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Genetic Sex Conditions and Redefining Sex

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Introduction

Western culture has a tendency to value binaries and discreet categories that separate its social structure and provide a sense of order and organization. The value placed on binaries and categories may be advantageous in some aspects, but when it starts to infringe upon the legal and medical rights of individuals not easily placed in either binary category, it can become less advantageous.

A baby is usually classified as either male or female shortly after birth, and all future legal, social, and economic actions and rights of that individual are more or less decided according to this classification. A problem with this system arises when children are born that do not neatly fit into either classification. These intersex individuals may be treated as abnormal in many spheres of their lives, which may have detrimental effects on their psyches. In the past, children determined to have ambiguous genitalia, defined as not fitting into either sexual classification, have often undergone infantile surgery in order to correct the ambiguity. In many ways, this surgical correction has had a major influence on the social and legal futures of these individuals, since a significant portion of Western culture depends on maintaining a sexual binary. One could say Western society may need to be more widely educated regarding the occurrence of medical conditions that may result in ambiguous genitalia and how to effectively integrate effected individuals into legal and social systems.

Because medical professionals are classifying the sex of each individual that is born and are faced with how to best treat intersex conditions in the context of a patient's physical, psychological, and legal needs, the medical community may need to consider adopting a strategic guide for effectively treating intersex individuals. The first section of this paper presents a few of the predominant genetic conditions that affect sexual development compared to typical sexual development. The second section aims to discuss how individuals with these conditions are typically approached in a clinical environment and discuss potential improvements in treatments. The final section examines a few societies in which intersex individuals are effectively integrated into the legal and social spheres and how they may serve as examples for how Western society might improve its treatment and classification of intersex individuals.

I.

Typical sexual development follows a specific pathway involving multiple genes, hormones, and organs over a considerable length of time. The presence and expression of certain genes only determine whether ovaries or testes will develop. The rest of sexual differentiation depends upon the characteristic secretions of the gonads that develop.

Undifferentiated urogenital ridges are present in both male and female embryos until the seventh week of gestation. At the seventh week, the sexual-determining region of the Y chromosome (SRY) is expressed in those individuals with a Y-chromosome, and they will eventually develop into males.[1] The absence of the SRY gene leads to ovarian development and will eventually result in a female phenotype. Before gonads begin to develop, a double genital duct system consisting of Wolffian and Müllerian ducts as well as a common external orifice exist in all embryos. As gonads develop, the single-duct system will differentiate and develop while the other degenerates.

As testes develop, they begin to secrete the steroid hormone testosterone, which is manufactured in the Leydig cells, and a peptide hormone called MIS (Müllerian-inhibiting substance), which is manufactured in the Sertoli cells.[1] The expression of the gene that encodes MIS is induced by an SRY-associated protein and thereby accompanies testicular development directly.[1] Testosterone secreted from the testes induces the differentiation of the Wolffian ducts into the vas deferens, epididymis, ejaculatory duct, and seminal vesicles. In combination with dihydrotestosterone (DHT), a derivative of testosterone formed by the enzyme 5-alpha-reductase, testosterone induces the fusion of the labioscrotal fold to form the scrotum.[1] It also stimulates the enlargement of the genital tubercle to form the penile glans tissue. The urogenital fold develops into the urethral groove and external anal sphincter, and the embryological cloaca develops into the bladder, urinary ducts, bulbourethral glands, and prostate.[1]

In females, neither MIS nor testosterone is typically produced because no Y chromosome accompanied by an SRY gene is present. Therefore, Müllerian ducts differentiate into the Fallopian tubes and uterus without an ovarian hormone signal, and the Wolffian ducts degenerate in the absence of testosterone and MIS.[1] In typical female development, the genital tubercle develops into the clitoris, and the urogenital fold develops into the labia minora/vestibule and anal sphincter. The labioscrotal fold develops into the labia majora, and the embryological cloaca develops into bladder, urinary ducts, and vagina.[1]

Pseudovaginal Perineoscrotal Hypospadias (PPSH), XX and XY sex reversal, Androgen Insensitivity Syndrome (AIS), and Congenital Adrenal Hyperplasia (CAH) are just a few frequently encountered genetic conditions in which the typical process of sexual development is altered, producing an atypical phenotype.

Pseudovaginal Perineoscrotal Hypospadias (PPSH), previously referred to as male pseudohermaphroditism, refers to a condition involving a genital configuration in which the urethral opening is located in the perineoscrotal region potentially accompanied by an incompletely closed genital opening resembling a small, shallow vagina. PPSH arises from a 5-alpha reductase enzyme deficiency. This enzyme converts testosterone to DHT in the testes of typical males, and therefore a deficiency in males can lead to the development of external genitalia resembling that of a typical female. The karyotypes of individuals with PPSH are typically 46, XY.[2] The SRY gene is usually present, which would typically lead to testicular differentiation and development. However, mutations in the SRD5A2 gene on the short arm of the second chromosome or the SRD5A1 gene on the fifth chromosome cause a translational error in manufacturing one form of the 5-alpha-reductase enzyme.[2] The mutations typically found in the SRD5A2 gene are multiple base deletions or missense mutations at positions 197 or 212.[3]

The external genitalia of individual with PPSH are often ambiguous at birth, and the phenotype could include perineoscrotal hypospadias and a blind pseudovaginal pouch mentioned before.[2] Individuals with 5-alpha-reductase deficiency are typically reared as females if a blind pseudovaginal pouch is present, and additional symptoms are usually not evident until the body undergoes alterations associated with puberty. At puberty, masculinization including typical male habitus, muscular development, voice change, phallic enlargement, and semen production can occur due to the formation of a small amount of DHT. Individuals may also have a small prostate and develop a scanty beard. Amenorrhea and a lack of breast development at puberty may also be signs of this condition.[2]

Biochemically, 5-alpha-reductase converts testosterone to DHT, reducing its steric strain, or the strain caused by the repulsion of electrons that are too close together. Molecules tend to assume the configuration where all electrons are equally spaced and flatter, and decreased steric strain allows DHT to bind to its receptors more easily.[4] Because the 5-alpha-reductase enzyme is defective, appropriate DHT transformation to a configuration with less steric strain is greatly inhibited. Testosterone and estrogen levels as well as testicular histology in individuals with PPSH usually resemble readings expected of typical males. This suggests that testosterone is converted into other substances to prevent negative feedback from inducing overproduction of testosterone. Müllerian structures are usually absent in these individuals, and Wolffian structures can be completely differentiated into the epididymis, ejaculatory ducts, and seminal vesicles.[5] Viscous and concentrated semen resulting from a small prostate and seminal vesicles, as well as micropenis, may be present.[5]

Two forms of 5-alpha-reductase deficiency have been suggested by the work of Leshin et al. (1978).[6] One form is postulated to be the result of the aforementioned structural alteration of 5-alpha-reductase as evidenced by an abnormal dissociation constant for its substrate . The second form is paradoxically characterized by undetectable 5-alpha reductase activity in biopsy specimens but a normal dissociation constant for its substrate, testosterone.[6] 5-alpha-DHT levels in these individuals are low, but 5-alpha-DHT is present in basal amounts, so some masculinization occurs.[7]

Individuals with 5-alpha-reductase deficiency typically choose to adopt a male gender identity at puberty, probably because the effects of testosterone in the brain can override sociocultural factors.[6] Therefore, many of these individuals may opt to undergo sexual reconstructive procedures. High dose androgen therapy has been effective in enhancing virilization and therefore improving self-image and sexual performance for individuals who self-identify with the male gender.[8]

Sex reversal, previously referred to as true hermaphroditism, is another condition resulting in atypical sexual development. It can occur in karyotypic males or females. A diagnosis of complete sex reversal is rare, but it is based on the presence of a portion of the SRY gene at Yp11.31 and the presence of some degree of both ovarian and testicular tissue.

In 46, XX individuals, sex reversal can arise from a translocation of a part of the Y chromosome containing the SRY gene onto an X chromosome.[9] Phenotypically, XX individuals may resemble a typical male, but because only the SRY gene is present, not accompanied by the gene encoding the H-Y antigen, 46, XX individuals still exhibit many phenotypic characteristics that resemble a typical female.[9] There are no Müllerian structures, but bilateral scrotal or maldescended ovotestes that produce both ova and

spermatozoa are usually present.[10] Individuals with genetic sex reversal are usually infertile. Clinical comparisons to individuals with Kleinfelter's Syndrome patients revealed that 46, XX individuals with genetic sex reversal were also significantly smaller in stature.[11] Short stature is common even though IGF1 and IGFBP2 levels are usually normal.[12]

Nonrandom X-chromosome inactivation ratios are common in the gonads of 46, XX males as the SRY gene translocated from the little arm of the Y chromosome to the little arm of an X chromosome may ensure the transcription of that chromosome by encouraging the hypomethylation of its 5'-flanking region.[13] In one case, however, reciprocal translocation of the SRY gene on the little arm of the Y-chromosome to the big arm of the X-chromosome may have resulted in the loss of X telomeric sequences and the subsequent differential inactivation of the X chromosome with the SRY gene.[14]

In 46, XY individuals, genetic sex reversal can arise from either point mutations or deletions of the SRY gene.[15] Phenotypically, individuals exhibit a phenotype mostly resembling that of typical females as normal uteri, fallopian tubes, and external genitalia are usually present, but many atypical secondary sex characteristics such as bilateral streak gonads that are misshapen and histologically homogenous are usually present accompanied by amenorrhea.[16]

Because genes on the X-chromosome as well as chromosomes 5, 9, 10, 12, and 17 have been shown to affect 46, XY sex reversal, the condition may exist in X-linked or autosomal recessive forms.[17] If mutations in any of these genes cause complete gonadal dysgenesis, defined as a loss of gonadal germ line cells, the resulting condition is classified as Swyer's syndrome. Those with the Sporadic Testicular Agenesis (STAS) form of Swyer's syndrome do not have the H-Y antigen that is produced from the expression of the H-Y gene typically found on the Y chromosome. Those with the Familial Testicular Agenesis (FTAS) form do not have the H-Y antigen but exhibit an X-linked recessive inheritance. Those with Familial Testicular Dysgenesis (FTDS) have the H-Y antigen but exhibit streak gonads and a phenotype resembling that of a typical female.[17]

A hypoestrogenized vagina and cervix are common in XX inviduals. These individuals are usually tall, and they may have an enlarged clitoris and a high incidence of neoplasia in the streak gonads.[18] There may be evidence that X and Y loci collaborate in determining the typical male phenotype in XY individuals, and there may be a gene on the X chromosome that blocks the function of the H-Y antigen and consequently inhibits typical male phenotypic development in these individuals.[19]

Androgen Insensitivity Syndrome (AIS) is another condition resulting in atypical sexual development. As its name suggests, AIS is the result of a decreased ability of androgens to bind to their receptors and induce their typical cellular response, and because androgens are in their greatest amounts in genotypic males, symptoms are most severe in genotypic males. Androgen insensitivity usually occurs because testosterone cannot effectively bind to the androgen receptors. This may be due to an abnormality in the DHT receptor, an inefficiency of the receptor-DHAT complex, a decreased affinity of testosterone for the receptor, or a decreased amount of receptors present.[20] Phenotypic variability in the effected population occurs because of a mutation in the AR gene on the long arm of the X chromosome that codes for the androgen receptor.[21] Point mutations and deletions associated with neighboring genes are common, but evidence for inversions that cause a break in the AR gene has also been found.[22]

The SRY gene induces testicular development and subsequent MIS and testosterone secretion when it is present. MIS causes the Müllerian ducts to degenerate, but because the Wolffian ducts and external structures cannot detect the androgens secreted by the testes, the signal needed to induce differentiation, the Wolffian ducts degenerate as well, and the external structures develop to resemble those of a typical female. Inguinal testes are usually the result. The typical neonatal testosterone surge is dampened because the hypothalamic-pituitary axis (HPA) cannot respond to testosterone, and positive feedback to drastically increase testosterone levels cannot be stimulated.[23] Insulin-like growth factors (IGF) are involved in mediating testosterone action and the growth of genital tissue, and IGFs are probably synthesized in genital tissue in response to a testosterone-induced signal cascade. Since testosterone cannot bind and initiate the typical signal to induce IGF synthesis, IGF1 levels are usually low in these individuals, resulting in a subsequent decreased bone mass density (BMD).[24] Gynecomastia, a blind vagina, absent uterus, and female adnexa are common, but most cases are presented when amenorrhea becomes evident or an inguinal hernia is presumed and determined to be inguinal testes.

Because there can be a variability in receptor dysfunction, there are a few different types of androgen insensitivity. Partial AIS, in which androgen receptors are only slightly insensitive to testosterone, can result in hypospadias, gynecomastia, and micropenis as expected of general AIS. However, variability in external genitalia phenotype is exhibited as higher concentrations of testosterone may saturate slightly insensitive androgen receptors and induce cellular responses similar to typical responses.[25] Incomplete AIS, in which androgen receptors are not completely desensitized to androgens but do not have the capacity to induce typical cellular responses to an adequate degree, can result in clitoral enlargement, virilization, the dorsal fusion of the labioscrotal folds, some spermatogenesis, and only partial androgen responsiveness. Because of these signs, the incomplete form may be mistaken as PPSH, but androgen sensitivity tests can be used to confirm AIS.[26] Testes are usually removed soon after an AIS diagnosis because of a high risk of cancer associated with inguinal testes.

Chymerism in heterozygous 46, XX females and linkage to other X chromosome genes suggest AIS exhibits a simple X-linked inheritance pattern.[28] The protein typically produced from the transcription and translation of the AR gene activates the expression of other genes. This ability depends on the structure of the N-terminal domain encoded in exon 1 of the gene, which contains polymorphic CAG repeats. A smaller number of repeats corresponds with a heightened ability of the AR protein to activate other genes involved in cell growth and metabolism, possibly resulting in a higher risk of prostate cancer.[27]

Topical androgen gel therapy exhibits a potential to be successful in treating individuals with partial or incomplete AIS that self-identify as male. However, according to a study of 14 women, clinical patients have a tendency to express complete satisfaction with their rearing, gender assignment, sexual function, and psychosexual development based on their answers to a questionnaire and a psychosexual analysis and do not seek gender reassignment surgery.[29]

In contrast to AIS, which results from the decreased ability of tissue to detect the presence of androgens and thereby respond to them, Congenital Adrenal Hyperplasia (CAH) is characterized by the overproduction of androgens, and therefore the hyper-masculinization of body tissues. CAH is the result of a problem defect in the cortisol synthesis pathway, most commonly the result of a mutation in the CYP21A2 gene on the

short arm of chromosome six that encodes the 21-hydroxylase enzyme.[30] This condition is therefore inherited according to an autosomal recessive pattern. A mutation in the CYP21A2 gene causes an abnormal translation of the enzyme 21-hydroxylase, a misconfiguration of the enzyme, and a subsequent deficiency in enzymatic activity. The enzyme cannot convert 17-OHP to 11-deoxycortisol in the cortisol synthesis pathway and therefore halts cortisol production.[30] A decrease in cortisol production results in decreased negative feedback to the HPA, resulting in increased adrenocorticotropic hormone (ACTH) secretion from the adenohypophysis. Increased ACTH overstimulates the adrenal cortex where cortisol is made in an attempt to increase cortisol production. As a result, because androgens are also produced in the adrenal cortex, androgen production increases, leading to masculinized external genitalia, postnatal clitoral enlargement, and early epiphyseal closure. Hyperpigmentation can also result from the hypersecretion of proopiomelanocortin (POMC) that accompanies the hypersecretion of ACTH and stimulates melanocytes.[31] The gonads and internal genitalia of these individuals usually resemble those of typical males. Salt wasting can result because the disruption of the cortisol synthesis pathway at the 21-hydroxylase reaction also causes a decrease in aldosterone secretion from the adrenal cortex, a huge decrease in salt reabsorption in the kidneys and sweat glands, and therefore large amounts of salt excreted.[32]

Because CAH can result from a disruption of any enzyme in the cortisol synthesis pathway, there are multiple types of CAH. The two main classifications are classic and non-classic. The classic type is further divided into the salt-wasting form and the simple virilizing form. Because classic CAH can result in massive salt loss, the classic type is usually more severe while the symptoms of the non-classic type are usually only found late in life and are therefore less sever. In XX individuals, the classic form produces a phenotype that includes clitoromegaly and the fusion of the urethra and vaginal canal, therefore it is usually diagnosed at birth. XY individuals are more commonly diagnosed with the salt wasting form of classic CAH than XX individuals. XY individuals with the simple virilizing form of CAH display early virilization, potentially including an enlarged penis and body hair, between the ages of 2 and 4. Individuals with the non-classic form of CAH exhibit similar virilization to the classic type including infertility, oligomenorrhea, amenorrhea, polycystic ovarian syndrome, and acne in XX individuals, but symptoms occur later in adolescence. Sometimes symptoms never appear and the diagnosis is not made until the individual is tested for another condition from which atypical test results provide evidence for CAH. Individuals with CAH may also be behaviorally masculinized, so there is a high incidence of homosexuality in females.[33]

Phenotypic variation is very broad in individuals with CAH because problems leading to CAH can arise during splicing, because the expression of 21-hydroxylase can be altered by genes in the renin-angiotensin systems, and because variable temporal and spatial gene expression occurs.[34, 35] Bilateral testicular masses have been observed in XY individuals as well as clitoromegaly, gynecomastia, and labial fusion in XX individuals. Late sexual maturation, decreased incidence of pregnancies, and early onset osteoporosis because of decreased BMD are also common in XX individuals. Adrenal stimulation by ACTH can cause adrenal hypertrophy (increased adrenal area), tumors, and adrenal atrophy from exhaustive stimulation.[36] Amygdala function may also be impaired by the hypersecretion of CRH in both XX and XY individuals leading to decreased emotional and fear responses.[37] Low thyrotropin-stimulating hormone (TSH) has been observed because

increased hypothalamic/pituitary/adrenal activity decreases TSH secretion, which also leads to decreased adrenomedullary function via epinephrine and norepinephrine.[38] Decreased levels of thyroxine from decreased TSH secretion leads to a decrease in the permissive action of thyroxine on epinephrine and can also disrupt glycemic control.[39] Testicular tumors or the impairment of Leydig cells as a result of decreased plasma testosterone can lead to decreased spermatogenesis, subsequent azoospermia, and poor semen quality in affected XY males as well.[40]

A fourth cryptic form of CAH is characterized by typical 21-hydroxylase deficiency that is accompanied by no symptoms with the exception of an increased incidence of tumors.

Amniotic fluid steroid analysis is only successful in diagnosing the salt-wasting form of CAH, but a first day urine analysis of 17-hydroxyprogesterone and androstenedione can provide an accurate diagnosis of all forms.[41,42] Nighttime low dosage dexamethasone therapy can dissipate adrenal masses and restore fertility. It is recommended during pregnancy because it crosses the placenta quickly, has a long half-life, and has a large suppressive effect on ACTH, although it may affect verbal working memory and self-perception.[43] The non-classic form of CAH may be treated by adrenocorticosteroids potentially accompanied by adrenalectomy.[44]

Non-classic CAH is the most frequent autosomal recessive genetic condition with an overall frequency of 1 in 5,000 births, although frequencies in Zurich are even higher and gene frequencies in Ashkenazi Jewish populations can reach 0.223.[45] In contrast to the severe symptoms that can occur as a result of CAH, there is a heterozygote advantage for carriers due to the fact that cortisol levels are higher and therefore stress response is heightened and the individuals is therefore more efficient in coping with physiological stress.[46]

II.

Many conditions like the ones described in Part I are diagnosed as Disorders of Sexual Development (DSD), a general category that includes all conditions that result in atypical sexual development. The treatment of these conditions can be very extensive, sometimes including hormone replacement, multiple surgeries, and a great number of medications. Historically, the sexual development of an individual along one of the two typical pathways is emphasized in medical professions, and therefore medical professionals are accustomed to treating patients classified as either male or female. Therefore, when a child is born with ambiguous genitalia or any number of other DSDs, many medical professionals may not be completely confident in how to treat these individuals. The pressure of potentially altering the physical, social, and psychological traits of these individuals combined with a low level of social and medical exposure to individuals with these conditions may make it difficult for medical professionals to know how to effectively treat them. Because the social structure of modern Western society includes such a distinct gender and sexual binary, doctors and other medical professionals are often unable to separate their concern with the social implications of intersex individuals and the medical consequences of certain DSDs for the individuals themselves.

Most of these complications stem from a previously perceived necessity for immediate medical or surgical intervention when an individual with a DSD is presented as well as the customary practice of determining sex from only two options.

Some DSDs impose large health risks on the effected individuals and should be treated in a way that minimizes these risks and detrimental effects. For example, because CAH involves cortisol and aldosterone deficiencies and subsequent salt wasting, hypotension, dehydration, hyponatremia, hyperkalemia, and even death, immediate action to minimize these issues is medically necessary.[47] Gonadal dysgenesis and hypospadias often accompanying DSDs result in higher frequencies of gonadoblastomas and urinary tract infections, which again should be treated to prevent detrimental health effects.[48] But many other DSDs have little to no detrimental side effects. Patients with Androgen Insensitivity Syndrome (AIS) have a theoretical risk for gonadoblastomas, but this risk can be drastically reduced by simply removing the gonads in one surgical procedure.[49] The effects of any treatment beyond what is medically necessary should be carefully considered.

The treatment of many DSDs have been historically linked to social placement and gender socialization because intersex individuals often do not fit into male/female binary categories so relied upon in traditional Western medical practice. Before the late 1970s, there was a minimal focus on how to treat intersex patients effectively considering what was in the best interest of the patient. For example, infantile clitoroplasty in individuals with clitoromegaly has been very common to conform ambiguous genitalia to the shape, size, and configuration seen in typical females. This procedure was generally used in any case of genital abnormality, usually defined as a morphology that made it difficult to identify the presence of an adequate penis. Used in an effort to ensure the classification of these babies as female, these surgical procedures can potentially reduce the individuals' genital sensations, which can be detrimental to their sexual pleasure, overall sexual satisfaction, self-image, and sexual performance, which can then lead to even more negative effects psychologically.

Any child born that had an atypical karyotype was considered a social and medical emergency. Following any infantile genital reconstruction surgeries, parents of the individual were advised to keep the nature of the condition confidential, and all intersex children were recommended to be reared as females as reductive surgery is quicker, easier, and cheaper than surgeries that required the addition of tissue.[50] In addition to unnecessary infantile sexual reconstructive surgeries, past studies used to determine the severity of CAH were even illogically based on which gender-charged toys affected children played with rather than on biochemical or physical symptoms.[33]

In the late 1970s, however, Dr. Milton Edgerton at Johns Hopkins University and the University of Virginia started producing a bulk of scientific literature recommending proper clinical treatment of intersex and transsexual individuals, including the psychological and surgical facets of their treatments. He started to separate the social and medical aspects of individuals with DSDs and transgendered individuals. His goal was to make the medical aspects of treatment more objective and to construct a comprehensive list of standard guidelines for treating these conditions in an attempt to make the treatment of these individuals more fulfilling for the patients themselves in regards to their clinical health and psychological satisfaction. Before long, "gender dysphoria" became an official diagnosis for intersex or transgendered individuals who felt that their gender

socialization did not correspond with the sex they felt they inhabited. Edgerton began calling reconstructive surgeries "sex-confirmation operations" rather than sexual-reassignment operations. Advocacy groups of medical professionals and social advocates began to construct and modify the guidelines on how to treat these individuals in a clinical setting. Eventually, necessary reconstructive surgery needed to improve healthy body function such as the cosmetic correction of hypospadias, previously conducted to appease a social binary, was separated from the type of reconstructive surgery desired by the patient utilized to re-enter society as a member of their self-identified sex. Similarly, the use of infantile clitoroplasty and other unnecessary procedures to alter ambiguous genitalia were restricted.[51]

A shift to patient centered medicine involving transgendered patients or patients with DSDs altered the way these individuals were treated. Steps were taken to ensure that gender dysphoria was authentic by a "gender team" of medical professionals across many fields. Professional thoroughly presented patients with the risks involved in "sex confirmation operations" and were required to be declared physically and mentally fit for gender reassignment by a group of psychologists and surgeons before the process could be initiated. Preliminary real-life tests were conducted, requiring a patient to publicly and privately assume the role of the opposite gender to ensure adequate transitioning following irreversible surgery.[51] Aesthetically satisfying cosmetic alterations were considered to be important, but proper functioning and sensation of surgically altered genitalia were considered very high priorities. Gender reassignment surgeries for transgendered men who identified as women aimed to produce a neovagina capable of intercourse and a sensate clitoris capable of inducing orgasms in order to maximize sexual satisfaction.[52] Genetic counseling services were also made available to inform the patient of their condition, and counseling was framed around being sensitive to the patient and explaining that their condition, although atypical, is normal and something that happened before they were born at no fault of their parents or themselves.[53]

Many legal battles then began to arise over how men and women who have undergone "sex-confirmation surgeries" should be categorized legally and who is legally responsible for children with DSDs. In 1999, the Constitutional Court of Columbia stated that children born with ambiguous genitalia were treated based on the wishes of their parents granted the parents were concerned for the wellbeing of the child, not themselves.[50] Although a step in the right direction, a more considerate model for treatment was developed later. Milton Diamond and Keith Sigmundson developed an extensive list of guidelines that should be strictly followed when treating individuals with DSDs and/or infants that may mature to be transgendered. This list included a full and concise genital inspection at birth, a primary focus on major health risks such as electrolyte imbalances and hypospadias associated with CAH, and patience during the meticulous inspection. This model included full disclosure of information to the parents and an encouragement to seek counseling while being reminded the condition arose due to fault of no one. A focus on the affected patient was paramount in this model, and while sex might be classified due to the likelihood of how that individual would develop psychologically and physiologically, no major operations would be performed to solidify the classification. Once the patient is able to make informed decisions about his or her condition, then physical changes can be made provided they are eligible according to the aforementioned criteria. Diamond and Sigmundson's model was built on communication and positive messages, an

approach finely tuned to both the psychological and medically aspects of treatment. And their main point was that most intersex conditions do not necessitate major surgery for the patient to feel socially and psychologically fulfilled.[54] This model is still widely used today, and has been modified to appeal to individuals in relation to their contexts. A book called *Transgender Emergence* also provides a very comprehensive guideline for an integrated treatment involving many sociocultural techniques to be used by health professionals and social workers to improve the quality of treatment for the patients.[55]

Presently, there are still many legal battles happening involving insurance coverage of sexual reassignment surgeries and other treatments regarding DSDs and transgendered identity. Twenty-eight states do not have explicit Medicaid regulations about coverage, 21 states have explicit regulations excluding coverage, and those that do not have explicitly exclusive regulations do explicitly exclude cosmetic or experimental procedures.[56] Of course, common legal arguments in favor of including "sex-confirmation surgeries" rest on the fact that reassignment surgery has been proven to be effective and fulfilling for the patient and that if denied surgery, a person's psychological health may be negatively impacted.

Knowledge and awareness about how to treat DSDs and how to improve the psychological health of transgendered individuals should be emphasized in medical communities. Many individuals with AIS and other DSDs have had less than quality medical evaluations and have undergone marginalization by their healthcare professionals and therefore less than effective treatments.[49] Sometimes, the biggest issue is how to cope with the social and psychological implications of DSDs, for example when doctors must decide how to manage masculinization at puberty of individuals with 5-Alpha Reductase Deficiency. Patient-centered care that involves a multidisciplinary approach by medical and other support teams well versed in how to convey sensitivity toward these individuals is of the utmost importance.[48] Because some intersex and transgendered individuals are undergoing changes that could potentially be traumatic, more follow up studies need to be conducted on how patients respond under these guidelines of care. Individuals need to supply informed consent on how they would like to be treated, which means some families may need to wait 10-15 years after their child is born with a DSD to make decisions about how to approach the condition medically if intervention is an option.[50]

Groups like the World Professional Association for Transgender Health (WPATH) constantly construct and revise the Standards of Care of intersex individuals. The Endocrine Society has created guidelines on how to properly diagnose DSDs and how to confer treatment. The Gay and Lesbian Medical Association (GLMA) aims to create a welcoming community of medical professionals prepared to treat DSDs and transgendered individuals, and Accord Alliance is an advocacy group for legal and social change surrounding the rights of transgendered individuals. Websites like YouthResource and Trans Basics are also immensely concerned with these individuals' experiences in the doctor's office.[57] These groups and many like them are making great strides toward informing medical professionals and families of patients with DSDs on how to manage these conditions medically and socially. A larger emphasis on integrating these methods into medical school curriculums as a part of sensitivity and ethical training has also been widely advocated.

Developing uniform standard guidelines for how to treat transgendered individuals and individuals with DSDs is becoming easier as the people developing them continue to

consider the comfort and well being of the patient, but we must also be careful in realizing that within the diagnosis of gender dysphoria or any of the many DSDs, individuals can vary widely with regard to medical needs and psychological states of mind. Not every individual can be treated the same way and yield optimal results. Just as in other fields, each patient must be treated as an individual, and these guidelines may need to be modified depending on the particular patient's needs. These challenges still comprise a large gray area of medicine that needs to be constantly modified and fine-tuned.[58]

The language used in the medical field regarding DSDs and intersex individuals also needs to be altered. Lee et al. (1996) proposed that a DSD should be redefined as a "congenital condition in which development of chromosomal, gonadal, or anatomic sex is atypical," which emphasizes that DSDs are not abnormal or disorderly, simply atypical. The renaming of true hermaphroditism, male pseudohermaphroditism, and testicular feminization as sex reversal, PPSH, and AIS are also steps in the right direction as they reflect the physiological and clinical aspects of the condition rather than traditional social responses to these atypical phenotypes. The connotation that words carry in a diagnosis can have a great impact on how the effected individual views himself or herself when the condition is not under his or her control, so medical jargon is worth considering in reference to these conditions in order to conform to the guidelines set forth by Midgerton, Diamond and Sigmundson, and countless other organizations.

III.

Although Western society typically has a tough time integrating individuals into society who do not fit into the widely accepted male-female binary, many societies around the world have found it relatively easy and simple to effectively incorporate these individuals into society by reorganizing society rather than by reclassifying these individuals. Intersex or transgendered individuals are even greatly admired or considered divine in some societies.

A significant percentage of the Dominican Republic population are effected by 5-alpha reductase deficiency or PPSH described in Part I. These individuals are called the *guevedoces*, and as implied by the Spanish term roughly translated to "testicles at 12," these individuals are born with ambiguous genitalia and raised as female until puberty, at which time they start to exhibit male secondary sexual characteristics including the descendance of testicles and penile growth. The *guevedoces* exhibit a typical male karyotype, but because of a lack or deformation of the 5-alpha reductase enzyme, these individuals are unable to convert testosterone to DHT.[59] This form of 5-alpha reductase deficiency or PPSH has been classified as Type 2 Familial Incomplete Male Pseudohermaphroditism while Type 1 has been understood to be Reifenstein syndrome.[60] PPSH is similar to Reifenstein syndrome but is characterized by autosomal inheritance and gynecomastia. It is characterized biochemically by a structural alteration of 5-alpha-reductase exhibited by an abnormal dissociation constant (K_m) and low levels of enzymatic activity.[6]

In the 1970s, Dr. Julianne Imperato-McGinley visited a small mountain village in the Dominican Republic to study the *guevedoces* and found that they composed about 2% of the general population.[5] In Dominican society, she found that these individuals were legally

and socially considered as a third sex. As their phenotypic transformations progress, the *guevedoces* assume a male gender role in society and usually identify as a heterosexual male with a common desire to father children despite being reared as females for over a decade. This major shift in gender association completely contradicted Money's theory that gender identity becomes fixed at three years old by insinuating that gender identity can completely reverse at least until puberty.[61] Dr. Imperato-McGinley's findings also suggest that gender identity is partly biological and partly sociological. Therefore, she wonders if these individuals assume a male identity at puberty because they are pressured to by society or if they are biologically prone to undergo a shift in gender identity due to physiological and psychological changes.

Regardless of the exact origin and cause of this gender shift, the classification of this subpopulation as a third sex in Dominican society provides a model for how sex and gender should be classified in Western culture. By recognizing the *guevedoces* as members of a separate sex, the people of the Dominican Republic recognize that a strict sexual dimorphism is not universal in humans.[62] The sexual transformation of these individuals is welcomed by joyous celebrations and although these individuals may encounter slight stigmas as a statistical minority, they are at least acknowledged as a third group. They aren't expected to fit into the strict sexual binary imposed by Western culture because they recognize that a strict sexual binary is inapplicable in nature, including the human species.

The recognition of these individuals has not only had social implications, but medical ones as well. Once the physiological effects of 5-alpha reductase deficiency were identified and studied, pharmacological treatments for benign prostate hyperplasia were developed. The discovery of the trophic effects on the prostate by DHT led to the development of 5-alpha reductase inhibitors like finasteride and dutasteride were in order to treat prostate hyperplasia by replicating the physiological effects that 5-alpha reductase deficiency has on the prostate of the *guevedoces*.[63]

The Dominican Republic is not the only country or society that embraces intersex and transgendered individuals as a normal part of society. Native-American "two-spirits" who identify with both their feminine and masculine spirits are considered divine in many North American tribes. The *hijra* of India and south Asia are sometimes holy people and carry out many sacred rituals. They are even included in many holy texts as divinities. The nation of Bangladesh has officially recognized their classification as a third sex. A *kathoey* of Thailand is a transgendered, homosexual, or intersex individual that is regarded as a product of *karma* and is widely recognized as a master within the entertainment and fashion businesses. The list of societies who recognize and embrace the presence of intersex or transgendered individuals is not exhausted here, and they serve as beautiful examples for Western society, proving societies that recognize and integrate transgendered or intersex individuals as integral parts of society often flourish.

Conclusion

Although it is often the genesis of social injustice towards intersex and transgendered individuals, the sexual dichotomy that is engrained in Western culture is not completely based on illusion. Sexual dimorphisms are very prevalent in nature and used to

classify the members of the species. Body structures can be vastly different in males and females of different species. For example, the neuronal cluster of the hypothalamus is markedly larger in males than in females of humans.[64] The purpose of this paper, however, is not to refute that strict sexual dimorphisms and dichotomies exist, but that in the wide variation of life, they should not be considered the only possibilities. And in a human context in which society is a major aspect of life, the sex of an individual that does not clearly fall into either category should not be the cause of being socially ostracized or labeled as abnormal. This philosophy can be extended to the variety of sexualities that exist in the human population as well. Evidence for linkage of human male homosexuality to a gene on the long arm of the X chromosome has been presented as well as a genetic mutation in fruit flies that causes homosexual male courtship behaviors.[65,66] And it is widely accepted among scientists that a huge variety of sexualities is exhibited in the rest of the animal kingdom. Physiology is a result of a very large number of molecules interacting together in complex ways determined by the genetic code in each living thing. This complex interaction of molecules is the machine that manufactures the variety of life. And every molecule in every pathway provides an opportunity for change that should be considered natural and normal. Everything we are as a member of the animal kingdom is determined, in some part, by our biology, and our social abilities should not seek to override this fact but to embrace it.

This paper has illustrated that there are many genetic and physiological origins of intersex conditions. Intersex and transgendered individuals, although statistically atypical, are not abnormal but naturally occurring individuals like any other individual that is considered typical. Medical standards acknowledging the rights of these individuals are transforming, and they should continue to be adjusted as more knowledge and experience is gained concerning how to effectively treat these individuals. Because sexual classification has dramatic effects on social integration, legal standing, a sense of sexuality, self-identity, and the overall sense of well being of an individual, these medical standards cannot be completely objective but must be continuously adjusted for each individual in the context of each individual's life. The acknowledgement and respectful incorporation of these treatments into the medical field can initiate a shift in social stigmas surrounding these individuals and progress toward establishing a society in which all human beings are treated with respect. So many cultures around the world have adopted policies of equality and justice for these individuals in social, medical, legal, and religious spheres, and it is time for Western society to follow in these footsteps. Every human being on earth has a certain amount of androgens and estrogens inside them, and the ratios of the two and the effects they have on the morphology of the body should not be considered a social emergency, but a social opportunity for progress and equality.

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