AMBIGUOUS GENITALIA

ESSAY
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BY

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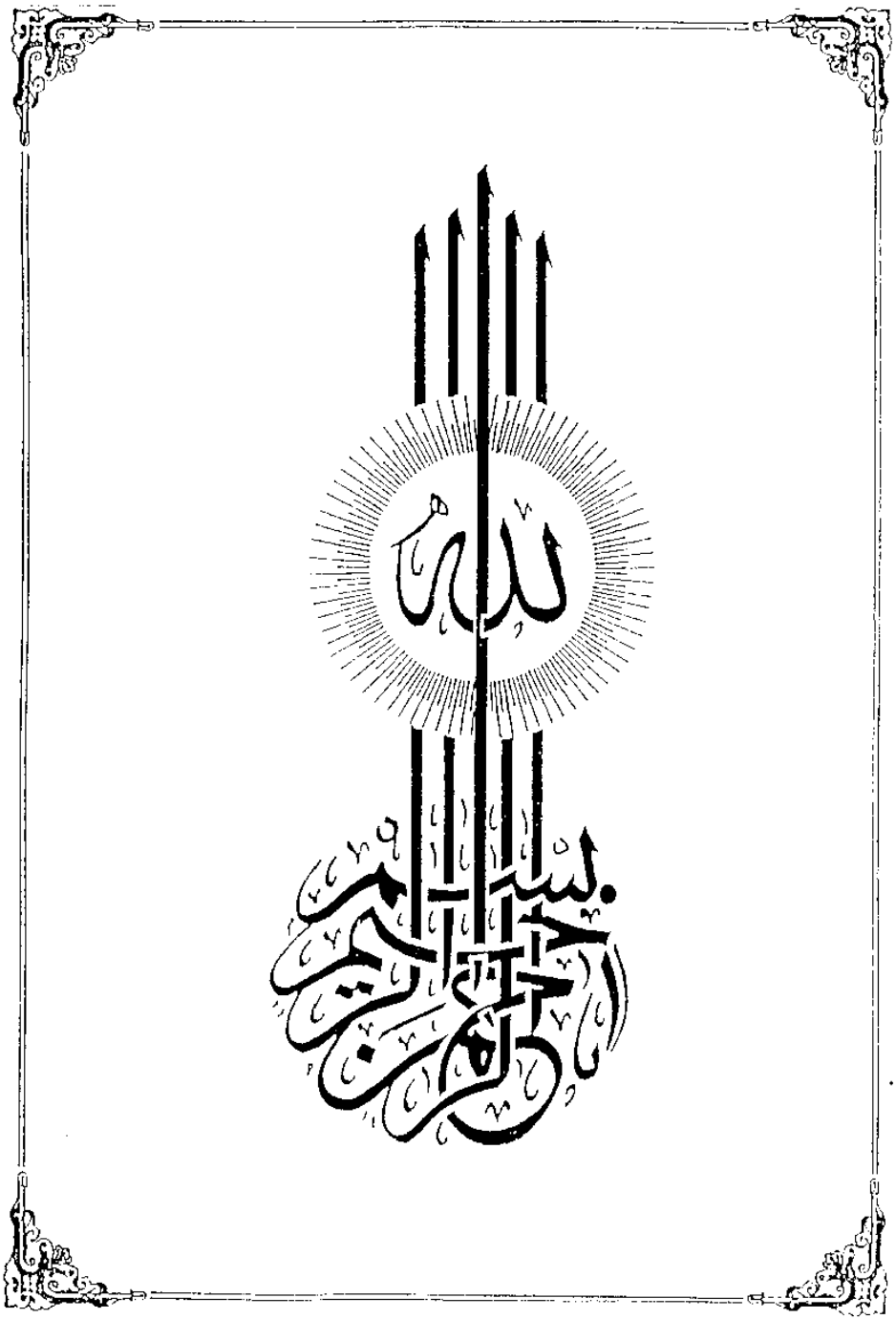

C O N T E N T S

AIM OF THE WORK

To throw light on the problem of intersex which is considered to be one of the most distressing problems for the patient and his family.

Our aim is to introduce a proper classification of the different types and causes of ambisexual development & to discuss the different phenotypic and chromosomal patterns of each type. Different diagnostic methods will be explained.

Management of those patients as regards gender identity and role, reassignment of sex, reconstructive surgery, and hormonal replacement therapy will be presented.

INTRODUCTION

The term ambiguous genitalia implies a discrepancy between the morphology of the gonads and of the external ganitalia. It is now well established that many conditions can result in ambiguity of the external genitalia.

An increasing number of such conditions can now be explained, owing to advance in the understanding of normal sexual differentiation.

The newborn infant who presents with genital ambiguity must be dealt with as an emergency.

Appropriate and rapid gender assignment will often determine the success of the outcome for child and family, regardless of the complexity of the problem. The decision is based on delineation of the existing anatomy and understanding of the pathologic and physiologic reasons for the ambiguity.

Classification of Anomalous Sexual Development.

I- **Disorders of gonadal differentiation:**

A) Seminiferous tubular dysgenesis (Klinefelter syndrome).

B) Syndrome of gonadal dysgenesis (Turner Syndrome).

C) True hermaphroditism.

II- **Female pseudohermaphroditism:**

A) Congenital virilizing adrenal hyperplasia.

B) Androgen and synthetic progestins transfered from maternal circulation.

C) Masculinizing maternal tumors.

D) Associated with malformations of intesine and urinary tract.

III- **Male pseudohermaphroditism:**

A) Testicular unresponsiveness to human chorionic gonadotrophins and leutinizing hormone

B) Inborn errors of testosterone biosynthesis:

1. Enzyme defects affecting synthesis of both corticosteroids and testosterone.

(a) Cholesterol desmolase complex deficiency

(b) 3B. hydroxysteroid dehydrogenase deficieny

(c) 17 hydroxylase deficiency.

2. Enzyme defects primarily affecting testosterone biosynthesis by the testes.

(a) 17,20-desmolase (lyase) deficiency.

(b) 17B-hydroxysteroid oxidoreductase deficiency.

C) Defects in androgen-dependent target tissues.

1- End organ isensitivity to androgenic hormones.

a) Complete syndrome of androgen insensitivity and its variants.

b) Incomplete synbdrome of andgrogen insensitivity and its variants.

2- Defects in testosterone metabolism by peripheral tissues.

a) 5α-reductase deficiency- male pseudo--hermaphroditism with normal virilization at puberty.

D) Dysgenetic male pseudohermaphroditism.

1- X chromatin-negative variants of the syndrome of gonadal dysgenesis.

2- Incomplete forms of Xy gonadal dysgensis.

3- Associated with degenerative renal disease.

4- Vanishing testes Syndrome.

F) Defects in synthesis, secretion, or response to mullerian duct inhibitory factor.

F) Maternal ingestion of estrogens and progestins.

IV- <u>Unclassified forms of abnormal sexual development.</u>

1- Hypospadias.

2- Cryptorchidism.

3- Absence or abnormal development of the vagina.

(Williams, 1981)

Embryology of the genital organs

Development of gonads:

Although the sex of the embryo is genetically determined at the time of fertilization, the gonads do not acquire male or female morphological characteristics until the seventh week of development. The gonads appear in a four week embryo as a pair of longitudinal ridges, on each side of the midline between the mesonephros and the dorsal mesentry. They are formed by proliferation of the coelomic epithelium and a condensation of the underlying mesenchyme. Germ cells do not appear in the genital ridges until the sixth week of development.

In mammalian and human embryos the primordial germ cells appear at an early stage of development, and are initially located in the wall of the yolk sac close to the allantois. From there they migrate by ameboid movement along the dorsal mesentry of the hind-gut toward the region of the genital ridges. In the sixth week of development the primordial germ cells invade the genital ridges.**(Fitz Gerald,1978)**

Indifferent Gonades.

Shortly before and during the arrival of the primordial germ cells the coelomic epithelium of

the genital ridge proliferates and epithelial cells penetrate the underlying mesenchyme.

Here they form a number of irrigularly shaped cords, the primitive sex cords, which surround the invading primordial germ cells, at this stage, it is impossible to differentiate between male and female gonad, so the gonad is known as the indifferent gonad. (Langman, 1976).

Development of the testis:

Troen and Oshima (1981), described more advanced stages in testicular development during the seventh and eighth weeks of development where the primitive sex cords continue to proliferate and penetrate deep into the medulla of the gonad. They form a series of well-defined cell cords, anastomosing with one another and known as the testis cords. Towards the hilus of the gland the cords break up into a network of tiny strands which later give rise to the tubules of rete testis.

During further development, the testis cords lose their contact with the surface epithelium, and by the end of the seventh week they are separated from it by a dense layer of fibrous connective tissue,

the tunica albugninea. The epithelium on the surface of the gonad flattens and becomes the mesothelium, the tunica albuginea forms the underlying capsule of the testis.

In the fourth month the testis cords become horseshoe-shaped, and their extremities are continuous with the cell cords of the rete testis. During fetal life the testis cords are composed of primitive germ cells and epithelial cells. The cords remain solid until puberty, where they acquire a lumen, thus forming the seminiferous tubules. Once the seminiferous tubules are canalized, they rapidly join the rete testis tubules, which in turn enter the ductuli efferentes. The interstitial cells of Leydig develop from the mesenchyme located between the seminiferous tubules and are particularly abundant in the fourth to sixth months of development.

(Langman, 1976)

During the final two months of gestation the testes descend along the inguinal canal. Descent to the serotum is usually completed before term, however it may lie anywhere along the inguinal canal at birth, gaining the scrotum during the first postnatal year. **(Shroch, 1971)**

Development of the ovary:

In the male the primitive sex cords are well-defined, but in the female they are broken up by invading mesenchyme into irrigular cell clusters. These clusters containing groups of primitive cells, are mainly located in the medullary part of the ovary. Later they disappear and are replaced by vascular stroma which forms the ovarian medulla. The typical characteristics of the ovary become recognizable much later than those of the testis.

The surface epithelium of the female gonad, unlike that of the male, remains thick and continues to proliferate. In the seventh week it gives rise to a second generation of cords, the cortical cords, which penetrate the underlying mesenchyme but remain close to the surface of the gland. In the fourth month these cords are split into isolated cell clusters, each surrounding one or more primitive germ cells. The germ cells subsequently develop into the oogonia, while the surrounding epithelial cells form the follicular cells.

It is generally accepted that the primary medullary cords are a distinctly male feature, where as the secondary cortical cords are characteristic of the female gonads. **(Speroff, 1981)**

Development of genital ducts

Indifferent Stage:

In the sixth week of development, both male and female embryos have two pair of genital ducts, the mesonephric or Wolffian ducts, and the paramesonephric or Mullerian ducts which run parallel to the Wolffian ducts.

The Mullerian duct arises as a longitudinal invagination of the coelomic epithelium on the antro-lateral surface of the urogenital ridge. On the inside of the sinus, the Mullerian ducts cause a small swelling, the Mullerian tubercle. The Wolffian ducts open into the urogenital sinus on either side of the Mullerian tubercle.

Depending upon the sex of the embryo, the fate of the Mullerian duct differs. If the embryo is male, the Wolffian duct forms the main genital duct and the Mullerian duct disappears almost entirely, if the embryo is female, the Mullerian duct comes to full development, thereby forming the oviducts and the uterus, while the Wolffian duct disappears except for a few remnants.

(Fitz Gerald, 1978)

Development of male and female genital ducts:

At the seventh week of intrauterine life, the fetus is equipped with primordia of both male and female genital ducts, derived from the mesonephros. The Mullerian ducts give rise to the uterus and fallopian tubes, whereas the Wolffian ducts have the potentiality of differentiating further into the epididymis, vas deferens, seminal vesicles, and the ejaculatory ducts of the male. During the third fetal month either the Mullerian or Wolffian ducts complete their development while involution occurs simultaneously in the opposite structures. **(Huff & Pauerstein, 1979)**

It has been proved by experiments of Jost and other embryologists (1972) that secretions from fetal testis play a decisive role determining the direction of the genital duct development. They reported that in the presence of functional testis, the Mullerian structures involute while the Wolffian ducts complete their development, whereas in the absence of testes the Wolffian ducts are resorbed and Mullerian structures mature. These two events are mediated by two different fetal testicular secretions.