimate physiological effectors in the cell. See Fig. 3.

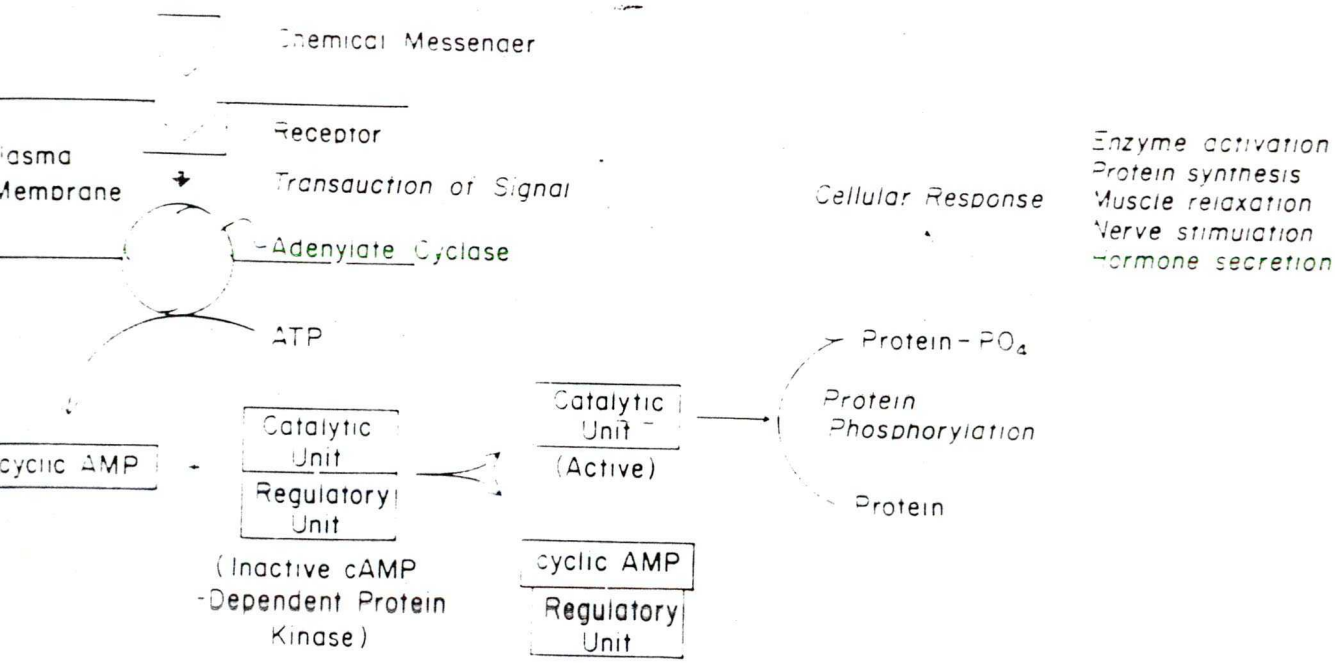

Fig. 3. Cyclic AMP and action

SEX DETERMINATION, DIFFERENTIATION AND DEVELOPMENT

Genetic sex, established at the time of conception, governs the development of gonadal sex of the individual /Davies 1981/. Gonadal Sex, in turn regulates the development of phenotypic sex, that is the differentiation of internal and external sex organs as well as attainment of adult secondary sexual characteristics /Kurtz 1986, Julesz J. 1990/.

CHROMOSOMAL /GENETIC/ BASIS OF SEX DETERMINATION

The genetic sex of an individual is realized at the moment of fertilization of the agg by a sperm. The genes related to the determination of sex are grouped together on particular chromosomes. Initially, all cells of the human body contain 22 pairs of somastic chromosomes /autosomes/ plus a pair of sex chromosomes. The female possesses a pair of X chromosomes /homogenetic sex/. During gametogenesis, the diplod number /46/ of chromosomes is reduced through meiotic division to the haploid number /23/ /Goldstein 1981/. The female can normally only contribute an X chromosome, whereas the male may contribute either X or Y chromosome /heterogenic sex/. During gametogeneses the diploid number /46/ of chromosomes is reduced through meiotic division to the haploid number /23/. The fertilized egg, the zygote will normally develope in a female or male direction depending on whether a pair of XX or XY chromosomes are present, respectively. The Y chromosome in the mammal appears to be mainly responsible for sex differentiation as any embryo without a Y chromosome developes as a female. Even humans with as many as four X chromosomes and

a single Y chromosome develop into males /Fincham 1984/.

The undifferentiated gonad has generally been considered to be composed of cortical and medullary regions. In the male, sex differentiation of gonads involves differentiation of the medullary primordium and suppression of the cortex. In the female, on the other hand, the cortical region develops, whereas medullary differentiation is suppressed. The development of these 2 anatomical components was for years theorized to be controlled by hypothetical cortico-medullary inductive substances. It is now proposed that the undifferentiated primordium normally tends to develop toward female in the mammal unless influenced by genes located on the Y chromosome /DE. Kretser et al. 1974/.

Mammalian testicular organogenesis is dependent on an H-Y antigen, a protein produced by cells containg XY chromosomes /DE.Kretser, Wachele, 1979a, 1979b/. This inducer substance is released early in embryonic development and causes differentiation of the somatic elements of the primordial gonads. In the absence of this H-Y antigen, the mammalian gonads will differentiate to form ovaries. The H-Y antigen can be considered as a protein hormone which is ubiquitous in its production by cells of early embryo. The H-Y receptor sites, on the other hand, are confined to gonadal cells of both sexes /Polani PE 1983/. Although the expression of the H-Y receptor is common to both the testes and ovary, this has no conseuence as production of H-Y antigen is male specific. Thus although the H-Y receptor is present in the prospective female

gonad, the H-Y antigen is not available for receptor occupancy /Ohno S,Y, et al. 1979/.

Normal testicular differentiation is invariably associated with the presence of the H-Y antigen. The testes differentiate under the influence of the Y chromosome during the seventh week of gestation in human whereas ovarian development usually does not proceed before 13-16 weeks /Wilson 1981/.

Two X chromosomes appear to be essential for the development of normal ovaries, as individuals with a single X chromosome develop gonads which are only partially differentiated. It has been argued that certain X-linked genes are regulatory and control the expression of H-Y antigen production by a structural gene located on the Y chromosome. It has also been suggested that H-Y structural genes may be X-linked or even autosomal /Gibbon et al./.

DIFFERENTIATION OF THE EXTERNAL GENITALIA

As with the ovary and internal urogenitalia develop a female phenotype in the absence of the Y chromosome. Differentiation of the male external genitalia is dependent solely on androgen production by the testes. Development of the penis and male urethra, and scrotum commences shortly after onset of Wolffian duct development. The genital folds elongate and fuse to form the penis and male urethra. The urogenital swellings on each side of the urethral orifice form a bilobed scrotum into which the testes descend. In the female emryo the genital tubercle becomes the clitoris and the adjacent genital swelling gives rise to the labia majora; the genital folds

become the labia minora. Removal of the gonads from indifferent embryos of either sex results in development of a female phenotype, demonstrating that the male is the induced phenotype /Bardin 1981, Ohno S.Y. et al. 1979/.

Of critical importance in development of the external genitalia is the timing of androgen action. In the female fetus, for example, the external genitalia may become masculinized if androgen levels are elevated as in "congenital adrenal hyperplasia". Androgens originating from the maternal circulation can also cause genital masculinization in the female fetus: except for clitoral hypertrophy, androgen excess at a late time /11-12 weeks/ is without effect.

GONADAL STEROID HORMONE SYNTHESIS AND CHEMISTRY

Gonadal steroids are produced by mesodermally derrived tissues of the testes and ovaries /Erickson 1985/. The same desmolase system is found in the adrenal and is responsible for this first biosynthetic step in steroidogenesis. The nature of the stimulus that activates testosterone biosynthesis in the fetal testes is unknown. There is experimental evidence that testes or ovaries of rabbit embryos synthetize testosterone or estradiol respectively, in media devoid of hormone. It appears, therefore that differentiation of gonads as endocrine organs is controlled by factors intrinsic to the gonads themselves /Wilson 1981/. See Fig. 4.

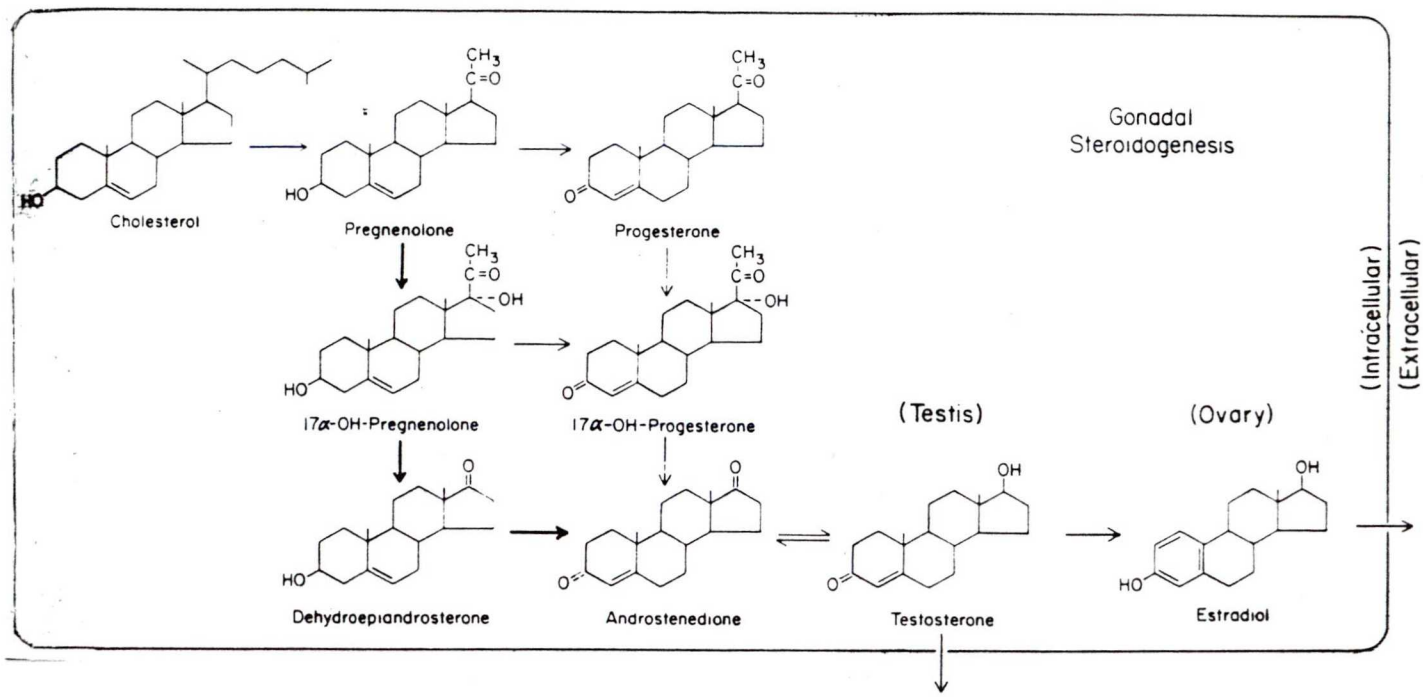

Fig. 4. Biosynthesis of gonadal steroid hormones in the vertebrate testes and ovaries. /Dufau 1978/.

Unlike the adrenal gland, the 17 -hydroxylase activity is dominant and through conversion of pregnenolone, to 17 hydroxy pregnenolone, and 17 hydroxy progesterone, provides substrates for androgen biosynthesis. In the testes, testosterone is the major androgen secreted. In the ovary androstendione and tes tosterone serve as precursors for estrogen formation. Estradiol is the major estrogen produced by the ovaries. The key reaction in the ovary is aromatization of the A ring of the steroid nucleus. The first step in this reaction involves the hydroxylation of the C-19 carbon

followed by removal of the newly formed hydroxymethyl group from the steroid nucleus. The A ring is then aromatized to yield a phenolic hydroxyl group at the c-3 position.

In some tissues testosterone is converted by 5∝ reductase activity to dihydro- testosterone /DHT/ See Fig. 5.

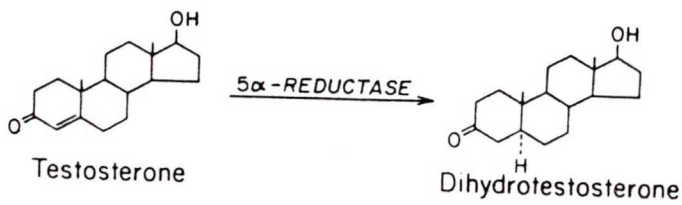

Fig. 5. Cellular conversion of testosterone to dihydrotestosterone /Dufau 1978/

The rudiments of the external genitalia and prostate convert testosterone to DHT which is then responsible for the development of these organs. The importance of DHT formation in certain tissues for normal virilization is revealed in rare anomalies of male development which are due to the absence of 5∝ reductase activity /Imperato et al. 1974, Imperato Mossing 1979/.

Although the ovary differentiates much later than the testes, the enzymatic machinery for estrogen synthesis is developed at the same time as the process for androgen biosynthesis in the testes.

GONADAL STEROIDS AND BRAIN DIFFERENTIATION

It has been shown that single injections of testosterone into a female rat during a critical period /few days postnatally/ resulted in adults that were acyclic. In addition these females exhibited male sexual behavior /mounting of other females/. These results were consistent with earlier observations that transplanted ovaries only became functional if the transplants were located into a neonatally castrated male rat, rather than an intact adult male rat. These studies suggest that deprivation of testosterone in the male animal during his species specific critical time of brain differentiation will result in a female pattern of sex dimorphic behavior. Such male animals will assume the female mating posture when administered estrogen, but will not mount females even when injected with testosterone. From these studies of androgen effects on the neonatal rodent emerged the hypothesis that testosteron was not only responsible for differentiation of the internal and external genitalia, but was critical importance of normal differentiation of the brain into the male type /McEwen 1976/. See Fig. 6.

One observation was particularly difficult to reconcile: estradiol also masculinized the brain of either male or female rodent. This dilema was solved when it was discovered that testosterone is aromatized to estradiol within the brain. Several experimental lines of evidence support the hypothesis

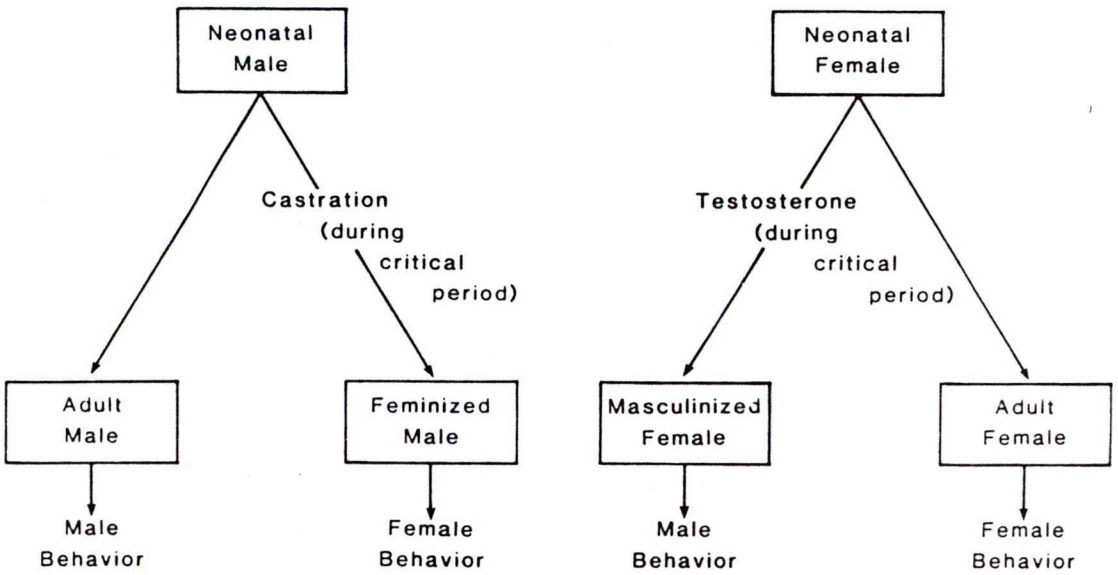

Fig. 6. Effects of castration and testosterone administration in the neonatal rat on subseqent adult male and female behavior /McEwen 1976/.

of androgen to estrogen conversion:

1/ The effects of testosterone therapy in neonatal female rats are inhibited by prior administration of specific estrogen /not androgen/ receptor antagonist.

2/ The brain possesses the aromatase enzymes required for conversion of testosterone to estradiol.

3/ Dihydrotestosterone does not mimick the effect of testosterone on neonatal brain differentiation, thus reveals that the action of testosterone are not mediated through conversion to DHT, in addition DHT cannot be converted to estradiol.

4/ /^{3}H/-labelled testosterone is recovered from the brain mainly as /^{3}H/ labelled estradiol.

5/ Aromatase inhibition impairs brain differentiation in response to perinatal testosterone administration.

6/ In testicular feminization mutation /mouse/ which has greatly reduced levels of androgen receptors, testosterone causes brain differentiation as it does in normal mice.

Thus it appears that in addition to its hormonal role on a number of target tissues, testosterone serves as a prohormone for dihydrotestosterone biosynthesis in some tissues and estradiol production within the brain /Machusky 1981/.

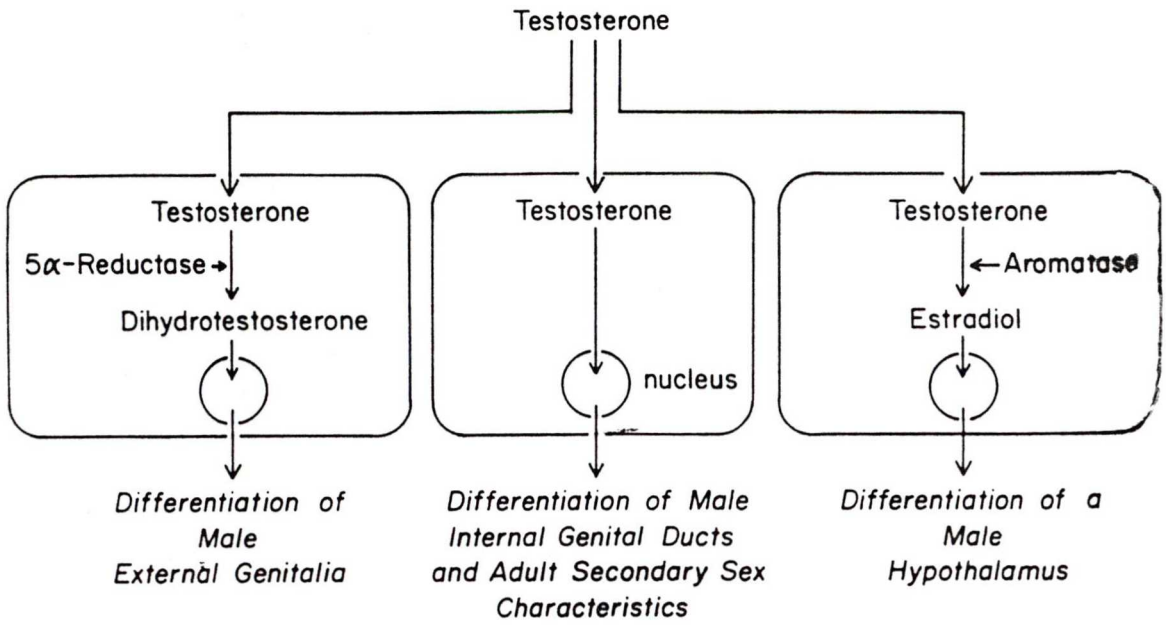

Fig. 7. Testosterone: prohormone for dihydrotestosterone and estradiol in certain target tissues.

If testosterone is indeed responsible for brain differentiation in the male, why is in not the brain of the female also masculinized as estradiol is the major gonadal steroid of the female? First, estradiol production by the fetal ovaries may be minimal. Second, a circulating α-fetoprotein /feto-neonatal estrogen-binding protein, FEBP/ is present in high levels within the blood of the fetus and apparently has a specific binding affinity for estradiol.Theoretically, therefore, no estradiol is available to reach the

brain of the female fetus /Machusky et al. 1981/.

Although estradiol is available in the male at a critical time in development to regulate the differentiation of the brain, the mechanism by which estradiol is able to alter irreversibly the brain and subsequent sexual behavior is unclear. The sexual differentiation of the CNS is of utmost importance, while we are treating sexuality-altering diseases, as we must keep in mind that behavior mechanisms may or may not be changed.

It is important to understand these basic fundamental entities in endocrinology for the pathomechanisms of the various diseases are not simply based on the hormone itself, rather one must comprehend that there are a multitude of intermediatory factors including those of hereditary and environmental character which when collected together and with the proper balance of all stimuli, will produce a normaly functioning human being.

This paper will discuss the diseases in endocrinology which show deviances from normal sexual phenotype, genotype and function, and the current diagnosis and therapy utilized at present.

PATHOPHYSIOLOGY OF SEX DIFFERENTIATION AND DEVELOPMENT

/Precocious and Delayed Puberty/

Sexual maturity may occur earlier or later than normal, a number of possible factors determine the etiology of such divergent development. True precocious puberty is defined as theattainment of sexual maturity at an earlier than normal age. This sexual precocity will result as either a genetic nature, or from disorders of the hypothalamus consistent with enhanced GnRH secretion. Precocious pseudopuberty characterizes the situation where there is a development of secondary sexual characteristics, without gametogenesis. The problem is that there are excessive levels of circulatory steroids of either gonadal or adrenal origin. In congenital adrenal hyperplasia, excessive amounts of adrenal androgens are produced and may cause virilization and pseudo-hermaphroditism in the female. Interstial cell tumor of the gonads or sex steroid secreting tumors of the adrenal glands are also sources of excessive levels of estrogen or androgen. The high levels of circulatory steroids exert a negative feedback inhibition on hypothalamic release of GnRH. In the absence of pituitary gonadotropin secretion, there is a failure of gametogenesis, but the secondary sexual characteristics that normally develop at puberty are well developed. The pubertal process can also be delayed due to panhypopituitarism where all pituitary hormones including the gonadotropins are absent. A defect at the level of the hypothalamus or an isolated deficiency in FSH or LH secretion could also be responsible for a delayed onset of puberty. /Textbook of

Endocrinology, Robert Williams ed., Pediatric and Adolescent Gynecology, vol. 19 3 Altchek/.

The major pathways of adrenal gland steroid synthesis are depicted below. The understanding of these enzymatic pathways allows us to understand the alteration in the individual outlook and behavior.

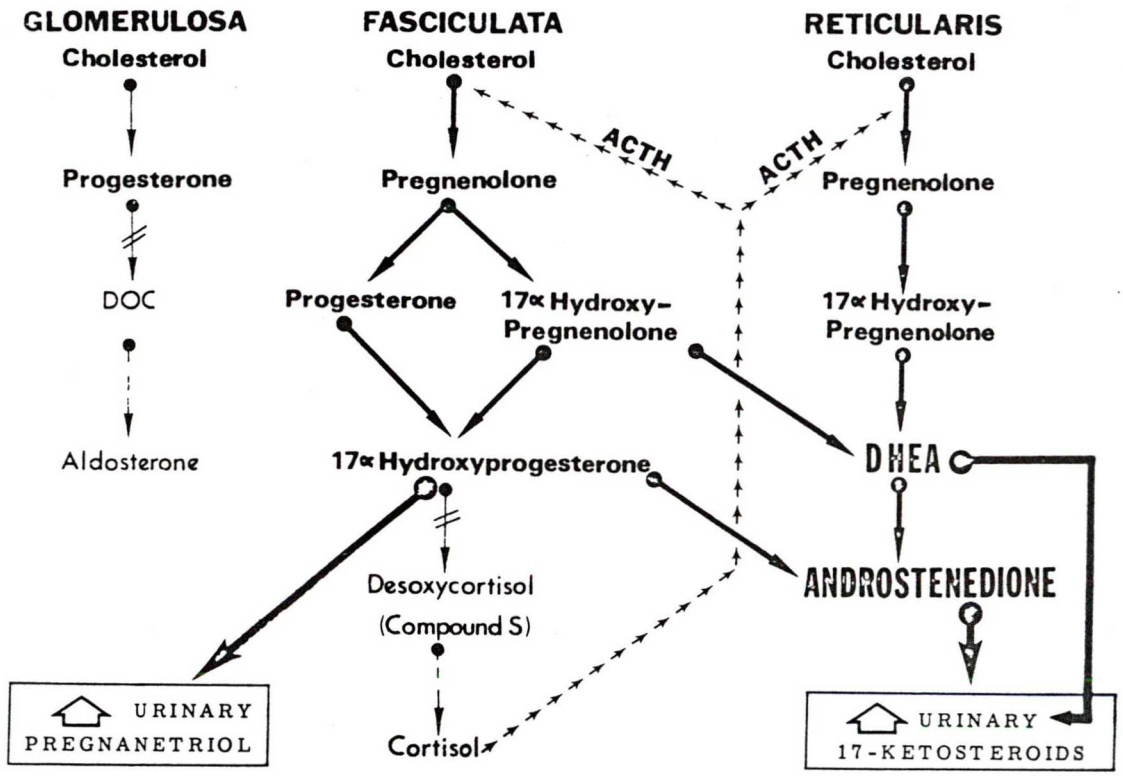

Fig. 8. The pathogenesis of 21 hydroxylase deficiency. Decreased cortisol production stimulates ACTH release, resulting in excess production of precursors and androgens. Deficient mineralocorticoid production may cause sodium waisting /Saba 1955/.

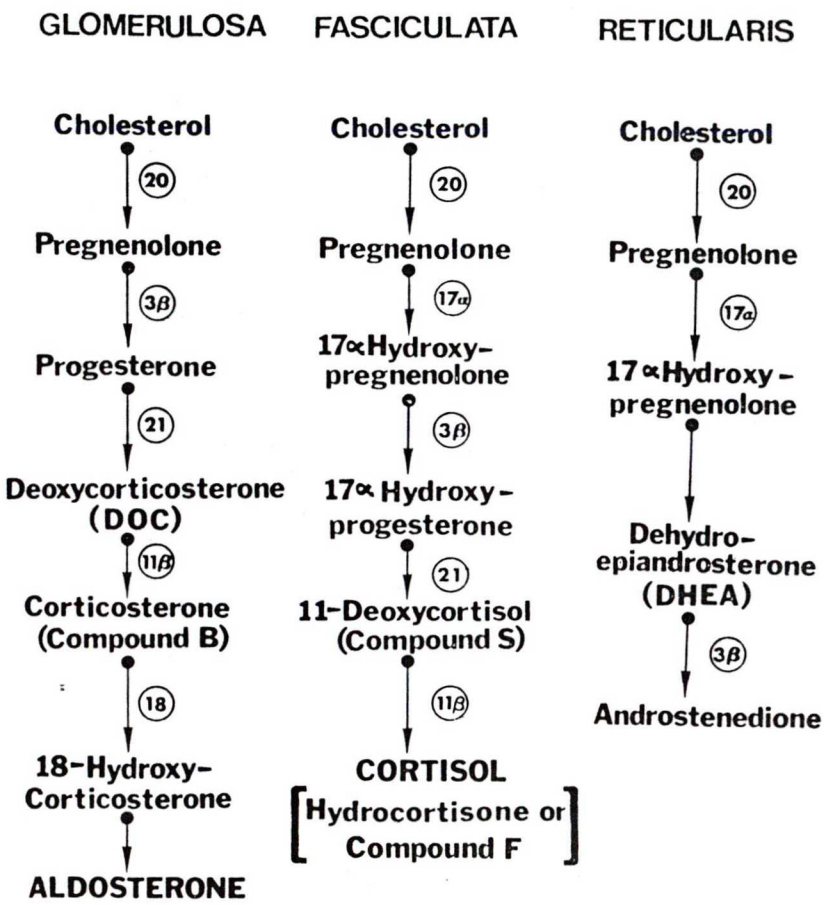

Fig. 9. Major pathways of adrenal steroid synthesis. Sites of enzyme action for each step are indicated by circled numbers /Saba 1955/.

There are at least five more or less distinct etiological entities which result in hypercortisolism.

1/ Bilateral adrenal hyperplasia

2/ ACTH secretory tumors /pituitary, lungs/

3/ Ectopic ACTH production
4/ Benign adrenal adenoma
5/ Functional adrenocortical CA

/Clinical Manifestations:/

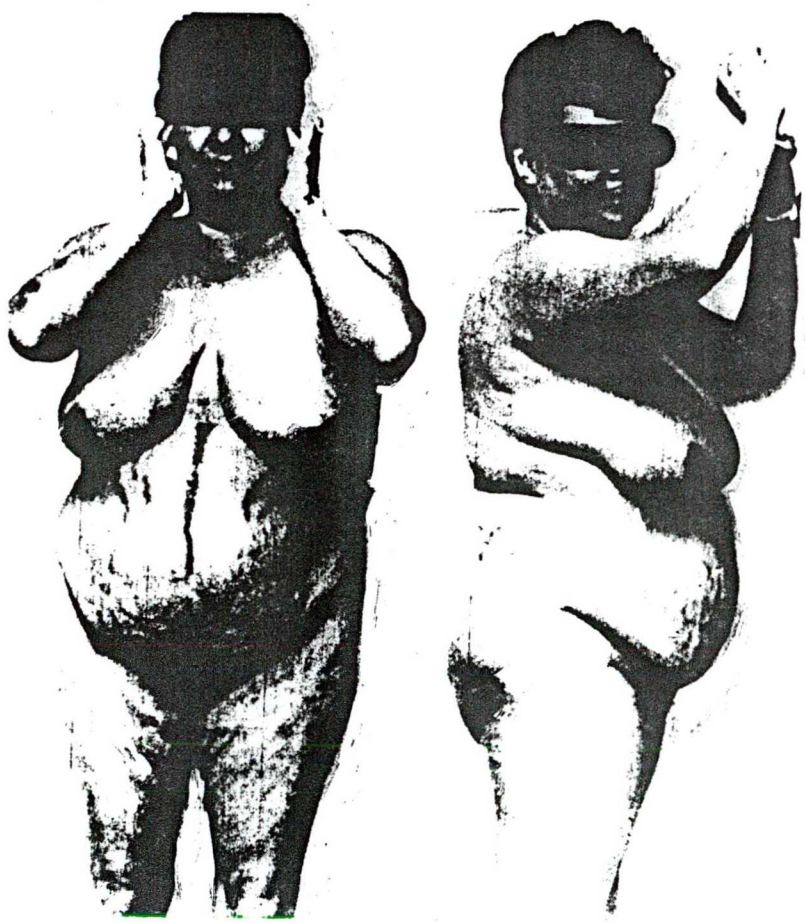

Fig. 10. Cushing's syndrome. Truncal obesity, moon facies, ecchymoses and striae are apparent. /Cope 1972/.

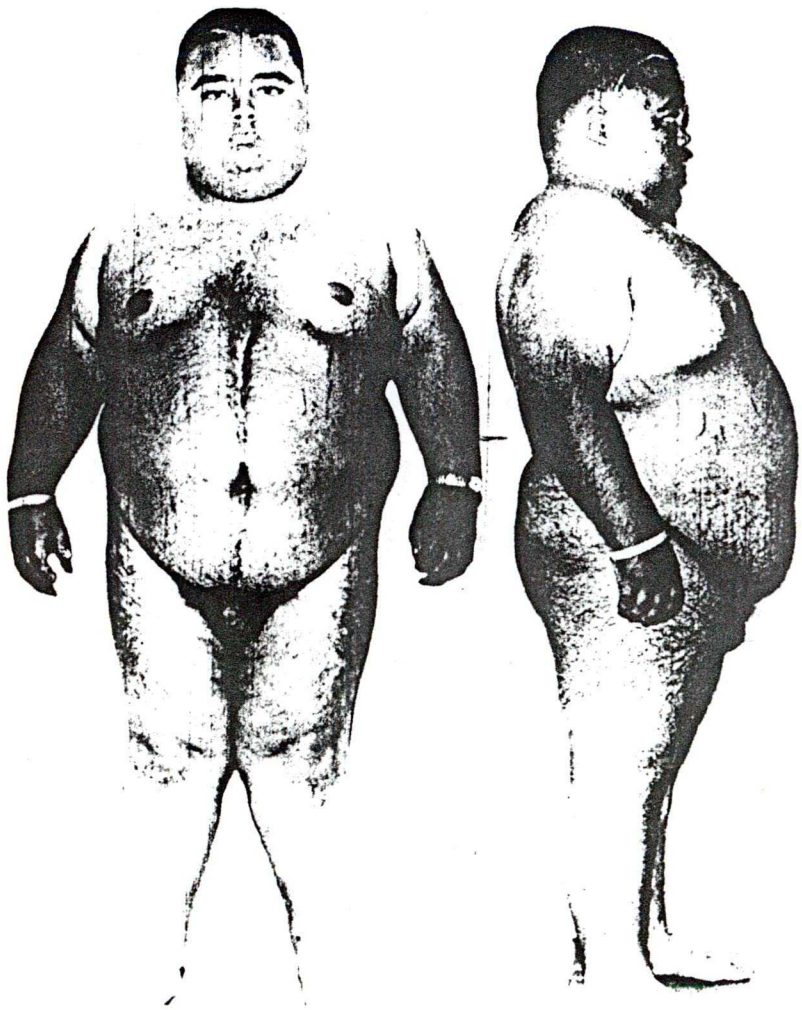

Fig. 11. Cushing's syndrome. Truncal obesity, moon facies, ecchymoses, and striae are apparent. /Cope/

Symptoms of excessive cortisol secretion include central redistribution of fat with demonstrable supraclavicular and cervicodorsal /buffalo hump/ fat deposition. The face is rounded /moon facies/ with fat above as well as below the zygomatic arches. There is generalized muscle wasting and concommittant loss of fat from the extremities. Muscle weakness is more proximal than distal. There is a loss of elastic fibers and skin develops a fine thin texture. Purple striae on abdomen, thighs, arms, and chest. Easy bruisability is common and poor wound healing. There is also a generalized osteoporosis due to the inhibitory effect of cortisol on osteoblastic activity.

Sign or Symptom	Occurrence %
Central Obesity	94
Hypertension	82
Glucose intolerance	80
Hirsutism	75
Amenorrhea or impotency	75
Purple striae	65
Plethoric facies	60
Easy bruisability	60
Osteoporosis	60
Personality change	55
Acne	50
Edema	50
Headache	40
Poor Wound Healing	40
Polyuria, polydipsia	20

Table 1. Frequency of signs and symptoms in Cushing's Syndrome.

/Diagnostic Procedure/

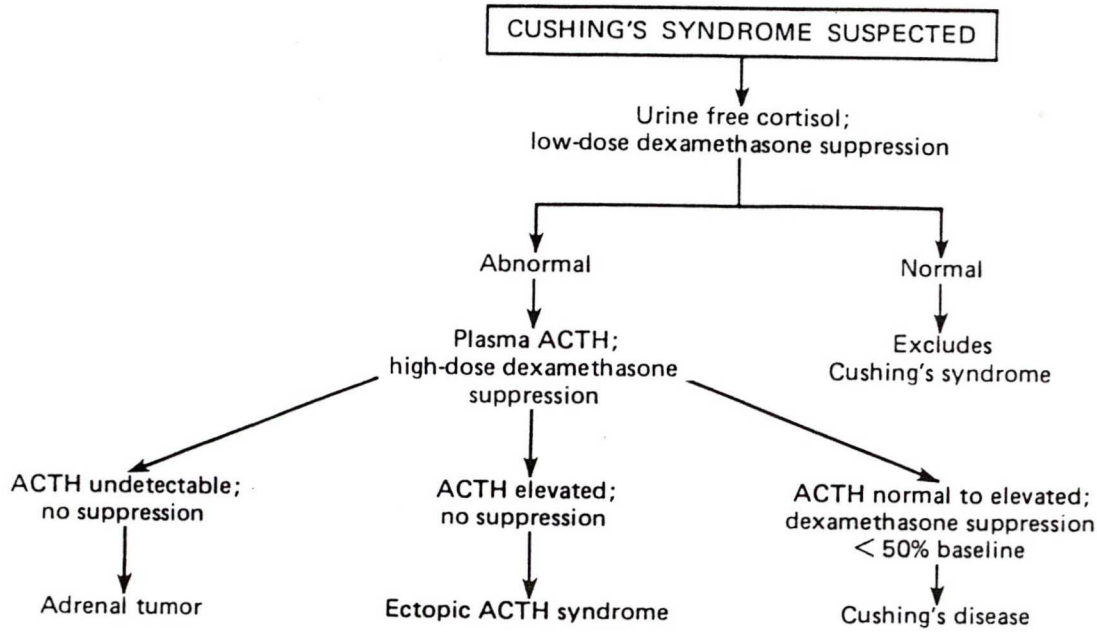

Fig. 12. Diagnostic evaluation of Cushing's syndrome and procedures for determining the cause. /From Los Angeles County University of S.Ca. Medical Center/.

1/ Overnight 1 mg dexamethasone suppression test. Plasma cortisol or free cortisol in a 24 hour urine specimen is to be measured.

If plasma cortisol less than 5 ug/dl=normal
If decrease urine cortisol =normal
no Cushing's disease.

If these tests are abnormal, hypercortisolism is present and diagnosis of Cushing's disease be considered.

2/ If patient is borderline. 2g low dose dexamethasone test.

normal response 17 OH cortico-steroid levels less than 4mg/24 hrs, which excludes Cushings disease.

3/ Other Tests

Basal morning cortisol levels
afternoon, evening cortisol
24 hr 17 OH steroids
17 Ketogenic steroids

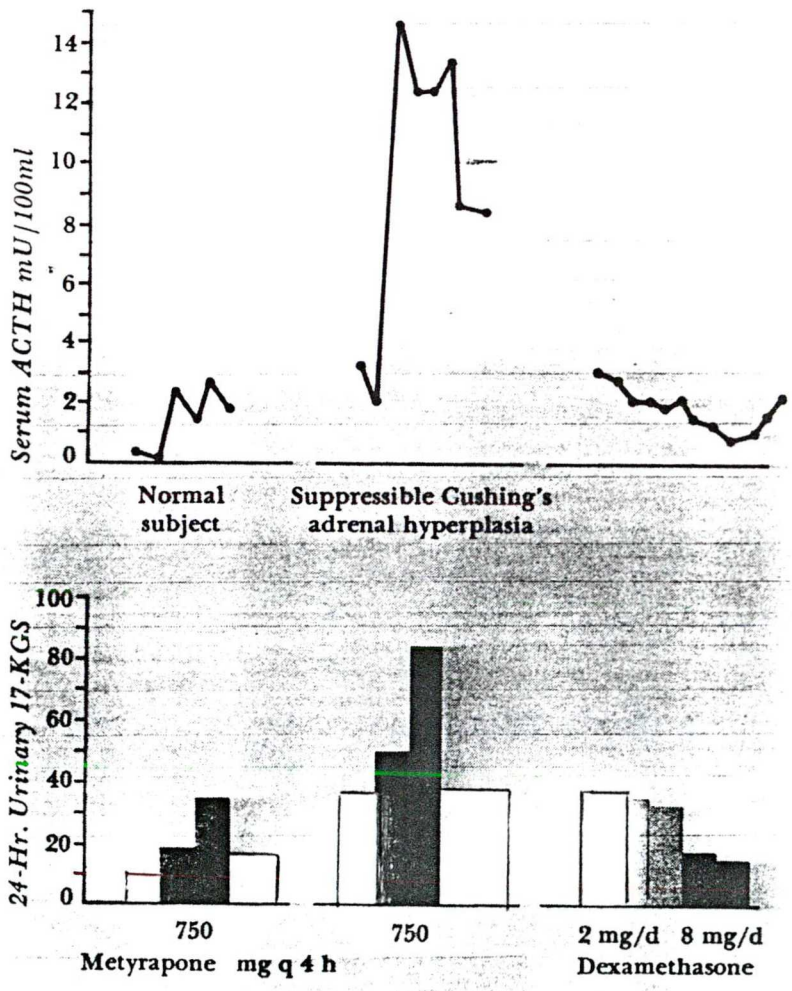

Fig. 13. Dexamethasone suppression tests.
/Los Angeles Medical Center/

/Diagnostic Procedures/

The most valuable early signs are the rounded face, hypertension, and some evidence of hirsutism, i.e. increased hair growth, acne, menstrual irregularities, and the presence of rather thin skin on extremities, perhaps with easy bruisability. When these features appear in the female child-bearing age, the disease of Cushing's Syndrome must be seriously considered. Of great value is the comparison of the patient's appearance with pictures taken some years earlier. The most frequent problem in the diagnosis occurs in the early stage of the syndrome when the patient may present only as a fat hairy girl with menstrual irregularities. More often than not, this is the final diagnosis and not Cushing's syndrome, since simple obesity may be associated with mild hirsutism and abnormalities of steroid metabolism.

Not infrequently in Cushing's syndrome signs and symptoms of excess androgenicity occur. These may lead to precocious puberty in the prepubertal boy and hirsutism or even virilism in the female. Such androgenic signs are more frequent in adrenal tumor-borne Cushing's Syndrome than in Pituitary Cushing's Disease.

/Therapy/

Depends on the Diagnosis.

Pituitary excess ACTH

If the patient has mild Cushing's symptoms, without severe osteoporosis, psychological problems

or hypertension, some authors propose to attempt pituitary irradiation, with up to 5000 rads. This will result in a cure in 6-12 months in 50% of the patients /Salassa 1979/. The causal therapy of Cushing's disease is the microsurgical removal of the ACTH producing pituitary tumor when accessible.

Bilateral Total Adrenalectomy

If Cushing's disease is very severe /nodular hyperplasia of the adrenal cortices/, or if there has been failure of pituitary intervention, bilateral total adrenalectomy is the only certain cure. However it cannot be looked upon as an ideal therapy, for the physician is thus substituting one lethal disease for another. The patient's Addison's Disease will now need to be therapeutically controlled during the rest of his life.

Medical therapy would be anticortisol drugs, which has been attempted on experimental trials, but at present no safe preparations are available for clinical use.

If an adrenal tumor is present, exploratory surgery and removal of an adrenal adenoma is curative. If cancer is found, the primary tumor is usually removed and adrenolytic drugs are utilized for therapy of the metastasis. The tumor is usually quite malignant, and death within 5 years is common.

/Congenital Adrenal Hyperplasia/

Adrenal Biosynthetic Disorder

The most common adrenal disorder encountered in pediatric practice is the adrenogenital syndrome.This form of congenital adrenal hyperplasia is due to an enzymatic block resulting in deficient hydroxylation at the C_{21} or C_{11} position of the steroid molecule. There have been to date a total of 5 such blocks described in the steroid synthetic pathway and there is every-likelihood that an enzyme deficient syndrome to fit each enzyme in the pathway will eventually be described. See Fig. 14. /Degenhart 1984/.

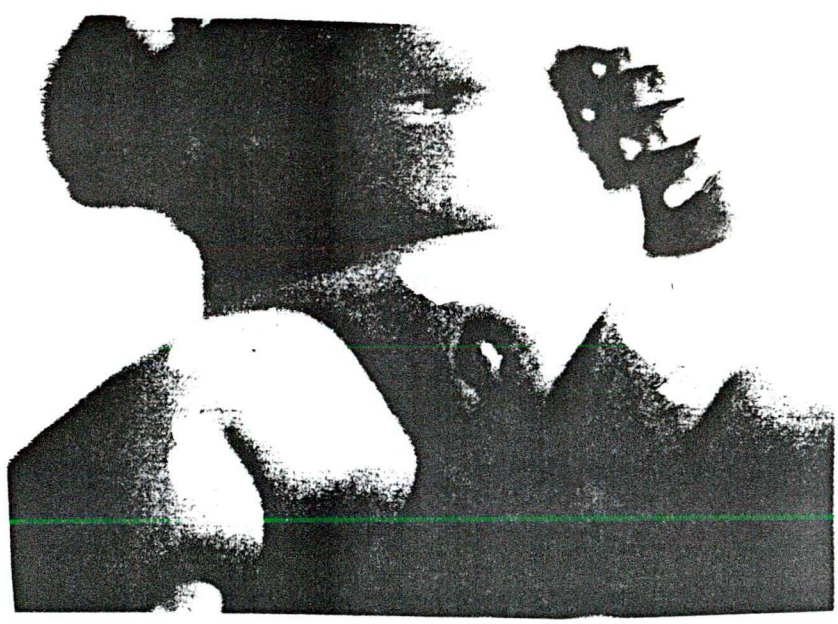

Fig. 13. Enlarged clitoris in an eight-month-old baby girl. Urinary 17 keto-steroid were 2x normal, pregnanetriol was 2x normal, and plasma testosterone level was 377 ng/100ml. /Los Angeles Medical Center/

There are usualy two immediate consequences of such a block 1/. The steroid intermediates directly behind the block build up in the adrenal spill out into the blood, 2/. There may be a deficiency of steroids normally produced beyond the block.

Since the last and most important of the steroids in the pathway is cortisol, ACTH is produced in excess in attempt to overcome the effect of glucocorticoid deficiency by restoring plasma cortisol to near normal levels. This leads to adrenal hyperplasia and often to a huge excess of adrenal steroid intermediates flooding the body. Normally they are found in the peripheral circulation only in trace quantities. The characteristics of all enzymatic defects are:

1/ Varying degree of cortisol deficiency
2/ Adrenal hyperplasia
3/ Various clinical manifestations due to excess preblock intermediates formed. /Bongiovanni 1984, Mantero 1984, Zachman 1984, Virdis 1984, D'Armiento 1983/.

a/ 21-OH ase deficiency

This is the most common defect which is due to an autosomal recessive inheritance and is observed with much more frequency in girls than boys. The incidence is controversial, being reported as often as 1/5000 births /Wilkins 1962, Prader 1985/.

The result of C-21 OH ase block is to inhibit both glucocorticoid and mineralocorticoid pathways. The ACTH excess due to the cortisol decrease pushes the steroid synthetic pathway to ward pregnenolone formation leading to an excess of precursors.

/17-OH pregnenolone, 17-OH progesterone and progesterone, which are then shunted toward the androgen pathway./ The excess androstenedion secreted is then converted by peripheral tissues to testosterone. The latter leads to virilization of the external genitalia. In utero and birth, varying degree of virilization in the female is found. The excess 17-OH progesterone and progesterone are metabolized in the liver and excreted in the urine as pregnanetriol and pregnanediol. Excess secretion of these in the infant are used to confirm the presence of this defect. The increase in dehydroepiandrosterone /DHEA/ and androstenedione gives rise to large quantities of urinary 17-OH keto-steroids /David J. Ped. 1984/.

The defect may vary in its severity. In the complete form of the disease the mineralocorticoid pathway may be so inhibited that salt wasting occurs and the infant will die of dehydration if untreated. In the mildest form, the androgenic effects may be manifest only at puberty, e.g. hirsutism, poor breast development and amenorrhoea.

usually the defect is intermediate in severity. A female infant is born with a large clitoris and if untreated she will grow rapidly with a masculine habitus. Pubic hair will appear early, a deep voice may appear in some years later and at puberty menarche does not occur. it must be emphasized that most of the biological androgenicity in this syndrome derives from the testosterone produced in non-adrenal tissues via the conversion of the androgenic precursors DHEA and androstenedione to testosterone. The simplest test for following adequate replacement therapy is to measure the serum testosterone levels and replace the cortisol until testosterone is maintained in the normal range. See Fig. 14.

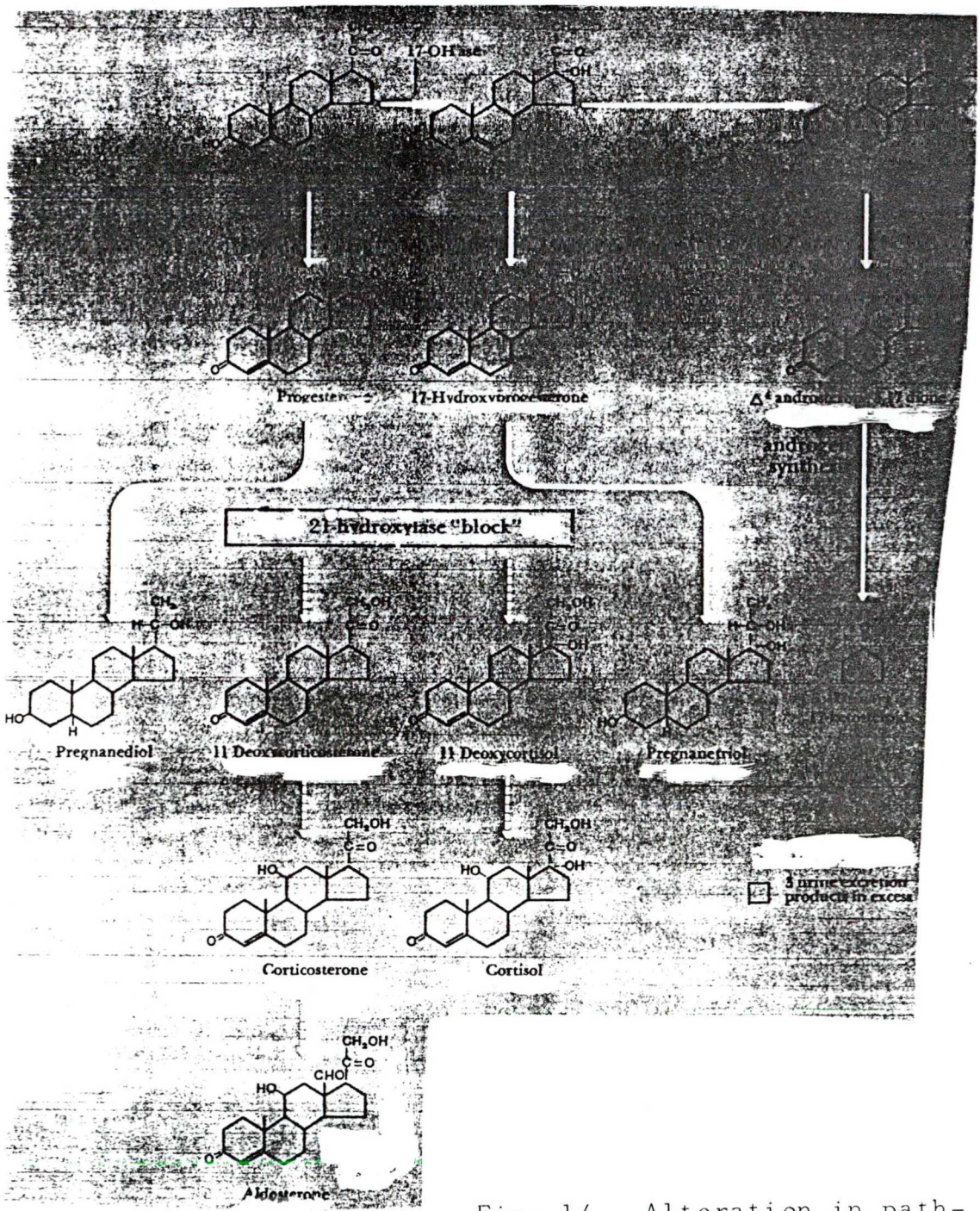

Fig. 14. Alteration in pathways by 21-hydroxylase block. /Los Angeles Medical Center/

OTHER ENZYMATIC DEFECTS

/Desmolase Decrease/

Since no steroid hormone can be produced in this defect it is incompatible with life when untreated. At autopsy, the infant is found te have large fat--laden adrenals.

/3ß-OH Dehydrogenase Decrease/

This defect is also incompatible with prolonged life and affected infants without hormone substitution therapy have survival no more than a few months.

/C-17 OH ase Deficiency/

This defect is compatible with life for C-17 OH steroid can effectively replaced by a weaker C-11 OH glucocorticoid precursor corticosterone. In this syndrome, corticosteroid secretion is excessive and controls the excess ACTH secretion relatively well. However, its immediate precursor 11-deoxy-corticosterone, a very active mineralocorticoid is also produced in excess, and therefore a hyperaldo-sterone like syndrome develops. Since, the C-17 defect is present in the ovaries and testes too, a deficiency of both male and female hormone occurs in both sexes and the patients are of the female phenotype, regardless of genetic sex.

/C-21 OH ase Deficiency/

Previously discussed.

/C-11 OH ase Deficiency/

The 11-hydroxy group is necesary for all biologically active corticosteroids and this defect results in a decrease of cortisol, corticosterone and aldosterone. This leads to a syndrome similar to C-12 OH ase defect except that a potent mineralocorticoid, deoxycorticosterone is formed in excess, and produces, in addition to virilization, a hyperaldosteronism--like picture.
See Fig. 15.

ANDROGEN DEFICIENCY SYNDROME

Provided the Leydig cells function normally, the male in adolescence shows progressive pubertal changes, normally beginning sometime between the ages of 9 and 16. These changes encompass many system. Growth prior to puberty /about 5 cm/year/ is probably regulated by the thyroid and growth hormone; the increased linear growth rate in early adolescence /7.5 cm/Yr/ has been ascribed to androgens. The overall increment in growth found in males can quite appropriately be ascribed to testosterone action: Fusion of the epiphyses is dependent upon sex hormones.

The anabolic effects of testosterone are manifested at puberty in many tissues. Both muscle, mass and bone tissue are increased under the influence of testosterone. The genital organs increase in size. The prostate and seminal vesicles enlarge; the voice becomes low pitched. The scrotum enlarges and becomes pigmented, and develops folds. Pubic hair grows upward in a typical diamond-shaped pattern. Hair appears

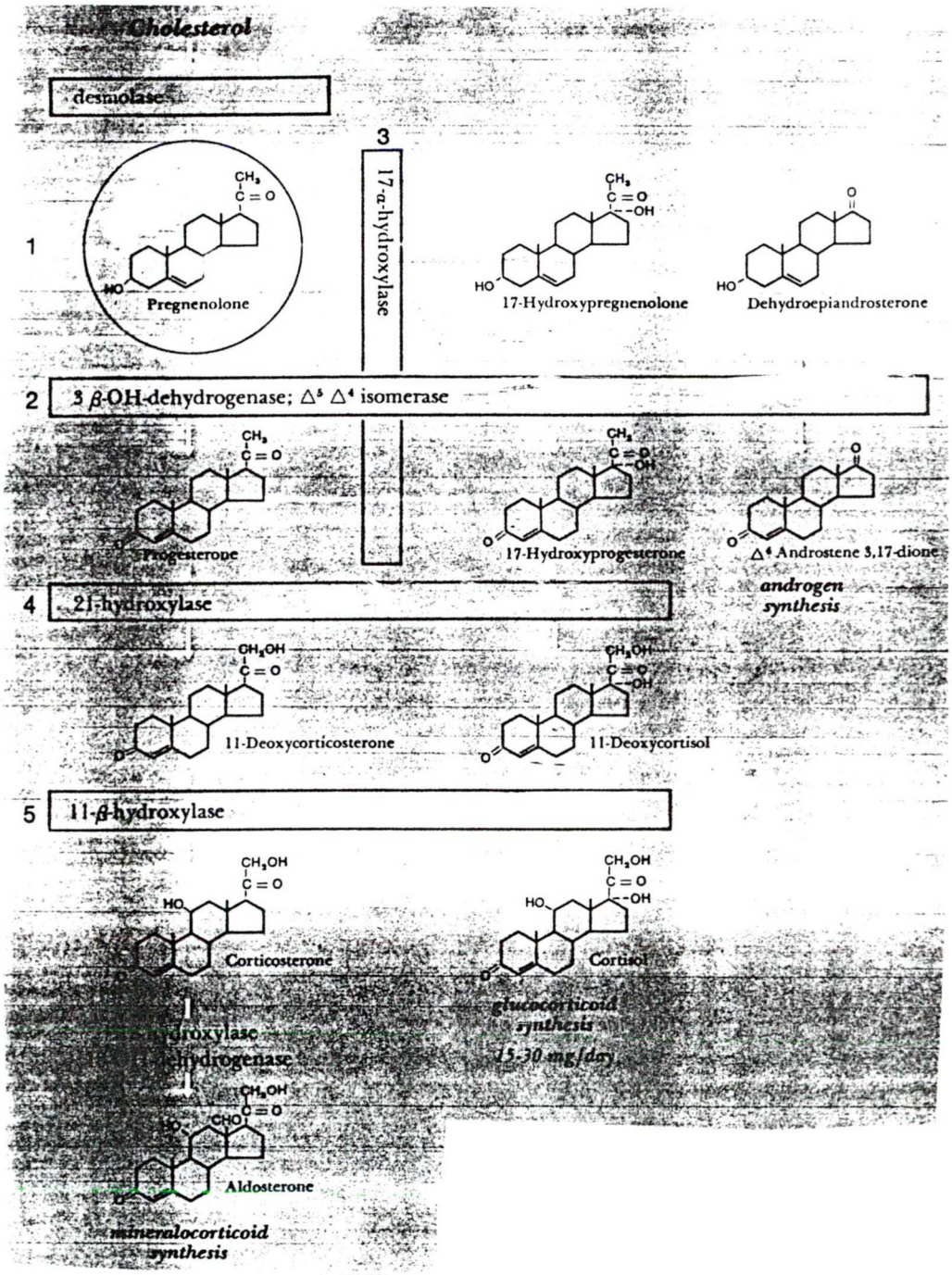

Fig. 15. Five Adrenal Biosynthetic Disorders. /Los Angeles Medical Center/

at the axilla, on the body, on the extremities, and around the anus. Facial hair develops and the scalp line undergoes the typical male recession. The psychological changes in the adolescent are equally profound.

If the Leydig cells fail to function at the usual age of adolescence, the pubertal changes normally brought on by testosterone will fail to appear. Most often the androgen deficiency is secondary to delayed function of the hypothalamic-pituitary gonadotropin system.

In the teenager who fails to manifest sexual maturation one must consider the possibility of primary gonadal failure. By far the most common example of male hypogonadism is Klinefelter Syndrome.

KLINEFELTER SYNDROME

The fundamental etiology of this disorder is the presence of supernumerary X chromosomes; most often the patients are XXY. Fig. 16 depicts the various sex chromosomal abnormalities possible.

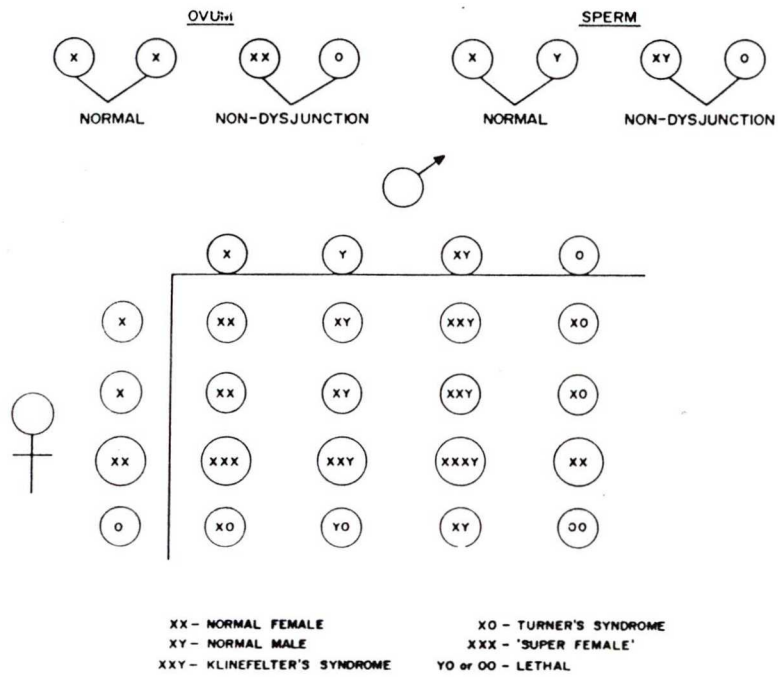

Fig. 16. The various contributions of sex chromosomes possible from ovum and sperm and results of different unions /de Grouchy 1984/.

It is characterized by tubular failure and decreased Leydig cell function. In 1942 Klinefelter described nine men with aspermia, gynecomastia, small testes, elevated urinary gonadotropins. Leydig cell function was obviously present to some degree /since each patient had a phallus of normal size and moderate amount of pubic hair, however diminished facial and body hair suggested some impairment of testosterone secretion /Klinefelter 1942, Jacobs 1959/. See Fig.17. for classification of Hypogonadism.

Classifcation of Hypogonadism

Primary Testicular Failure (Hypergonadotropic Hypogonadism)

- **Klinefelter's Syndrome**
- **Variants of Klinefelter's Syndrome**
- **Male Turner's Syndrome**
- **Reifenstein's Syndrome**
- **Familial Syndromes of Primary Hypogonadism with Normal Karyotype**
- **Anorchia**
- **Germinal Cell Aplasia**
- **Adult Seminiferous Tubular Failure**
- **Adult Leydig Cell Failure**

Secondary Testicular Failure (Hypogonadotropic Hypogonadism)

- **Delayed Puberty**
- **Isolated Gonadotropin Deficiency**
- **Fertile Eunuch Syndrome**
- **Hypopitutarism**

Fig. 17. Classification of the hypogonadisms possible /Grumbach 1985/

The incidence of this disorder is surprisingly high, it occurs in 1/400 live born males. Apparently the presences of one or more extra X chromosomes in testicular tissue brings about the typical Klinefelter testicular dysgenesis. At birth the testes of affected patients appear normal, and during the prepubertal years the growth and histological appearance of the testes are normal, although there is some evidence of a gradual loss in germ cells. At puberty the rise in gonadotropins brings about a progressive hyalinization and fibrosis of the seminiferous tubules, which therefore fail to develop, and testes remain small in size. Rarely doe the testes of a patient with Klinefelter's Syndrome exceed 2.0-1.5x1.5 cm in dimensions. Normally the adult testes measure 4.6 cm in length and 2.6 cm in width. The small, firm testes of Klinefelter syndrome are characteristic /Paulsen 1968/.

It is interesting that many patients with Klinefelter's syndrome show excessive long bone growth prior to puberty; the bone age, however, is appropriate for the chronological age. The growth of the long bones is greater in the lower extremity than in the upper extremity, resulting in a ratio of arm span to height of one or less.

Explanation for other aspects of Klinefelter's syndrome are also lacking. The gynecomastia is bilateral and involves hyperplasia of the interductal tissues. In contrast, estrogens produce ductal hyperplasia. Subnormal intelligence /I.Q. less than 80/ and characteristic behavior alterations are found in many patients. Individuals with Klinefelter's syndrome

have an increased incidence of diabetes mellitus, chronic bronchitis, neoplasia, and autoimmune disorders /Lubs 1962, Forssman 1963/.

More than two "X" may be present in cells from patients with Klinefelter's Syndrome. Variants include XXXY, XXXXY and mosaicism. Mental retardation in the XXXY, and XXXXY patients is usually severe, whereas the mosaic patients, particularly those with XY cell line show far less severe symptoms and may even have normal gonadal function. It is important to ascertain the gonadal genotype since only supernumerary X's in testicular tissue produce testicular dysgenesis. Buccal smears and karyotyping of skin and blood will not necessarily reveal the abnormal genotype /Lubs 1962/.

A testicular biopsy is important in the diagnosis of Klinefelter's syndrome. The tissue should be examined histologically and the testicular cells should be karyotyped.

Azoospermia is also a classical finding in Klinefelter's syndrome. There are no unique changes in seminal fluid volume; however, with severe androgen deficiency, the volume of ejaculate is small, and the concentrations of fructose and phosphate are decreased.

The treatment of patients with Klinefelter's syndrome is direct toward androgen replacement, if necessary. Testosterone in oil, 200 mg intramuscularily every 2 weeks is recommended. Gynecomastia and infertility are irreversible, the former one may require

plastic surgery /See Fig. 18. and 19./.

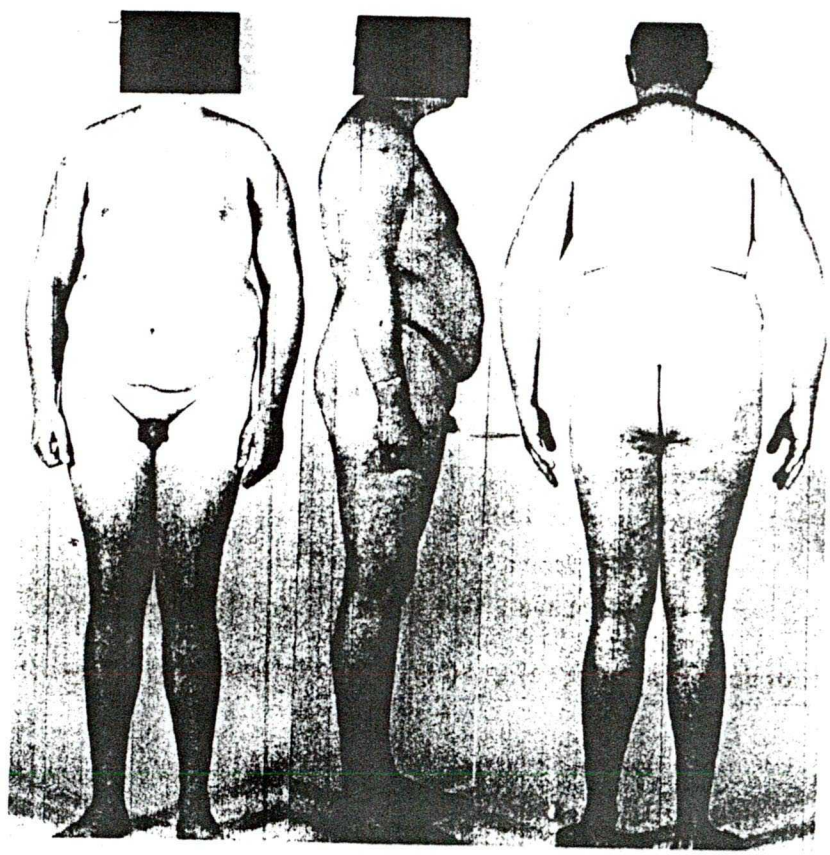

Fig. 18. An untreated patient with Klinefelter's syndrome. Note the ennuchoidal features, gynecomastia, lack of body hair, and underdeveloped external genitalia. /University of California, Klinefelters/

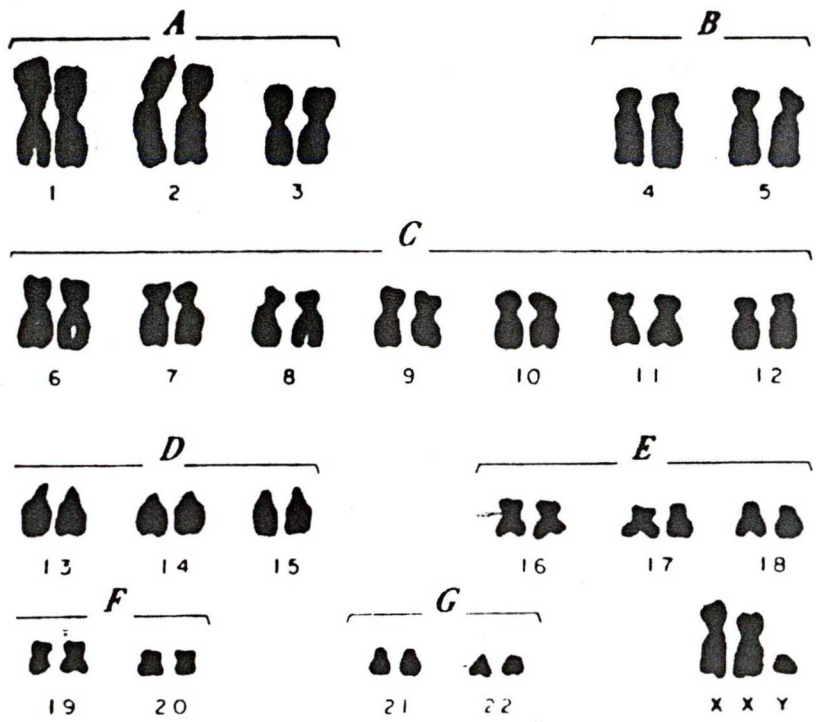

Fig. 19. The characteristic XXY karyotype in a patient with Klinefelter's syndrome. /University of California/

REIFENSTEIN'S SYNDROME

This syndrome may belong to the category of inborn errors of testosterone synthesis. This heredity disorder is characterized by hypospadias of varying degree and incomplete fusion of the labioscrotal folds. Atrophy of seminiferous tubules occurs after the onset of puberty and gynecomastia develops. Testosterone concentrations are usually reduced, possibly owing to a defect in the conversion of androstenedione to testosterone /17ß-OH steroid dehydrogenase defi-

ciency/. Gonadotropins are usually elevated. Affected patients respond to androgen therapy /Klinefelter 1949/.

TESTICULAR FEMINIZATION SYNDROME

This disorder does not represent a failure of testosterone synthesis; rather in all probability, it is the result of a genetic defect in androgen receptors in target tissues. In addition some patients have reduced 5 α - reductase activity in androgen target tissues. The patient is sex chromatin negative and the karyotype is 46XY, however the phenotype is completely female /See Fig. 20./

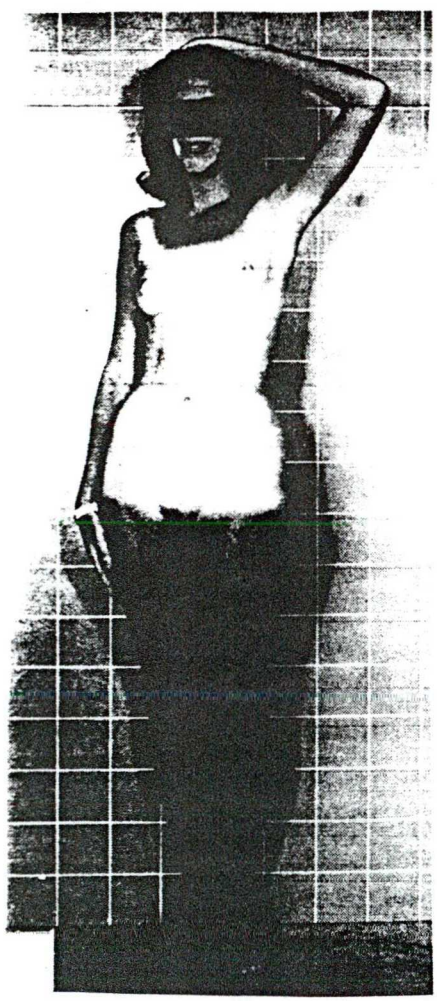

Fig. 20. Testicular feminization syndrome. This girl is chromatin negative and has total absence of sexual hair with feminine secondary sexual development.

/Textbook of Endocrinology/ Fifth Edition. Saunders 1974.

At puberty the breast development is marked, but pubic and axillary hair are scarce, and no menses occur. Colposcopy usually reveals a small vagina, but no uterus, tubes, or ovaries; the testes are either abdominal or inguinal.

Patients with the testicular feminization syndrome fail to respond to androgen at any time in life; and fetal development reflects this. The external genitalia are female. The testis secretes both wolffian duct inducer, and Mullerian inhibitor; and response to these substances is normal. Thus the male genital ducts develop, but becuase of the lack of response to androgens they tend to be hypoplastic. As mentioned the female genitalia are incomplete; the uterus and tubes are absent and the upper portion of the vagina does not develop. The shallow vagina ends in a blind pouch /Skordis 1987, Josso N. 1965/.

The testis is capable of forming testosterone and estrogens. Indeed, after removal of the testes. the breasts regress, suggesting that testicular estrogens are implicated in gynecomastia. Usually the testes are removed because of the increased incidence of testicular malignancy in affected patients. After orchidectomy, the patient is maintained on estrogens /Fergusen-Smith MA 1965/.

As one might predict, affected patients are totally feminine in behavior, dress and attitude. Indeed, they are among the most strikingly feminine individuals one is likely to encounter. The disorder is transmitted

by the heterozygous female to half her male offspring. As for her female offspring, half will carry the trait /Fitzgerald PH 1984/.

DISORDERS CONSISTENT WITH ESTROGEN DEFICIENCY: HYPOGONADISM

Deficient production of estrogen of the ovary may be due to primary or secondary hypogonadism. Any interruption of the hypothalamic-pituitary-ovarian axis will produce a secondary hypogonadism. Whatever the cause of hypogonadism, one of the major symptoms is amenorrhea. If menstrual periods have never occured the condition is called primary amenorrhea. The abnormal cessation of menstrual periods that are already established is called secondary amenorrhea. Infrequent menstruation is termed oligomenorrhea.

If a girl has not menstruated by the age of 15, and has not matured physically, an investigative study should be initiated. One half of all girls who have not menstruated by the age of 18 have primary ovarian failure or a congenital anomaly of the reproductive system. Primary ovarian failure can result from congenital or acquired conditions either of which may involve defective steroidogenesis and/or germ cell failure.

CONGENITAL OVARIAN FAILURE

Although occasionally a child is born with total absence of gonads /gonadal agenesis/, more often

gonadal function is present for some time in fetal life and subsequently becomes impaired. Most affected patients are short, but some are normal in height or even tall. Other stigmata may be present, such as webbed neck, wide carrying angle /cubitus valgus/, short metatarsals, and coarctation of the aorta. Streak gonads, short stature, webbed neck, and cubitus valgus are symptoms of Turner's Syndrome when consistent with an XO karyotype.

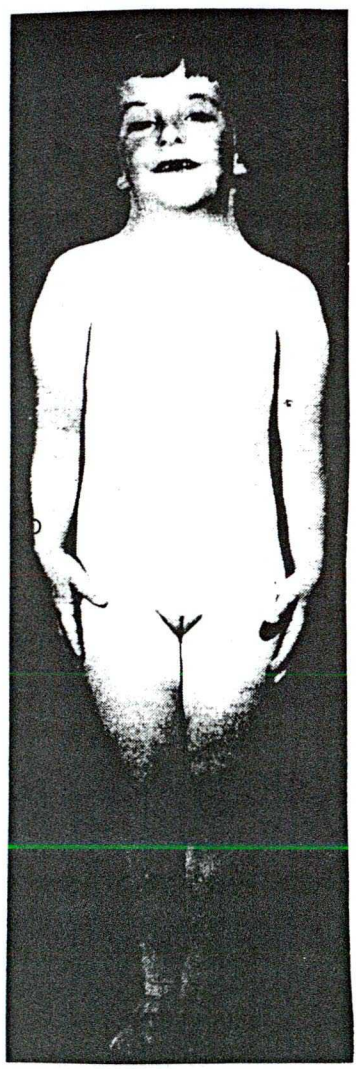

Fig. 21. Thirteen-year-old patient with Turner's syndrome showing webbed neck, low set ears, and widely spaced nipples. In the first few months of life the patient was moted to have edema of the feet which disappeared spontaneously. Her growth rate fell below the third percentile. Her buccal smear was chromatin negative, and the karyotype was 45XO. Urinary excretion of FSH was high; 17KS were 1.4 to 1.6 mg/24 hr urine. No evidence of sexual maturation could be seen. An exploratory operation was performed, streak gonads and a very small uterus were found and removed. Estrogen therapy was instituted.

/Courtesy of Dr. John Crigler, Childrens Hospital Medical Center, Boston, Mass./

This phenotype is not difficult to recognize. At the other end of the spectrum is the genetically normal /46XX or 46 XY/ individual with streak gonads and no osmotic anomalies. This is known as pure gonadal dysgenesis, and the individuals with this form of gonadal dysgenesis invariably have normal stature. Primary amenorrhea is associated with all of the variants of gonadal dysgenesis /Kohn G. 1980/.

Patients with XO karyotype can be easily recognized during infancy usually because of lymphedema of the extremities and loose skin folds over the nape of the neck. Later in life the patients are distinctly recognizable by their distinctive facies:

1/ micrognathia
2/ epicanthal folds
3/ prominent low set ears
4/ fish like mouth
5/ ptosis

The chest is shieldlike and the neck subsequently is short; broad, and webbed /40% of patients/. Additional anomalies associated with Turner's syndrome include coarctation of the aorta /10%/ hypertension, renal abnormalities /50%/ pigmented nevi, cubitus valgus, tendency to keloid formation, short fourth metacarpal, and recurrent otitis media.

Short stature is a marked feature. Mean final height is approximately 142 cm with a mean range of 133-153 cm. The current data suggest that the short stature found in patients with the syndrome

of gonadal dysgenesis is not simply due to a decrease of GH, somatomedin, sex steroid, or thyroid hormone. The literature also suggests that no significant increase in final height has been documented in these patients after therapy with GH, anabolic steroids and estrogens. However, there have been some promising trials as to the positive effects of estrogens on growth in these individuals. These therapeutic efforts have been initiated by the fact that the subdued GH reserve of Turner patients can be improved by the administration of minute amounts of estrogens /Laczi F. et al. 1979, etc./.

In order to appreciate new experimental therapy done in Turner's syndrome, we have to acknowledge that growth in Turner's syndrome can be divided into the following four phases:

1/ Intrauterine growth is retarded, mean length at birth is around term but below normal

2/ Early childhood /up to three years/ retardation of bone age; height is relatively normal.

3/ Later childhood /up to bone age of about 10 years, growth is slow. Bone age progresses normally at the rate of 1 cm/yr.

4/ Adolescent age; patients accumulate fat and thus the weight to height ratio increases.

There is no prepubertal growth spurt. Bone age slows down, however the total growth gain is slightly different from normal. This subsequently suggests that the presence or absence of puberty

does not influence final height. Evidence has shown that the characteristics in Turner's syndrome is completely different from those diseases in which there is a true GH deficiency.

Dr. Van Vliet reviewed the possibilities of hormonal changes during development in Turner's Syndrome; Obviously there are several abnormalities.

1/ Gonadotropins are increased in infancy and adolescence, due to ovarian failure.

2/ Adrenal androgens may be normal

3/ The GH secretion was found to be subnormal /results showed decrease in estrogens and relative obesity/; ethinylestradiol administration increased the concentration of GH in the blood plasma/. See table 2.

	Mean ± SD	Range
Chronological age (years)	14.2 ± 3.3	6.3-21.2
Bone age (years)	12.3 ± 2.7	6.5-17.0
Height (SD score)	-3.2 ± 0.67	-4.3 -2.2
Weight (SD score)	+2.0 ± 1.4	+0.8 +6.8

	Before ethinyloestradiol	After ethinyloestradiol	p value
GH (ng/ml)	2.4 ± 0.45	5.3 ± 1.16	<0.02
Somatomedin C (IU/ml)	1.45 ± 0.15	1.77 ± 0.15	0.06
LH (mIU/ml)	28.9 ± 4.6	10.4 ± 3.6	<0.01
FSH (mIU/ml)	91.6 ± 5.5	17.2 ± 5.7	<0.01

Table 2. Basal hormone concentrations before and after ethinylestradiol. Values are means ± SEM.

Frequently in Turner's syndrome, glucose tolerance is somewhat distorted. To this date: GH has not been found to further alter glucose metabolism; this suggests an intermediate mediator.

Dr. Joss et al, questioned the possibility of anabolic steroid treatment, particularly with oxandrolone. Subsequently after therapy with anabolic steroids is stopped, the bone age may continue to progress inappropriately. Dr. Joss evaluated the final height data after therapy with oxandrolone. The data from the literature are still controversial. Syber shows that there is no effect on final height. A more positive result was published by Heideman. He showed that 27 patients with therapy for 6 years reached a mean height of 150 cm. This is approximately 5 cm above the mean for controls. See Fig. 21.

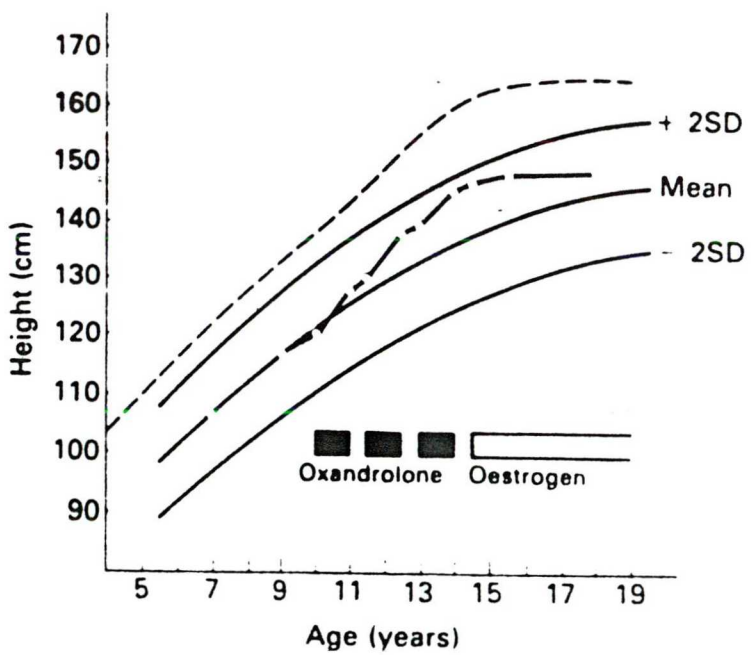

Fig. 21. Growth curve of a girl with Turner's Syndrome treated for three 1 year periods with oxandrolone, 0.1 mg/kg/day. Standards /mean±2SD/ for Turner's syndrome from Joss and Ranke. The broken line is the mean height for normal girls.

Dr. Karstrup had started to investigate the effect of low dose estrogen doses on the growth in Turner's syndrome. He suggested that estrogens may regulate the tempo of growth during development rather than influencing the final height. I believe this is an important statement because we are subsequently dealing with two different growth modulators: 1/ GH-somatomedins which are obviously related to difference in stature in normal development, whereas 2/ pubertal steroids may influence the dynamics of growth.

The growth effects of low dose estradiol are partially independent of the GH-somatomedin axis, it seems to have a direct effect on bone too as osteocalcin increases with this therapy. It has been suggested in the literature that trials with GH should also be conducted.

After all these studies we question ourselves which procedures are the most beneficial ones on the final height of a Turner patient.

As a conclusion: a general protocol can be drawn up for Turner's Syndrome with all the data compiled:

1/ GH may be applied subcutaneously every /other/ day at early years of age.

2/ Oxandrolone at bone age of approx. 8 yrs.

3/ Estrogen at bone age of 8-10 years not to induce growth, but rather to modulate it.

and to induce female secondary characteristics, initially using a low dose.

It is becoming widely recognized that many sexually dimorphic patterns of body growth, hepatic steroid metabolism, and hormone and growth factor receptors' concentrations are largely attributable to the difference in patterns of GH secretion /O.G.P. Isaksson, A.A.L. Lindahl, A. Nilsson, Acta Paedr. 1988/.

With the advent of estrogen therapy, it should be noted that chronic estrogen administration can cause chromosomal changes in rat pituitary /Lloyd et al. 1973/ and estrogens have also been shown to induce prolactin release by a potent antidopaminergic effect at the pituitary level /Raymond et al. 1978/. It is also plausible that the primary ovarian failure in some cases of gonadal dysgenesis can induce pituitary tumors which may secrete gonadotropins /Kelly 1902, Woof and Schenk 1974/.

In a case report, Gaspar and Julesz have shown that mosaic Turner's syndrome / 45XO/46XX / and prolactin secreting pituitary microadenoma may coexist. In such a case, when hyperprolactinemia is properly treated, a regular menstrual cycle may be restored. See Fig. 22. and 23.

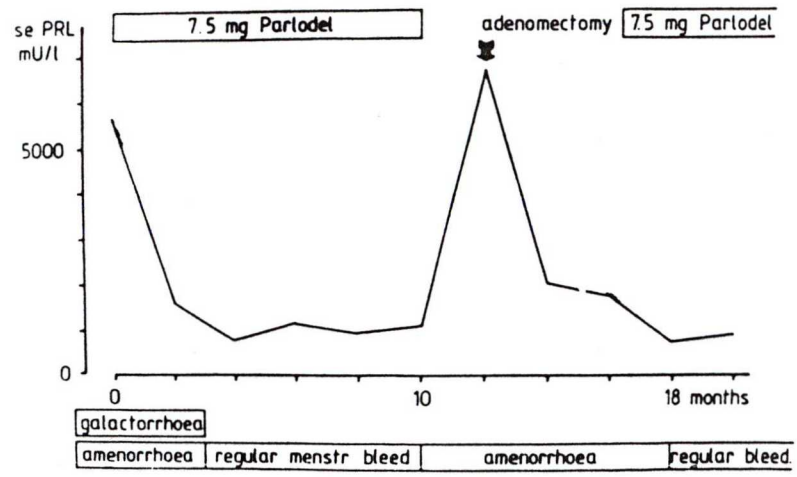

Fig. 22. The effect of bromocriptine treatment and adenomectomy followed by postoperative bromocriptine administration on serum prolactin level and menstrual cycle in patient with Turner's syndrome and microprolactinoma.

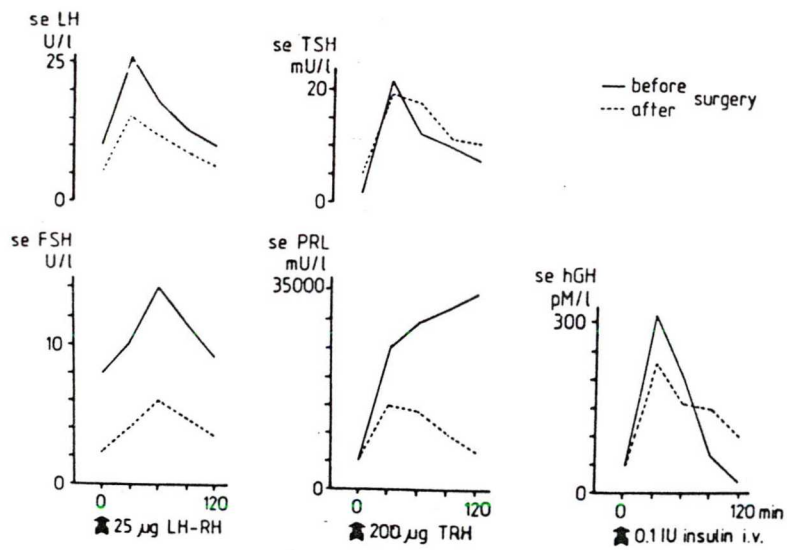

Fig. 23. Reserve capacities of FSH, TSH, PRL and hGH of the patient with mosaic Turner's syndrome and prolactinoma before and after surgical treatment.

SUMMARY

The attainment of adult sexual function occupies the years of adolescence. The characteristic growth spurt, probably due to GH secretion modulated by steroids, and the enhanced secretion of androgen precursors by the adrenal, heralds gonadal maturation and the onset of secondary sexual characteristics. The target tissues for testosterone or it's metabolite dihydrotestosterone includes the penis, testis, prostate, seminal vesicle, skin, muscle, bone, kidney, and brain. Estrogens stimulate ovarian follicles and the breast, alter the structure and foundation of endometrial and vaginal cell, and change the distribution of fat in the body.

Any interruption in the pathway from hypothalamus to pituitary and gonad disrupts the process of sexual maturation and function. If this pathway has never functioned normally, the resulting hypogonadism produces amenorrhea and lack of breast development in girls and azoospermia with small genitals in boys.

Primary disorders of the gonads can produce a similar state of hypogonadism. Often these primary gonadal disorders are due to chromosomal aberration /gonadal dysgenesis, Klinefelter's syndrome/. A failure of target tissue to respond to testosterone can produce "amenorrhea" in a seemingly normal female with 46,XY karyogram /Testicular Feminizing Syndrome/.

Once sexual maturation occurs, disruption of the hypothalamic-pituitary-gonadal-axis produces secondary amenorrhea in girls, and impotence and sterility in boys.

Primary disorders of gonads after sexual maturation usually involve infection or space occupying lesions /cysts or tumors/. If such lesions produce excessive amounts of estrogens or androgens, appropriate changes in physical characteristic will ensue. Gonadal tumors producing hormones must be differentiated from androgen-producing and estrogen-producing tumors of the adrenal.

The remarkable physical changes in puberty are mirrored by psychological changes. Androgens, produced in increased quantities in both girls and boys, heighten sexual desire. Intrauterine and perinatal imprinting of sexual identity by androgens plus a variety of environmental factors determine the completeness of this identity. Failure to identify with the sex rear, creates great problems as our society thinks in terms of all or none and can not or will not recognize the individual of ambiguous identity. Furthermore, the legal problems associated with surgical alteration of the sex of an individual are enourmous.

As a result of new research in the field of Turner's syndrome, the disease has gained a more positive outcome with the possible therapy of growth disturbances. Although the therapy at present is still controversial, it is feasible to acknowledge

the plausible interactions between various factors in producing some increase in growth.

In conclusion, appropriate secretion of hormones by the gonads and their action on the target tissues are major organic factors which determine sexual identity.

The hormonal secretion of course, depends upon structurally and functionally normal gonads, the condition of the gonads in turn depends on the chromosomal arrangement. The hormonal secretion also depends upon the presence of various enzymes and cofactors necessary for hormone synthesis.

The action of testicular hormones on the target tissues should bring about unequivical male sexual differentiation of the external genitalia and should stabilize Wolffian ducts induced by testicular hormones The lack of testicular hormones should bring about female sexual differentiation. The sex of rearing must be determined by the appearence of external genitalia, the karyotype, and the functional potential of the gonads. Any abnormality which precludes the interaction of appropriate sex hormone and target cells may cause physical and probably, psychological disturbances in sexual identity.

Of all the areas of medicine, it is in the realm of sexual maturation and identity that the most patience and understanding is required. The young adolescent needs assurance and guidance as he or she explores this world, and should be guided in coping with problems of puberty.

REFERENCES

1 Berthold A.A. 1849. Transplantatio der Hoden, Arch. Anat. Phys. Wiss Med. 16: 43-46.

2 Harris G.W. 1955. Neural Control of Pit. Gland. London Edward , Arnold, Ltd.

3 Moss R.I. 1979. Actions of Hypothalamic-Hypophysiotrophic hormones on the Brain. Ann. Rev. Physiology. 41: 617-32.

4 Seatlo G. and B. Flerko. 1978. Brain Cells as Producers of Relasing and Inhibitory Hormones. Intern. Rev. Cytol. 7 /Suppl. 1-50/.

5 Vala W., C. Rivier, M. Brown. 1977. Regulatory Peptides of the Hypothalamus. Ann. Rev. Physiology. 309: 473-527.

6 Wade N. 1978. Guillemin and Schally. Science 200: 279-282. 411-414. 510-513.

7 Rayyis S.S. and J.E. Bethone. Radioimmunoassay, Acth in Dexamethasone Nonsuppressible Cushing Syndrome. J. Clin. Endocrinol. and Meatb. 29: 1231. 1969.

8 Davies A.G. 1981. Role of FSH in the Control of testicular Function. Arch. Androl. 7: 97--108.

9 Kurtz E.M., DR. Sengelaub and A.P. Arnold. 1986. Androgens Regulate the Dendrite length of Mammalian Motor neurons in adulthood. Science 232: 395--398.

10 DE Kretser, S.M. H.G. Burger B. Hunson. 1974. The relationship between germinal cells. Serum FSH levels in Males with Infertility. J.Clin. Endocrinol. and Metab. 38: 787-793.

11 Wachell S.S. 1979a. Immunogenetic aspect of Abnormal Sexual Differentation. Cell 16: 691-695.

12 Wachelle S.S. 1979b. The genetic of Intersexually Clinical and theoretical perspectives. Oby. Gyn. 54: 671-685. New York Harper and Row Inc.

13 Ohno S.Y. Nagai, S. Ciccaress and H.G. Wais. 1979. Testes organizing HY antigen and the Primary Sex Determination mechanism of Mammal. Rec. Prop. Horn. Res. 25: 449-476.

14 Gibbon M.J.D. and kreiger H.M. Charlton E.A. Zimmerman Mating and pregnancy can occur in Genetically Hypogonadal Mice with Peptide in Preoptic Area Brain Grafts.

15 Bardin, C.W. and J.F. Cateerwal. 1981. Testosterone: a major determinant of Extragenital Sexual Dimorphism. Science 211: 1285-94.

16 Erickson G.F. PA. Mafiffin CA. 1985. The ovary and Androgen Producing Cells. A review of Structure and Function Relationships. Endocrine Rev. 6: 371-99.

17 Wilson J.D. FW George, JE Griffin. 1981. The Hormonal control of Sexual Development. Science 211: 1278-84.

18 Imperato-McGinley J.J., Guerneao, T. Gautier, R. Peterson. 1974. Steroid 5 Réductase decreased in Man, and Inherited Form of Male Pseudohermaphrodism. Science 186: 1213-15.

19 Imperato-McGiney, J.RE Peterson, T. Gautier, E. Sturla. 1979. Androgen and the Evolution of Male Gender Identity Primary Male Pseudohermaphrodites with 5 Reductase Deficiency. New. Eng. Journal Med. 300: 1233-37.

20 McEwen B.S. 1976. Interactions Between Hormones and Nerve Tissue. Sci. Assoc. 235: 48-58.

21 Machusky N.S. and F. Nayftoli. 1981. Sexual Differentiation of CNS. Science 211:1294-1302.

22 Motta M.F. Fraschini and L. Martini. 1969. Short Feedback Mechanisms in the Control of Anterior Pituitary Function in Frontiers in Neuroendocrinology. ed. Ganing W.F. and L. Martini, Oxford Press, p. 211.

23 Motta M. 1968. The Brain and the Physiological Interplay of Long and Short Feedback Systems. Excerpta Medica Int. Cong. No. 184. Prog. In Endocrin. p. 533.

24 Gibson T. and R.J. Jarrett. 1972. Diurnal Variation of Insulin Sensitivity. Lancet 2: 947.

25 Goldstein JL, Motulsky AG. 1981. Genetics and Endocrinology. In: Williams RH ed. Textbook of Endocrinology, 6th Ed. Philadelphia, London, Toronto: W.B. Saunders Company 1125-1148.

26 Fincham Jrs. 1984. Genetics. Bristol, London, Boston: Wright PSG.

27 Polani PE, Adinolfi M. The H-Y Antigen and its Functions: A review and Hypothesis. J. Immunogent. 1983, 10: 95-102.

28 Wilson JD. Griffin, George et al. The Role of Gonadal Steroids in Sexual Differentiation. Rec. Prog. Horm. Res. 1981. 37: 1-39.

29 Dufau M.J. and K.J. Cath. 1978. Gonadotropin Receptors and Regulation of Steroidogenesis in the Testis and Ovary. Vit. Horm. 36:461-592.

30 Textbook of Endocrinology, Edited by Robert Williams, W.B. Saunders Company, Philadelphia 1974. Ch. 678.

31 Pediatric and Adolescent Gynecology, Pediatric Clinics of North America Vol. 19 No. 3, Edited by A. Altchek, W.B. Saunders Co. 1973.

32 Saba N.O. Hechter. Cholesterol $4C^{14}$ Metabolism in Adrenal Homogenate. Fed. Proc. 14: 775. 1955.

33 Cope C.L. Adrenal Steroids and Diseases. J.B. Lippincott. Philadelphia 1972. pg. 232.

34 Los Angeles County University of Southern California. / LAC/USC / Medical Center, Los Angeles,CA.

35 Salassa, R.M., Kearns, J.W. Kernohan et al.: Pituitary Tumors in patients with Cushing's Syndrome. J.Clin. Endocrinol. Metab. 1979. 19: 1523.

36 Glenn, F. and H. Mannix, Jr. Diagnosis and Prognosis of Cushing's Syndrome. Surg. Gynec. and Obststrics. 126: 765. 1986.

37 Liddle, G.W. Cushing's Syndrome in the Adrenal Cortex ed. Einstein, A.B. Littles Brown. Boston. 1967. p. 533.

38 Degenhardt HJ. Prader's Syndrome /Congenital Lipoid Adrenal Hyperplasia/ In: New MI Levin LS, eds. Adrenal diseases in Childhood. Vol. 13. Pediatric and Adolescent Endocrinology. Laron Z. ed. New York, S. Karger. 1984. 125--144.

39 Bongiovanni AM. Congenital Adrenal Hyperplasia due to 3ß-hydroxysteroid Dehydrogenase deficiency. In New MI Levin LS. eds, Adrenal diseases in Childhood/ vol. 13. of Pediatric and Adolescent Endocrinology. laron Z. Ed. New York, S. Karger, 1984. 72-82.

40 Mantero F. Scaroni C. Enzymatic Defects of Steroidogenesis; 17-hydroxylase deficiency. In: New MI,Levin LS. eds. Adrenal diseases in Childhood/ vol. 13. of Pediatric and Adolescent Endocrinology, Laron Z. ed. New York, S. Karger, 1984. 83-94.

41 Zachman M, Prader, A. 17,20-desmolase deficiency. In New MI Levin LS, ed. Adrenal diseases in Childhood. Vol. 13. of Pediatric and Adolescent Endocrinology, Laron Z. ed. New York, S. Karger, 1984. 95-109.

42 Virdis R. Saenger P. 17ß-hydroxysteroid dehydrogenase deficiency. In New MI Levin LS. Eds. Adrenal diseases in Childhood/ Vol. 13. of Pediatric and Adolescent Endocrinology, Laron Z. ed. New York, S. Karger, 1984. 110-124.

43 D'Armiento M, Peda G, Bisignani B. et al. No linkage between HLA and Congenital Adrenal Hyperplasia due to 17-alpha-hydroxylase deficiency. New Eng. J. Med. 1983. 308: 970.

44 New MI Levine LS. Congenital Adrenal Hyperplasia. Berlin, Heidelberg, New York, Tokyo: Springer Verlag 1984. 44-67.

45 Prader A. Hereditary Defects of Adrenal Cortical Steroid Biosynthesis. In Papadatos CJ, Bartsocas CS eds, Endocrine Genetics and Genetics of Growth. New York: Alan R. Liss Inc. 1985. 219-231.

46 New MI Genetics of Congenital Adrenal Hyperplasia, In Papadatos CJ. Bartsocas CS. eds. Endocrine Genetics and Genetics of Growth. New York: Alan R. Liss Inc. 1985. 233-242.

47 Wilkins L. Adrenal Disorder 11. Congenital Virilizing Adrenal Hyperplasia. ARch. Dis. Child. 1962. 37: 231-242.

48 David M. Forest MG. Prenatal Treatment of Congenital Adrenal Hyperplasia resulting from 21-hydroxylase deficiency. J. Ped. 1984. 105: 799-803.

49 Grumbach MM, Conte FA. Disorders of Sexual Differentiation. In: Wilson JD. Foster, DW eds. Williams Textbook of Endocrinology, 7th ed. Philadelphia, London, Toronto, W, B. Saunders Co., 1985. 312--401.

50 de Grouchy, J. Turleau C. Clinical Atlas of Human Chromosomes, 2nd ed. New York Chichester, Brisbane, Toronto, Singapore: John Wiley and Sons Inc, 1984.

51 Klinefelter HF jr. Reifenstein EC jr, Albright F Syndrome Characterized by gynecomastia, aspermatogenesis without a-leydigism and increased excretion of follicle stimulating hormone. J. Clin. Endocrinol. 1942. 2: 615-627.

52 Jacobs PA, Strong JA, A case of Human Intersexuality having a possible XXY sex determining mechanism Nature 1959. 83: 302-303.

53 Lubs, HA JR. Testicular Size in Klinefelter's Syndrome in Men over 50. Report of a Case with XXY/XY Mosaicism. New Eng. J. Med. 267: 325-1962.

54 Forssman,J., G. Hambert. Incidence of Klinefelter's Syndrome Among Mental Patients. Lancet 1: 1327, 1963.

55 Paulsen, C.A. The Testes in Textbook of Endocrinology ed. Williams, R.H. W.B. Saunders Co. Philadelphia 1968. p. 405.

56 Ferguson-Smith MA. Karyotype-Phenotype Correlations in Gonadal Dysgenesis and their Bearing on the Pathogenesis of Malformations. J. Med. Gent. 1965. 2: 142-155.

57 Josso N, de Grouchy J, Auvert J. et al. True Hermaphroditism with XX/XY Mosaicism, probably due to double fertilization of the ovum. J. Clin. Endocrinol. Metab. 1965. 25: 114-126.

58 Skordis NA, Stetka DG, Mac Gillivray MH, Greenfield SP. Familial 46,XX males coexisting with Familial 46XX True Hermaphrodites in same pedigree. J. Pediat. St. Louis 1987. 110: 244-248.

59 Fitzgerald PH, Donald RA,. McCormick P. Reduced Fertility in women with X Chromosome Abnormality. Clinical Gen. 1984. 25: 301-309.

60 Kohn G., Yarkoni S., Cohen MM. Two Conceptions in a 45X woman. Am.J. Med. Genet. 1980. 5: 339--34.

61 Dr. Van Vliet, Dept. of Paed. Hospital Universitaire des Enfants, Universitaire Libré de Bruxelles Brussels Belgium Hormonal changes during development in Turner's Syndrome. Acta Paed. Scand. Suppl. 343: 31. 1988.

62 Dr. EE Joss From The Dept. of Paed., University of Berlin switz. Anabloic Steroids in Girls with Turner's Syndrome. Acta Paed. Scand. 343: 38-42. 1988.

63 Loyd, H Meases. J. Jacobi, J Secretory and Mitotic Response of the male rat Pituitary Gland to Replacing doses of Estrogen. Internal J. Cancer. 11: 90-94. 1973.

64 Raymond V., Beaulieu, M. Labine F., Biossia JR. Potent Antidopaminergic activity of Estradiol at the pituitary level in Prolactin Release. Science 200: 1173-1175. 1978.

65 L. Gaspar, J. Julesz, J. Kocsis, E. Pásztor, F.A. Laszlo. Endocrine Unit, First Department of Medicine, Szeged, University Medical School Szeged, Dept. of Radiology, and National Inst. of Neurosurgery, Budapest, Hungary. "Mosaic Turner's Syndrome and Pituitary Microadenoma". Exp. Clin. Endocrinol. Vol. 86, No.1. 1985. pp. 87-92.

66 Laczi F., Julesz J., Janáky T., László F.A.: Growth hormone reserve capacity in Turner's syndrome. Horm. Metab. Res. 1979. 11:664-666.

67 Julesz J. Heredity. In: Functional Endocrine pathology /Kovacs K., Asa SL eds./ Blackwell. Boston-Oxford-London. 1990. 862-876.