Consequences of the ESPE/LWPES guidelines for diagnosis and treatment of disorders of sex development

Ieuan A. Hughes*
Professor of Paediatrics
Department of Paediatrics, University of Cambridge, Addenbrooke’s Hospital, Box 116, Cambridge CB2 0QQ, UK

C. Nihoul-Fékété
Paediatric Surgeon
Department of Paediatric Surgery, Hopital des Enfants-Malades, Paris, France

B. Thomas
Support group counsellor

P.T. Cohen-Kettenis
Clinical Psychologist
Department of Medical Psychology, VU University Medical Center, P.O. Box 7057, 1007 MB Amsterdam, Netherlands

Ambiguous genitalia of the newborn is the paradigm of a disorder of sex development that demands a multidisciplinary team approach to management. The problem is immediately apparent at birth. Abnormalities of the external genitalia sufficient to warrant genetic and endocrine studies occur in one in 4500 births. In recent decades there have been improvements in diagnosis and early management, particularly with respect to congenital adrenal hyperplasia, the commonest cause of ambiguous genitalia of the newborn. However, dissatisfaction with overall management remains. A Clinical Guidelines and Handbook for Parents generated by a partnership of health professionals and support groups is available on the internet. The professional societies representing paediatric endocrinology responded by organizing a consensus meeting on the
management of intersex. This resulted in the publication of a Consensus Statement encompassing many aspects of management, extending from birth to adulthood.

**Key words:** Intersex; Disorder of sex development (DSD); Consensus; Disclosure; Consent; Ethics.

Ambiguous genitalia of the newborn is, *sine qua non*, the paradigm of a disorder of sex development (DSD) that demands a multidisciplinary team approach to management. The problem is immediately apparent at birth, and what is conveyed to the family in the ensuing hours and days will have a long-lasting impact. Assignment to either male or female gender is instantaneous when a baby is born. That in rare instances this may not be possible is immensely distressing to affected families. Abnormalities of the external genitalia sufficient to warrant genetic and endocrine studies occur in one in 4500 births.1 There have been improvements in diagnosis and early management in recent decades, particularly with respect to congenital adrenal hyperplasia (CAH), the commonest cause of ambiguous genitalia of the newborn.2 Dissatisfaction remains with overall management, including decisions on gender assignment, the need for and timing of surgical intervention, aspects of disclosure and consent, and the lack of evidence from outcome studies. The demand for improvements has come largely from affected families and patient advocacy groups. A Clinical Guidelines and Handbook for Parents is available on the internet (www.dsdguidelines.org) and was generated by a partnership between health professionals and support groups. The professional societies representing paediatric endocrinology – primarily the European Society for Paediatric Endocrinology (ESPE) and the Lawson Wilkins Pediatric Endocrine Society (LWPES) – responded by organizing a consensus meeting on the management of intersex. This resulted in the publication of a consensus statement encompassing many aspects of management extending from birth to adulthood.3–5

A consensus is a general agreement or an accord which recognizes that the objections of a minority of participants in the process should be resolved as far as is practicable. It is about ‘splitting the difference’ and reaching a solution which is workable and represents positive developments. Difficulties in the management of intersex have been compounded by the use of complex nomenclature which confuses health professionals and affected families alike. The term *intersex* particularly needed addressing, as many families regard this term as pejorative. In addressing this question, the process was a catalyst for a major revamp of a swathe of nomenclature relating to disorders of sex development.

**GENETICS AND NOMENCLATURE**

The dimorphic pathway of sex determination from an initial bipotential gonad and the subsequent sex differentiation of the male/female phenotype are now remarkably well established, and a plethora of genes and hormones involved in the process has been identified (Figure 1). Nevertheless, many genes required for testis or ovary determination remain to be identified. The Consensus anticipated that application of techniques such as microarray, comparative genomic hybridization (CGH), and tissue-selective disruption of candidate genes will enable progress to be made. There are many genes that, when disrupted, have been demonstrated to lead to a disorder of sex development in the mouse, but no syndromes have yet been described in humans as a result of mutations in their homologues.
It has been a truism that ovarian determination occurs only in the absence of testis-determining genes. Figure 1 indicates that a number of genes can act in an anti-testis fashion in a dosage-sensitive manner; examples include \( \text{DAX1} \) and \( \text{WNT4} \). Furthermore, genes such as \( \text{FOXL2} \) and \( \text{RSPO1} \) appear to be involved directly in ovarian determination. \( \text{RSPO1} \) was identified by studying a consanguineous family that included four 46,XX individuals who were SRY-negative and had complete male sex reversal.\(^6\) Palmoplantar hyperkeratosis and a predisposition to squamous-cell skin carcinoma were additional findings. Affected members had a homozygous nonsense mutation in the \( \text{RSPO1} \) gene, a gene that encodes one of the family of R-spondins. These function as growth factors that interact with \( \beta \)-catenin and, via \( \beta \)-catenin stabilization, may also synergize with WNT proteins. The interaction appears critical for early genital development and ovarian determination. This observation in a disorder of sex development is another example of how analysis of human syndromes can lead to an improved understanding of normal sex determination. \( \text{RSPO1} \) is not required for testis determination, a conclusion based on the observation of normal male development and fertility in a 46,XY member of the family who carried the homozygous nonsense \( \text{RSPO1} \) mutation.

With respect to nomenclature, it is customary for basic geneticists to use terms such as sex reversal (complete or partial) prefaced by XX or XY chromosomal definition. These terms, and the term intersex, have been found unacceptable by some affected individuals and support groups. Hence the umbrella term ‘disorder of sex development’ (DSD) has been proposed and defined as a congenital condition in which development of chromosomal, gonadal, or anatomical sex is atypical. This broadly based definition makes it possible to include a range of genital variations, from ambiguous genitalia to micropenis, cryptorchidism, and congenital malformation syndromes such as cloacal exstrophy. The inclusion of ‘congenital’ in the definition of DSD excludes disorders such as precocious or delayed puberty.

The new nomenclature is outlined in Table 1. The karyotype prefaces the acronym, so that female pseudohermaphroditism is replaced by 46,XX DSD and male
pseudohermaphroditism by 46,XY DSD. Ovotesticular DSD defines a DSD characterized histologically by the presence of testicular and follicle-containing ovarian tissue and replaces the terminology ‘true hermaphrodite’. Table 2 shows a classification system for causes of DSD which is now being incorporated in standard endocrine texts and used for teaching modules. It is simple, logical, and workable in clinical practice. The literature is now also becoming replete with the DSD acronym usage when reporting clinical studies or more fundamental studies on mechanisms of fetal sex development.

**MEDICAL MANAGEMENT**

It is axiomatic that initial management of DSD is dependent on establishing a diagnosis, although it is recognized that this may be difficult in many cases of XY,DSD. In this category of DSD a precise diagnosis may not be possible in more than 50% of the cases. Nevertheless, it is recommended that all newborns with ambiguous genitalia should be assigned a gender, but only after expert evaluation has been performed at a centre with an experienced multidisciplinary team. Discussion with the parents at this critical early stage must be open, and parents’ participation in decision-making should be encouraged.

Various endocrine protocols are included within reviews of the investigation and management of ambiguous genitalia in the newborn. It is not practical to recommend a uniform ‘catch-all’ protocol that can be rolled out in all centres. Tests need to be tailored according to the findings on clinical examination and should be consonant with the laboratory facilities available in each centre. First-line testing will include fluorescence in-situ hybridization (FISH) analysis with X- and Y-specific DNA probes and a full karyotype, abdominal/pelvic ultrasound, and serum measurement of 17-OH-progesterone, testosterone, gonadotrophins, anti-Müllerian hormone (AMH), electrolytes and urinalysis. This will rapidly delineate the category of DSD.

Second-line investigations are generally needed in XY and XO/XY DSD. Here, the human chorionic gonadotropin (hCG) stimulation test is pivotal in determining the presence of testes and whether they are capable of producing age-related normal concentrations of androgens. A concomitant adrenocorticotropic hormone (ACTH) stimulation test may also be required if a biosynthetic defect shared by both the adrenals and gonads is suspected. Some uniformity in the protocol for the hCG stimulation test is certainly needed. No consensus has emerged either for the dose and frequency of injections or the age at which the test should be performed in infants. A frequently used protocol is 1500 Units daily for 3 days, with post-hCG serum samples collected.
<table>
<thead>
<tr>
<th>Sex chromosome DSD</th>
<th>46,XY DSD</th>
<th>46,XX DSD</th>
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<tr>
<td><strong>A: 47,XXY</strong></td>
<td><strong>A: Disorders of gonadal (testicular) development</strong></td>
<td><strong>A: Disorders of gonadal (ovarian) development</strong></td>
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<td>(Klinefelter syndrome and variants)</td>
<td>1. Complete or partial gonadal dysgenesis (e.g. SRY, SOX9, SF1, WT1, DHH etc)</td>
<td>1. Gonadal dysgenesis</td>
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<td>2. Ovotesticular DSD</td>
<td>2. Ovotesticular DSD (e.g. SRY+, dup SOX9, RSP01)</td>
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<td>3. Testicular regression</td>
<td>3. Testicular DSD</td>
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<td><strong>B: 45,X</strong></td>
<td><strong>B: Disorders in androgen synthesis or action</strong></td>
<td><strong>B: Androgen excess</strong></td>
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<td>(Turner syndrome and variants)</td>
<td>1. Disorders of androgen synthesis</td>
<td>1. Fetal</td>
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<td>Luteinizing hormone receptor mutations</td>
<td>3β-hydroxysteroid dehydrogenase 2 (HSD3B2)</td>
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<td>Smith—Lemli—Opitz syndrome</td>
<td>21-hydroxylase (CYP21A2)</td>
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<td>Steroidogenic acute regulatory protein mutations</td>
<td>P450 oxidoreductase (POR)</td>
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<td>Cholesterol side-chain cleavage (CYP11A1)</td>
<td>11β-hydroxylase (CYP11B1)</td>
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<td>3β-hydroxysteroid dehydrogenase 2 (HSD3B2)</td>
<td>Glucocorticoid receptor mutations</td>
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<td>17α-hydroxylase/17,20-lyase (CYP17) P450 oxidoreductase (POR)</td>
<td>2. Fetoplacental</td>
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<td>17β-hydroxysteroid dehydrogenase (HSD17B3) 5α-reductase 2 (SRD5A2)</td>
<td>Aromatase (CYP19) deficiency</td>
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<td>2. Disorders of androgen action</td>
<td>Oxidoreductase (POR) deficiency</td>
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<td>Androgen insensitivity syndrome</td>
<td>3. Maternal</td>
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<td>Drugs and environmental modulators</td>
<td>Maternal virilizing tumours (e.g. luteomas)</td>
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<td></td>
<td></td>
<td>Androgenic drugs</td>
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<tr>
<td><strong>C: 45,X/46,XY</strong></td>
<td><strong>C: Other</strong></td>
<td><strong>C: Other</strong></td>
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<tr>
<td>(mixed gonadal dysgenesis)</td>
<td>1. Syndromic associations of male genital development (e.g. cloacal anomalies, Robinow, Aarskog, hand-foot-genital, popliteal pterygium)</td>
<td>1. Syndromic associations (e.g. cloacal anomalies)</td>
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<td>2. Persistent Müllerian duct syndrome</td>
<td>2. Müllerian agenesis/hypoplasia (e.g. MURCS)</td>
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<td>3. Vanishing testis syndrome</td>
<td>3. Uterine abnormalities (e.g. MODY5)</td>
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<td>4. Isolated hypospadias (CXorf6)</td>
<td>4. Vaginal atresis (e.g. KcKusick—Kaufman)</td>
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<td>5. Congenital hypogonadotrophic hypogonadism</td>
<td>5. Labial adhesions</td>
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<td>6. Cryptorchidism (INSL3, GREAT)</td>
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<td>7. Environmental influences</td>
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24 hours after the last injection. A prolonged stimulation test using twice-weekly injections for 3 weeks may also be employed. How soon after birth should the test be performed? It is tempting to proceed early while the infant is still in hospital, but this may give spurious results due to the effects of placental and fetal adrenal clearance of steroids and lack of assay specificity if standard unextracted assays are used. There is merit in delaying the tests until the infant is about 4 weeks of age to take advantage of the increased Leydig-cell activity at this age.

More specialized investigations include urinary steroid analysis by specific gas chromatography/mass spectrometry techniques, and DNA analysis of key genes in the pathway of testis determination and function (see Figure 1). Urinary steroid analysis is particularly valuable in 46,XY disorders such as 5α-reductase deficiency and P450-oxidoreductase deficiency, but is less informative in the neonatal period for the diagnosis of 17β-hydroxysteroid dehydrogenase deficiency. Later, it may be necessary to obtain gonadal biopsies for histology if a definitive diagnosis such as gonadal dysgenesis or ovotesticular DSD is to be made. Table 3 summarizes the modes of presentation of DSD, not only during the newborn period but also later at puberty. Some are not obvious; the apparent male with bilateral cryptorchidism may be a fully masculinized female with CAH. The female infant with bilateral inguinal swellings may have herniated testes and a diagnosis of complete androgen insensitivity syndrome or 17β-hydroxysteroid dehydrogenase deficiency. The latter disorder classically presents at puberty with virilization of a child raised female, also to be seen in 5α-reductase deficiency. A girl with delayed onset of puberty may have XY gonadal dysgenesis or 17α-hydroxylase deficiency. If breast development is normal but menses are delayed, this may be due to complete androgen insensitivity syndrome. Within these clinical contexts it is important that appropriate investigations are undertaken following discussion of plans with laboratory staff.

### PSYCHOSOCIAL MANAGEMENT

The proposal that psychosocial care should be an integral part of DSD management is an important general recommendation and recognizes that management is not solely focused on medical/surgical issues. The sensitivity of the subject means that children and adults with DSD are particularly vulnerable to psychological, social and iatrogenic harm. To prevent this, mental health issues in DSD need to be allocated a high priority, both in clinical practice and in research. It is important to translate this recommendation into a procedural role for the clinical psychologist. For example, at the initial

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<th>Table 3. Clinical modes of presentation for disorders of sex development (DSD).</th>
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<td><strong>Late</strong></td>
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consultation with the family of a DSD child, the psychologist should be present with
the endocrinologist when crucial information about the diagnosis is disclosed. This
provides an opportunity to observe the reactions of parents, to know how informa-
tion has been conveyed, and if necessary to add supplementary advice. It is so impor-
tant at this early stage to avoid a common problem that families receive information
from different team members which may be contradictory.

Decisions on gender assignment and/or timing and the type of medical intervention can
be made only after careful consideration of the medical and psychosocial issues. During
the neonatal period, intensive sessions – and perhaps support by the use of psychological
instruments – may be needed to estimate to what extent parents are able to cope emo-
tionally with the complexity of their child’s condition. Furthermore, religious and
cultural factors may also need to be taken into account. How parents understand and
assimilate this information is critical in decisions on gender assignment and the timing
of surgery.

If a family is already vulnerable to psychological distress, educational sessions alone
may not suffice. Parents who are experiencing escalating distress may compound the
problem for the child. Psychologists sometimes need to train parents in problem-
solving skills, although DSD-specific programmes currently do not exist. There is
a need to develop tools that identify families at risk. Some are available for use in other
areas of child health psychology practice which could be adapted for use in DSD. Once
developed, such tools need to be available in several languages and readily available on
websites.

The current literature suggests that gender assignment should only cautiously be
based on prenatal androgen brain exposure. Also, care should be taken in drawing
conclusions on gender identity development based on genital appearance at birth. The
strongest evidence of direct sex-chromosome influences on behaviour involves as-
pects such as aggression and social cognition. There is currently no evidence to
indicate that chromosomes directly influence gender identity. It is often thought
that atypical gender role behaviour is a sign that the child wants a gender change or
will apply for a gender change in young adulthood. However, masculinized behaviour
in children assigned female is not an indication of incorrect assignment, although
some individuals may want to change gender later in life. There are two issues of in-
terest with respect to gender reassignment. The first relates to the upper bound age
for physician- or parent-initiated gender reassignment. Studies in developmental psy-
chology suggest caution when considering physician-initiated reassignment when chil-
dren are older than 18 months of age. However, there remains debate on this age
limit. The second issue concerns clinical management. While knowledge about predic-
tors of persisting gender dysphoria remain scanty, a comprehensive assessment by
professionals skilled in the management of gender change is essential before gender
change is imposed on a child, or indeed instituted at a later age. Ideally, such specialists
would be members of the DSD team, but there should at least be access to and
and collaboration with centres that specialize in gender dysphoria.

Disclosure is a matter of great concern to parents and encompasses a number of
aspects. The first relates to disclosure of information to the child. The Consensus rec-
ommendation on disclosure of karyotype, gonadal status, and infertility reflects an in-
creased emphasis on the rights of the child, changing views on health care by clinicians
and patients, and evidence gleaned from studies in other chronic medical conditions.
Early planning of a strategy with the parents and the development of a gradual process
of reinforced education, coupled with professional counselling, is likely to result in
fewer psychological problems than is currently the case. When well informed, children
will have better opportunities to develop coping skills and are likely to have a more positive self-image. The second aspect of disclosure deals with the social environment. It is still an open question whether sharing information with the wider environment will have positive or negative consequences for the child. Is living a 'normal' life with a secret more harmful than living a life without secrets but with a risk of stigma or shame? The advice currently given to parents is still largely empirical based on a clinical judgement of what option is best suited to the individual.

Another important aspect of information management is informed consent; this was only covered briefly in the Consensus document. The ability of children to fully understand relevant aspects of their condition is essential when they are expected to make decisions about medical interventions.

Little research has been conducted on information management. How is care influenced by the timing and type of information disclosed and the manner in which it is conveyed? What is the influence of cultural, family and child factors on how the information is received? Effects may vary according to diagnostic categories and how the condition evolves over time. Research is needed to compare the development of children managed in an information-sharing environment with those not so exposed, recognizing that such studies are a challenge to conduct. Protocols on information management would be most helpful if adapted to individual needs and accompanied by appropriate educational materials which ensure that children and parents are fully informed when taking decisions on treatment options.

Sexuality and pair-bonding are important elements in quality of life. How one feels about this life domain will be closely related to insecurities, fear of rejection and body image. Repeated genital examinations and medical photography may create unnecessary trauma. Yet these aspects have been largely underestimated in the past. The Consensus document provides some specific recommendations on how any adverse effects on sexuality and relationships can be prevented. It is recommended that adolescents with DSD be allowed counselling sessions where they can talk confidentially (without their parents) about interpersonal as well as sexual relationships. Such sessions are also an opportunity to continue medical and sexual education. This requires a resource of up-to-date educational materials and manualized protocols that are readily accessible by clinicians. The sensitive nature of the topics means that the educational materials need to be customized by professionals who have psychotherapeutic experience with adolescents.

The Consensus statement is an important milestone in DSD management. For psychologists, there is a need to develop additional instruments, treatment protocols, and educational materials, and to undertake research on gender development and information management. Resources developed for use in clinical practice have to be tailored to the needs of the individual. Input from professionals working in other mental health areas should be encouraged as appropriate. The psychologist has an important role in ensuring that members of the multidisciplinary team for DSD management communicate effectively and strive towards consensus operation, irrespective of individual personal or cultural differences. It is the psychologist who is best equipped to understand group dynamics and harness the talents of individual members for optimal benefit to the individual with a DSD.

THE PATIENT PERSPECTIVE

The conference which subsequently resulted in the Consensus statement was a historic event as it was the first occasion that members of patient advocacy groups
had participated as equals in a multi-professional meeting to discuss DSD. There has been an encouraging shift towards focusing on broader issues compared with a previous preoccupation with gender-identity issues. This is exemplified by the following three observations: (1) sex assignment does not inevitably mean surgical intervention; (2) there is a shortfall in evidence justifying treatment methods; and (3) each case needs to be considered on its own terms.

Terminology

Advocacy groups have expressed a grievance about the use of inaccurate, discriminatory terminology which also causes unnecessary distress. The Consensus addressed this concern and formulated a proposal for terminology which is not misleading to professionals or lay people, and which explains the individual condition as clearly and as logically as possible. The umbrella term ‘disorder of sex development’ (DSD) has been proposed. It is noteworthy that the term had already been included in the Handbook for Parents by the Consortium on Management of DSD (www.dsdguidelines.org). The Handbook refers to the DSD concept as follows: ‘Because there are so many stages of sex development in human life, there are lots of opportunities for a person to develop along a path that isn’t the average one for boys or girls. When a less common path of sex development is taken, the condition is often called a disorder of sex development or DSD’.

Arguments in favour of embracing the new terminology include the following. (1) It has clarity, and is more inclusive of all conditions which affect the urogenital tract. (2) It includes conditions which belong together (for example, CAH, Turner syndrome, hypospadias), unlike the term ‘intersex’ which is perceived to be inappropriate and unacceptable to many people with these conditions. (3) When used medically, the term should refer only to the biological manifestation of the condition and not the person as an individual; this includes statements about social behaviour, gender role, and gender identity outcome, and its usage in making treatment decisions that are not founded on professional competence. (4) Transsexualism and intersex are no longer so easily confused. (5) Bracketing several conditions of the urogenital tract under one generic umbrella term may lead to improved chances of optimal care, including the provision of psychological support.

There are also arguments against adopting the DSD terminology. (1) There is a view that the word ‘disorder’ has too much of a pathological connotation, and the alternative word ‘variant’ has been proposed. (2) When translated into German, the word ‘disorder’ has negative overtones of ‘disturbed’ (Du störst, er ist gestört, Störenfried etc). (3) Acronyms like DSD are perceived as too abstract. (4) Some affected individuals have become ‘attached’ to the term ‘intersex’ as it has become associated with community and empowerment.

It is probably not helpful to interpret the proposal of the term DSD as a wish by professionals to replace or usurp the word ‘intersex’. Using DSD can also be interpreted as a tactful withdrawal by the medical world from the private sphere of the term ‘intersex’ to which only those affected have access and choose to belong to. If the new guiding principle is to see cases in individual terms, the name for the individual condition (whether it be CAH or hypospadias) will be the automatic term of preference, while the umbrella term is retained as appropriate.

Management

The requirement that long-term care should be provided by multidisciplinary teams in centres of excellence is a major statement of intent and of considerable benefit to
affected families. The importance and impact of the first encounter with a family affected by DSD is paramount. It is essential to emphasize the potential of the child, and not what is lacking, as is open communication with full participation of affected individuals and families in the decision-making process.

The trauma caused by the deeply shaming experience of photography, display, and some medical interventions is now acknowledged. Any photography must be consented to and, if absolutely necessary, should only be undertaken at the time of an examination or surgical procedure under anaesthetic. Some individuals never recover from the emotional scars of being displayed and subjected to medical photography. The usefulness of the continuing practice of displaying photographs of genitalia at medical conferences should be questioned, considering the emotional trauma that many of the individuals being displayed will have suffered in the process of obtaining the information.

**Surgical issues**

The Consensus underlines the responsibility of surgeons to explain the consequences of surgical interventions, and stipulates that these complex procedures should only be undertaken by experts. Too often, parents and affected adults are not advised of possible complications or made aware of the alternative of postponing surgery. What is meant by 'successful' surgery must be considered in a holistic context and with a realistic view of what a particular surgical technique can and cannot deliver. Unrealistic expectations of what can be achieved serve no useful purpose to the patient or the surgeon. The Consensus recommends guidelines that should be followed in the case of any clitoral surgery, and no intervention is recommended for Prader stages I and II. This already appears to be the case in clinical practice.

There is now more specific advice concerning when gonadectomy should be performed in the androgen insensitivity syndrome. It is clear that this is not necessary before puberty, but the Consensus statement recommending subsequent automatic removal in the complete form of the syndrome remains controversial. The need for gonadectomy, and the timing of the procedure, in the partial form of the syndrome is dependent on the sex of rearing.

The more cautious approach to childhood cosmetic surgery is a step in the right direction. Further evidence of long-term satisfaction is still needed to justify the practice of childhood cosmetic surgery and to compare this with the practice of non-intervention and observation. There is an impression that surgical intervention takes place on the premise that if the procedure is technically possible, then surgery will be performed. There are now data in the literature documenting a wide variation in the appearance of the external genitalia in women who do not have a DSD. This must be borne in mind when discussing the question of surgery. As a general rule, it would be preferable to avoid surgery in infancy and childhood, or at least delay it whenever possible. Preservation of tissue, particularly gonadal tissue, and maintenance of the integrity of the body as a whole are aspects of care that should receive higher priority.

**Psychological issues**

Recognizing the importance of the clinical psychologist as a key member of the multidisciplinary team is a welcome development and is emphasized elsewhere in this
chapter. There has been a tendency to focus too much on the physical components of the condition rather than on coping mechanisms needed to come to terms with the problem and move forwards. Some families still receive no psychological support, or just a couple of clinic appointments is deemed sufficient. The psychological issues for individuals with DSD extend beyond just consideration of genetic, surgical or gender identity aspects. There must be opportunities to discuss concerns about how to approach relationships and deal with sexual encounters, and sex therapy should be offered if requested.

Psychology sessions for affected families should ensure that information is understood and an assessment made as to how the individual has processed the information emotionally; this is often very different from what professionals think or hope they have communicated. If an offer of psychological support is declined, this should not be interpreted as a long-lasting or finite decision. The person may not yet be ready or able to talk about their condition and what it means for them at a given stage of development. Families who are at risk for maladaptive coping with their child’s condition should be identified and given extra support.

The Consensus statement rightly emphasizes that children’s psychosocial adaptation is enhanced by disclosure. This is known from experience with other conditions such as cancer. Knowledge of the condition empowers the child, increases self-confidence, and often results in the child being better able to cope than the parents when faced with a challenging diagnosis.

The future

A multidisciplinary approach to management is essential, but more emphasis on patient-centred care is required. Regional centres of excellence should be the norm. Patients will choose the best quality care and recommend centres where the teamwork is efficient. Team-building and better training of health professionals is an urgent priority.

A change in nomenclature is a sign that attitudes and assumptions about the condition are also changing. The way in which professionals perceive DSDs needs to be examined in comparison with other chronic medical conditions. In turn, affected individuals should not have to waste their energies dealing with the abnormal and unhelpful reactions of society to their condition. The culture of secrecy and non-disclosure is unhealthy. The situation pervading DSD is not unlike that espoused by Alcoholics Anonymous: ‘we are as sick as our secrets’.

The greater role of support groups is to be encouraged. Where appropriate, links to support groups should be provided in medical publications on DSD. It should be common practice to provide families with information about support groups, and comments on what experiences families may encounter should not be prejudicial. Parents are often relieved when their isolation comes to an end and they can put matters in perspective by talking to other families. All too often there are still reports that parents have been told by health professionals that no support groups exist and that no other family is known with a similar condition.

Suppositions, speculations, and personal anecdotes are not a sound basis for medical interventions. It is axiomatic that evidence based on long-term outcome studies is necessary. The data can only be generated by the centres providing care, but perhaps analysis of the results should be undertaken by independent external assessors. This way, any suggestion of bias may be countered, and the standard of care can be assessed
more objectively if individuals are not constrained from making comments in an open manner.

Planning of Consensus meetings, with appropriate input from consumer groups at an early stage, would improve confidence in the validity of findings and proposals. For example, the change in nomenclature resulting from this particular Consensus might have been refined had patient advocacy groups been able to consult more widely ahead of the meeting. There are also constraints on constructive debate if the number of delegates is too large and unwieldy.

There have been too few occasions in the past for opportunities for dialogue and exchange of views between health professionals and families with DSD. Working together on practical tasks which improve patient care is the way forward to avoid both groups spending unproductive time and energy getting embroiled in ideological discussions. Getting members of advocacy groups more involved in relevant conferences on DSD can only lead to improved care and outcome in the longer term.


**SURGICAL MANAGEMENT**

The Consensus statement is a promising start which now needs to be translated into surgical management that works in practice. The surgeon will be increasingly involved in the multidisciplinary team, working within clearly delineated surgical networks and having the specific expertise for DSD surgery.

The concept of early surgery is accepted by the Consensus according to guidelines issued by the American Academy of Pediatrics. The excess skin of the labio-scrotal flaps and the preputial shaft provides tissue with an abundant vascularity and nerve supply should vaginoplasty also be considered at this time. There is no place for vaginal dilatation in childhood. Early genitoplasty is feasible only if the precise cause of DSD has been established and gender assignment has been based on certain knowledge of post-pubertal sexual outcome. Otherwise surgery should be postponed, as genitoplasty involves irreversible procedures such as castration and phallic reduction in individuals raised female and resection of utero-vaginal tissue in those raised male.

Sometimes the diagnosis is missed in infancy and only comes to light at puberty. Examples include girls with CAH raised as boys, or males with 17β-hydroxysteroid dehydrogenase and 5α-reductase deficiencies raised as girls. There will be pressure from the parents to proceed to surgery urgently, but this must not be undertaken before full endocrine evaluation and psychological assessment have been undertaken. The Consensus statement does stress that the upper age limit for imposed gender reassignment should be viewed conservatively.

There is an emphasis on functional outcome rather than on cosmetic appearance of the genitalia. With respect to erectile tissue, a decision regarding clitoral reduction should be taken with the knowledge of potential damage to the neurovascular bundle and of the possibility that the clitoris will reduce in size if excess androgen secretion in CAH is controlled adequately. In the case of boys, it should be emphasized that erectile function can be damaged with every genitoplasty procedure. Consequently, a one-stage procedure should be recommended for masculinizing genitoplasty.

Urinary function must be given due consideration. In girls care must be taken not to perform extensive mobilization of the urogenital sinus, as this can shorten the urethra and lead to urinary incontinence. Preserving urinary function requires techniques that
avoid urethral structure, urethral lithiasis on hairy grafts, and episodes of epididymo-orchitis arising from urine refluxing into the vas deferens from an enlarged utricle. The Consensus discusses the question of preserving fertility. For boys, this could lead to recurrent epididymo-orchitis, testicular endocrine dysfunction, and an outcome where fertility is seldom achieved. The surgeon may be faced with performing several genitoplasties, including penile reconstruction, in order to aim for improvements in cosmetic and functional outcome. That this goal may be unrealistic is emphasized in the Consensus statement.

The Consensus statement relating to gonadal surgery is very important. There is at last an evidence base for the risk of gonadal tumours according to diagnostic category. This is rare in complete androgen insensitivity syndrome, for example, and is confined to adulthood. Spontaneous female puberty can be achieved. Surgeons need only remove gonads in other conditions when XY children are raised female. For the child raised as a boy, it may be questioned whether the Consensus statement relating to the management of post-pubertal scrotal testis is risky. There is no evidence that a normal biopsy excludes the presence of tumoral tissue. Regular ultrasound examinations and endocrine markers can be used to monitor dysgenetic testes. Each biopsy has the potential to damage the testis which may need to be cryopreserved for future in-vitro maturation of spermatogenesis. The Consensus statement overstates the risk of malignancy in a neovagina. This is small, and occurs only with the use of skin grafts with chronic inflammatory scarring.

The importance of gathering evidence on outcome in DSD is particularly apposite for the surgeon, but cannot be taken in isolation from the impact of medical and psychosocial management. It is essential to engage input from adult surgical specialists, also working in multidisciplinary teams, if meaningful results on DSD outcome are to be realized.

CULTURAL, ETHICAL AND LEGAL ISSUES

These important subjects related to the management of DSD were not covered in detail in the Consensus statement. This was partly the result of a strategic decision, taken at the planning stage, not to do so, but also because of the enormity and complexity of the issues which vary among societies worldwide. It was decided from the outset that the Consensus statement would have to be broadly based on prevailing practice in Western societies. Nevertheless, there are interesting parallels to be drawn by considering practices in other societies.19–23 For example, there is greater gender diversity in some cultures, with gender not always neatly dividing into male and female. On the Indian subcontinent it is often frank poverty that is the determining factor which dictates staying with the status quo, as access to specialized services is not possible. The dominant role of males in some cultures is clearly illustrated by the desire to assign gender as male whatever the ‘cost’ in terms of sexual function, rather than a female assignment associated with an inability to marry. This is not a practice that is just of interest in far-off clinics. The mobility of world populations means that Western countries now have a significant percentage of their population which is immigrant (8.3% in the UK) and are becoming multicultural. Just recently, statistics have been released that UK passports have been issued to one million immigrants in the last decade. The cultural perspective on DSD management is increasingly important and should be considered in any future developments to modify the Consensus statement.

Consequences of the ESPE/LWPES guidelines 363
The ethical and legal aspects of DSD management are somewhat intertwined and are covered, albeit briefly, in the Consensus document. The major issues of continuing concern include informed consent, information disclosure, and human rights. It is against the backdrop of consent that the question of a complete moratorium on all surgery in DSD that is not medically necessary became prominent on the management agenda. The Consensus statement does not endorse this proposal, but there has been a change in practice noted by clinicians working in DSD which is reflected in the more conservative approach to surgery recommended in the statement. A recent publication on ethics and intersex (International Library of Ethics, Law and the New Medicine, edited by Sharon Sytsma, Springer 2006) comprises a series of essays, some of which provide useful information on legal aspects, human rights, consent, the boundaries between clinical practice and research, and even a perspective on DSD from a Christian religious viewpoint. Nevertheless, the medical profession is still portrayed in negative terms by reference to decision-making that is too cavalier. Phrases such as ‘the concealment model of intersex’, that intersex is a ‘hotbed of deception’, and chapter headings such as ‘Sex, Lies and Paediatricians’ amply illustrate the tenor of dissent.

Times have moved on. No longer is non-disclosure a practice acceptable to those enlightened multidisciplinary teams working in DSD. The challenge is the recruitment of enough trained personnel to put the skills of information-sharing into practice throughout development from childhood to adulthood. The practice of informed consent within a clear legal framework has also improved, although it is recognized that the way in which this is undertaken varies considerably among countries. It has been proposed that a committee of experts drawn from the relevant disciplines should be charged with the responsibility of providing guidance to families of children with DSD. The committee should ensure that any consent proffered by parents is qualified and persistent, must accumulate outcome data on various treatments, and provide continuing education to persons with DSD, their families and their physicians. This is an ambitious goal and perhaps lacks some realism, yet it deserves to be given due consideration.

THE IMPACT OF THE CONSENSUS STATEMENT ON DSD

The product of the Consensus initiative on DSD management has certainly brought the subject matter to the fore and has created a greater awareness of the problems that need addressing. The change in nomenclature is a movement of almost seismic proportions, and is apparently becoming generally accepted. It will take time for the historical and unhelpful terms to disappear from the standard texts. There is a greater spirit of collaboration between health professionals and patient support groups which must surely be to the betterment of patient care. The medical profession is listening to criticism and is striving to make changes. This can be successfully achieved only by teamwork which includes patients and their advocates as equal partners.

The Consensus statement has raised more questions than it has answered, mainly because of the lack of outcome data across the whole range of issues that comprise DSD management from infancy to adulthood. It is incumbent on practitioners interested in DSD to ensure that the current Consensus statement is merely a catalyst to enable further strides to be made to improve care for the individual and families with DSD.
REFERENCES


