SEXUAL IDENTITY: TRANSEXUAL AND PATIENTS WITH DEVELOPMENTAL GONADAL DISORDERS “THERE ARE NO SEXES, ONLY ROLES”: AN ANTHROPOLOGICAL EXPERIMENT BADLY NEEDED OF BIOTECHNOLOGY
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We are witnesses to an anthropological experiment, that relies on Biotechnology with the pretension of leading towards a type of human being for whom sexes does not exist, “only roles”, and according to whom the sexual identity, be male or female is of free election. Does this mean that it is not important or even that it is not necessary, the psychological connection between “I and my body”?

We live in an increasing preoccupation for health, physical well-being and physical appearance. Does this mean that it is possible to understand ourselves, understand what happens in our interior, apart from our own body?

When something or someone affects us and awakens an emotion, we notice it precisely in our body. Our body communicates us with others and the inverse occurs with the body of others. Can we make ourselves understood and understand others if we create a situation of discord between “I”, my intimacy and my body?

Current knowledge of human biology especially the data of neurosciences, about the sexual identity, allows us to analyze with serenity, without prejudices and prosecutions of whatever type, or trans-phobias, than can suppose one moving away from one's own body.

Corporal sex is determined by the biological inheritance received from one's parents. In the first place, this is because of the different genetic information of the XX female chromosomal pair or of the XY male. Secondly because the patterns of femininity and of masculinity are orderly put into operation by specific components of the Y chromosome or of the XX pair. The same genetic inheritance-23 pairs of chromosomes are present in all the cells of the organism.

Genes of the cells that constitute the gonads-ovaries or testicles-, that in turn generate the cells for the transmission of life, either feminine -ova- or masculine -sperm- as well as the cells that form the genitals and the brain cells are activated or are silenced to the rhythm of the sexual hormones, whose synthesis controls the absence of a chromosome Y in the female or its presence in the male.

The reproductive organs and the brain have a sex. Only a female body forms and matures ova and only a male body produces sperm. The DNA state of the ova is different from the state of the genetic material of the sperm. That DNA state specific of sex is called parental imprinting.

It is well known that for an individual to live and develop an inherited genetic endowment is required, consisting of 23 pairs of chromosomes, has maternal imprinting in one of each of the pairs and the other chromosome has the paternal imprinting. There exists, in primates, a biological barrier which for now is impassable, that shatters the possibility that a child be born to a father without a mother or from a mother without a father. At least nowadays, and it does not seem to be any other way, each human being has to be the son/daughter of one and the other. For now and possibly forever, the idea of asexual reproduction, naturally or artificially, or by the manipulation of two ova or two sperm is none other than science fiction. Biotechnology has not accomplished surpassing the limits
The artificial production of ova and sperm from immature mother cells of a female or of a male has not yielded results, at least until the moment. Artificial reproduction calls for human donors in whose body the gametes have been formed, ova or sperm, or their precursors.

It is possible that the biotechnology overlooks the need that it be formed in the body of a female or a male, respectively. But, not because of that would it cease to be humanely very significant the fact that the identity itself of each person would necessarily be provided by “biological” father and mother. You can technically store gametes and fertilize them, but the genetic inheritance has its story, it comes from a family tree, with its predispositions, its propensity to certain diseases, apart from the ethnicity and the features of the countenances, etc. Hence that each person has the right to know from where they precede and with it what their biological identity is.

Sexual identity forms part of the biological identity of each person. The “I” is somatized in the body, which is sexed-based. The cerebral sex, psychological, coincides with the corporal and gives rise to an ample margin of styles of the males and females. The brain has a sex.

This does not suppose ignoring that there are transsexual people, that feel they are of the opposite sex to that of their body, nor to ignore that there are people who have a gonadal developmental disorder -”ova-testicular”- that presents ambiguity in the gonadal structures and in the genitals.

Nowadays we know that the cause of both conditions is genetic. The alteration of one or more genes entails an impairment in one of the enzymes associated to the metabolism of the sexual hormones thus and with it a deficit or an excess of the action that these exert over the regulation of other genes.

During the prenatal stage the genes of the sexual chromosomes establish the structures of the testicles or of the fetal ovaries that produce the hormones. The brain also receives and metabolizes the hormones, in adequate moments and different of the consolidation of the gonads. It maintains a delicate hormonal equilibrium that shapes the broad outline of the feminine or masculine brain pattern.

Unlike any other organ, the brain is plastic its entire life. It is structured and functions to the beat of hormones in some early stages of life, and above all of life’s lessons, experiences, addictions and decisions. The action of hormones is especially intense in infancy -first puberty- and in the puberty where adolescence commences.

It can be affirmed that the direct action of the sexual hormones on the brain is a crucial factor in the development of gender identity, masculine or feminine. Nevertheless, it is not enough. In fact, there are differences in the sensibility of the androgens, there are different hormonal levels and of the receptors, that capture them to exert their specific action on the cells so much so on the reproductive organs as on the brain.
Thus, transsexual people exist where their body does not say the same as their “I”. There exists people, who before were called “inter-sexed” or “hermaphrodites” in which their body gives them an ambiguous message, because they suffer from ova-testicular development disorder.

Current knowledge points, as in the case of trans-sexuality, to a dysfunction of the cerebral perception of one’s own body, are not a simple question of preference dependent on the social environment or of schooling. And, because of it, biomedical investigation challenges the notion that psyche/corporal harmony is reached with the surgical procedures and the hormonal treatments that change the sexual genital and the secondary sexual characteristics and in turn affects the brain.

People with genetic disorder of gonadal development have body structures with sexual ambiguity, but without cerebral effects. Children that are born genetically and hormonally as males identify themselves as such, in spite of having been, in many cases, raised and educated as females, and even after having undergone at birth a feminizing and des-masculinization surgery.

Also, girls subjected to high levels of androgens -that come from the supra-renal glands- in the prenatal stage have masculinized genitals and, only in extreme cases, present transsexualism. Today we can know what has caused gonadal ambiguity and can educate the individual as how he/she is in reality. The times if when in doubt then “be it a girl” have fortunately passed.

It is a general principle that the human body does not lie, and always advises of what occurs. On the contrary, the brain can make mistakes in its perceptions. But, even so, everything that happens in the physique the body somatizes.

Information on the advancements of neuroendocrinology and of neuroimaging, in this field, should be made known, and should be taken into account in the education of new generations. The slogans in use “sexes do not exist, only roles”, imposed on since infancy, does not recognize what science proves: human nature demands coherence on the genetic and gonadal levels, because the “I” is somatized in a body that is sexed.

Since more than a decade ago, that slogan has been converted in the icon of modernism and some defend that this perspective should be accepted and transmitted from infancy. The underlying idea is to liberate oneself from the demands of one's own body, be autonomous and to self-build oneself. Sex -is said- is nothing more than a physiological function- that offers being a male or a female as its only possibilities-, while gender refers to the preferences and these are social realities subject to change as many times as one wants.

Nevertheless, the equal rights of females regarding males are a social, cultural and judicial question, the overcoming of gender demands the intervention of biotechnology. It deals with a revolution of humanity contrary to the processes of the biological evolution. Hence there is a strong gap in the approach to this experiment on gender identity. Human biology, that is not mere zoology, shows the specific of a cultural living being. However, biology is not culture and does not change easily, without paying a high price. It is the person, each of
the men and women, is a cultural human being.

Protocol of this experiment requires passing the science tribune. What is implied in playing off against in a person the biological sex and the psychological and social? What is innate in it and what is cultural? What does biotechnology offer, in fact, to the sex change? What guarantees of success are there?

And if it resulted that the experiment was not valid: How could we palliate the consequences of the possible victims that have not been given option to choose to participate or not in the experiment?
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Abstract

An anthropological experiment with the application of biotechnology is being conducted, although without any guarantees of success. It might be summarized within the cultural idea of overcoming the existence of two sexes. However, it is a fact that body sex is determined by a heritage of sex chromosomes XX or XY. Gonads and brain, as well as secondary sexual structures, “have” sex. Biotechnology experiments with rodents to obtain gametes in vitro from immature cells of male or female, or change the type of gamete generating a male body or vice versa, have yielded no results that could be extrapolated to humans. Today, transfer of life independently of body's biological identity is mere science fiction. The harmonious development, which provides and maintains personal identity, can match brain sex and psychological, with the body. Transsexual people feel the opposite sex of their body. The cause is genetic, generated in the prenatal stage of life when the brain is exposed to excessive steroids. Recent research suggests a dysfunction in brain's own body perception and not a simple matter of choice depending on social or learning environment. Thus, it is argued that harmony psyche/body is achieved with surgery and hormone treatments that change the genital sex and secondary sexual characteristics. There are also people with inter-sex condition, genetically based, with a disorder of gonadal development -"ova-testicular"- that have ambiguity in the gonadal structures and genitals. This is a malformation that involves no brain effects of transsexualism. The researchers recommend no hurry to assign a sex at birth, arbitrarily.

Key words: asexual reproduction, genetic and gonadal sex, transsexuals, ovotesticular developmental disorders

1. Beyond the XX and XY pair of chromosomes of the sexual identity and the transmission of life

The evolutionary mechanisms made possible more than 500 million years ago with the appearance of mammals, a precise system of reproduction, based on that each individual, male or female, is the child of one male and one female of the same species. A system that tunes up by natural selection and reaches a great specificity in the primates present on Earth more than some 20 million years ago. The system of sexual reproduction gave biological way to the constitution of the human family nucleus, base not only of personal development of each one, but also of the construction of the progressive technique and of culture.

For each person the biological level is always the first and the basic, and that level contains the two determinations of their biological identity: of whom -father and mother- have
inherited their genes and what sex the inherited genetic endowment has indicated for him. This first level is founded with the specific level and humanly genuine, that makes biological life, necessary and inseparably, biographical life in relation to others. The relationships, experiences, life experiences, decisions, knowledge, aptitudes, memories, preferences, addictions, etc., leave a biological mark in the brain and modulate the personality and psyche of each one, that makes it one's own and personal.

Nowadays, with the progress of the neurosciences, that show how our brain functions and how it modifies its structure with time and with the life of each one, we can go further on than the sterile debate “nature versus culture” knowing that it is a given in some form -as a determination or as a predisposition- and that it possesses the enormous amplitude of the eligible, acquirable or optional. The knowledge of how it affects each person the technological interventions and the knowledge of the neurosciences, has to be present for a rational analysis of viability and the consequences for the present and for future generations, of this anthropological experiment. An experiment that searches for a new form of human being that becomes independent and opposes its psychological dimension of its native corporal dimension can not be accepted -or rechargeable- only by opinions. On the contrary, it demands founded reasons and prevision of the consequences.

1.1 Sex and genetic inheritance

When life is transmitted be it engendered or by Portland their reproductive cells to artificially and technically produce a new life with the resources in the laboratory, the parents transmit the genetic inheritance.

Evidently, they both contribute the back-up material, the DNA that contains the baseline material for the child to form and develop the offspring. The DNA is a double strand of a very long polymer, formed by four ashlars that are packed forming the chromosomes. The two copies of those chromosomes, one coming from the father and the other from the mother, constitute the one's own patrimony or genetic background. It is the inherited biological identity that does not change throughout one's life and will be present in each cell of the body. It says in the first place who he is and who his parents are1.

The copies that each one contributes as one's own material are two non identical halves and that together constitute a complete version of the patrimony. Of the total of 23 chromosomes, one pair determines its sex: XX female, XY male. The maternal half can only provide one X chromosome, either the one that comes from its mother Xm or of its father Xp. The paternal half can only carry the maternal Xm and the Y that obviously comes from its father. The sex of the child definitely depends on the spermatozoa that fertilizes the ovum carries a chromosome X or a Y.

The chromosome Y contains the necessary genetic information to initiate the corporal pattern of a male child -the masculine pattern- at the very start of life, while the double genetic dose of the two X chromosomes, of the daughter, controls the pattern of

femininity\textsuperscript{2}. In that case, the biological identity of each one, that includes being XX or XY, is to say male or female, is not consigned by nature only to the presence or absence of one type of chromosome of the pair 23. In fact, for example, women exist with Turner syndrome with having only one X chromosome (X0), and males with two XX chromosomes and one Y (XXY) with Klinefelter syndrome. It is also known that some twins with Turner were genetically identical in everything except in cerebral processes dependent on genes with the X chromosome in that logically only one was endowed with the maternal Xm and the other with the paternal Xp that are different among themselves\textsuperscript{3}.

Therefore, sex depends in the first place on a pair of sexual chromosomes -XX or XY- and precisely because the dose of genes is not the same of the two X chromosomes as in a pair of XY, each feminine embryo has an additional task: inactivate one of the two cells of its organism with the exception of those that will produce ova in the ovaries. Logically when the genetic prevision is divided in two halves, both chromosomes should be active in order to ensure that if the ovum is fertilized, the resulting zygote always contains an active X. What is more, the female embryo and the masculine in its first days of life can be differentiated in their rate of growth, in the proteins that they synthesize and in their metabolism\textsuperscript{4}.

But not only the sexual pair has to do but also the determinism of sex is more intense. The germinal cells-ova or sperm- of each woman and of each male have in their DNA all and each of the 22 pairs of remaining chromosomes some specific chemical marks and a different spatial configuration. The child distinguishes the chromosome of each pair coming from the father and from the mother. And, especially, in the first phases of development, what is inherited from the father and what is inherited from the mother intervenes in a different way in the formation of its body\textsuperscript{5}. This phenomenon is known as parental imprinting is very strong in mammals and even more so in primates and in men. It is this parental imprinting that necessarily makes each individual be the son/daughter of a female and a male.

Each male and each female during its development needs to gradually eliminate its inherited chromosomal imprinting. In the first place, during the process of gamete fertilization, that gave it its origin, will eliminate markings of the paternal and of the maternal chromosomes at a different rate and in different sites of the DNA. This loss of the great part of the own markings of the ova and the spermatozoa make possible for the zygote, in the first stage of its new life, unveiling a genetic patrimony, whose state is obviously different from the sum of the contribution provided by its progenitors and necessarily XX or XY.

\textsuperscript{2}Arnold, A.P., Burgoyne, P.S. «Are XX and XY brain cells intrinsically different?» TRENDS in Endocrinology and Metabolism 15, 2004, 6-11.
Hereto, the corporal sex is determined in the inheritance received, in the first place, by the different genetic information of a pair of XX or XY chromosomes. In turn, different gametes are generated according to sex having specific markings in the DNA in each one of the components of the 22 remaining pairs.

In the first days of life, the embryo progressively erases the parental imprinting that it has inherited and this how the instruction frame contained in the genes and new instructions that remain occult, in a manner that the cells will see their development guided until they are integrated in tissues and in organs with its own functions and morphology. This information, that step by step arises, differs between the male and the female of each species, including in the construction of organs not related with the transmission of life. The same genes act in a different manner according to the sex. For an amplification of genetic material contained in the nucleus of an individual's cell, more or less young, should reach in all of its chromosomes the own parental imprinting of a zygote, that step by step arises, differs between the male and the female of each species, including in the construction of organs not related with the transmission of life. The same genes act in a different manner according to the sex. For an amplification of genetic material contained in the nucleus of an individual's cell, more or less young, should reach in all of its chromosomes the own parental imprinting of a zygote, newly generated in a precise, harmonious and complex fertilization process, to give way to a clone.

Mammals have, therefore an impassable barrier that shatters the possibility that in a natural manner a child be born to a father without a mother, of to a mother without a father.

### 1.2 Genetic Asymmetry of the XX-XY pair controls the differences between the organs and sexual cells

The presence or absence of the Y chromosome determines the gonadal sex of the embryo and assure with it the stable generation of the gametes. In region 1 of the short arm of the Y chromosome is localized in the gene called Sry that has the data for a protein to be synthesized that is called the factor determinate of the testicle.

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9 Sekido, R., Lovell-Badge, R. «Sex determination involves synergistic action of SRY and SF1 on a specific Sox9 enhancer». 

This factor makes that in the seventh week of gestation the masculinization process of the human embryo take place, activating in cascade the genes -Sox9 and Fgf9 and silencing Wnt4- that cause the formation of fetal testicles and, with it, masculine hormones are synthesized, principally testosterone and masculine gametes are formed. At the same time it impedes that the process deviates to the fetal ova formation. The receptor of the masculine hormones is codified by the gene Tfm located on the chromosome X. Therefore, for the normal masculine differentiation chromosome X and chromosome Y is needed the same.

The absence of chromosome Y is necessary, but not sufficient, for the process of feminization of the embryo- The XX pair permits the expression of an inhibitor of the process in the masculine line -Fox12-, and of other activating genes de la via of feminine development and inhibitors of testicle formation. To the inverse of the XY pair, the cascade of the regulated expression of the genes is initiated with the activation of Wnt4 and Fgf9 and Sox9 are silenced. The ova will direct the production of the corresponding hormones.

Of all the cells of the organism only the sperms and the ova are marked during their formation in the fetal testicles or the fetal ovaries respectively with a labeling totally masculine or totally feminine in the totality of the chromosome pairs. Because they are the cells that transmit life, they do not exist according to that the individual who produces them lives, but to transmit “their life. In both cases an adequate nest is needed: respectively a masculine or feminine body that has already developed testicles or ovaries. Beforehand, the starting cells –known as primordial germ cells- should have erased the markings -parental imprinting- of the chromosomes of the other 22 pairs to the end of acquiring exclusively what is inherent of the sex, defined in the first place by the absence or the presence of the Y chromosome.

This specific pattern of markings is very thorough in the gametes. From puberty on, the sperm mature in a lineal manner and the ova in a cyclical manner directed by the changes of the hormonal cycle. On the other hand, the markings change with age in the different cells of the organism: it is natural aging. From this process the sperm is liberated but not the ova. This is why a female fertility clock exists but not a male. Because of this, the state of the gametes is not independent of the body where it is generated and matured. In natural procreation it is the personal body of a male and of a female who engender and in artificial reproduction the gametes generate in a body that has its story. Biological father and mother contribute, in one way or another, the genetic and sexual identity of their children. Also, to a certain extent, the markings of their age, their eating habits, their lifestyle, their possible

exposure to environmental toxics, etc. And, of course it breaks off from the history of their own family tree, such as predispositions to illnesses or of musical abilities, etc.

Hence, neither in natural procreation nor in the artificial, be father or mother can, in fact, reduce to contribute or receive gametes for others, or from others. Gametes are not just like any other ordinary cells, like those of the blood for example, but that they are implicated in the transmission of life of that precise person in whose body they have been formed, not of human life in general.

Considering the fact that genetic inheritance has its history, each person has the right to know from whom they originate: Who their “biological” father and mother is, has shaped his/her own identity.

2. Biotechnology in the search for an asexual human reproduction

Biology sets a limit on the transmission of human life, since necessarily, as with all mammals each conception has to be carried out on behalf of a male and of a female. What does biotechnology try to achieve to skip the natural barriers of procreation or at least to expand and broaden their frontiers? What is looked for with biomedical manipulation or biotechnologically of the gametes?

2.1. Gamete Production

a) The production of spermatozoa and ova from immature cells has been a recurring topic in the search for solutions to the problem of sterility or infertility and achieve logically an adequate sexed fertilization.

In mice it has been tried so much in vivo as in in vitro. In vitro, using immature cells coming from embryos, it has been attained a cell prior to the sperm capable of fertilizing a natural ovum. However, it has not been possible to produce ova. Possibly, in the human case, these sperm precursors are not fertile.

Several experiments have shown that a complete maturing of the precursors cells of the ova will only be achieved if said cells reside for a time in the ovary, their natural place of formation and maturation; the experiment consisted in introducing stem cells in the ovary


of an infertile female mouse and the injected cells reversed the infertility that had previously been produced and had offspring. It seems, therefore, necessary for the generation of ova and spermatozoa that at least one stage of its production happens in the body of a female or a male respectively.\textsuperscript{14}

\subsection*{2.2. Clones, parthenotes and chimeras}

The intents to produce individuals from only one type of cell, masculine or feminine, without fertilization, have not given any results in primates. As it has been commented, with cloning technology it is not possible to achieve a primate clone because of the natural barriers that their cells offer to a \textit{backward programming}, until reaching the zygote state where an individual is developed, a \textit{clone} of the first\textsuperscript{15}.

What also has not been achieved and does not seem possible is that through the activation of an ovum without fertilizing it, this becomes a woman, a \textit{parthenote}\textsuperscript{16}.

In mice \textit{chimeras} have been accomplished; this is individuals developed from an embryo formed by the mix of cells from two different embryos. The technique consists in introducing in a normal embryo, of a short while and before it is in a state to nest, embryonic type cells attained from an adult and programmed backwards, until the embryonic state. The development of this “mixed” embryo results in a chimera mouse with the genetic background of the original embryo and gametes with the endowment of the other adult mouse from where the cell was taken and was rejuvenated. The cross by fertilization of chimera mice, female or male, gave way to a variety of mice whose gametes had only the genetic background of the cell donor. In definite, a coy is achieved based on sexual crossing during various generations\textsuperscript{17}. In another type of experiment, pursuing the same, an embryo has been generated of tetraploid mouse (double set of genetic material), to leave it later as diploid\textsuperscript{18}. And, in definite, in both cases, it is a procedure too unsuitable for extrapolating to men.

Presently at least, and there does not seem to be any other form, each human person as to be the son/daughter of a male and a female. Clones are not possible neither parthenotes nor human chimeras.

\subsection*{2.3. One individual from two progenitors of the same sex: two fathers?}

In December 2010 it came out in the media the publication of an \textit{online} article from the

\begin{itemize}
  \item[\textsuperscript{14}] Daley, G.Q. “Gametes from embryonic stem cells: a cup half empty or half full?” \textit{Science} 316, 2007, 409-410.
  \item[\textsuperscript{17}] Boland, M.J., Hazen, J.L., Nazor, K.L.,Rodríguez, A.R., Gifford, W., Martin, G., Kupriyova nov, S., Baldwin, K.K. «Adult mice generated from induced pluripotent stem cells». \textit{Nature} 461, 2009, 91-96.
\end{itemize}
magazine Biology of Reproduction that said to have obtained male and female mice from two male fetuses. It was made known in the article that with this a door was opening to the provocative possibility that a pair of the same sex could have a child with the contribution of both of their genetic material. Theoretically for their to be a human generated by two fathers or two mothers it would be necessary to form ova XX from XY cells and inversely sperm XY from XX cells; also needed would be the passing of the gonads from another male in one case or of another woman in the other case for the final maturation of each of the gametes. Before the acquisition in the 22 pairs of non-sexual chromosomes, there is the proper imprinting of the ova or of the sperm. Besides all of this, if it all were possible the fathers or the mothers would be fetus and not adults.

How did this experiment take place with the fetuses of mice? In the first place, immature skin cells have been manipulated, fibroblast, of a male mouse (XY) with the aim of converting them in reprogrammed cells backwards this was progenitor 1. During the cultivating some of these cells XY spontaneously and by chance lost the Y chromosome remain as X0 cells, this is devoid of an X. Subsequently, these X0 cells were injecting in a female embryo in the stage previous to implantation, blastocyst, and this chimera was transferred to the uterus of a female mouse. Later on a female chimera whose oocytes where derived from the X0 cells, initially coming from a male, was crossed with normal males that therefore did the function of progenitor 2. In such a way that some offspring appeared that had the genetic material of two males: one manipulated to be X0, a female derived really after generations of a male fetus XY, and the other a natural male.

It is a “new” reproduction mode that definitely ends as a crossbreed between a male and a female. It merely needs to add the idea of extrapolating that system to humans that the manipulations seen in a mouse demand, apart from all that has been said, to pose as an X0 female and women X0, with Turner's syndrome, are sterile.

2.4. And two mothers without a father?

It is possible to generate sperm from a feminine cell be as impossible as the inverse. The gene that codifies the factor that sets forth the masculine program has to necessarily come from a male, contributing, although be it by genetic engineering, the possibility of reverting the sex of a cell. What two women can do, with the obvious resort of a male who becomes a father, is to share in an asymmetric form motherhood: the genetic material present in the mitochondria of one could form part of the other's ovum, in the scenario that the mix did not generate immunological rejection; and of course only one could be the pregnant one. At least for now, and possibly forever, the idea of asexual reproduction, natural or artificial, is not anything more than science fiction.

3. The brain is a sexed organ: male-female identity

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The gonads and the brain are sexed organs in the human body. Both are determined in feminine or masculine direction according to the genetic sex XX or XY, in the first place not exclusively. On the one hand a great number of genes intervene -that codify the sexual hormones, their receptors and the enzymes of the metabolism of the hormones, etc.- localized in different chromosomes and, so much so their variants as the regulation of their synthesis, plays an important role in the construction of these organs, and determine the sexual pattern.

Sexual hormones are very important for sexual identity and a good number of genes also play an essential role in sexed cerebral differentiation\(^1\); it has even been found in rodent that there is a differential expression of 50 genes in the brain of fetal males and females, before the hormones begin to act\(^2\). And the gene SRY, of the Y chromosome, that starts the masculinity pattern of the fetal gonads, is also expressed in the adult human brain\(^3\).

From birth, behavior expresses the prenatal differences organized during development in the maternal womb. It is described, for example, that in the first days of life girls prefer to look at the faces while the boys look at the moving mechanisms\(^4\), choose different types of toys between three and eight months independently of possible social pressures\(^5\), that can not occur at such an early age.

3.1. *In the prenatal stage sexual identity is determined*

The different levels of the gonadal hormones act in the prenatal period an in the postnatal. The direct action of the testosterone in the developing nervous cells in the fetal brain develops in the masculine direction and in the absence of this hormone, in the feminine direction\(^6\).

Therefore, during fetal development an immature draft is set up in which the design of the adult is initiated. The differences in brain weight are already present at age two\(^7\). The different layout of the neuronal circuits is innate and caused by the genetic background that each one receives in their conception. For example, among other characteristics, there begins to establish in the fetal stage a greater asymmetric function of the two female hemispheres, than the masculine.

Subsequently the hormonal levels boosts the functionality of the areas of greater

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\(^{1}\) Bocklandt, S., Vilain, E. «Sex differences in brain and behavior: hormones versus genes». *Advances in Genetics* 59, 2007, 245–266.


concentration of the receptors with which the hormones interact specifically and the key function surge of the specific sexual neuronal circuit that involves the cerebral region known as the hypothalamus.

Some hypothalamus nuclei are of a different size according to sex. The hypothalamus forms part of the limbic system and coordinates the corporal expression of the emotional states: it is a coordinating center of responses be they either somatic as autonomous or vegetative. Therefore, it is the principal regulating center of sexual conduct. In human beings, the reciprocal connections of the hypothalamus and the limbic system, with the brain cortex provoke that the emotional states are made conscious generating feelings and permit that the instinctive behavior is transformed in conduct.

Also there exists differences between the sexes in the distribution of the cerebral receptor of steroids during development, genetically determined, that extends to other stages of life.

The production of testosterone by the testicles of the boy fetus is high and its peripheral conversion of dihydrotestosterone is essential for the formation of the masculine genitals. It reaches the brain in two waves. A first is produced during the half of the pregnancy with a peak in the fetal serum between weeks 12 and 18, and in weeks 34-41. The levels of testosterone in boys are ten times superior to that of girls. The second wave is produced in the first three months after birth. The estrogens not only reach the brain by circulation but are produced by the action of the aromatase enzyme on testosterone. The levels produced by the male fetus exert a defeminizing action.

The estrogens support the brain cells to guarantee the feminine differentiation on the neural mechanisms that control the sexual brain. The fetal brain is protected against the effect of the circulating estrogens of the mother by the protein alphafetoprotein that is produced by the fetus and that links with force the estrogens. At the end of the pregnancy, when the levels of alphafetoprotein is reduced, the fetus is more exposed to the estrogens of the placenta, by which it loses the inhibition of the axis that from the pituitary sends signals to the gonads. Thus, at the moment of birth a testosterone peak occurs in males and an estrogen peak in females.

Studies with animals have shown that estrogens have on the brain a double action: feminizing and defeminizing. They propose that the defeminizing action of estradiol is produced in males before birth and is avoided in fetal women due to the protective actions of alphafetoprotein, while the feminizing action of estradiol normally occurs between birth and puberty when the ovaries produce high levels of estrogen and the alphafetoprotein does not play an important role anymore.

Therefore, during the intrauterine period the interaction between hormones and genes in the development of the brain cells is decisive in the programming of the brain sex, harmonized to the genetic sex, gonadal and genital. Harmony that permits the sexual identity of each person: the conviction of belonging to the masculine or feminine gender.

The first component of feeling male or female is ascertained in children. It was thought that the sexual identity was psychologically derived through social cues received by the child according to the appearance of their external genital organs. However, it is now clear that there exists a genetic and hormonal determination in the corporal constitution and in the cerebral structure, different in each sex.

3.2. Temporal differences during the gonadal and cerebral developmental

In that case, the fact that the differentiation of the sexual organs takes place in the first few months of gestation while the sexual differentiation of the brain, dependent on the hormones, occurs in the second half makes for, in fact, that the sexual organs and the brain follow different routes and express the corresponding genes at different moments. This is, a person can have gonadal structures and genitals of their genetic sex and feminine cerebral structures in a masculine brain and vice-versa. It is the human phenomenon of Transexuality.

And on the contrary, there can be some genetic alterations that lead to gonadal malformations -intersex or even of both sexes, hermaphroditism- while the brain has followed its own structural pattern of its genetic sex. It is known as ovo-testicular development disorder.

4. Transsexuality

Transsexuality or gender identity disorder is defined as a feeling of inadequacy with the biological sex and a constant and persistent identification with the opposite sex. Transsexual people have, with frequency in their infancy, the sensation of having been born with the mistaken sex. For the majority, the onset of symptoms appears in early childhood and frequently in this period the preference for dressing with clothes of the other sex is present.

Generally, they wish to be accepted as what they feel and some solicit hormonal treatment and sex reassignment surgery. It produces in them a great suffering, so much so the deep unease with their own body and the need to carry out the change of sexual reassignment, as the frequent family and social rejection.

In other people the disorder appears at adulthood, and in a gradual manner: sometimes even

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spontaneous remissions are produced. The time of emergence helps with the diagnosis of the causes and, therefore, of the treatment. The problem of sexual identity seems to depend on a dysfunction, possible temporary, of hormonal action during embryonic development between the gonads and the brain.

The processing of the sexual identity differs in the brain of sexual orientation although some of the mechanisms that predispose the identity and the sexual orientation can be related. The sexual orientation of transsexual people largely corresponds to its chromosomal sex, as generally occurs with the population.

4.1. Genes and their regulation

Trans-sexuality has its origin in genetic inheritance. The implication of genetic factors in the male-to-female transsexualism has been confirmed by the studies of twins, of transsexual brothers and sisters and with the family studies of more than one member. The genes that encrypt for the androgen receptor, the aromatase enzyme of the metabolism of androgens and the estrogen receptor are reasonable candidates between the genes that can influence in trans-sexuality, to modify the level of the hormones that reach the brain, or are produced in them.

a) The receptor gene of androgens is localized on the X chromosome, and presents in the human species, two genetic variants that give a high or a low activity, and with it contribute an excessive sensibility, or on the contrary, insensitivity to this hormone action. It is one of the genes that escape from the inactivation of the X chromosome and, therefore, in males only one copy of the gene appears while in females two copies appear, that can be the same or different, creating in this way intermediate levels of activity. Such polymorphism has been linked to the male-to-female transsexualism and also, in the case of females, with disorders due to the elevated effect of the androgens.

b) Gen CYP19A1 codifies the enzyme aromatase that participated in the biosynthesis of estrogens from androgens; its effect is known in relationship with male-to-female transsexualism due, that during development, the brain has been exposed to a less amount of masculinising estrogens, proceeding from androgens.

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c) It also seems to be involved in female-to-male transsexualism but not in male-to-female\textsuperscript{36}, the gene CYP17, found on chromosome 10, and that encodes an enzyme that catalyzes two reactions in the metabolism of the androgenic hormones in the gonads. It produces a variant associated to an excess of circulating androgens.

4.2. Structuring of the hypothalamic cerebral zone before and after hormonal treatment

Trans-sexuality is due, firstly according to the data described, to an alteration of the early influence to steroids in brain development\textsuperscript{37}. Coherent with that idea, the neurobiological studies about the hypothalamus of transsexual people show that some parameters have similarity with those of the sex they feel they belong to, and opposite to their body, of their sexual organs\textsuperscript{38}.

From there the hypothesis that trans-sexuality has been associated to sexual differentiation, in such a way that certain hypothalamus netting related with sex would be altered and they would be due to the early exposure to steroids.

To put to the test this hypothesis various parameters have been studied that reflect the hypothalamic brain structure and the possibility that these brain changes has been caused by the prenatal exposition to sexual hormones.

For this, it was necessary to find people with rejection to their corporal sex, that had not taken hormones for sex reassignment, with the fin to detect the innate from the acquired by hormonal treatments.

In the studies of functional neuroimaging areas are detected that are activated or silenced by the procedures of the emotions aroused. We can simplify by saying that the “emotion is measured” of what underlies a process.


a) One of the parameters is the activation pattern of the hypothalamus in response to the smell stimuli of substances derived by the sexual hormones, a specific parameter of sex. The areas that are activated in women by the odor of substances derived by androgens differs from the hypothalamic area that is also activated in males by odor derived from estrogens; and neither in males nor in females no areas are activated when they smell hormones derived from their corresponding genetic and gonadal sex. They do not feel any emotion ante those stimuli.

Chosen for this study were 12 transsexual men, not homosexual, so that the result could not be attributed to an effect of sexual practice. Apart from this condition, none of these people had had hormonal treatment that could affect the response. They were all given to smell odors derived from androgens or from estrogens and the results showed that the activating pattern of the hippocampus is intermediate: similar to the pattern of women when they smell androgens and to the pattern of activation characteristic to males when they smell estrogens.

That is to say, that there was not in their brain a pattern contrary merely only intermediate.

b) In other studies the response to erotic visual stimuli has been measured, of people with the transsexual condition prior to having had hormonal treatment. Males responded with much more intensity than women with these stimuli and with a different area activation pattern. Transsexual people with male-to-female showed areas less active- less degree of sexual arousal- than males, and more similar to that of females.

These analyses show a sex-atypical response to the hypothalamic circuits, possibly as a consequence of a variation of brain organization of the areas that process sexual excitation.

When this cerebral change was taken as sufficient to explain the human phenomenon of trans-sexuality, it was established as a dogma that transsexual people simply have an inverted sexual dimorphism of the brain in relation with their genetic and corporal sex. Therefore, the solution would consist in changing their corporal genital sex by surgery, extirpating of their gonads and hormonal treatment, although with it they would be infertile.

In the first place, the sexual pattern as regards the size and activity of the hypothalamus

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40 Berglund, H., Lindström, P., Dhejne-Helmy, C., Savic, I. «Male-to-female transsexuals show sex- atypical hypothalamus activation when smelling odorous steroids». Cerebral Cortex 18, 2008, 1900-1908.
nuclei, does not express itself until early adulthood\textsuperscript{42}, which means -that not only this parameter can not be used for an early diagnosis of trans-sexuality-, but that there are many other factors that vary throughout time.

This is, that they are not directly reflected the prenatal exposure to hormones but the emotions that their own situation, education, relationships with others, etc. raises and exceed what is primitively biological.

What happens therefore when they have been subjected to hormonal treatment in brain areas that are different in males and females but that have no relationship with sexual activity?

Transsexual people male-to-female present then intermediate values, in those that are typical for males and females, in what refers to brain structuring as the lateralization of the brain hemispheres and the cognitive abilities\textsuperscript{43}, independent areas from those that regulate sexuality.

This is that hormonal treatment after birth reaffirms prenatal circuits and creates others.

\textit{4.3. Structuring of the cerebral areas not related with sexual processes}

Various studies coincide in the effect of hormones after birth.

a) Cerebral studies to resolve tasks of mental rotation of an object is space, activities in which men, in general, surpass women, transsexual people so much so male-to-female as with female-to-male present an intense activation of occipital-parietal-frontal pattern as in control groups of men and women. However, in comparison with control men, the activation of male-to-female transsexuals, during the task, was less in superior parietal lobe; and in comparison with the control group of women they showed greater activation in the right dorsolateral-orbitalprefrontal region and less activation in the left prefrontal convolution region.

There exists therefore a specific pattern for male-to-female transsexual people. And curiously the diminishing of activity of the parietal lobe and the occipital and temporal regions was correlated with the years of estrogen treatment\textsuperscript{44}. This intermediate pattern was not innate but would have been caused by supplemental hormonal treatment.

On the contrary, female-to- male transsexual people differ from the control group of men in the parietal region and of the control group of women in the orbital-prefrontal region. A typical pattern has not been identified, nor is there the inverse correlation with the treatment time with estrogens\textsuperscript{45}. What abounds in the idea of changes with respect to one's own brain

\textsuperscript{42} Chung y cols., op.\textit{cit.}29.
\textsuperscript{45} Carrillo y cols., \textit{op. cit.} 44.
pattern of the corporal sex is generated by the treatments, as we remember the estrogens only generate masculinizing effects in the fetal stage.

b) Other studies showed that the microstructure of the neuronal fibers in female-to-male transsexuals, before hormonal treatment, was in diverse regions more similar to male controls, than those of females.\(^{46}\)

More longitudinal studies will be needed with the aim of confirming if the supplemental hormonal treatment causes changes in the brain structures or can simply reflect an a priori of the differences.\(^{47}\) Nevertheless, the anatomical findings also question the dogma that transsexual people simply have an inverted cerebral sexual dimorphism in relation with their biological sex.

In effect, if the hypothesis was correct, it would have to be found in transsexual people, feminine structures in a masculine brain and vice versa, and in fact such inversions have not been found in the brain areas implicated in sexual conduct: the hypothalamic characteristics of transsexual people were halfway between masculine and feminine rates.

5. Self-perception of the body and transsexualism

Savic's group poses a creative hypothesis when they formulate the question whether transsexuality could be associated with changes in the cerebral networks implicated in the auto-perception of the body.

Actually the neurosciences describe with precision the interaction of the cerebral areas that process the sense of identity; this is the conscience of one's own body and the perception of existing in that body.\(^{48}\)

The identity and conscience of “I in my body” is processed in the neuronal networks that include the region of union of the temporal and parietal lobes, the thalamus and the anterior insular cortex.\(^{49}\) The results of the analysis of neuroimaging of male-to-female transsexual people had reduced structural volumes of putamen and thalamus in comparison with the two control groups of males and females. Also the grey substance in the right insular cortex and the right temporal-parietal union was greater than in the two control study groups. This clearly points to the implication of a dysfunction in the auto-perception, because of modification in the areas that precisely carry out the function of somatizing one's own “I”.

In the following outline the areas of the limbic system are distinguished that process the


sexual stimuli and some of the areas that process one’s own identity, the “I” in my body, and that have been found to be affected in transsexual people.

5.1. Psychological treatments

If as the results point to that the results of trans-sexuality has to do with a dysfunction of the perception of one’s body, always obviously sexed, that leads to feel a sexual identity contrary to the corporal sex, the data suggests that what would have to adapt is the brain to the body and not the opposite.

Progress in neuroimaging is gradually making it is rethink what are the best treatments and the best psychological follow-up since infancy. Transsexual surgery can condition the genitals to the psychological sex, but it always has to go accompanied and followed by hormonal treatment. Hormones, apart from influencing the gonads and the genitals, at the same time modify the brain structures with greater or lesser intensity according to age, and at a different rhythm in males and females.

And, as in all that is human, so much so these modifications as with personal experiences with the social environment or learning generate psychological changes.

This offers an understanding that can be valuable: cerebral sex determines the psychological sex and therefore gender identity. There exist principles of permanent programming of cerebral sex because of biological factors and exposure to androgens in such a way that the sexual identity simply is not an option. The alteration of the early influence of steroids in brain development can originate trans-sexuality, a disorder at a psyche level.

Early exposure to steroids, as an original cause to the transsexual condition comes approved by known experiences. In 1999 it was published that a group of 243 women that had received compounds of the phenobarbital type during pregnancy had a higher risk of giving birth to a transsexual child; in fact, three transsexual children were born and some others with less radical gender problems, that are rates relatively high for a not so frequent condition. Both substances modify the metabolism of sexual hormones and can act on the sexual differentiation of the fetus’ brain. It has also been stated, although it has not been confirmed that it be general nor the reason, that some male-to-female transsexual people have been born after several brothers and have more brothers than sisters; what suggests the presence of immunological processes of the mother during the pregnancy targeted at the proteins generated by the Y chromosome, that would affect the cerebral masculinization process in the fetal process.

In the first prenatal stage and during the first infancy the influence of the hormones on the


brain is very pronounced. The hormones manufactured by the brain propitiate connections between zones of the central nervous system that regulates the traffic of external and internal information in the first two years of life. After, hormonal changes in puberty reinforce the connections and create other new ones.

Thus, there is not any evidence that after it be the social factors the ones responsible for the emergence of transsexuality.

6. Ova-testicular developmental disorders: states of intersexuality

These types of disorders, occurring during the gonadal development in the early prenatal stage, generate an insufficient gonadal and genital differentiation. Genital ambiguity and/or of the gonads made that it be known as intersexuality, even that hermaphroditism be talked about.

Only in some cases is trans-sexuality studied. However, until a short time ago, it was accustomed to rear as girls people born with genital ambiguity. Fortunately such a custom was eliminated, the assignation of sex has been made, generally with great precipitation in many cases, eliminating gonadal structures and/or genitals and boosting others through surgical interventions and hormone treatments.

Current knowledge allows guiding them towards a better harmony with their corporal characteristics.

For some of these types of disorders there exists an ample scientific bibliography so we take them as an example.

6.1. Cloacal Exstrophy

Cloacal Exstrophy (CE) is a rare and complex defect of the entire pelvis and its content, that is produced during the gestation of an XY fetus, male, and that involves a grave phallic insufficiency. The cause of the malformation is an alteration of 5alpha-reductase-2 deficiency and 17beta-hydroxysteroid dehydrogenase-3 enzymes. As newborns they seem like girls with a great clitoris. The neonatal allocation of the feminine social and legal sex allowed these males to overcome the phallic insufficiency problem, including if their internal testicles were removed. However, when they were assigned the masculine sex at birth, during puberty they had a strong virilization, penis growth and their testicles descended and a many of them adopted a masculine identity, being heterosexual men.
An interesting study evaluated 16 youths, males genetically, that suffered EC from the age of 5 until the age of 16 years. 14 of them had undergone a neonatal assignation to the feminine sex; the parents of the other two refused to do so. Through very detailed questionnaires the development of the sexual function and identity was evaluated. 8 of the 14 subjects assigned to the female sex were declared as males during this study, and the two educated as males maintained their masculine identity. The 16 had between moderate and marked interests and masculine attitudes, with independence of their upbringing as girls or boys.

Clinical interventions in these children should be reexamined in the light of these findings. Cloacal extrophy is not an inter sex condition: the phallic insufficiency is an anomaly of corporal structures.

The fact that patients with EC possess histologically normal testicles, although not having had them descended in the neonatal period, implies that they have developed in a typically prenatal masculine hormonal medium.

Therefore, these children, genetically and hormonally are born as males, are identified from infancy as males in spite of having been raised as females, and having undergone a feminizing surgery after birth.

6.2. Complete Androgen Insensitivity Syndrome

An extreme type of hormonal alteration is constituted by people with complete androgen insensitivity syndrome. In XY fetuses the lack of testosterone effect generates a female body and brain. They develop as heterosexual females.

6.3. Congenital Adrenal Hyperplasia

Another gonadal developmental disorder is Congenital Adrenal Hyperplasia (CAH), that XX women suffer, due to a deficiency in 21-hydroxilasa, that maintain an excessive level of circulating androgens that proceed from adrenal glands. They show different variable degrees of masculinization of the body and some more virile features in their behavior, but do not exhibit masculinization in the circuits of the brain’s limbic system. However, the more severe forms, because of having been exposed to extreme levels of testosterone,

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58 Ciumas, C., Linden Hirschberg, A., Savic, I. «High Fetal Testosterone and Sexually Dimorphic Cerebral Networks in Females». Cerebral Cortex 19, 2009, 1167-1174.
presented a greater probability of suffering *female-to-male* transsexualism\(^59\).

On the other hand, although the majority of these women are heterosexual\(^60\), the levels abnormally high, in which severe cases are exposed to hormones coming from the same fetus, seems that it supposes a predisposition to a homosexual orientation, as is released from the great percentage of girls with CAH that are bisexual and homosexual\(^61\).

The characteristics of ambiguous sex syndrome at birth, shows that the degree of masculinization of the genitals does not reflect the degree of masculinization of the brain. The identity and the sexual orientation are not only dependent on the prenatal exposure of androgens or the appearance of the genitals.

This indicates that the sex assignment of girls with CAH should not be based on the appearance of genitals or on the levels of prenatal androgens, could be inferred. Moreover, the feminine identity does not require genital organs of a normal aspect. The chromosomal sex and the gametes should be taken into account in the first place and proceed to psychological help\(^62\) to notice those aspects of their behavior, like play style preferences and the election of playmates\(^63\), are not the “typical” of the members of their same sex. This would be sufficient for the onset of a gender identity conflict would only happen in exceptional and very extreme cases\(^64\).

A greater sensibility to androgens, and even lower levels of ovarian hormones than the habitual for girls, would be at the basis of the gender dysfunctions in girls with CAH. While in boys, a partial insensitivity to androgens would constitute a predisposition to such dysfunctions since the androgen receptors are essential for the masculinization of the brain\(^65\).

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\(^{62}\) Resnick, S.M. «Psychological adjustment in children and adults with congenital adrenal hyperplasia».


\(^{64}\) Berenbaum, S.A., Bailey, J.M. «Effects on gender identity of prenatal androgens and genital appearance: evidence from girls with congenital adrenal hyperplasia».

The variables observed show that the brain circuits that regulate the sexual behavior are not exclusively due to a direct effect of androgens on the brain; they are independent genetic factors\textsuperscript{66} and also the interaction of social factors that broaden the identification with certain aspects of the masculine function during infancy and its behavior during that period, that can later on give way to transsexualism\textsuperscript{67}.

We conclude therefore that the direct action of the testosterone on the brain development of boys and the lack of it in the brain development of girls is a crucial factor-although it is not the only one- for sexual identity, masculine or feminine and sexual orientation.

The complex origins of gender identity and the behavior related with gender should be taken into account in the medical treatment of children with intersexual conditions.

Progress in neuroendocrinology and of neuroimaging should be taken into account in the upbringing of new generations. The use of slogans such as ”there are no sexes, only roles” imposed since infancy, does not acknowledge what science shows/demonstrates: human nature demands coherence at the genetic, gonadal, genital and psychological levels. Sex is determined by inheritance and, with it, one’s own identity. The “I” is somatized in a body that necessarily is of a female or a male.

It is a natural principle that the human body does not lie and always informs of what occurs to the person “bearer” of that body. On the contrary, the brain can err in its perceptions. But, even so, all that occurs in the psyche our body somatizes it.

7. Reviews of materials that can be found “online” in: