Statistical Management of Ambiguity: Bodies that defy the algorithm of sex classification

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The aim of this article is to challenge the current management of intersex cases, a management that is based on statistical principles of strict binary classification. The concept of "algorithm of sex classification" is introduced based on the current guidelines for the management of intersexuality proposed by the American Academy of Pediatrics. Although this three-step algorithm is rooted on scientific principles that shape our views on what constitutes 'sex', it is argued that its applicability is not universal as it does not properly encode every case. The clinical criteria to define the proportions of non-ambiguous sexual anatomy, that are based on a Gausssian distribution to define normalcy, is analyzed. An analysis of published reports during the past fifteen years showing the number of cases that are assigned to the male or the female sex categories when confronting an intersex case is contrasted with an analysis of the number of cases that self-initiate a change in gender identity according to specific clinical diagnoses. Discordant results between clinical assignment of sex and self-ascribed gender identity by intersex individuals are shown. The practice of encoding intersex cases by etiology and not phenotype is examined as it perpetuates the idea of "rare events." It is concluded that the current algorithm of sex classification must be substituted by another algorithm that allows the encoding of random events that occur during the sexual differentiation of the human body. A desirable consequence of this new algorithm is to validate the phenotypic expression of intersex cases by medicine, the law, and society.

A look at sex classification through the lens of critical statistics

The cover of a recent issue of a weekly USA magazine portrays an attractive hairless blue-eyed White baby sucking the index finger and wearing a short jumpsuit, pink on the front and blue on the back. The body of the baby in a sitting position appears as if suspended in mid-air over a white background, underlining the purity and innocence of this character. The question that poses the cover is: "The mistery of gender: aside from the obvious, what makes us male or female? The new visibility of transgender America is shedding light on the ancient riddle of identity" (Newsweek, May 21, 2007). This is the kind of magazine cover that will catch the attention of people from all walks of life as they wait in line to pay for midnight cravings at the local supermarket. But the premise of the question with regard to sex, "aside from the obvious", is questionable. For instance, what happens when the neonatal medical staff cannot announce to the happy parents "It's a boy!" or "It's a girl!"? This apparent medical and social emergency is managed through the algorithm of sex classification as it guides the decision-making process for sex assignment. This algorithm confers authority and presumed objectivity to physicians, but more importantly, it reproduces the binary system of sex classification when facing a baby whose genitalia cannot be easily recognized as male or female. The broad term "intersex" is commonly used to refer to individuals whose phenotype falls between the male and female sexes. The medical establishment has expanded this definition to label cases where chromosomal, gonadal, or hormonal sex does not coincide with the anatomy of the genitalia. However, this algorithm proves to be defective in the process of sex assignment when confronting an intersex phenotype.

Professional statisticians, and scientists whose work heavily depends on statistics, make sense of the world by quantifying phenomena or by creating categories to classify all phenomenon. Statisticians aim at generating taxonomies that include categories that are mutually exclusive and that encompass the full spectrum of alternatives. In so doing, the use of nomenclatures as classification systems has the consequence of equating the typical, the most frequent, with the normal. One of the simplest and the most pervasive forms of binary

classification is that of "sex," since it poses two distinct acceptable anatomical phenotypes of male or female that are mutually exclusive and preclude other typologies. Therefore, this classification system is consistent with the statistical worldview. Although it seems a matter of common sense to accept this simple binary system, thousands of babies around the world are born with "ambiguous genitalia" according to current medical standards of sex classification. The problematic algorithm of sex classification proposed by medicine is reinforced at birth for the consequent sexual classification of every baby into the birth certificate to guarantee the socio-legal expression of such system.

At the turn of the 21st century, the American Academy of Pediatrics published the clinical criteria that defines an intersex case and its recommended management, which follows the logic of an algorithm (AAP, 2000). This article reconstructs these series of guidelines as a three-step algorithm of sex classification in order to uncover the scientific logic behind each step. After having this algorithm, a critical question remains: does the algorithm work? The number of intersex cases that are assigned to the male versus the female sex according to discrete clinical diagnoses is examined followed by an account of the number of cases that self-initiate a change from the assigned sex category. This analysis reveals that in spite of its presumed objectivity, the algorithm of sex classification is not universal as it does not properly encode every case. Given the paucity of studies reporting sex assignment and long-term outcomes on gender identity among intersex cases, it is assumed that intersexuality is a 'rare event'. This view is supported by reported incidence rates and prevalence estimates that are based on current clinical classification systems of disease such as the International Code of Disease (ICD-10) by the World Health Organization (WHO) and the classification system followed by the American National Organization of Rare Disorders (NORD). Even though intersexuality is first recognized by the phenotype of the sex organs and the management of these cases is typically considered complete once the sex organs are surgically reconfigured to the assigned sex category, these classification systems are based on etiology and not phenotype. Therefore, it is pertinent to ask whether the current algorithm of sex classification that perpetuates a binary system and that excludes other cases as "rare events" should be substituted by a new algorithm that includes non-typical cases as "random events" with regard to the biological processes that lead to the sexual differentiation of the external genitalia as established in developmental biology. Finally, the cases of Colombia and Puerto Rico are discussed in terms of their potential contribution towards a new algorithm of sex classification fueled by their initiatives.

Recommended management of intersex cases according to the American Academy of Pediatrics

The birth of an intersex baby provokes a sense of medical and social emergency. Doctors ask themselves; how to classify him/her? While parents ask themselves; how to raise him/her, as a boy or as a girl? Ultimately, all are constrained by a social mandate: every child must have an assigned sex category as determined by a medical expert. The law enforces that mandate in that a birth certificate must be issued to register the legal identity of all newborns. Limited by our current binary system, scientists and physicians are required to discover the "true sex" of an intersex phenotype as if this sexual body is a trickery played by nature (Lee 2004).

The field of statistics greatly influences the practice of medicine, in fact, many XIX century statisticians were physicians (Désrosieres 1998). For instance, the medical practice of diagnosis is based exclusively on the principle of identifying and classifying cases and of treatment on the basis of knowledge previously accumulated in taxonomies. The analysis of sex classification reveals that the pertinence of established criteria is *a priori* arbitrary, and can only be apparent *a posteriori* only if one assumes that each classification criteria are real, natural, and universal. The Committee on Genetics, Section on Endocrinology, and Section on Urology of the American Academy of Pediatrics (AAP) provided the recommended standard operating procedures for the clinical management of intersex infants in 2000.

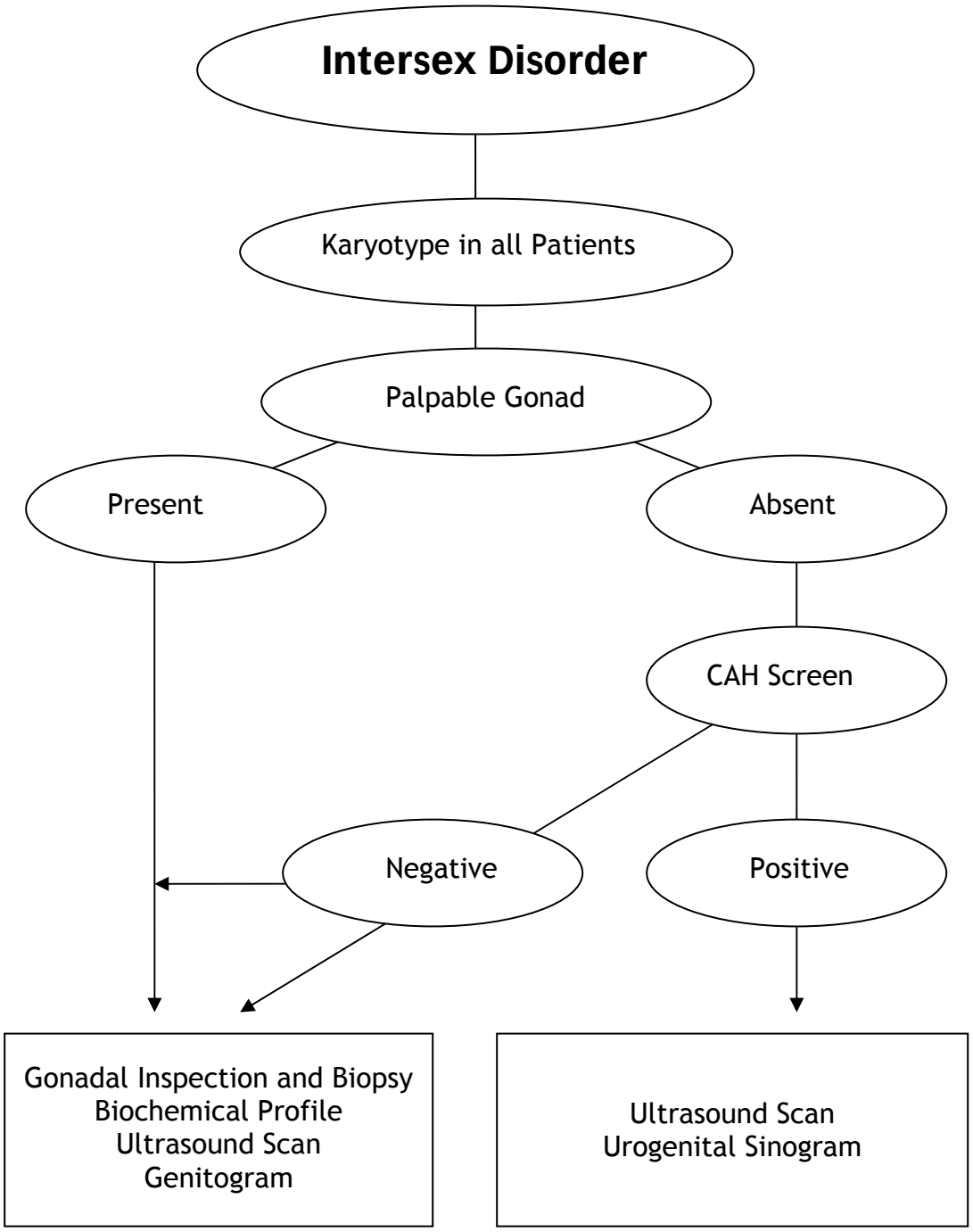


Figure 1.
Recommended management of intersex infants according to the American Academy of Pediatrics.
Adapted from the American Academy of Pediatrics. Committee on Genetics, Section on Endocrinology, Section on Urology (2000). Evaluation of the newborn with developmental anomalies of the external genitalia. Pediatrics, 106: 138-142.

Once "true sex" has been assigned following the prescribed steps, the ultimate medical intervention to safeguard the classification system must be performed: "sex" must become apparent in the proportions of the sex organs. The criteria for establishing whether the sexual anatomy at birth is normal or not, comes from statistical reasoning. "A micropenis is… defined as having a stretched length of less than two and a half standard deviations below the mean for age or stage of sexual development" (Kessler, 1998). The consensus in the literature is that the measurement of a stretched penis is preferable over the measurements of a flaccid penis since the first correlates better with the size of an erect penis. Although there is also a correlation between lengths and diameter or circumference, the latter is usually not taken into consideration for establishing normality. Overall, a neonate penis is defined as "normal" if it has a length of between 2.8 and 4.5 centimeters and a circumference of 0.9 to 1.3 centimeters (Castro-Magna et. al., 1984). Current medical standards accept a penis as normal if it measures at least 2.5 centimeters (1 inch), but again, there is no accepted consensus on normal size especially if this phenotype is accompanied by an urethral opening located elsewhere but the tip of the glans and/or if the scrotal bags do not contain the gonads. In other words, a 2.5 centimeters case could be assigned to the female sex. In contrast, Kessler (1998) notes that tables of normative clitoral values appeared more than forty years after similar values for penile size. Published values for a normal clitoris are: length between 0.2 to 0.85 centimeters and width of 0.2 to 0.6 centimeters (Oberfeld et al 1989), which gives a "clitoral index" (Sane and Pescovitz, 1992). In general, a normal clitoris according to medical standards measures up to 0.9 centimeters (about 3/8 of an inch). In fact, the literature is open about the variable anatomical appearance of the labia majora and minora with regard to their sizes and their relative positions. Therefore, as with the penis, a measurement of 0.9 centimeters is not necessarily an absolute value for establishing normalcy of the clitoris.

The algorithm of sex classification

Physicians have resorted to an "algorithm of sex classification" that specifies the steps to be taken to discover the "true sex" of an intersex phenotype. An algorithm is a finite set of instructions or steps that are required to execute a task and/or to solve a problem. Such instructions or steps must be achievable and non-ambiguous since the ultimate goal is problem solving in a finite period of time.

Step 1:
Perform a karyotype
to assign sex according to "chromosomal sex"

"Chromosomal sex" refers to the karyotype of the individual revealing either an "X" or a "Y" chromosome leading to the "XX" pattern typically expressed in females versus the "XY" pattern typically expressed in males on the twenty third pair of human chromosomes. One may think that karyotype testing is only done in rare cases of congenital malformations, a concept that I will discuss below. But the truth is that an adult individual may need to know his or her chromosomal make-up as part of routine check ups in reproductive clinics. It turns out that some females seeking medical treatment for infertility discover that their "chromosomal sex" is XY and not the expected "XX" pattern. Therefore, as defined by the algorithm of sex classification these females are "intersex" since their phenotype including the external genitalia is that of a female but their chromosomal make-up is that of a male. An example of this "intersex conditon", to use the medical terminology, is "complete androgen insensitivity syndrome". These individuals are XY, their androgen receptors cannot be activated by testosterone and consequently, their bodies develop more in tune with a female body. It is now possible to identify "XY females" long before these individuals seek medical help for infertility due to recent technical advancements in genetics and molecular biology (Minto et al 2005). The existence of these individuals questions the validity of defining "sex" according to the Step 1 of the algorithm of sex classification.

Unfortunately, every current textbook in human embryology subscribes to the idea that the gene encoding the "testis-determining factor" (TDF gene) in the Y chromosome, a transcription factor that mediates the differentiation of the primordial undifferentiated gonad into testis is determinant of the male sex. According to the current model, the absence of this gene in the Y chromosome leads to the "default sex": female. But again, this chauvinistic simplification of sexual differentiation has been challenged by the anatomy of intersex individuals. The existence of males who lack a Y chromosome, the so-called "XX males" in the scientific literature, has been explained by a recent model proposing that a yet unidentified gene in the X chromosome must be suppressed by the TDF gene in the Y chromosome to avoid differentiation into female (Kolon et al 1998). Therefore, the first step in the algorithm is not universal as it does not solve the problem of sex assignment in every case.

Step 2:
Perform a biopsy
to assign sex according to "gonadal sex"

As established in Step 1, the TDF gene within the Y chromosome allows for the formation of the testis during fetal development, whereas the absence of TDF presumably allows for the formation of the default ovaries. According to this step then, the presence of testicular tissue confers the male sex whereas the presence of ovarian tissue confers the female sex. The historian Alice D. Dreger has called the 1870-1915 period the "Age of Gonads", a period that unequivocally established the histological confirmation of the gonads as testis versus ovary as the scientific determinant of sex in cases of "ambiguous genitalia" (Dreger 1998). At the end of the 19th and the beginning of the 20th century, photographs of naked intersex individuals frequently depict the scar in the lower abdominal wall as testimony of a laparatomy procedure to confirm the identity of the gonads (Dreger 1998; Graille 2001). But there is a problem, it is possible to find gonads comprised of both ovarian and testicular tissues. The scientific literature named this type of gonad "ovotestis". In fact, this is precisely the ultimate diagnostic criterion for "true hermaphroditism" according to current medical practices. True hermaphrodites usually exhibit a mosaic pattern of XX and XY complements, it is common to assign these individuals to the female sex but if they are clinically managed well after birth, they have also been raised as males. Even though hermaphroditism is perhaps the phenotype that first comes to mind when speaking of intersex cases, it is ironic that it is perhaps one of the least understood in terms of etiology and clinical management. This evidences that culture greatly influences our views on the perception of non-typical sexual bodies and that to equate the concept of "gender" to "gonads" has serious theoretical deficiencies (Fausto-Sterling 2000; Kessler 2003).

Step 3:
Perform a blood test
to assign sex according to "hormonal sex"

The cellular composition of the testis includes the Sertoli cells and the Leydig cells. The latter are responsible for producing "testosterone", the so-called "male hormone". Further chemical modification of testosterone into dihydrotestosterone in the skin of the developing genitalia allows for the sexual differentiation of the un-sexed fetus into a penis and a scrotum. In contrast, production of estrogens by the fetal ovaries as well as from maternal sources, mainly the placenta, mediates the differentiation of the fetal pelvic region into a clitoris, vagina, and associated structures. The precursor of hormones is cholesterol and they share a common chemical structure, that is, seventeen carbons arranged in four rings. In fact, this strong structural design, "steros", confers the name to these compounds, "steroids". It turns out that males and females share the same biosynthetic pathways for steroid production, they only differ in the plasma levels of certain hormones, for example, males have more testosterone than females. But the majority of intersex individuals with XX karyotype are medically diagnosed with "Congenital Adrenal Hyperplasia" if they were exposed to high levels of androgens during fetal and early postnatal development due to excess production of androgens by hypertrophied adrenal glands due to a number of enzymatic deficiencies. Clinicians consider these individuals as "females with male-like genitalia", while here again, nature does not coincide with Step 3 in the current algorithm for sex classification. Some of these CAH "females" consider themselves males (see Byne 2006; Meyer-Balhburg et al 1996; Jorge et al 2007).

Taken together, the recommended management of intersex cases according to the AAP clearly delineates Step 1 ("Karyotype on all Patients"), Step 2 ("Palpable Gonad" and Gonadal inspection and Biopsy") and Step 3 ("CAH screen" and "Biochemical Profile") of the current algorithm of sex classification (see Figure 1). The following table summarizes the steps taken to discover the 'true sex' of an intersex phenotype according to this algorithm. It also presents the length values that are taken as normal for the sexual organs to fit an intersex case back into the algorithm through genital surgeries.

Table 1
The algorithm of sex classification

Karyotype (Step 1)	Gonad (Step 2)	Hormone (Step 3)	Sexual phenotype	Sex classification
XY	testis	androgens	penis (2.5-4.8 cm)	MALE
XX	ovary	estrogens progestins	clitoris (0-0.9 cm)	FEMALE

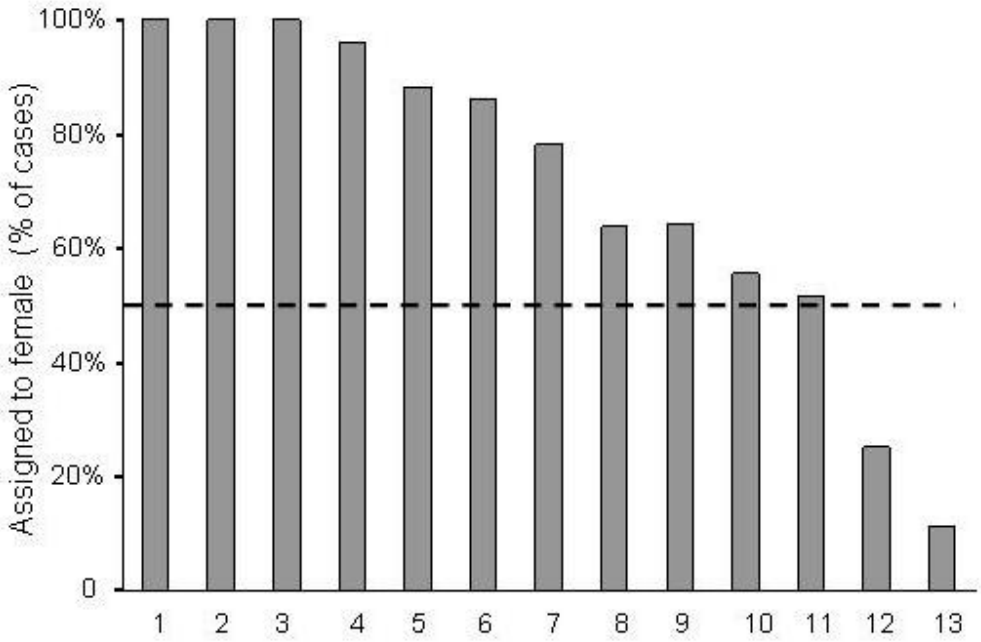
Therefore, well beyond the purpose of classification, the algorithm is also utilized to prescribe genital normalizing surgeries to conform phenotypic cases that fall outside the algorithm so that they can fit back into the algorithm that originally defined them as "intersex" (see below). The ultimate outcome of this algorithm is simple; intersex cases only exist for diagnostic purposes as this phenotype is erased by the prescribed clinical management of these cases and by their invisibility in our coding of sex in the birth certificates. The question is: do physicians discover the "true sex" of every ambiguous case by employing this algorithm?

Clinical outcomes of the algorithm of sex classification

According to the established algorithm of sex classification, when confronting an intersex case, the chromosomal make-up, the identification of gonads by imaging techniques or by histological procedures, and the biochemical profile of the individual must lead to an unequivocal sex assignment according to these objective clinical criteria.

The analysis that follows is based on a literature review using PubMed search engine on sex assignment and reported changes in gender role according to various clinical diagnoses. The terms used included intersex*, hermaphrod*, gender and identity, sex and identity, intersex and surgery from year 1995 to 2006. Collectively, these studies report a sample size of 1,081 individuals. Our analysis of the combined empirical information presented in these journals aimed at determining what proportion of cases where assigned to male and females for each individual clinical condition related to intersex cases. Most of these categories show that more than 50% of the cases were assigned to the female sex (see dotted line in Figure 2). It is evident that, within the past fifteen years, individuals that exhibit anatomical ambiguity of sex organs are more likely to be assigned to the "Female" rather than to the "Male" sex category. Other authors coincide with this assertion (see below).

Figure 2:



1. CAIS	6. Intersex (XX/YY)	11. Intersex (XX/YY/mosaic)
2. 5a-RD-2	7. PAIS	12. True hermaphrodite
3. Traumatic loss of penis	8. 17__-HSD-3	13. Micropenis
4. CAH	9. Penile agenesis	
5. Cloacal exstrophy	10. CAIS/PAIS/Micropenis	

Proportion of cases assigned to "Female" according to clinical diagnosis

A logical interpretation for this discrepancy may argue that even though clinical practitioners use the algorithm of sex classification to assign sex with a set of objective criteria, other considerations beyond the algorithm come into play in the decision-making process. Let us now assume that the algorithm of sex classification proposed here misses a clinical step. Although theoretically impossible, but for the sake of argument, let us assume that clinical practitioners take into account the *predicted* gender of the infant before deciding h/is/er "true sex." The standard practice of care specifies that sex assignment or sex re-assignment must occur prior to the second year of age. But science has not shed light on the mechanisms of gender formation nor in the developmental time frame where such process takes place. This is a fundamental gap in the field: an understanding of the time scale for gender formation should be taken into consideration before establishing the course of clinical management of intersexuality; including the desirability of sex re-assignment surgeries. Ironically, even though we are not certain of how gender identity is formed, there are standardized scales based on statistical principles to measure it! The underlying assumption is that "gender" cannot exist in the absence of

clearly defined genitals (Preves 1998). Historically, a critical issue in cases where an intersex individual wanted to change h/is/er assigned sex later in life was how to rule out that s/he suffered from a gender disorder or whether h/is/er desire was based on the fact that s/he was assigned to the wrong sex category during infancy. According to the Diagnostic and Statistical Manual IV (DSM-IV-TR) the diagnosis of "gender identity disorder" (GID), which appeared in 1994 for the first time, should not be applied to intersex cases (302.85C in the coding system of mental diseases). Interestingly, it is important to point out that the original term for GID was 'transsexualism", a category introduced in the DSM III in 1980. Intersex individuals that were evaluated prior to 1994 were at the risk of receiving a diagnosis and/or treatment for a gender disorder. For this reason, it may still not be a trivial task for an intersex individual to convince mental health practitioners that s/he does not suffer gender dysphoria (personal communication with an intersex individual, see Jorge et al 2007). Nevertheless, the final decision for the clinical management in cases where a gender change is desirable can be based, in large part, on the assumption that "gender" is quantifiable, and therefore, unequivocally established.

Long-term outcome studies on gender identity were also quantified in order to determine if pubertal or adult intersex individuals changed their original sex assignment during infancy

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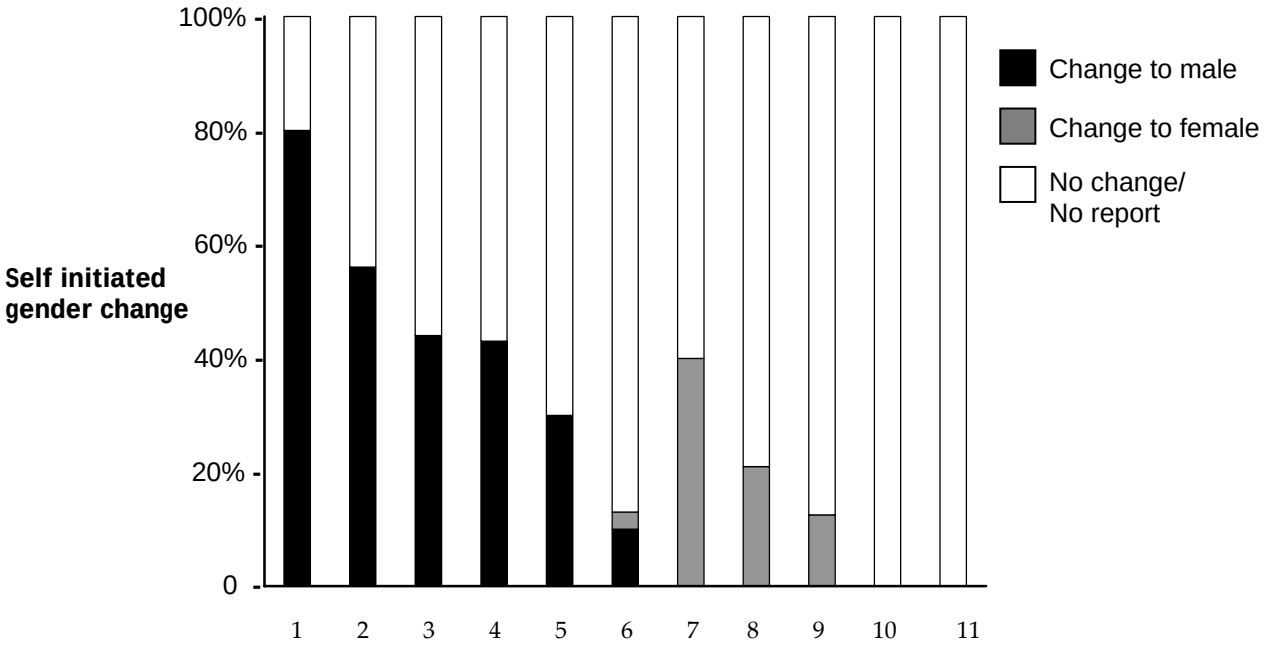
Figure 3:



Self-initiated gender change according to clinical diagnosis

Clinical diagnosis		
1: micropenis	5: cloacal exstrophy	9: penile agenesis
2: 5α-RD-2	6: PAIS	10: true hermaphrodite
3: 17β-HSD-3	7: CAIS/PAIS/micropenis	11: CAIS
4: Traumatic loss of penis	8: cloacal exstrophy	

Table 2:
Note on sources of information for Figure 3.

Clinical Diagnosis	number of cases	% change to male	% change to female	Description of the clinical diagnosis
CAIS [A]	166	0	100	Complete androgen insensitivity syndrome, androgen receptors are non-functional and the body develops as a typical anatomical female.
5α-Reductase [B]	99	0	100	Lack of this enzyme does not allow the conversion of testosterone into dihydrotestosterone (DHT), which is necessary for the sexual differentiation of the external genitalia and formation of the prostate in an XY fetus. Individuals with this diagnosis are commonly known as "gueve doce" because the newborn is recognized as a "female" but, during puberty, the individual develops secondary sexual characteristics typical of males including elongation of the phallus and descent of testicles on what was considered labia majora.
Traumatic loss penis [C]	7	0	100	This is not an intersex phenotype but it was included it in this analysis since cases of infants who have lost their penis by accident (e.g. during circumcision) have been clinically managed as intersex cases. The infamous John/Joanna case is the best documented case in the scientific and lay literature on this type of accident (Colapinto 2000).
CAH [D]	270	4	96	It is caused by the enzymatic deficiency of 21-hydroxylase (CYP21). Inefficient cortisol signals the hypothalamus and pituitary to increase CRH and ACTH production, respectively. As a consequence, the adrenal glands become hyperplastic and produce excess hormone precursors that do not require CYP21 for their synthesis. These hormonal products are metabolized to testosterone and dihydrotestosterone mainly. The net anatomical effect is prenatal virilization of girls and rapid somatic growth followed by early epiphyseal fusion in both sexes. Depending of the timing of androgen exposure in an XX fetus, the external genitalia may resemble that of the male due to hypertrophy of the clitoris and closure of labia majora and minora along the midline giving the appearance of an empty scrotum. CAH males do not exhibit an intersex phenotype.
Cloacal exstrophy [E]	66	12	88	It refers to the outpouching of an anatomical structure that during embryonic development collected excretory waste products before the formation of the anus and sex organs through the anterior abdominal wall.

Intersex [1 F]	64	14	86	This study did not make the distinction between XX or XY karyotype and it pooled their data based on intersex phenotype and not etiology (see text for implications on the reporting of incidence rates).
PAIS [G]	99	22	78	Partial androgen insensitivity syndrome, refers to a condition were androgen receptors are not completely activated by androgens. The intersex phenotype is varied.
17-B-HSD-3 [H]	77	36	64	It refers to an enzymatic deficiency of 17-β-hydroxysteroid dehydrogenase-3, which impedes the formation of testosterone. However, due to the presence of other isoenzymes that aid in the formation of testosterone, individuals lacking this specific enzyme have sub-optimal levels of testosterone that are below the values typical for an XY individual. The intersex phenotype is varied.
Penile agenesis [I]	33	36	64	It refers to a condition where infants are born without a penis but with scrotum-containing testicles that are functional. The etiology of this condition is mixed.
CAIS, PAIS, Micropenis [J]	72	44	56	CAIS and PAIS as defined above. Micropenis usually defined as a penis with a length less than 1 cm at birth (see text).
Intersex [2 K]	35	49	51	This study did not make the distinction between XX or XY karyotype in their sample. Mosaic karyotype refers to a number of "X" and "Y" combinations. The study pooled the data based on intersex phenotype and not etiology (see text for implications on the reporting of incidence rates).
True hermaphrodite [L]	4	75	25	It refers to individuals with gonadal tissue known as ovotestis as it contains cells that are characteristic of the testicle and the ovary (see text).
Micropenis [M]	89	89	11	As defined above.
TOTAL CASES	1081			

Pooled data taken from: A= Diamond and Sigmundson 1997, Wisniewski et al 2000; B= Cohen-Kettenis 2005; C= Kristic et al 2000; D= Hines et al 2004, Meyer-Bahlburg et al 1996, Dessens et al 2005; E= Meyer-Bahlburg 2005 , Reiner 2004, Byne 2006; F= Eroglu et al 2004, Zucker 1999; G= Diamond and Sigmundson 1997; H= Cohen-Kettenis 2005; I= Meyer-Bahlburg 2005; J= Migeon et al 2002 ab; K= Rajendran and Hariharan 1994; L= Kristic et al 2000; M= Mazur 2005. (Care was taken not to include the same cohort of intersex cases as some of these studies include literature reviews of previous studies).

In Figure 3, the black color denotes the percent (%) of cases that self-initiated a gender change to male as these individuals were assigned as "females" during infancy. Grey color denotes the percent (%) of cases that self-initiated a gender change to female as these individuals were assigned as "males" during infancy. White color denotes the percent (%) of cases that did not change their assigned sex. It also denotes that no information has been published with regard to long-term outcome in gender identity for these conditions. (Please, refer to Figure 2 for the abbreviations and source of data depicted here.)

Figure 3 shows that the number of individuals who self-initiated a gender change from the assigned female sex category to male is greater than the number of individuals who changed their gender identity from the assigned male category to female. Cases that self-initiated a gender change during puberty or adulthood, but not during childhood, were included in this analysis. This cut-off developmental stage is based on the fact that gender identity during childhood is most likely influenced, if not determined, by parents and physicians (Cohen-Kettenis 2005). In descending order, reported changes in gender identity from female to male according to intersex condition are: micropenis, 5α-reductase-2, 17β-HSD-3, traumatic loss of penis, cloacal exstrophy, and PAIS (see figure legend 2 for abbreviations). In contrast, reported self-initiated changes from male to female are: CAIS/PAIS/micropenis, cloacal exstrophy, penile agenesis, and PAIS (see figure legend 2 for abbreviations). It is worth-noting the scarcity of reports on long-term outcomes studies with regard to gender identity and the sexual life of intersex individuals after their clinical management. In spite of this significant limitation, it is becoming increasingly clear that many intersex conditions should be assigned to male and not to the female sex category. These include: penile agenesis, micropenis, cloacal exstrophy, 5α-reductase-2, and 17β-HSD-3 (for a discussion see Byne 2006).

Although it has not been clearly established that gender identity is determined by chromosomal sex, sex of rearing, or prenatal hormone exposure, androgens constitute a common ground for sex researchers and clinicians to argue about male gender identity. The debate is based on a wealth of animal research showing that exposure to androgens affects the sexual differentiation of the brain and behavior. To date, it is yet unclear whether prenatal, postnatal, or perinatal androgen environments play a role, if any, in establishing gender identity. Nevertheless, contrary to animal studies, humans may require functional androgen receptors for "male" brain development, which in turn may contribute to male gender identity. Data on individuals with CAIS support this hypothesis as these XY individuals live as females. Notice that a 100% of CAIS cases were assigned to the female sex (Figure 2) and to date, there has not been a published result on self-initiated gender change to male (Figure 3). This interpretation is consistent with that presented by Meyer-Bahlburg (1999) and Byne (2006). A recent developmental neuroendocrine model for humans proposes that an effect of prenatal androgens on gender may be reinforced further by androgen secretions during the neonatal period and puberty (Byne 2006). If this hypothesis is correct, the second birthday is way too early for sex assignment procedures including genital surgery. It is worth-noting the lack of agreement on long-term outcomes studies on gender identity among XX individuals with congenital adrenal hyperplasia (CAH). The official standpoint is that these individuals should always be assigned to the female sex (AAP 2000; Meyer-Bahlburg et al 2004) even though there is evidence that some of these individuals live as males (Meyer-Bahlburg et al 1996, Jorge et al 2007) and have weaker identification as females than non-CAH females (Hines et al 2004).

Taken together, this analysis has revealed that a greater proportion of intersex cases are assigned to the female than to male sex category (Figure 2) and that, when given the opportunity, more cases change from the assigned female category to male than from the assigned male category to female (Figure 3). These changes may compensate for the greater number of sex assignments to female than to male.

The current clinical management of intersex cases poses great ethical and sociopolitical challenges. Most of these individuals were submitted to anatomical reconfiguration of their sex organs in order to fit them into the assigned sex category. In intersex cases, it is clear that the sexual anatomy is no longer a collection of vessels, nerves, and tissues during the decision-making process to assign or re-assign sex to an intersex case. In this process the flesh becomes a body, a sociopolitical matter. As we have seen, even though the algorithm of sex classification should guarantee a proportional assignment to the male sex versus the female sex categories, the reality is that the female sex is over-represented among intersex individuals. The notion is that, surgically, "it is easier to make a hole than to build a pole" as it is expressed in a German website www.nadir.org/nadir/initiativ/kombo/k_34isar.htm . The clinical goal in the case of the male is to preserve a functional penis as defined by the ability to urinate while standing and to be able to be inserted into a vagina during intercourse. In contrast, the clinical goal in the

case of the female is to preserve the potential for reproduction. A genital surgery to conform to the assigned sex is, by large, a sophisticated strategy to suture a female out of an otherwise 'defective male'. Once again, here comes into play the notion that 'female' is the 'default sex' and that in the absence of a full embryological program for a *natural* male, a female can be artificially constructed. It seems that technical limitations with regard to genital surgery overrides any other clinical consideration in the decision-making process for sex assignment and clinical management of individual cases. In this sense, in spite of the scientific justification behind each step of the algorithm of sex classification, the cosmetic reconfiguration of the sex organs to match "anatomy" and "sex" remains as a clinical priority in these cases. It is not surprising that the Intersex Society of North America (ISNA), the leading advocacy group in the USA for intersex clinical and civil rights, has been proposing a moratorium to intersex genital surgeries for a number of years. Their views on this matter is consistent with other international advocacy groups such as the Peer Support for Intersexuals in Japan (formerly Hijra Nippon, and the United Kingdom Intersex Society (Chase 1999). Fortunately, the medical establishment is now listening to the recurrent request of intersex individuals to consult them with regard to the desirability of genital surgeries.

However, in spite of this significant progress in the field, there is still lack of consensus among experts regarding clinical management of intersexuality around the world (Table 3). Three predominant ideologies are apparent in their opinions. First, a healthy sexual identity is defined as a "female" who has a "male" partner and viceversa. Second, a healthy sexual life refers to functional genitalia with regard to heterosexual intercourse as defined by penile insertion into the vagina. Third, it is an emergency situation when the sexual anatomy does not support these heteronormative values, and the medical establishment must interfere to restore such values.

Encoding intersexuality as a "rare congenital disease"

Justifications for the current inadequate management of intersex cases at times use the statistical label of "rare disorders." The American National Organization of Rare Disorders (NORD) lists several intersex phenotypes as rare or "orphan" diseases under different categories. NORD provides the following definition: "A rare or 'orphan' disease affects fewer than 200,000 people in the United Sates" (NORD, 2007). Similarly, the International Classification of Disease (ICD) provided by the World Health Organization (WHO) clearly exemplifies two stages of statistical reasoning applied to medicine: first, the use of nomenclatures as systems of naming, and second, the encoding through the use of algorithms. According to this system of classification, the intersex phenotype can be found under three different categories based on etiology as the criterion for classification. These are: endocrine, nutritional, metabolic, and immunity disorders (codes 240-279), diseases of genitourinary system (codes 580-629), congenital anomalies of genital organs (code 752). Even though the appearance of the external genitalia is the most easily recognized feature and first criterion for diagnosis of the intersex phenotype, the clinical criterion for classification is etiology and not the anatomy of the sexual organs. Indeed, the criterion for a complete clinical management of these cases is precisely the cosmetic appearance of the sexual organs. The discrepancy between the current classification system and the clinical treatments of such cases has a profound impact on how intersexuality is managed by physicians and by society. According to this international system of classification, intersex cases are "rare" as individual cases can be encoded under different categories; some of which has nothing to do with "sex." This system of encoding, then, has a direct impact on incidence rates and prevalence estimates of intersex cases as it encodes them as "rare" events.

According to Durkheim and Mauss seminal work on statistics in 1903, *De quelques formes primitives de classification: contribution a l'etude des representations collectives*, systems of classification are "a first philosophy of nature" (Desrosieres 1998). Systems of classification, beyond providing order, provide comfort as they name and encode the real and the natural around us to give universal character to individual phenomenon. At the outskirts of these systems we find the un-real, the un-natural, or simply, the freakish and the monstrous: the things that cannot be named. But if named, they should be systematically encoded; therefore, sabotaging the social strategy of reinforcing the idea of a rare event in order to avoid its proper management. As mentioned earlier, systems of classification require the assumption that each criterion for classification is *real*, *natural*, and *universal*. In this context, it is not surprising that incidence rates for intersex births remains a mystery today. One should ask the impolite question of how "rare" is intersexuality? Some estimates for intersexuality include: 1 to 3 cases for each 2,000 births (Dreger, 1998), 1 in 2000 (Blackless et al 2000), 1 in 4,500

(Warne 1988), and 1 in 5,000 live births (Olaf Hort et al 2005). The frequency reported by Fausto-Sterling and Dreger is similar to the incident rates for cystic fibrosis (approximately, 1 in 2,000 Caucasian births) and for Down Syndrome (approximately, 1 in 800 live births). Even for the most common condition within the intersex category, there is no agreement with regard to its frequency. As Dreger (1998) points out, three well-respected medical texts report CAH frequencies spanning from 1 in 60,000 births, 1 in 20,000 births and greater than 1 in 12,500. NORD lists CAH as a rare disorder, but given the lack of agreement with regard to prevalence estimates, is CAH really "rare"? Given that intersex phenotypes are encoded under different categories according to etiology as the criterion for classification, one may assume that each phenotype is 'rare'. But, what if intersexuality (CAH, true hermaphroditism, partial and complete androgen insensitivity syndrome, 5α-reductase syndrome, etc.) is encoded under a single category based on the anatomy of the sexual organs? Would intersexuality still be "rare" if the incidence rates are calculated based on phenotype and not etiology? The answer to this question is well beyond the realm of numbers since the system of encoding is used to justify the medical management of intersex births as it reinforces the idea of a rare event. The current system of encoding of these cases is not consistent with their clinical management as the ultimate goal is "to correct" the appearance of sex organs that are not typical. By including phenotypes such as Kinefelter syndrome, Turner syndrome, and late-onset adrenal hyperplasia in her encoding system, Fausto-Sterling estimated that 1.7% of the population can be classified as intersex (Fausto-Sterling 2000a). Others have argued that this figure is an over-estimation of the true prevalence of intersex of about 0.018%, almost 100 times lower than the original estimate by Fausto-Sterling (Sax 2002). It has also been estimated that at least 300,000 people are intersex in the USA to date, and that possibly an equal number whose intersexuality becomes apparent during puberty (Armstrong 2003), but again, the prevalence estimates depends on the system of encoding individual cases. Therefore, it is not clear that the intersex phenotype is a *rare* congenital disease even under NORD's definition. It is also important to keep in mind that a number of intersex phenotypes are a result of a given enzymatic deficiency in the biosynthetic pathway of steroids due to recessive mutations of specific genes. This means that inheritance of such mutations tend to occur in population clusters. For example, the incidence of CAH is higher among Latinos, Yugoslavs (1 to 2 % of the general population), and Ashkenazi (Eastern European) Jews (3 to 4 % of the general population) (White and Spiser 2000). Therefore, the political geography of intersexuality cannot be overlooked when considering incidence and prevalence rates. For instance, what are the relationships between social class, race, and geographic distribution of intersex cases across time? Nevertheless, the inconsistent reports of intersex incidence rates stem from clinical codification systems that are deficient when it comes to sex.

Table 3: Experts' opinions of the clinical management of intersexuality
Selected countries

Country	Opinion	Reference
Yugoslavia	"The basis of surgical; treatment of intersex disorders is not to coordinate the phenotype and the genotype, but rather to form the external genital organs which will allow functional sexuality. It is much easier to create a vagina as a passive organ than an erectile phallus with sufficient dimension. Therefore, the authors suggest that such infants be reared as females."	Kristic Z, Perovic S, Radmanovic S, Necic S, Smoljanic Z, Jevtic P (1995) Surgical treatment of intersex disorders. Journal of Pediatric Surgery, 30 (9): 1273-1281.
France	"When a baby is born with genital ambiguity, the normally routine announcement of the baby's gender cannot be made to parents, and the medical team suddenly finds itself faced with a medical and psychological emergency that requires immediate and rational management. The infant's future identity will be based in great part on gender, which is usually apparent at birth."	Sultan C, Paris F, Jeandel C, Lumbroso S, Benoit Galifer R (2002) Seminars in reproductive medicine, 20 (3): 181-188
India	"Parents prefer the intersex children to be raised as male possibly because of the less social stigma attached to an impotent male than to sterile female, and because males are socially independent".	R. Rajendran & S.Hariharan (1995) Profile of intersex children in

Table 3: Experts' opinions of the clinical management of intersexuality
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		South India. Indian Pediatrics, 32: 666- 671.
Australia	"A newborn with genital ambiguity represents a medical emergency. With rapid, systematic investigations, early gender assignment and appropriate treatment, this child can have a well-adjusted life. If the anomaly remains unrecognized, the diagnosis is late, or the gender chosen is not associated with functional genitalia, the consequences can prove disastrous."	Hrabovsky Z & Hutson JM (2002) Surgical treatment of intersex abnormalities: A review. Surgery, 131 (1): 92- 104.
USA	"The birth of a child with intersex is a true emergency situation and an immediate transfer to a medical center familiar with the diagnosis and management of intersex conditions should occur. (...) Further data are necessary to formulate guidelines and recommendations fitting for the individual situation of each patient. Until then, the parents have to be supplied with the current data and outcome studies to make the correct choice for the child."	Frimberger D and Gearhart JP (2005) Ambiguous genitalia and Intersex. Urologia Internationalis, 75: 291-297.

Overcoming the strict binary classification of sex

Is the current algorithm for sex classification the best possible one?

> *At first sight, the best algorithm is the one that most often approached the truth, in other words, that assigns in every case the degree of causality that best corresponds to reality. But we do not know the truth, since that is what we are looking for. The best algorithm is therefore the one whose imputations coincide with those of the best expert. But who is the best expert? Fine: the best algorithm is the one that judges like a consensus among experts. And if there is no consensus among experts? Then the best algorithm is the one that creates consensus, by combining the viewpoints of the experts who agree to submit to it. Good: but what if all algorithms do that, each in its own way? Then the best algorithm is the one whose judgments differ least from those of the other algorithms. Unless no better algorithm can be found? (Fagot-Largeault 1989, quoted in Desrosieres, 1998).*

There has been a significant shift in management policies with regard to sex assignment or re-assignment of intersex infants in recent years (Daaboul and Frader 2001; Nelson and Gearhart 2004; Thyen et al 2005). The "optimal gender policy," proposed in the 1950s, stated that humans are born psychosexually neutral, and that the sex of rearing plays a pivotal role in gender identity formation. They proposed that a clinical decision regarding sex assignment should take place prior to the second year of life and that intersex children should not become aware of their sex history in order to avoid psychological distress or doubts about the assigned sex (Hampson et al 1956; Money et al 1957). An important shift in the clinical management of these cases is full disclosure of medical information to the affected parents and their participation in the decision-making process, a paradigm that is known as "full consent policy" (Diamond 1999, 2004; Diamond and Sigmundson 1997; Wilson and Reiner 1998; Lee 2004). Under this policy, one has to assume that parents are actually capable of influencing the final decision with regard to sex assignment of their baby.

Colombia is the only Western society where the courts participate in the decision making process of infant sex re-assignment surgery based on their Constitution (Haas 2004 and Martin 2002). In Colombia, intersex cases are discussed to establish the desirability for genital surgeries, and in some cases, surgeries are deferred so that the individual can decide for himself/herself. However, in the end, the participation of the law may only have the effect of guarantying that the "full-consent policy" is truly in place during the decision-making process for sex assignment. Legal intervention does not solve the main issue at stake, and that is, to insist in fitting intersex cases into a binary classification system. The official position continues to view intersexuality as an emergency that requires clinical intervention,

including surgery (Hrabovszky and Hutson, 2002; Nelson and Gearhardt, 2004; Frimberger and Gearhart, 2005).

As stated earlier, in the case of congenital adrenal hyperplasia (CAH), the American Academy of Pediatrics (AAP) officially recommends that XX individuals are unequivocally assigned to the female sex in spite of evidence that a proportion of these individuals consider themselves males (Byne 2006). The only logical explanation for this position is that to officially recognize that some CAH cases can be "male" is to evidence the failure of the algorithm constructed, validated, and protected by the medical establishment. This is a self-perpetuating system where cases that fail the algorithm are considered 'rare events' that must be brought back into the algorithm. Nevertheless, the AAP recommends:

> *Because of remaining uncertainties with regard to the long-term psychological and physical aspects of treatment among these patients, ongoing counseling of the parents and the affected child is apparent. Although it appears that most individuals are able to function in the normal range and are well-adjusted, few studies have been done that address the social, psychological, and sexual outcomes for affected adolescents and adults* (AAP, Pediatrics 2000).

Since 2005, the Puerto Rico Health Department changed its birth certificate form, creating a mechanism for encoding intersex cases, an alternative that defies the traditional statistical management of ambiguity (D Valencia and L Alvelo, personal communication). However, changes in statistical forms, does not necessarily change the worldview of health professionals, who must be educated about the possibility for classifying the infant as "intersex" until a clinical management program for the infant is established. The birth certificate changes allows for the possibility of a relatively accurate estimation of the incidence rate of intersex. This is an unique opportunity, for it will provide a basis for examining the incidence rates according to the ICD and the NORD systems. Taking advantage of these changes, the Puerto Rico Health Department should even propose its own classification system. A new birth certificate policy opens the possibility for initiating other changes for the creation of a public policy regarding the management of intersexuality and for the scientific study of the implementation of this policy.

The Puerto Rico Department of Health should recommend that genital normalizing surgeries should not be performed and that the coding of intersex into the birth certificate be temporary or permanent, allowing for sex changes if the individual so requires. The establishment of an intersexuality management policy requires a new algorithm of sex classification.

A new algorithm must allow for the coding of cases that are best described by a continuum of phenotypic variations. These variations should be understood as normal randomness in the multiplicity of biological processes underlying the sexual differentiation of the human body. Although some of these events may not be the most frequent or typical to occur during the first trimester of fetal life, it is not the task of medicine to view these events as "abnormal". It is clear that even the discipline of developmental biology has not been exempt of the social pressures and ideologies with regard to what constitutes normality (Gilbert and Fausto-Sterling 2003). A recent initiative championed by ISNA aims to replace the term "intersexuality" with "disorders of sex development" to bring agreement upon the cases that should be considered as intersex for the purpose of coding and estimating incidence rates, and presumably to de-stigmatize biological sexual diversity (Hughes et al 2006; visit **www.isna.org** for "Clinical guidelines for the management of disorders of sex development in childhood" and "Handbook for parents").

The proposition of a new codification system based on etiology and phenotypes is a great initiative. However, the effectiveness of the de-stigmatization of intersexuality when labeled as a "disorder" should be evaluated. What is truly needed is an algorithm that does not question such biological diversity by allowing a non-binary system of classification that view these non-typical cases as 'random', but not 'rare', biological events. Last, the medical establishment should avoid surgeries that aim to make a sex organ more in tune with a male or a female phenotype, as opposed to surgeries that aims to bring organs back into the pelvic cavity, as in cloacal exstrophy cases, or surgeries that aims to exteriorize the urethrae to allow voiding of the bladder. The first case is a cosmetic surgery that imposes anatomical constraints to the future sexual life of the individual, the second case preserves life, and the third case greatly improves the person's quality of life by allowing everyday normal functioning. A clear set of clinical criteria can be established to define the desirability of some surgeries while classifying others as elective surgeries. Patient input is essential but, historically, the issue of timing genital surgeries has provided the clinical justification for submitting the infant or the child to such surgeries. At the core of this controversy is the lack of knowledge with regard to the "embryology of gender". For how long should these surgeries be deferred? Can we take the patient's word for revealing h/is/er "true sex" or must we somehow confirm h/is/er gender? The notion here is that nature 'tricked' the body, and that the individual can now trick us by living a gender that is not congruent with h/is/er sex. The current management of intersexuality demonstrates that medicine has taken up the

responsibility of protecting the dyad sex:gender to preserve social agreements on what constitutes livable sex.

Taken together, it is appropriate to revise our current classification system as the management of intersex cases does not guarantee that an assigned sex category under a binary system that is based *a priori* on sexual anatomy will match gender identity later in life. More importantly, there is now sufficient data showing the insufficiencies of one of the most heavily used categories in statistical classification: sex. It is an attainable goal for the medical and legal fields to re-define this category for the coding into the birth certificate the cases that do not follow the binary system. What is true about "sex" then? That: (i) our current classification system of sex is ambiguous, (ii) our current classification system of sex is faulty, and (iii) our current classification system of sex must be statistically revised with a critical and open mind.

But until then, what seems obvious about sex, the innocent classification of the infant's sex organs and the dichotomy of the pink and the blue, will continue to be engrailed in our brains even as we gaze through magazine covers waiting in line to pay for our secret cravings at night.

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