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Human Sexual Differentiation and Aberration Spectrum

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Abstract

Human Sexual Differentiation process starts with the fusion of an ovum, carrying a maternal X chromosome with a spermatozoon, carrying a paternal either X or Y chromosome. It evolves up to a certain stage during pregnancy and gets completed by the sex hormones in puberty, when female and male human beings become mature for reproduction.

In the absence of a Y chromosome, the bipotential primordial genital structures of the embryo, develop into female internal and external genital organs and the dimorphic brain remains female. In presence of an intact and functional Y chromosome, the embryonic primordia develop into male internal and external genital organs during the 1st trimester and the dimorphic brain gets masculinised during the 2nd half of pregnancy.

The differentiation mechanism is extremely complicated and sensitive to any alteration or mutation of parental genital cells, chromosomes and genes, as well as of embryonal hormones, enzymes, receptors and neurotransmitters, not neglecting the influence of the environmental factors and the detrimental effect of endocrine disruptors. Thus, the final target of development of a perfect female or male, may not be totally successful in every descendant.

Due to these eventual influences on the embryo, there are newborns with errors in the formation of the internal or external genital organs and hormones. Exactly in the same way, there may be newborns with normal internal and external genital organs , but with aberrations in the cellular structure and function of specific brain areas, which determine Gender Identity and Sexual Orientation.

Regarding the anatomical and hormonal disorders, we are able , with special surgical interventions and hormonal manipulations, to offer these people, to a great extend, the sexual characteristics, organs and functions, which best correspond to the Gender Identity and Sexual Orientation, they identify with. In contrast, regarding inborn Gender Identity (the conviction that a person belongs to the male or female gender) and Sexual Orientation (heterosexuality, homosexuality and bisexuality) which have been programmed in the dimorphic brain during the endometrial life, there is no proof that any postnatal medical manipulation or influence of the social environment, can have any crucial effect.

Key words: sexual differentiation

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Dear Readers,

It is a pleasure and an honour to me, to be amongst you today, and try to inform you on such an important issue, as **The Differentiation of Sexes** in humans.

It is about a process, which evolves during the embryonal and fetal (intrauterine) life, and gets integrated during puberty, when maturation of female and male human beings is reached.

Furthermore, we are going to touch some extremely interesting aspects, such as **Gender identity** and its varieties, **Sexual orientation** and **Gender Dysphoria**, **Sexual reassignment** or **Transsexualism** (recently **Transgenderism**), and **homosexual,** (gay or lesbian), or **bisexual behavior**.

I would like to start from the fact, that at the beginning of the **"Evolution**" or "**Creation**", according to any ones respected beliefs, Reproduction was "**Asexual**", and did not require specific cells or organs, which appeared later, and were best organized in birds and mammals

The discovery of sex chromosomes occurred in 1923 in insects, and correlation of human X and Y chromosomes to the sex differentiation, was understood in 1959,

The development of sexual differences starts at the time of fertilization, by the fusion of an ovum or egg, bearing an X maternal chromosome, with the head of a spermatozoon, bearing an X or a Y, paternal chromosome

Thus, the cells of a genetically **Female fetus,** contain two X chromosomes, one Maternal and one Paternal, and the cells of a genetically **Male fetus,** contain a Maternal X and a Paternal Y, chromosomes. This situation is called **"Chromosomal Sex"** and, theoretically, could be expected to regulate (govern) the whole Sexual Development.

The Female and Male Reproductive systems are derived from "**Bipotential**" fetal and embryonic tissues, and consist of **three** main parts: the **Gonads,** the **Internal genitalia** and the **External genitalia**. Nevertheless, finally, the function and role of all these parts are mastered by the **Brain**.

GONADS

Under the influence of specific **genes**, selected embryonic cells migrate to the place where they will form the primitive, **undifferentiated Gonads**, and the **Mullerian** and **Wolffian ducts**, which are the precursors of the Female and Male Genital Organs.

In the 4 week old embryo, the presence of a **Y chromosome**, with a functional" **SRY gene** " (**Sex Reversal Y**) on its short arm, induces the anatomic and hormonal events, which will finally lead to the development of the **Testes** and the **Male genital organs**. The expression of the SRY gene on **Sertoli** cells of the testes, on the 7th week, results in a cascade of events leading to the formation of the **seminiferous tubules**, containing the **primordial germ cells** (PMG).The **Sertoli cells** secrete **Antimullerian hormone (AMH**) ,which **a)** causes regression of the Mullerian Ducts, **b)** Keeps primordial germ cells arrested in meiotic phase and inactive, until puberty and **c)** stimulates the development of the interstitial cells (lying between the seminiferous tubules) to testosterone secreting, **Leydig** cells .

On the other hand, the "absence" of the Y chromosome in the embryo, in cooperation with other genes and a down-regulated **DAX-1 gene** on the **X chromosome**, allows the primitive **gonad to evolve into Ovary**. Ovarian development becomes apparent later than testicular one, on 10th to 11th week, when primordial germ cells, **oogonia**, move from the cortex of the female gonad to the medulla, surrounded by **granulosa** and **theca cells**, to form the **primordial follicles**, on t 16th week, witch rest until puberty.

GONADAL DESCENT

But the Gonads do not stay permanently, where the first appeared**. During the intrauterine life**, both **ovaries** and **testes** descend from their initial formation place, in the thorax, to the **bottom of pelvis**.

The ovaries remain in the female pelvis, but the testes continue migrating, until they get out of the abdomen, through the inguinal canal, and reach the scrotum. This migration begins around the end of 7th embryonal month and is regulated by testosterone and **dihydrotestosterone,** on a chord like structure, called **gubernaculum,** extending between the testes

and the scrotum. In some cases, it may be completed during the first four to six weeks after birth. The reason for this "out of the body" position of the testes, is thought to be that the spermatogenesis, (the production of spermatozoa) requires lower than the body temperatures.

At this point it should be made clear that, **if there is any delay or malfunction**, at any stage of development, due to gene error or mutation, or lack of hormone or its receptors, or processing enzymes, either in the gonads, or genital organs, or other target structures, **the result will be both anatomical and functional aberration**, from what is normally expected.

INTERNAL GENITAL ORGANS

At the end of the 7th week, when the gonads are, already, sex determined, the precursors of the other parts of the reproductive system are still **bipotential** and, transiently, coexist.

In Males, the embryonal testes secrete **Antimullerian** hormone, which causes regression of the Mullerian ducts, and **testosterone** witch (with **DHT**), are responsible for the differentiation of the Wolffian Ducts, to male Internal and External Genital organs, through the action of specific enzymes and receptors. **The Internal genital organs** are **epididymis**, **vas deferens**, **seminal vesicles** and the **prostate**. Especially, the timely and unopposed action of testosterone, is crucial to the further evolution, and integration, of the male genital organs, add later **the Brain**.

In Females, in the **absence of testosterone and AMH**, the Wolffian Ducts degenerate, and the Mullerian Ducts evolve to the formation of **Fallopian tubes**, **Uterus** and **upper 2/3 of the Vagina**. As this development occurs, simply in the absence of ovaries, it is evident that the **internal Female reproductive tract,** is independent of gonadal steroids, (mainly estrogens),

EXTERNAL GENITAL ORGANS

The development of **External Genitalia** goes also through a **Bipotential state**, till the 8th week. It starts from a pair of **Labioscrotal folds**, a pair of **Urogenital folds** and a **Genital Tubercle**.

In Males, all the transformations are due to the most potent androgen Dihydrotestosterone, (**DHT**), derived locally, from testosterone, by the action of the enzyme **5a-Reductase**. In the 10th week, an elongation of the genital tubercle, forms the **shaft and the glans of penis** and, fusion of the urogenital folds forms, the **penile urethra**. Further fuse of the Labioscrotal folds, forms the **scrotum**, awaiting for the" out of the body" installation of the testes, later.

In the Female, in the absence of androgen action, the genital tubercle bends below and forms the **clitoris**, the genital folds do not fuse and become the **Labia minora**, the Labioscrotal folds remain separated and become the **Labia majora**, and the posterior wall of the Sinuvaginal bulbs (or Urogenital folds) , forms **the lower 1/3 of the vagina** and **the urethral meatus.**

PUBERTY

From a Biological point of view, **Puberty** is **the stage of physical and emotional maturation,** which allows the individuals to become capable of reproduction. Several **neurosecretory** and **hormonal factors** modulate the somatic growth and the final development and function of gonads, and internal and external genital organs. **The sex steroids** will ensure the appearance and the maintenance of **secondary sexual characteristics** and the capacity for reproduction. Finally, in collaboration with **genetic factors**, they will influence some **brain functions**, which will express (induce) the profound psychological changes of adolescence.

The Reproductive System remains almost unchanged during childhood, simply following the somatic growth. After the age of 7-8 years, a very small and slow increase of **Gonadotrophin**s, **FSH** and **LH**, is observed. The primary **triggering mechanism**, which activates at the age of 12.5 to 14 in girls and 12 to 16 in boys, the hypothalamo-pituitary-gonadal axis, (at puberty) remains **still hypothetical**. Both **Genetic** and **Environmental factors,** are involved. It has been advocated that, when boys and girls, achieve a certain amount of body fat or body composition, an adipose tissue hormone, called **Leptin** increases. This is sensed by some specific central nervous system neurons, expressing the **Kiss-1 gene** and producing **kisspeptin** , which stimulates the secretion of the Hypothalamic

Gonadotrophin-Releasing-Hormone (GnRH.) **GnRH** drives the Pituitary to increase the **Follicle stimulating hormone** (FSH)and the **Luteinising hormone** (LH) secretion. The increase in frequency and amplitude of FSH and LH surges, **wakes up the testes** to start progressively producing testosterone and later, spermatozoa, **and the ovaries** to produce estrogens and later, ovulate.

In the Female, the size of the **ovary** increases, from 0.5cc to around 4 cc, and **estradiol** induces the development of **secondary sexual characteristics**, that is growth of **breasts** and the **female type o fat distribution** (hips, thighs, buttocks, upper arms and all over the body), which is going to serve as energy deposits , in case of future pregnancy .At the same time, the **adrenal androgens** start the **axillary hair** and shape the inverted triangle of female **pubic hair**.

Vagina gets thicker walls and mucus secretions and **Uterus** with the **Fallopian tubes**, reach their adult size. **Endometrium**, the internal lining of uterus, undergoes gradual proliferation, until it reaches substantial growth, to be able to cycle. When **FSH** and **LH**, through estrogen feedback, start their **cyclical secretion** and cause **ovulation** and production of progesterone, the endometrium becomes secretory and is able, either to host the fertilized ovum and become placenta or, losing its ovarian hormonal support, be discarded as **menstruation** and allow a new cycle to begin. The FSH, peaks at about the 13th day of the cycle, and the LH one day later and, before and after, they fluctuate at lower levels.

In the Male, the **testicular volume** increases from to 2-3 cc to 15-20 cc, mainly due to the development of **seminiferous tubules**, under the stimulation o FSH. Concomitantly, the pulsatile LH secretion induces further differentiation of interstitial cells, to **Leydig cells**, secreting **testosterone**, which dominates, thereafter, the whole male body. It exerts negative feedback control, on the LH release and, as puberty progresses, it initiates and maintains, with FSH, the **spermatogenesis**. Testosterone is responsible for the development of male **secondary sex characteristics**. The **penile size** increases to reach 7 to 15cm, in relaxation, and the **pubic hair**, obtains the male pattern, spreading up to the umbilicus, the internal surface of the thighs, the perianal area and, possibly, the chest and back. **Axillary hair** appears, with body odour. The **voice deepens**, due to elongation of vocal cords in the increasing larynx. The **muscular system** is developed, and the **height** increased so as the male habitus is completed.

SEXUAL DIFFERENTIATION OF THE HUMAN BRAIN

IN RELATION TO GENDER IDENTITY AND SEXUAL ORIENTATION- AND ABERRATIONS

There has been evidence that humans present a vast **array of brain differences**, related, not only to gender identity, but also to the sexual orientation.

During the intrauterine life, the **fetal brain** can develop **in the male direction**, through a direct action of the embryonic testicular testosterone and other genetic and environmental factors, on the developing hypothalamic neurons and circuitries and other brain structures. Nevertheless, the brain can, as well develop **in the female direction**, if testosterone action is absent or delayed. In this way **"human gender identity**", i.e. the conviction of belonging to the male or female gender, and "**sexual orientation**", are programmed into the human brain structures **before birth** and are believed to be **irreversible.** In more details, since **sexual differentiation of the genital organs**, (due to SRY gene of Y chromosome and other factors), takes place in the **first two to three months of pregnancy**, and **gender differentiation of the brain** is determined **during the second half**, these two processes can evolve **independently**. This means that it is just possible to exist a **"non coincidence"** of the **"sex of the genitalia"** and the "**brain gender identity and sexual orientation",** fact which can result **in transgenderism or transsexuality**. It also means that **Aberrations of Gender Identity and Sexual Orientation**, **are not a Choice** of an individual but **rather errors** in his-hers **Brain Differentiation**. It addition that, in the event of "**ambiguous sex**" at birth, the degree of masculinization of the genitalia may not reflect the degree of masculinization of the brain.

As a final note, which should be taken into consideration, is that there has been **no proof** that hormones or social environment may have an effect, after birth, on gender identity or sexual orientation.

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