BOOK REVIEWS:

Garner D M, Garfinkel P E (eds.): Diagnostic Issues in Anorexia Nervosa and Bulimia Nervosa. Reviewed for Journal of Nervous and Mental Diseases, 177(5):307-308, 1989.

Kanas N: Group Therapy for Schizophrenic Patients. Reviewed for Psychiatric Times, June, 1997.

PROFESSIONAL PUBLICATIONS REVIEWED/EDITED:

Reviewer, Journal of Clinical Psychiatry, 1987 to present
Reviewer, Psychosomatics, 1989 to present
Reviewer, Journal of AIDS, 1990 to 2001
Reviewer, Psychology and Health, 1992
Editorial Board, San Antonio M.D., 1991-1993
Reviewer, International Journal of Psychiatry in Medicine, 1994-2006
Reviewer, CNS Drugs, 1995-2002.
Reviewer, Southern Medical Journal, 1995-2013
Reviewer, AIDS Patient Care, 1996-2003
Editorial Board, International Journal of Transgenderism, 1997-present
Reviewer, Federal Practitioner, 2000-present
Reviewer, Journal of the American Geriatrics Society, 2000-2003
Reviewer, Bipolar Disorders, 2005-present
Reviewer, Journal of Sexual Medicine, 2009-present
Reviewer, European Psychiatry, 2010-present
Reviewer, International Journal of Sexual Health, 2011-present
Reviewer, American Journal of Public Health, 2011-present
Editorial Board, LGBT Health, 2013-present
Reviewer, Canadian Medical Association Journal, 2013-present
Reviewer, Suicide and Life-Threatening Behavior, 2015-present
Editorial Board, Transgender Health, 2015-present

PRESENTATIONS:

Behavioral Medicine Lecture Series, Kettering Medical Center, Kettering, Ohio. Ten parts. January 24-June 25, 1985.
"Sex Reassignment Surgery: Surgical Cure or Well-Meaning Mutilation?", Good Samaritan Hospital, Dayton, Ohio. March 5, 1985.
"The Difficult Patient: Recognition, Understanding, and Management", The Marriott Hotel, Dayton, Ohio. March 6, 1985, (Category I, CME credit).
"Transsexualism: Literature Review and Case Report", Wright State University, Dayton, Ohio. March 19, 1985.
"Pseudoseizures: When is a Jerk not a Fit?", Bergamo Conference Center, Kettering, Ohio. April 19, 1985. (Category I, CME credit).
"Transsexualism: What Sex am I?", University Center, Wright State University, Dayton, Ohio. September 17, 1985.
"Transsexualism and the Military", Good Samaritan Hospital, Dayton, Ohio. March 18, 1986.
"Clinical Utility of the House-Tree-Person Test", Diversion Program, Dayton, Ohio. April 9, 1986.
"The Silent Mitwelt", Bergamo Conference Center, Kettering, Ohio. April 18, 1986. (Category I, CME credit).
"Clinical Recognition of Alexithymia", Diversion Program, Dayton, Ohio. June 3, 1986.
"Male-to-Female Transsexualism - Case Study", Case Western Reserve University,

Cleveland, Ohio. July 18, 1986.
"Zoophilia: Literature Review and Case Study", Case Western Reserve University, Cleveland, Ohio. July 31, 1986.
"Neuropsychiatry of Alexithymia", Good Samaritan Hospital, Dayton, Ohio. October 14, 1986.
"Penile Auto-Injection: New Treatment for Organic Impotence", Diversion Program, Dayton, Ohio. August 12, 1986.
"Gender Identity Development in Children and Adolescents", Diversion Program, Dayton, Ohio. August 26, 1986.
"Paraphilias", Good Samaritan Hospital Seminar, Dayton, Ohio. November 17, 1986.
"Introduction to Gender Disorders", Good Samaritan Hospital, Dayton, Ohio. December 15, 1986, January 5, 1987.
"Strategic Psychotherapy, Part I", Wright State University, Department of Psychiatry, Dayton, Ohio. December 23, 1986.
"Strategic Psychotherapy, Part II", Wright State University, Department of Psychiatry, Dayton, Ohio. December 30, 1986.
"Transsexualism: Dilemmas in Diagnosis", Good Samaritan Hospital, Dayton, Ohio. January 19, 1987.
"Transsexualism: Live Interview Presentation", Wright State University, Department of Psychiatry, Dayton, Ohio. January 20, 1987.
"Anxiety Disorders: New Treatment Approaches", Wright State University, Department of Family Practice, Dayton, Ohio. January 29, 1987.
"Gender Dysphoria", Wright State University Medical School, Dayton, Ohio. February 10, 1987.
"Bioethical Issues in Sex Reassignment", Good Samaritan Hospital, Dayton, Ohio. February 2, 1987.
"Mycobacterium xenopi Pulmonary Infection Complicated by Anorexia Nervosa", presentation at the 29th Annual Meeting of the Society of Air Force Physicians, New Orleans, Louisiana. March 23, 1987.
"The Transsexual Flight into Hypermasculinity", presentation at the Tenth International Symposium on Gender Dysphoria, Amsterdam, The Netherlands. June 10, 1987.
"Grand Rounds: Gender Disorders", Institute of Living, Hartford, Connecticut, April 30, 1987.
"Affective Disorders", three hour lecture series, Wilford Hall Medical Center, San Antonio, Texas, September, 1987.
"Grand Rounds: Transsexualism", Maine Medical Center, Portland, Maine, November 4, 1987.
"Opportunistic Infection in Anorexia Nervosa", 34th Annual Meeting of The Acadamy of Psychosomatic Medicine, Las Vegas, Nevada, November 14, 1987.
"Grand Rounds: Gender Disorders, An Overview", Wilford Hall Medical Center, San Antonio, Texas, December 17, 1987.
"Women Who Marry Transvestites", accepted for presentation at XXI Annual Meeting of AASECT, San Francisco, California, April 26, 1988 (no funding available).
"Psychiatric Manifestations of HIV Infection", Texas Medical Association Annual Session, San Antonio, Texas, May 13, 1988.
"Introduction to Gender Disorders", University of Texas Health Science Center, San Antonio, Grand Rounds, September 27, 1988.
"Transsexualism and Gender Disorders", Bexar County Psychiatric Society, San Antonio, Texas, October 18, 1988.
"Psychiatric Diagnoses in HIV-seropositive Air Force Personnel", Maine Medical Center, Portland, Maine, November 5, 1988.
"Symposium on HIV-seropositivity and Psychiatry", Program Coordinator, Behavioral Health Sciences Symposium, Sheppard AFB, Wichita Falls, Texas, November 8, 1988.
"Childhood Gender Disorders", Laurel Ridge Hospital, San Antonio, Texas, January 24, 1989.
"Prospective Study of Psychiatric Morbidity in HIV-seropositive Women", Annual Meeting of the American Psychosomatic Society, San Francisco, California, March 10, 1989.

"Psychiatric Findings in HIV-seropositive Air Force Women", Walter Reed Army Institute of Research, Bethesda, Maryland, March 31, 1989.

"Psychiatric findings in HIV-seropositive persons in a mandatory HIV screening program", (abstract and poster session, with J Rundell, S Paolucci), Fifth International Conference on AIDS, Montreal, Canada, June 5, 1989.

"Alcohol Use and HIV-seropositivity", (poster presentation, with K Drexler, J Rundell), American Psychiatric Association Annual Meeting, San Francisco, California, May, 1989.

"Current Legal Status of Transsexualism in the Military Setting", Eleventh International Symposium on Gender Dysphoria, Cleveland, Ohio, September, 1989.

"Grand Rounds: Transsexualism in the Military", Wilford Hall Medical Center, December 14, 1989 (videotape available on request).

"Psychosexual and Gender Disorders", 6 session advanced seminar for psychiatric residents, University of Texas Health Science Center, San Antonio, January to February, 1990.

"Update on HIV Psychiatric Research in the USAF: 1990", Behavioral Health Sciences Symposium, Wichita Falls, Texas, 25 April, 1990.

"Psychiatric Morbidity in HIV-seropositive Women without AIDS", 143rd Annual Meeting of the American Psychiatric Association, New York, May 14, 1990.

"HIV Infection and Perception of Social Support", (Rundell, Ursano, Brown), 143rd Annual Meeting of the American Psychiatric Association, New York, May 14, 1990.

"Relative Frequency of HIV Disease as a Cause of Mood Disorder in a General Hospital", (Rundell, Brown), Neurological and Neuropsychological Complications of HIV Infection Conference, Monterrey, California, June 17, 1990.

"CSF Parameters, Immune Status, Serum Viral Titers, Anxiety, and Depression in HIV Disease", (Rundell, Praus, Brown), Neurological and Neuropsychological Complications of HIV Infection Conference, Monterrey, California, June 17, 1990.

"CSF Findings and Request for Psychiatric Examination in HIV-Infected Patients", (Rundell, Brown, et al.), poster presentation, Neurological and Neuropsychological Complications of HIV Infection Conference, Monterrey, California, June 17-19, 1990.

"Methods Employed by and Length of Knowledge of HIV-Seropositivity of HIV-infected Suicide Attempters", (Rundell, Brown, Kyle, et al.), 37th Annual Meeting of the Academy of Psychosomatic Medicine, Phoenix, Arizona, November 18, 1990.

"Psychiatric Morbidity in HIV-seropositive Women: Results of a Three Year Prospective Study", (Brown, Rundell, Temoshok, et al.), 37th Annual Meeting of the Academy of Psychosomatic Medicine, Phoenix, Arizona, November 16, 1990.

"Psychiatric Issues in the Evaluation of Spouses of Cross-dressers," Fairfax Hospital, Falls Church, Virginia, November 30, 1990.

"Measurement of Negative Affect in HIV-seropositive Individuals," (Jenkins, Carey, Temoshok, Brown, et al.), 12th Annual Meeting of The Society of Behavioral Medicine, Washington, D.C., March 20, 1991.

"Psychiatric and Neuropsychiatric Morbidity in Early HIV Disease," Grand Rounds presentation with S. McManis, University of Texas Health Science Center, San Antonio, Texas, April 30, 1991.

"Neuropsychiatric Impairment Early in the Course of HIV Infection," (McManis, Brown, Zachary, et al.), 7th International Conference on AIDS, Florence, Italy, June 17, 1991.

Nine presentations/new research posters/symposia presented at the 144th Annual Meeting of the American Psychiatric Association, New Orleans, Louisiana, May 11-15, 1991 (see Publications section, #50-58, for titles).

Two presentations at the 7th International Conference on AIDS, Florence, Italy, June 15-17, 1991 (see Publications section, #59-60, for titles).

"Methodological Advantages of Comprehensive Multidisciplinary Consultation-Liaison Psychiatry Research: HIV Research as a Model," (Rundell, Temoshok, Brown, et al.), Annual Meeting of the Academy of Psychosomatic Medicine, Atlanta, Georgia, October 17, 1991.

"HIV Psychiatric Research in the Air Force," Grand Rounds presentation, Mayo Clinic, Rochester, Minnesota, July 9, 1991.

"Neuropsychiatric Morbidity in early HIV Disease: Implications for Military Occupational Function," (Brown, Rundell, McManis, Kendall), Aerospace Medicine Symposium on Allergic, Immunological, and Infectious Disease Problems in Aerospace Medicine, NATO Advisory Group for Aerospace Research and Development Conference, Rome, Italy, October, 1991; presented by J. Rundell in my absence due to lack of funding.

Four oral presentations and two poster presentations at the First International Conference on the Biopsychosocial Aspects of HIV Infection, Amsterdam, The Netherlands, 22-25 September, 1991 (see Publications section, #61-66, for titles).

"Biopsychosocial HIV Research in the U.S. Military," Invited Grand Rounds presentation, University of South Dakota School of Medicine, Sioux Falls, South Dakota, October 25, 1991.

"Biopsychosocial Issues in Treating HIV-seropositive Women," Fairfax Hospital Evening CME Lecture Series, Falls Church, Virginia, December 11, 1991.

"Psychiatric Issues in Women with HIV," Fairfax County Health Department, Falls Church, Virginia, December 12, 1991.

"Suicidality in Men with Early HIV Disease," American Psychosomatic Society 50th Annual Meeting, New York, New York, April 1, 1992.

USAF HIV "Train-the-Trainer" Course; course organizer, presenter, and comprehensive course assessment (pretest, posttests), San Antonio, Texas, April 7-9, 1992.

"Clinical Utility and Diagnostic Sensitivity of the Michigan Alcoholism Screening Test in Patients with HIV Disease," (Rundell, Brown), Annual Meeting of the Academy of Psychosomatic Medicine, San Diego, CA, October 31, 1992.

"Longitudinal Neuropsychological Findings in HIV Positive Males," (Goethe, Richie, Brown, et al), 8th International AIDS Conference, Amsterdam, The Netherlands, July 20, 1992.

"HIV and Women: Challenge for the 90's," Grand Rounds presentation, Geisinger Medical Center, Danville, PA, August 6, 1992.

"Psychosocial Dimensions of Depression in Early HIV Disease," (Jenkins R, Rundell J, Brown G, Law W, Temoshok L), Annual Meeting of the American Psychological Association, Washington, D.C., August 15, 1992.

"Psychiatric Presentations of HIV Disease," AIDS and Mental Health Program sponsored by San Antonio VA and UTHSC-SA, Corpus Christi, TX, September 18, 1992.

"Major Depression in HIV Disease Before AIDS: Clinical Features and Associated Factors," (Rundell J, Brown G, Jenkins R, Kendall S, Temoshok L), Annual Meeting of the Academy of Psychosomatic Medicine, San Diego, CA, 29 October, 1992.

"HIV Risk Behavior Surveys in the U.S. Military -- What Have We Learned?," Wilford Hall Medical Center Scientific Group Meeting, San Antonio, TX, 16 November 1992.

"Biopsychosocial Aspects of Early HIV Disease in Women," Grand Rounds, Michigan State University/St. Lawrence Hospital, Lansing, MI, 18 December 1992.

"Methodological Issues in Assessing Risk Behaviors in an HIV Sero-positive Military Sample," (Coyle C, Blake S, Brown GR, Ledsky R, Temoshok L), Special Citation Poster Presentation, Proceedings of the Fourteenth Annual Meeting of the Society of Behavioral Medicine, San Francisco, CA, March 10, 1993.

"Gender differences in transmission risk behavior, affect, and social support in HIV-positive individuals," (Nannis E, Temoshok L, Jenkins R, Blake S, Sharp E,Jenkins P, Brown G, Patterson T, Coyle C, Brandt U, Johnson C),Proceedings of the Fourteenth Annual Meeting of The Society of Behavioral Medicine, San Francisco, CA, March 10, 1993.

"Psychosocial stressors and vulnerability to psychiatric distress in early-stage HIV," (Zachary R, Brown GR, Kendall S, Coyle C, McManis S), Proceedings of the Fourteenth Annual Meeting of The Society of Behavioral Medicine, San Francisco, CA, March 10, 1993.

"Establishing databased research in an academic department of psychiatry," invited address to the Department of Psychiatry, Jefferson Medical College, College of Physicians, Philadelphia, PA, April 30, 1993.

Two Workshops, three poster sessions, 1993 Annual Meeting of the American Psychiatric Association, San Francisco, CA, May 22-24, 1993.

"Treating Depression in Early HIV Disease," Grand Rounds, Oklahoma University School of Medicine, Oklahoma City, OK, December 1, 1993.

"Diagnosis and Treatment of Transvestism," Tulane University School of Medicine, Department of Psychiatry presentation, December 2, 1993.

"Psychiatric Disorders in Early HIV Disease," Grand Rounds, Tulane University School of Medicine, New Orleans, LA, December 3, 1993.

"Diagnosis and Treatment of Gender Identity Disorders," invited presentation at Keesler Air Force Base Medical Center, Biloxi, MS, January 13, 1994.

"Personality Disorders in HIV-positive Persons: Association with Other Measures of Psychiatric Morbidity," poster presentation, (Richards J, McManis S, Brown G), Annual Meeting of the American Psychiatric Association, Philadelphia, PA, May 23, 1994.

"Psychiatric Issues in HIV/AIDS," invited presentation, Huntsville Mental Health Community, Huntsville Space and Science Center, Huntsville, AL, November 12, 1994.

"Diagnosis and Treatment of Gender Identity Disorders," Grand Rounds, Tulane University School of Medicine, New Orleans, LA, April 29, 1994.

"Management of Depression in Early HIV Disease," Upper East Tennessee Psychiatric Association Meeting, Kingsport, TN, June 2, 1994.

"Sertindole in the Treatment of Chronic Schizophrenia: a Phase III Controlled Trial," Grand Rounds, East Tennessee State University, Johnson City, TN, September 30, 1994.

"New Onset of Sexual Dysfunction in HIV-seropositive Women: Results of a Prospective Study," 88th Annual Scientific Assembly of the Southern Medical Association, Orlando, Florida, November 3, 1994.

"Gender Identity Disorders in the VAMC Setting," Grand Rounds, Atlanta VAMC, December 13, 1994.

"Managing Depression in Early Stage HIV Disease," Grand Rounds, Salem VAMC, December 22, 1994.

"Biopsychosocial Aspects of HIV Disease in Men," Invited Speaker, Mississippi Pharmacists Association MidWinter Meeting, Jackson, MS, February 12, 1995.

"Biopsychosocial Aspects of HIV Disease in Men," Invited Speaker, Mississippi Pharmacists Association MidWinter Meeting, Oxford, MS, February 19, 1995.

"Biopsychosocial Aspects of HIV Disease in Women," Grand Rounds, East Tennessee State University, Johnson City, TN, March 17, 1995.

"Managing Insomnia," primary care provider educational meeting, Bristol, TN, May 22, 1995.

"Diagnosis and Treatment of Gender Identity Disorders: DSM-IV Approach," Grand Rounds, Geisinger Medical Center, Danville, PA, June 15, 1995.

"Psychosocial Characteristics of 739 Transgendered Men," (Brooks G, Brown GR, Askew J), 41st Annual Meeting of the Southeastern Psychological Association, Savannah, GA, March 12, 1995.

"Personality Characteristics and Sexual Functioning of 188 American Transgendered Men: Comparison of Patients with Nonpatients." 14th Harry Benjamin International Gender Dysphoria Symposium, Irsee/Ulm Germany, September 9, 1995.

"Sertindole HCl: A Novel Antipsychotic With a Favorable Side Effect Profile." 89th Scientific Assembly of the Southern Medical Association, Kansas City, Missouri, November 17, 1995.

"Long term Safety of Treatment with Sertindole, a Novel Antipsychotic." (Radford M, Brown GR, Matthew H) poster, 89th Scientific Assembly of the Southern Medical

Association, Kansas City, Missouri, November 17, 1995.
"Diagnosis and Newer Treatments for Schizophrenia." Invited Presentation. Central Appalachia Services, Kingsport, TN, December 7, 1995.
"Personality and Sexuality in Transvestism." Grand Rounds, University of Texas Health Sciences Center, San Antonio, Texas, December 12, 1995.
"HIV/AIDS and Sexuality." Grand Rounds, Wilford Hall Medical Center, San Antonio, Texas, December 14, 1995.
"How Research Can Enhance Your Career." Invited Presentation to Department of Psychiatry, Wilford Hall Medical Center, San Antonio, Texas, December 13, 1995.
"Conducting Research With Stigmatized Populations." Journal Club Presentation, University of Texas Health Sciences Center, Department of Psychiatry, San Antonio, Texas, December 12, 1995.
"Sexuality in HIV/AIDS." Grand Rounds, Bowman Gray Medical School, Department of Psychiatry, Wake Forest University, Winston-Salem, North Carolina, January 19, 1996.
"Gender Identity Disorders." Grand Rounds, Lakeshore Mental Health Institute, Knoxville, Tennessee, February 14, 1996.
"New Approaches to the Management of Schizophrenia," Helen Ross McNabb Center, Knoxville, Tennessee, February 14, 1996.
"Diagnosis and Management of Gender Dysphoria," Grand Rounds, University of Alabama at Birmingham, March 5, 1996.
"Depression and Primary Care," Morristown, TN Primary Care Provider's CE Group, Morristown, TN, June 27, 1996.
"Personality and Sexuality in Transgendered Men," paper presentation, American Psychological Association, Toronto, Canada, August 13, 1996.
"Gender Identity Disorders," paper presentation at Southern Psychiatric Association Annual Meeting, Santa Fe, New Mexico, September 25, 1996.
"Sleep Disorders," Grand Rounds, Salisbury VAMC, Salisbury, North Carolina, August 21, 1996.
"Depression in Primary Care Settings," Nurse Practitioner-Physician Assistant Association of Northeast Tennessee, Johnson City, Tennessee, September 11, 1996.
Visiting Professorship, Menninger Clinic and Foundation; included Grand Rounds, case presentation and discussion, meetings with residents and staff; Topeka, KS, October 10-11, 1996.
"New Approaches to the Treatment of Schizophrenia," Grand Rounds, Lakeshore Mental Health Institute, Knoxville, Tennessee, October 30, 1996.
"HIV Disease in Women: Sexual Manifestations," symposium presentation at Academy of Psychosomatic Medicine Annual Meeting, San Antonio, Texas, November 14, 1996.
"HIV and Sexuality," Grand Rounds, Atlanta VAMC/Emery University, Atlanta, Georgia, December 3, 1996.
"Santa Claus is a Cross-Dresser (and so are his little elves)," invited address for the Upper East Tennessee Psychiatric Association, a component of the Tennessee District Branch of the American Psychiatric Association, Johnson City, TN, December 9, 1996.
"Depression and Sexuality," Tazewell County Medical Society, Richlands, Virginia, March 25, 1997.
"Identifying and Treating Depression in Primary Care," Annual Meeting of the Nurse Practitioner's and Physician's Assistants of East Tennessee, Johnson City, TN, March 25, 1997.
"Managing Sexual Side Effects of Antidepressant Treatment," Harlan County Medical Society, Harlan, Kentucky, March 11, 1997.
"Depression and Intimacy," Chatanooga Psychiatric Society, Chatanooga, TN, April 21, 1997.
"Depression and Sexuality," Lakeshore Mental Health Institute Grand Rounds, Knoxville, TN, April 9, 1997.
"Managing Sexual Side Effects of Antidepressants," Southern Highlands Pharmacist's

Society, Abingdon, Virginia, April 29, 1997.
"Transgendered Families," Lakeshore Mental Health Institute Grand Rounds, Knoxville, TN, April 30, 1997.
"Depression and Intimacy," Buchanan County Medical Society, Grundy, VA, May 8, 1997.
"Depression, Sexuality, and Treatment," Highlands Psychiatric Society, Abingdon, VA, May 9, 1997.
"Managing Sexual Side Effects of Antidepressants in Primary Care," Chatanooga Family Practice Association, Chatanooga, TN, May 20, 1997.
"Double Trouble: Depression and Anxiety in Primary Care," LeFlore County Medical Center, Greenwood Mississippi, May 29, 1997.
"HIV and Sexuality," ETSU Medicine and Sexuality Symposium, Johnson City, TN, June 13, 1997.
"Depression and Sexuality," ETSU Medicine and Sexuality Symposium, Johnson City, TN, June13, 1997.
"Transgenderism," Grand Rounds, Overlook Mental Health Center, Knoxville, TN, June 25, 1997.
"Managing Sexual Side Effects of Antidepressants in Primary Care," Wise County Medical Society, Norton, Virginia, July 11, 1997.
"APA Guideline on the Treatment of Schizophrenia," Smoky Mountain Chapter of the Tennessee Psychiatric Association, Knoxville, TN, July 22, 1997.
"Nicotine Dependence: Kicking the Habit," August Monthly Meeting of the Tricities Nurse Practitioner-Physician Assistants Association, Johnson City, TN, August 14, 1997.
"Biopsychosocial Issues in Women with HIV Disease," Monthly Meeting of OB-GYN Society of Tricities, Johnson City, TN, August 26, 1997.
"Revision of the HBIGDA Standards of Care: Opportunities and Controversies," Biannual Meeting of the Harry Benjamin International Gender Dysphoria Association, Vancouver, British Columbia, Canada, September 11, 1997.
"Anxiety and Depression in Primary Care: Double Trouble," Primary Care Grand Rounds, Fort Campbell, KY, October 1, 1997.
"Treatment Guidelines for Schizophrenia," Psychiatry Grand Rounds, Lexington VAMC, Lexington, KY, September 17, 1997.
"Gender Dysphoria in the Military Setting," Grand Rounds, Wilford Hall Medical Center, San Antonio, TX, December 18, 1997.
"Clinical Issues in Transgendered Families," Grand Rounds, University of Texas Health Sciences Center, San Antonio, December 16, 1997.
"Depression and Sexuality," Southwest Virginia Counsel of Nurse Practitioners, Abingdon, Virginia, November 1, 1997.
"Depression and Anxiety Disorders in Primary Care," Annual Meeting of the Nurse Practitioner Physician Assistant Association of Northeast TN, Johnson City, TN, February 23, 1998.
"Differentiating SSRI's in Clinical Practice," Richmond Psychiatric Society Meeting, Richmond, VA, January 22, 1998.
"Gender Identity Disorders," Grand Rounds, University of VA, Roanoke, VA, February 19, 1998.
"Smoking Cessation: Modern Approaches," Monthly Meeting of the East TN Hospital Pharmacists Association, Kingsport, TN, February 24, 1998.
"Identification and Treatment of Gender Dysphoria Syndromes," Grand Rounds, University of Mississippi, Jackson, MS, February 27, 1998.
"Gender Dysphoria Syndromes in Primary Care," Nurse Practitioner Physician Assistant Association of Northeast TN, Kingsport, TN, March 19, 1998.
"Treatment Guidelines for Schizophrenia," Grand Rounds, University of Kentucky, Louisville, KY, April 23, 1998.
"Gender Identity Disorders," Grand Rounds, University of Alabama at Huntsville, Huntsville, AL, May 21, 1998.
"Nicotine Reduction Strategies," Grand Rounds, Southwest Virginia Mental Health

Institute, Marion, VA, May 27, 1998.
"Depression and Anxiety Management in Primary Care," East Tennessee State University Dept. of Psychiatry Symposium on "Psychiatry in the Trenches", Johnson City, TN, June 12, 1998.
"Managing Depression in Primary Care," Grand Rounds, Internal Medicine Department, East Tennessee State University, Johnson City, TN, June 16, 1998.
"Mood Disorders in Women," Roanoke Psychiatric Society, Roanoke, VA, June 17, 1998.
"Gender Identity Disorders," Grand Rounds, Loyola University Strich School of Medicine, Chicago, IL, June 18, 1998.
"Standards of Care for Gender Identity Disorders," Grand Rounds, University of Louisiana, Baton Rouge, LA, July 21, 1998.
"Depression and Sexuality," Fall Symposium of the Mental Health Association of Knoxville, September 11, 1998.
"Pharmacotherapy of Agitation in the Elderly," Kentucky Pharmacists' Association, Lexington, Kentucky, September 20, 1998.
"Women and Mood/Anxiety Disorders," monthly meeting of the Nurse Practitioners-Physician Assistants, Johnson City, TN, October 1, 1998.
"Killing the Bore: How to Give Effective Medical Presentations That Keep an Audience Awake," Grand Rounds, ETSU Dept. of Psychiatry, Johnson City, TN, October 16,1998.
"Pharmacologic Management of Agitation in the Elderly," Detroit Psychiatric Society, Detroit, Michigan, December 22, 1998.
"Nicotine Dependence: Kicking the "Habit," Wise County Medical Society, Wise, Virginia, January 14, 1999.
"Mood Disorders in Women," Chatanooga Psychiatric Society, Chatanooga, TN, January 18, 1999.
"From Menarche to Menopause: Mood and Anxiety Disorders in Women," Greene County Medical Society, Greeneville, TN, February 2, 1999.
"From Menarche to Menopause: Mood and Anxiety Disorders in Women," Annual Meeting of the TriCities Nurse Practitioner-Physician Assistant Association, Johnson City, TN, February 23, 1999.
"Comparison of Risperidone and Olanzapine: RIS-112 Study," Upper East TN Psychiatric Society, Johnson City, TN, March 4, 1999.
"New Directions in Treating Schizophrenia," CME, Inc. sponsored faculty member, Los Angeles, California, March 27, 1999.
"Pharmacologic Management of Agitation in Dementia," University of Alabama Pharmacotherapeutics Conference, Huntsville, AL, April 24, 1999.
"Mood and Anxiety Disorders in Women," University of Alabama Pharmacotherapeutics Conference, Huntsville, AL, April 24, 1999.
"Behavioral Problems in Dementia," Grand Rounds, Alvin York VAMC, Murfreesboro, TN, April 29, 1999.
Pharmacological Management of Agitation in Dementia," Grand Rounds, Lakeshore Mental Health Institute, Knoxville, TN, May 7, 1999.
"Psychiatric Disorders in Women," Women's Health Symposium, University of Alabama, Huntsville, AL, May 14, 1999.
"Loxitane: A New Look at an Old Drug," Lakeshore Mental Health Institute, Knoxville, TN, June 4, 1999.
"Psychiatric Disorders in Women," University of Tennessee at Knoxville, OB-GYN Grand Rounds, June 4, 1999.
"Working With Transgendered Clients," workshop presented at A Search for New Understanding of Lesbian, Gay, and Bisexual Issues, East Tennessee State University, Johnson City, TN, September 24, 1999.
"Optimizing Treatment for Schizophrenia", CME, Inc. Symposium, Cleveland, Ohio, September 25, 1999.
"Diagnosis and Treatment of Depression in Primary Care," Grand Rounds, James H. Quillen VA

Medical Center-ETSU Department of Medicine, Johnson City, TN, September 28, 1999
"Gender Identity Disorder," Annual Meeting of the Southern Psychiatric Association, Hot Springs, Virginia, September 30, 1999.
"Management of Insomnia," Annual Meeting of the Tennessee Association of Physicians' Assistants, Gatlinburg, TN, October 12, 1999.
"Sexual Dysfunction in Primary Care Practice," Behavioral Health in Primary Care Symposium, East Tennessee State University, Johnson City, TN, October 16, 1999.
"Management of Insomnia: New Directions," monthly meeting of the Upper East Tennessee Psychiatric Association, Bristol, TN, October 19, 1999.
"Depression and Anxiety in Women Through the Life Cycle," Johnson City Women's Health Center Grand Rounds, Johnson City, TN, October 27, 1999.
"Selecting Antidepressant Treatment," invited presentation and panel discussion, New Orleans Academy of Internal Medicine, January 10, 2000.
"Managing Insomnia in Primary Care," Grand Rounds, Holston Valley Medical Center, Kingsport, TN, January 31, 2000.
"Gender Identity Disorders." Grand Rounds, University of Cincinnati, Cincinnati, OH, January 26, 2000.
"Selecting Antidepressants in Primary Care, " Rural Health Cooperative, Kingsport, TN, February 7, 2000.
Visiting Professor, Loyola University Medical School, Chicago, IL (two presentations), February 10, 2000.
"Managing Insomnia in the New Millennium," Annual Meeting of the East TN Nurse Practitioner's and Physicians' Assistants Association, Johnson City, TN, February 22, 2000.
"Sexual Dysfunction in Primary Care," Annual Meeting of the East TN Nurse Practitioner's and Physicians' Assistants Association, Johnson City, TN, February 22, 2000.
"Depression and PTSD in Women," Grand Rounds, Department of OB-GYN, University of Tennessee, Knoxville, March 17, 2000.
"Depression and Anxiety in Primary Care Practice," Grand Rounds, Department of Internal Medicine, University of Tennessee, Knoxville, March 16, 2000.
"Diabetes, Glucose Regulation, and Schizophrenia," Upper East Tennessee Psychiatric Society, Johnson City, TN, April 13, 2000
"Sexual Dysfunction in Primary Care Practice," Annual Meeting of the Tennessee Osteopathic Medicine Association, Chatanooga, TN, May 7, 2000.
"Diabetes, Weight Gain, and Schizophrenia," Grand Rounds, Lakeshore Mental Health Institute, Knoxville, TN, July 20, 2000.
"Bipolar Disorder: Monotherapy versus Combination Therapy", national CME Category I lecture series sponsored by Medical Education Resources and Curry, Martin, and Schiavelli, to 17 cities between May and November, 2000.
"Managing Depression and Anxiety Disorders," invited presentation to the Annual Meeting of the Tennessee Academy of Family Practice, Jackson, TN, August 19, 2000.
"Managing Insomnia," monthly meeting of the Tazwell County Medical Society, Richlands, Virginia, August 23, 2000.
"Sexual Dysfunction," Grand Rounds, ETSU Department of OB/GYN, Johnson City, TN, September 6, 2000.
"Depression and Sexuality," Grand Rounds, Holston Valley Hospital, Bristol, TN, September 25, 2000.
"Depression and Anxiety in Primary Care: Case Conference/Grand Rounds," Southern Medical Association Annual Meeting, Orlando, Florida, November 2, 2000.
"Depression in Primary Care Settings," Hamblen County Medical Society, Morristown, TN, November 21, 2000.
"Sleep Disorders," Nurse Practitioners-Physicians Assistant Association Monthly Meeting, Johnson City, TN, December 7, 2000.
"CD-ROM Workshop, Anxiety and Depression", Annual Meeting of the Holston Valley Nurse Practitioners-Physicians Assistants Association, Johnson City, TN, February 26, 2001.
"The Harry Benjamin Standards of Care in Prison: Benefits for Transsexual Healthcare," International Foundation for Gender Education Annual Symposium, Chicago, Il, March

24, 2001.
"Why Internists Should Care About Treating Depression," Grand Rounds, Department of Internal Medicine, ETSU, Johnson City, TN, April 3, 2001.
"Antidepressants: Effective Side Effect Management," Annual Meeting of the Tennessee Osteopathic Medicine Association, Memphis, TN, April 21, 2001.
"Gender Identity Disorder: Management," invited presentation, Smokey Mountain Chapter of the Tennessee Psychiatric Association, Knoxville, TN, April 24, 2001.
"Gender Identity Disorder," Grand Rounds, Department of Psychiatry, Memphis VAMC, May 24, 2001.
"Antipsychotic Efficacy Uncompromised by Side Effects," Grand Rounds, Department of Psychiatry, UT Memphis, May 25, 2001.
"Sexual Dysfunctions in Primary Care," International Medical Update Symposium, Johnson City, TN, August 2, 2001.
"Diagnosis and Treatment of Gender Dysphoria," Grand Rounds, Department of Psychology, James H. Quillen VAMC, August 3, 2001.
"Management of Bipolar Disorder," Grand Rounds, Meharry Medical College, Nashville, TN, August 21, 2001.
"Medical Treatment of Agitation in Dementia," Fall Symposium of the Mental Health Association of Knoxville, September 13, Knoxville, TN.
"Monotherapy vs. Combination Therapy in the Management of Mania," Fall Symposium of the Mental Health Association of Knoxville, September 14, Knoxville, TN
"Optimizing Treatment for Bipolar Disorder," quarterly meeting of the Upper East Tennessee Psychiatric Association, Johnson City, TN, September 20, 2001.
"Gender Identity Disorders: Diagnosis and Management," Grand Rounds, Institute of Living/Hartford Hospital Departments of Psychiatry and Psychology, Hartford, CT, October 17, 2001.
"Gender Identity Disorder Complicated by Dissociative Identity Disorder: Report of a Successful Case," XVII Symposium of the Harry Benjamin International Gender Dysphoria Association, Galveston, TX, November 3, 2001.
"Mood Disorders in Women," monthly meeting of the TriCities Nurse Practitioners Association, Johnson City, TN, December 10, 2001.
"Substance Use Disorders Complicating Common Psychiatric Disorders," Grand Rounds, Holston Valley Hospital, Bristol, TN, December 18, 2001.
"Women's Health Issues in Psychiatry," OB-GYN Grand Rounds, East Tennessee State University, Johnson City, TN, May 8, 2002.
"Matching the Neurotransmitter to the Patient," ½ day CME presentation, World Medical Conferences, Jackson, Mississippi, May 18, 2002.
"Matching the Neurotransmitter to the Patient," ½ day CME presentation, World Medical Conferences, Albany, New York, June 1, 2002.
"Killing the Bore: How to Give Effective Medical Presentations That Keep People Awake," Grand Rounds, Dept. of Psychiatry, ETSU, Johnson City, TN, August 9, 2002.
"Current Issues in Treatment of Dementia," Roanoke Psychiatric Society, Roanoke, VA, June 26, 2002.
"Comfort Foods: Should We Just Surrender Now?," Northeast Tennessee Nurse Practitioner's Association Annual Meeting, Bristol, TN, September 14, 2002.
"Gender Identity Disorders: Diagnosis and Management," Psychiatry Grand Rounds, University of Florida, Gainesville, Florida, September 20, 2002.
"Gender Identity Disorders: Diagnosis and Management," Psychiatry Grand Rounds, Meharry Medical College, Nashville, TN, October 9, 2002.
"New Issues in the Management of Bipolar Disorder," Grand Rounds, Lakeshore Mental Health Institute, Knoxville, TN, October 5, 2002.
"Pharmacological Management of Dementia," Psychiatry Grand Rounds, Western State Hospital, Staunton, Virginia, March 19, 2003.
"Appropriate Use of Antipsychotics in Primary Care Practice," Tricounty Medical Society Meeting, Johnson City, TN, April 3, 2003.
"Appropriate Use of Antipsychotics in Primary Care Practice," 2003 Primary Care Conference,

Johnson City, TN, April 1, 2003.
"Pharmacological Management of Dementia," Grand Rounds, Gaston Memorial Hospital, Gastonia, NC, May 13, 2003.
"Brown G R, McBride L, Williford W, Bauer M: Impact of childhood sexual abuse on bipolar disorder. Proceedings of the 5th International Conference on Bipolar Disorders, Pittsburgh, PA, 2003 (poster presented by Dr. Bauer in my absence).
"Aripiprazole Use in Psychiatry," Grand Rounds, Lakeshore Mental Health Institute, Knoxville, TN, August 22, 2003.
"Use of Anticonvulsants in Psychotic Disorders," Tennessee Psychiatric Association, Smoky Mountain Chapter Meeting, Knoxville, TN, August 28, 2003.
"Application of the Harry Benjamin International Gender Dysphoria Association's Standards of Care to the Prison Setting: Recent Victories for Transgender Healthcare in the USA," 18th Biennial Symposium of the HBIGDA, Gent, Belgium, September 11, 2003.
"Family and Systems Aggression Towards Therapists Working with Transgendered Clients," 18th Biennial Symposium of the HBIGDA, Gent, Belgium, September 12, 2003.
"Impact of Childhood Abuse on Disease Course in Veterans with Bipolar Disorder," 97th Annual Meeting of the Southern Medical Association, Atlanta, Georgia, November 8, 2003.
"Gender Dysphoria: Diagnosis and Management," Grand Rounds presentation, Marshall Medical School, Huntington, West Virginia, January 9, 2004.
"Gender Dysphoria: Diagnosis and Management," Grand Rounds presentation, Catawba State Hospital, Roanoke, Virginia, March 17, 2004.
"Treatment Resistant Schizophrenia," Grand Rounds presentation, Broughton State Hospital, Morganton, North Carolina, March 25, 2004.
"Antipsychotic Use in Geriatric Populations," Grand Rounds presentation, Tampa VAMC, Tampa, Florida, April 23, 2004.
"Gender Identity Disorders,", Grand Rounds presentation, University of TN College of Medicine, Memphis, TN, May 14, 2004.
"Overcoming Barriers to Treatment Success in Chronic Mental Illnesses," Grand Rounds, Salisbury VAMC, Salisbury, NC, June 3, 2004.
"Dissociative Identity Disorder Comorbid with Gender Identity Disorder: Review of the Literature and Long-term Case Presentation," Southern Psychiatric Association, Savannah, Georgia, October 2, 2004.
"Bipolar Disorder in Primary Care," CME Cat 1 presentation, Knoxville, TN, December 1, 2004.
"Bipolar Disorder and Impulsive Aggression in Primary Care Settings," CME Cat 1 presentation to Tricities Nurse Practitioner Association, December 16, 2004.
"Overcoming Barriers to Treatment in Chronic Mental Illnesses," North Carolina Advanced Practice Nurses Association, Greensboro, NC, February 13, 2005.
"Bipolar Disorder in the Primary Care Setting: What to do?," 9th Annual Update for Nurse Practitioners, Johnson City, TN, March 21, 2005.
"Current Controversies in the Use of SSRI's," TriCounty Medical Society, Johnson City, TN, May 5, 2005.
"Transgender client aggression towards therapists," XIX Biennial Symposium of the Harry Benjamin International Gender Dysphoria Association, Bologna, Italy, April 9, 2005.
"Gender identity disorder comorbid with dissociative identity disorder: review of the literature and 7 year followup case presentation. XIX Biennial Symposium of the Harry Benjamin International Gender Dysphoria Association, Bologna, Italy, April 9, 2005.
"Current Controversies in the Use of SSRI's," CME symposium, Southern Medical Association 9th Annual Scientific Symposium, San Antonio, TX, November 12, 2005.
"Gender Identity Disorder: Diagnosis and Management,", Grand Rounds, University of South Florida, Tampa, Florida, January 6, 2006 (Videotaped version of presentation available at www.TheCJC.com).
"Gender Identity Disorders," East Tennessee State University Women's Health Program, CME Cat 1 symposium, Johnson City, TN, March 24, 2006.
"Update on Bipolar Disorder," Millennium Center, CME Cat I program, Johnson City, TN, March 31, 2006.
"Dealing with Chronic Mental Illness: Barriers to Treatment Success," Southside Virginia

Psychiatric Society Quarterly Meeting, Richmond, Virginia, April 3, 2006.
"Management of Gender Identity Disorders," Intermountain Psychological Association, invited presentation, Johnson City, TN, June 8, 2006.
"Transgender Health Issues," Emory and Henry Lyceum Series, Emory, Virginia, September 18, 2006.
"Impact of Childhood Abuse in Veterans with Bipolar Disorder," 65th Annual Scientific Meeting of the Southern Psychiatric Association, Baltimore, Maryland, September 29, 2006.
"Appropriate Use of Antipsychotics in Primary Care Settings," 100th Annual Meeting of the Southern Medical Association, Charlotte, NC, October 14, 2006.
"Impact of Childhood Abuse on the Course of Bipolar Disorder," Keynote speaker, Perspectives In Health, Texas Department of State Health Services Annual CME Symposium, Austin, Texas, October 27, 2006.
"Autocastration as Surgical Self-Treatment in Incarcerated Persons with Gender Identity Disorder," Southern Psychiatric Association Annual Meeting, Memphis, TN, August, 2007.
"Autocastration as Surgical Self-Treatment in Incarcerated Persons with Gender Identity Disorder," XX Biennial Symposium of the World Professional Association for Transgender Health, Chicago, Illinois, September, 2007.
"Gender Identity Disorders in the Military and VA," Panel discussion and presentation. XX Biennial Symposium of the World Professional Association for Transgender Health, Chicago, Illinois, September, 2007.
"Diagnosis and Treatment of Gender Identity Disorders," Mountain Update on Psychiatry, ETSU CME Symposium, October 19, 2007.
"Voice Parameters That Result in Identification or Misidentification of Biological Gender in Male-to-Female Transgender Veterans," poster presentation at the First Annual Gender Spectrum Health Fair, Sponsored by the Alliance for Gender Awareness, Inc and Rutgers Office of Social Justice Education LGBT Communities Rutgers University College, New Brunswick, NJ, November 8, 2007 (with R King et al, coauthors).
"Voice Parameters That Result in Identification or Misidentification of Biological Gender in Male-to-Female Transgender Veterans," poster presentation at the XX Biennial Symposium of the World Professional Association for Transgender Health, Chicago, Illinois, September, 2007 (with R King, et al, coauthors).
"Voice Parameters That Result in Identification or Misidentification of Biological Gender in Male-to-Female Transgender Veterans," poster presentation at the Southern Medical Association Annual Scientific Meeting, Nashville, TN, September, 2008 (presented by E McDuffie on behalf of Brown, King, et al, coauthors).
"Evaluation and Management of Gender Identity Disorders," Cat I, 1.5 hour CME program, Annual Meeting of the Alaska Psychiatric Association, Alyeska, Alaska, April 18, 2009.
"Forensic Issues and Case Presentations on GID," Cat I, 1.5 hour CME program, Annual Meeting of the Alaska Psychiatric Association, Alyeska, Alaska, April 18, 2009.
"70 Veterans with Gender Identity Disturbances: A Descriptive Study," XXI Biennial Symposium of the World Professional Association for Transgender Health, Oslo, Norway, June 18, 2009.
"70 Veterans with Gender Identity Disturbances: A Descriptive Study", Annual Scientific Meeting of the Southern Medical Association, Dallas , Texas, December 4, 2009.
"Overview of Autocastration and Surgical Self Treatment in Prisons", National Commission on Correctional Healthcare Annual Meeting, October 10, 2010, Las Vegas, Nevada (invited two hour CME CAT I program)
"Autocastration- Overview and Case Series Presentation," Grand Rounds, East Tennessee State University, Johnson City, TN, April 29, 2011.
"Providing Healthcare for Transgender and Intersex Veterans," Live Meeting Series broadcast nationally by VA Talent Management System. Co-Presenters Leonard Pogache, MD, Meri Mallard, RN; CME category I credit for each of 3 programs completed, November 22 (2 programs) and November 30, 2011.
"PBM Guidelines for Providing Care for Transgender and Intersex Veterans," copresenter with Lisa Longo, Pharm.D, Live Meeting Series broadcast nationally by VA Talent

Management System, May 10 and May 14, 2012.

"Providing Culturally Competent Care for Transgender Veterans," invited Keynote address at Houston VAMC for symposium (CEU accredited) on LGBT Veteran healthcare, Houston, TX, August 17, 2012.

"Update on Version 7 of the WPATH Standards of Care," invited Keynote address for Mountain Area Health Education Center's Southeastern Summit on Transgender Healthcare, Category 1 CME accredited, Asheville, NC, August 24, 2012.

"History of Transgender Healthcare in the Department of Veterans Affairs," invited Keynote address for Mountain Area Health Education Center's Southeastern Summit on Transgender Healthcare, Category 1 CME accredited, Asheville, NC, August 25, 2012.

"Qualitative Analysis of Transgender Inmates' Correspondence: Implications for health Services in Departments of Correction", National Commission on Correctional Healthcare Annual Meeting, October 14, 2012, Las Vegas, Nevada (invited one hour CME CAT I program).

"Cross Sex Hormonal Treatment for Transgender Veterans," national Live Meeting for Women's Health Program, Department of Veterans Affairs, July 16, 2013.

"Transgender Health Care Training for VA Health Care Providers", 3 hours Category 1 CME accredited , Minneapolis, MN, September 26, 2013.

"Sex Reassignment Options", national presentation to VA SCAN-ECHO and regional consultation teams responsible for VA transgender health consultations, July 2, 2013.

"Access to Care for Gender Dysphoric Inmates: Issues and Cases," Invited plenary speaker for the 21st Annual Forensic Rights and Treatment Conference, sponsored by Drexel University College of Medicine, Category 1 CME credit (1.5 hours), Harrisburg, PA, December 5, 2013.

"Forensic Aspects of Transgender Health Care in Prison," Grand Rounds, East Tennessee State University, Category 1 CME, March 7, 2014.

"Health Disparities Research: Suicidality in Gender Minorities as a Research Model," Grand Rounds, East Tennessee State University, Category 1 CME credit, May 20, 2014.

"Sex reassignment surgeries: female-to-male," national presentation to VA SCAN-ECHO and regional consultation teams responsible for VA transgender health consultations, Cat I CME, June 24, 2014.

"Sex reassignment surgeries: male-to-female," national presentation to VA SCAN-ECHO and regional consultation teams responsible for VA transgender health consultations, Cat I CME, July 8, 2014.; December 2, 9, 16, 23, 2014; February 24, 20-15.

"Medico-Legal Aspects of Providing Transgender Healthcare for Inmates," invited 2.5 hour presentation for national training program in LGBT healthcare for the Federal Bureau of Prisons, September 4, 2014.

"Mental health and medical outcome disparities in 5,135 transgender veterans: a case-control study," 32nd Annual Conference of the Gay and Lesbian Medical Association, Category 1 CME credit, Baltimore, MD, September 11, 2014.

"Mental health and medical outcome disparities in 5,135 transgender veterans: a case-control study," Vanderbilt University Grand Rounds, Department of Psychiatry, Cat 1 CME credit, Nashville, TN, September 26, 2014.

"Mental health and medical outcome disparities in 5,135 transgender veterans: a case-control study," Drexel University Grand Rounds, Department of Psychiatry, Cat 1 CME credit, Philadelphia, PA, October 23, 2014.

"Pharmacotherapy issues with gender dysphoria," College of Psychiatric and Neuropsychiatric Pharmacists, Annual Meeting, Cat I CME credit, Tampa, FL, April 19, 2015.

"Lesbian, gay, bisexual, and transgender (LGBT) sociopolitical indicators and mental health diagnoses among transgender Veterans receiving VA care. Blosnich, J.R., Marsiglio, M.C., Gao, S., Gordon, A.J., Shipherd, J.C., Kauth, M., Brown, G.R., Fine, M.J. (2015, July). Department of Veterans Affairs Health Services Research & Development/Quality Enhancement Research Initiative National Conference, Philadelphia, PA, July, 2015.

"Killing the Bore: How to Give Effective Medical Presentations," East Tennessee State University Department of Psychiatry and Behavioral Sciences Grand Rounds (Cat I CME), May 1, 2015.

"Sex reassignment surgeries: male-to-female," national presentation to VA SCAN-ECHO and regional consultation teams responsible for VA transgender health consultations, Cat I CME, July 21, July 28, 2015

"Sex reassignment surgeries: female-to-male," national presentation to VA SCAN-ECHO and regional consultation teams responsible for VA transgender health consultations, Cat I CME, September 15, September 22, 2015.

"Transgender military service: Moving past ignorance in DoD and VHA," invited Keynote Address, Rush Medical University, Cat I CME credit, Chicago, IL, October 9, 2015.

"Health correlates of criminal justice involvement in 4,793 transgender veterans. Poster Presentation at the Annual National Conference on Correctional Health Care, Denver, CO, October 18, 2015.

"Open Transgender Military Service: Health Considerations," presentation to medical leadership of the USMC, Washington, DC, by videolink, January 27, 2016.

"Sex reassignment surgeries; masculinizing and feminizing," national presentations to VA SCAN-ECHO and regional consultation teams responsible for VA transgender health consultations, Cat I CME, June 7 and 28, 2016.

"Orange is not the new black—yet," Symposium on prison transgender mental health care and update on recent court cases supporting access to transgender health care in US prisons, 24th Biennial Scientific Symposium of the World Professional Association for Transgender Health, Amsterdam, The Netherlands, Cat I CME (1.5 hours), June 20, 2016.

"Harry Benjamin Plenary Lecture," invited Keynote address for the 24th Biennial Scientific Symposium of the World Professional Association for Transgender Health, Amsterdam, The Netherlands, Cat 1 CME, June 18, 2016. Available at www.wpath2016.com, timer marker 4:20.

"Health correlates of criminal justice involvement in 4,793 transgender veterans. Poster Presentation at the 24th Biennial Scientific Symposium of the World Professional Association for Transgender Health, Amsterdam, The Netherlands, June 18, 2016.

"Breast cancer in a cohort of 5,135 transgender veterans over time," 24th Biennial Scientific Symposium of the World Professional Association for Transgender Health, Amsterdam, The Netherlands, Cat 1 CME, June 20, 2016.

SYMPOSIA ORGANIZED AND/OR MODERATED:

1. Psychosocial Aspects of HIV Disease in the Military, organizer/moderator/ presenter, Wichita Falls, Texas, 25 April, 1990.

2. Full Day Roundtable Symposium on Atypical Antipsychotics, organizer/moderator, Excerpta Medica, Asheville, North Carolina, 22 April, 1995.

3. Mountain Update on Anxiety Disorders, Course Director, East Tennessee State University, Blowing Rock, North Carolina, 28-29 April, 1995.

4. Medicine and Sexuality Course, Course Director, East Tennessee State University and James H. Quillen VAMC, Johnson City, TN, 13 June, 1997.

5. Half Day audiotaped symposium moderater/organizer on Innovative Uses of Atypical Antipsychotics, Excerpta Medica, Blackberry Inn, Townsend, TN, 16 November, 1997.

6. Novel Uses of Atypical Antipsychotics, Symposium Moderator, Marriot Griffin Resort, Janssen Research Foundation, Lexington, KY, 4 December, 1998.

7. Novel Uses of Atypical Antipsychotics, Symposium Moderator, Blackberry Inn, Townsend, TN, 10 April, 1999.

8. Psychiatry and Neurology Poster Session Moderator for Southern Medical Association's 97th Annual Scientific Assembly, Atlanta, Georgia, November 6, 2003.

9. Moderator for East Tennessee State University Department of Psychiatry monthly Journal Club/Critical Evaluation of the Literature series, 2002-2011.

TELEVISED and TAPED MEDIA EVENTS:

WKPT local television interview on sleep disorders, Johnson City, 1995.

TNN (The Nashville Network), filmed winning an international revolver competition and then interviewed on silhouette handgun shooting, Oakridge, TN, 1998.

CME, Inc. audiotaped faculty presentations as advertised in "Psychiatric Times," various cities and topics.

Channel 5, London, England; documentary on psychiatric aspects of firearms, 2004.

"Cruel and Unusual", documentary on transgender health care issues in the prison setting, 2005 release, available from jbaus@aol.com; aired on Women's Entertainment channel on July 2, 2007

ABC 20/20, "Becoming Diane" segment on gender identity disorders, October 12, 2005.

The Carter Jenkins Center, www.thecjc.org, taped CME cat I lecture available on the internet, "Evaluation and Management of Gender Identity Disorder," January 6, 2006.

CNN, Kosilek Trial testimony/interview, June 1, 2006.

CNBC, "The Big Idea with Donny Deutsch," interview, June 6, 2006.

PBS News Hour, Transgender Soldiers Gain Ground as US Military Transitions, May 9, 2016, http://www.pbs.org/newshour/bb/transgender-soldiers-gain-ground-as-u-s-military-transitions/

RESEARCH PROJECTS AND GRANT SUPPORT:

Principal Investigator, "Phase III Comparison of Two Doses of Risperidone For Acute Exacerbations of Chronic Schizophrenia." Inpatient setting, grant support from Janssen Pharmaceutica, approximately $50,000. Completed 1996.

Principal Investigator, Sexual Functioning and Personality Characteristics of Transgendered Men in a Nonclinical Setting. Collaboration with Tom Wise, M.D. (Chair, Dept. of Psychiatry, Fairfax Hospital, Falls Church, VA), Peter Fagan, Ph.D. (Johns Hopkins Sexual Behaviors Consultation Unit), and Paul Costa, Ph.D. (NIMH). Completed 1990-1995.

DSM-IV Reliability Field Trials, Site Coordinator, 10 investigators, completed in 1995.

Principal Investigator, Psychosocial Adjustment of Spouses of Transgendered Men; study involving long-term support group work and nationwide questionnaire data collection from 1986 to 1997. Completed. Private non-profit organization grant support received.

Coinvestigator, International Study of 800 Transgender Men: The Boulton and Park Experience. 1988-1992. This was the largest community based survey study of transgender people in the U.S. conducted to date. Completed.

Principal Investigator, "A Double-Blind, Placebo-Controlled, Dose-Response Comparison of the Safety and Efficacy of Three Doses of Sertindole and Three Doses of Haloperidol in Schizophrenic Patients." Phase III trial, inpatient setting. Grant support by Abbott Laboratories, approximately $60,000 over one year. Completed 1994-1995. Contributed to FDA consideration of Serlect for U.S. marketing, 1996-1997.

Principal Investigator, "An Open Label, Long Term, Safety Study of Sertindole in Schizophrenic Patients." Phase II trial, outpatient setting. Grant support from Abbott Laboratories, approximately $50,000 over two years. Completed 1996.

Principal Investigator, "Biopsychosocial Natural History Study of HIV Infection in the USAF." RO-1 equivalent grant from Henry M. Jackson Foundation for the Advancement of Military Medicine, approximately $2,000,000. Completed 1987-1993, including pilot data collection.

Unrestricted Educational Grants, $19,000, for Mountain Update on Anxiety Disorders CME conference (SKB, Lilly, Mead-Johnson), 1995.

Unrestricted Educational Grants totaling approximately $30,000 annually in support of the VAMC/ETSU Psychiatry Grand Rounds and Visiting Professor Program, 1994-2000; 2002-2006. Grant funding following CME guidelines and administered through the ETSU Office of Continuing Education.

Principal Investigator, "Double-Blind Crossover Study of Zolpidem and Temazepam in Elderly, Hospitalized Patients." Funded through Psychiatry Research Fund, Mountain Home VAMC, and Chair of Excellence in Geriatrics, ETSU. Approved study, ultimately closed due to lack of appropriate subjects available for recruitment.

Principal Investigator, "A Randomized, Double-Blind Placebo Controlled Study of Risperidone for Treatment of Behavioral Disturbances in Subjects with Dementia." Collaboration with R. Hamdy, Cecile Quillen Chair of Excellence in Geriatrics, approximately $100,000 at full recruitment, 1995-1997; completed.

Associate Investigator, "Use of Nefazodone in Depressed Women with Premenstrual Amplification of Symptoms: a Pilot Study." Principal Investigator: Merry Miller, M.D. $5,000 pilot study grant, 1996-1999; completed.

Associate Investigator, "Voice Characteristics Associated with Gender Misidentification: A Pilot Study." Principal Investigator: Robert King, M.A. Unfunded study in data analysis phase, 2001-2005; completed in 2007.

Principal Investigator, Johnson City site, VA Cooperative Study #430, "Reducing the Efficacy-Effectiveness Gap in Bipolar Disorder." Health services research conducted at 12 sites nationwide. Grant for this site's operations total $435,000 over five years of study, 1997-2003; completed.

Coinvestigator, "Treatment for Erectile Disorder with Viagra in a VA Population: Efficacy and

Patient and Partner Satisfaction." Principal Investigator: William Finger, Ph.D. Approximately $30,000 total grant over two year period, 2000-2001; study concluded.

Principal Investigator, Johnson City site, "A Multicenter, Randomized, Double-Blind, Placebo Controlled Study of Three Fixed Doses of Aripiprazole in the Treatment of Institutionalized Patients with Psychosis Associated with Dementia of the Alzheimer's Type." Phase III clinical trial, sponsored by Bristol-Meyers Squibb, 2000-2001, $174,000 at full recruitment. Extension phase, 42 weeks, separate grant at maximum of $232,800. Approved April, 2000; completed.

Coinvestigator, "Effects of zaleplon on postural stability in the elderly." Principal Investigator: Faith Akin, Ph.D. $1000 grant for subject recruitment expenses, 2000-2001.

Principal Investigator, James H. Quillen VA site, "ZODIAK study; An International, Multicenter Large Simple Trial (LST) To Compare the Cardiovascular Safety of Ziprasidone and Olanzapine." Pfizer Pharmaceuticals, approximately $20,000 at full recruitment. Approved April, 2002, recruitment completed and closed in 2004. Results published: Strom B, Eng S, Faich G, et al: comparative mortality associated with ziprasidone and olanzapine in real-world use among 18,154 patients with schizophrenia: The ziprasidone Observational Study of Cardiac Outcomes (ZODIAC). Amer J Psychiatry 168(2):193-201, 2011.

Coinvestigator, "Survey of Family and Systems Aggression Against Therapists." Unfunded study, completed between 2002 and 2003; Randi Ettner, Ph.D., Principle Investigator; completed.

Coinvestigator, "Effect of Olanzapine on the Auditory Gating Deficit in Patients with Schizophrenia." Principal Investigator: Barney Miller, Ph.D. Investigator-initiated study funded by Lilly, approximately $85,000. 2002. Study did not recruit subjects at ETSU and was closed 2003.

Principal Investigator, multicenter study, "The SOURCE Study: Schizophrenia Outcomes, Utilization, Relapse, and Clinical Evaluation." Janssen Research, $100,000 grant at full recruitment (two year open label followup study of risperidone Consta), 2005-2007; second highest recruitment of 43 centers in multicenter study. Completed. See publications from this study under the Publications section, numbers 128 and 129.

Coauthor on grants to VA Central Office for program enhancements to mental health programs at Mountain Home VAMC; approximately $2,000,000 received for additional staff and support for residential treatment programs and PTSD clinic expansion, 2006-2007.

Principal Investigator in conjunction with Herbert Meltzer, MD, Vanderbilt University, " High Dose Risperidone Consta for Patients with Schizophrenia with Unsatisfactory Response to Standard Dose Risperidone or Long-Acting Injectable." Phase IV study of outpatients with schizophrenia who are partially responsive to risperidone oral and/or long-acting injectable, using a double-blind methodology to study doses between 50 and 100 mg every two weeks. Site funding of approximately $100,000. 2008-2010. Approved by ETSU IRB but negotiations between sponsor and Department of Veterans Affairs were not completed on intellectual property rights. Study not initiated at Mountain Home VAMC.

Principal Investigator (Everett McDuffie, MD, coinvestigator), "Descriptive study of veterans with gender identity disturbances: Characteristics and comorbidities, 1987-2007." Unfunded study that is first to characterize a population of 75 U.S. veterans with gender identity disturbances over a 20 year time frame. Completed 2009.

Principal Investigator: "Analysis of State and Federal Prison Directives Related to Transgender Inmate Medical Care and Placement." Unfunded review of existing prison policies through the end of 2007. Completed 2008.

Principal Investigator: "Qualitative Analysis of Concerns of Transgender Inmates in the United States. Unfunded analysis of 129 letters from self-identified transgender inmates across the US." Completed 2012.

Coinvestigator, "Prevalence and Suicidality in Transgender Veterans"; coinvestigator with collaborators at the VA Center of Excellence for Suicide Prevention. 2011-2013. Completed; publication of results in October, 2013.

Principal Investigator, "Assessing Health Outcomes, Health Care Utilization, and Health Disparities in Transgender Veterans Receiving Care in the Veterans Health Administration." Approved by ETSU IRB 7/1/13; protocol remains open. Six manuscripts published; one in preparation.

Consultant, Patient-Centered Outcomes Research Institute grant on transgender healthcare outcomes (STRONG), Michael Goodman, MD, Principal Investigator, Emery University, 2014-present.

References available upon request.

EXHIBIT B

Exhibit B to George Brown Declaration

Bibliography

Altschiller, Donald, *Hate Crimes: A Reference Handbook* (3d ed. 2015)

American Medical Association, Committee on Human Sexuality, *Human Sexuality* (1972).

American Psychoanalytic Association, *Position Statement on Attempts to Change Sexual Orientation, Gender Identity, or Gender Expression* (June 2012), *available at* http://www.apsa.org/content/2012-position-statement-attempts-change-sexual-orientation-gender-identity-or-gender.

American Psychological Association, *Transgender, Gender Identity, & Gender Expression Non-Discrimination* (Aug. 2008), *available at* http://www.apa.org/about/policy/transgender.aspx.

American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* (5th ed. 2013).

Arcelus, J., et al., *Systematic review and meta-analysis of prevalence studies in transsexualism*, 30 Eur. Psychiatry 807 (2015).

Auyeung, Bonnie, et al., *Fetal Testosterone Predicts Sexually Differentiated Childhood Behavior in Girls and in Boys*, 20 Psychol. Sci. 144 (2009).

Baker, Howard J., *Transsexualism—Problems in Treatment*, 125 Am. J. Psychiatry 1412 (1969).

Berglund, Hans, et al., *Brain response to putative pheromones in lesbian women*, 103 Proc. Nat'l Acad. Sci. 8269 (Gustafsson, Jan-Åke, et al. eds., 2006).

Blosnich, John R., et al., *Mental Health of Transgender Veterans in US States With and Without Discrimination and Hate Crime Legal Protection*, 106 Am. J. Pub. Health 534 (2016).

Bradford, Judith, et al., *Experiences of Transgender-Related Discrimination and Implications for Health: Results From the Virginia Transgender Health Initiative Study*, 103 Am. J. Pub. Health 1820 (2013).

Bradley, Susan J., *Gender Disorders in Childhood: A Formulation*, in *Gender Dysphoria: Development, Research, Management* 175 (Steiner, Betty W., ed., 1985).

Brown, George R., *Transsexuals in the Military: Flight Into Hypermasculinity*, 17 Archives Sexual Behav. 527 (1988).

Brown, George R. & Jones, Kenneth T., *Mental Health and Medical Health Disparities in 5135 Transgender Veterans Receiving Healthcare in the Veterans Health Administration: A Case–Control Study*, 3 LGBT Health 122 (2016).

Burgess, Diana, et al., *Effects of Perceived Discrimination on Mental Health and Mental Health Services Utilization Among Gay, Lesbian, Bisexual and Transgender Persons*, J. LGBT Health Res., Oct. 11, 2008, at 1.

Clements-Nolle, Kristen, et al., *Attempted Suicide Among Transgender Persons: The Influence of Gender-Based Discrimination and Victimization*, J. Homosexuality, June 2006, at 53.

Cohen-Kettenis, P. T., & Gooren, L.J.G, *Transsexualism: A review of etiology, diagnosis and treatment*, 46 J. Psychosomatic Res. 315 (1999).

Coleman, Eli, et al., *Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Version 7*, 13 Int'l J. Transgenderism 165 (2011).

Daniel, Hilary & Butkus, Renee, *Lesbian, Gay, Bisexual, and Transgender Health Disparities: Executive Summary of a Policy Position Paper From the American College of Physicians*, 163 Annals Internal Med. 135 (2015).

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Ettner, Randi, *The Etiology of Transsexualism*, in *Principles of Transgender Medicine and Surgery* 1 (Ettner, Randi, et al. eds., 1st ed. 2007).

Giedd, Jay N., et al., *Sexual dimorphism of the developing human brain*, 21 Progress Neuro-Psychopharmacology & Biological Psychiatry 1185 (1997).

Goldblum, Peter, et al., *The Relationship Between Gender-Based Victimization and Suicide Attempts in Transgender People*, 43 Prof. Psychol.: Res. & Prac. 468 (2012).

Golden, Carla, *Diversity and Variability in Women's Sexual Identities*, in *Lesbian Psychologies: Explorations and Challenges* 19 (Boston Lesbian Psychologies Collective ed., 1987).

Green, Richard & Keverne, E.B., *The Disparate Maternal Aunt–Uncle Ratio in Male Transsexuals: an Explanation Invoking Genomic Imprinting*, 202 J. Theoretical Biology 55 (2000).

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Haas, Ann P., et al., *Suicide Attempts among Transgender and Gender Non-Conforming Adults: Findings of the National Transgender Discrimination Study* (Jan. 2014), *available at* http://williamsinstitute.law.ucla.edu/wp-content/uploads/AFSP-Williams-Suicide-Report-Final.pdf.

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Kruijver, Frank P.M., et al., Male-to-Female Transsexuals Have Female Neuron Numbers in a Limbic Nucleus, 85 J. Clinical Endocrinology & Metabolism 2034 (2000).

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UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF NORTH CAROLINA

UNITED STATES OF AMERICA,

Plaintiff,

v.

STATE OF NORTH CAROLINA; PATRICK MCCRORY, in his official capacity as Governor of North Carolina; NORTH CAROLINA DEPARTMENT OF PUBLIC SAFETY; UNIVERSITY OF NORTH CAROLINA; and BOARD OF GOVERNORS OF THE UNIVERSITY OF NORTH CAROLINA,

Defendants.

Case No. 1:16-cv-425

SUPPLEMENTAL EXPERT DECLARATION OF GEORGE R. BROWN, MD, DFAPA IN SUPPORT OF THE UNITED STATES' MOTION FOR PRELIMINARY INJUNCTION

1. As is detailed in my June 20, 2016 declaration submitted in support of the United States' preliminary injunction motion, I am a Professor of Psychiatry and Associate Chairman of the Department of Psychiatry at East Tennessee State University and I have been retained by counsel for the United States as an expert in this litigation. I submit this supplemental declaration to address opinions offered by Defendants' expert witnesses in opposition to the motion.

2. I have been publishing books and articles on the subject of the diagnosis and treatment of Gender Dysphoria for over three decades, as my June 20 declaration makes clear. During this time, I have kept up with published research, continued to contribute original research to the literature on this topic, and I have consistently been deeply engaged with the community of experts in this field through conferences, consultations, lecturing, and other professional activities. I have never before heard of any of Defendants' medical experts prior to reviewing their declarations. To my knowledge, I have never encountered them at any professional conferences

on this subject. I am not aware of any publications by them concerning Gender Dysphoria, or related issues in any book or peer-reviewed scientific journal, and I see none listed on their CVs.

Medical Standards Established in the DSM and WPATH Standards of Care

3. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition ("DSM-5") is the authoritative source for psychiatric diagnoses in the United States and many other countries. The process of determining the diagnoses and diagnostic criteria included in the DSM involves a robust review of available evidence by numerous experts with varying perspectives in the relevant field over the course of several years of research, planning and debate. There is no sound basis for concluding that its contents are the product of influence from "political interest groups." (Josephson ¶ 24). The process by which this 947 page document was developed was well publicized, interactive with thousands of clinicians and researchers, and well described in the literature (DSM-5, pp. 5-10, 897-916).

4. There is no basis for Dr. Josephson's assertion that the change to the current diagnosis and nomenclature for Gender Dysphoria was the result of "political interest groups" as opposed to "scientific information." (Josephson ¶ 24). Having been present for discussions about these changes, presented by the Chair of Sexual and Gender Identity Disorders Committee, Dr. Kenneth Zucker, the reasons for the title change from "Gender Identity Disorder" to "Gender Dysphoria" was based on a more thorough understanding of this condition in the intervening 13 years between the publication of DSM's Fourth Edition, Text Revision ("DSM-IV-TR") and DSM-5. Gender Dysphoria, as a diagnosis, focuses on the treatable symptoms that a patient experiences. "Dysphoria," rather than "Identity," is the focus of treatment, and there is substantial evidence that Dysphoria can be treated successfully.

5. Likewise, Dr. Mayer's critique of the DSM-5's diagnosis of Gender Dysphoria in children reveals a lack of understanding of both the DSM and how it is used in practice. He isolates one aspect of a comprehensive set of criteria (gender atypical play preferences) and notes that it would not be a sound basis for a diagnosis. (Mayer ¶¶ 46-47). But that is precisely why it is only part of a comprehensive set of criteria provided to clinical professionals to use in the context of their practice to make a diagnosis. In fact, to arrive at a diagnosis of Gender Dysphoria in a child, a minimum of 6 of 8 specified "A" criteria must be met, accompanied by a minimum time frame criterion and a clinical significance criterion "B." All of these requirements must be met to arrive at a diagnosis. As with all psychiatric diagnoses, patients must be reassessed over time, and diagnoses may or may not be present at future time points.

6. Defendants' medical experts further situate themselves outside the mainstream of the field by rejecting well-accepted treatment protocols recognized by the major medical and mental health professional associations in the United States. As set forth in my June 20 declaration, the World Professional Association of Transgender Health ("WPATH") publishes Standards of Care for treating Gender Dysphoria. WPATH is an internationally recognized association comprising nearly 1,000 medical, surgical, mental health, and other professionals who specialize in the treatment of transgender and gender non-conforming people. The WPATH Standards of Care ("SOC"), which are in their seventh revision, represent the evidence-based consensus of experts in the field and have been recognized as the authoritative treatment protocols by the major medical and mental health associations in the United States, including the American Psychiatric Association, the American Medical Association, and the American Psychological Association. The largest health care system in the United States, the Veterans Health Administration ("VHA"), treats transgender veterans largely based on the guidelines set forth in

the current version of the WPATH SOC, and references these standards in their national training programs. I have been directly involved with the national VHA training program since its inception in 2012.

7. Some of Defendants' expert witnesses characterized WPATH as an advocacy organization with a social and political agenda (Van Meter ¶ 53), as opposed to a professional medical association that uses evidence-based standards. WPATH is a medical association in the same mold as every other medical association dedicated to the treatment of a particular condition— it creates a community of experts to share research and clinical experience; it establishes best practices for treatment based on experts in the field engaging in a robust review of the available evidence; and it supports policies that enhance the well-being of its patient population. There is ample evidence supporting the WPATH SOC, which are in widespread use throughout the United States and other countries. Any psychiatrist or other clinician trained in or with experience in this field would be aware of this.

Illustrative Errors in Defendants' Experts Opinions

8. Many of the opinions offered by Defendants' experts are unsound, reflecting a lack of experience in this field. The following are some pertinent examples.

The Suggestion That Transgender People are Delusional

9. I have not heard the theory that transgender people are suffering from a delusion articulated by any credible mental health professional in over thirty years. That theory has been soundly disproven and rejected by the medical profession.

10. In suggesting that transgender people are suffering from a delusion, Defendants' experts use a dictionary definition of "delusion" to oversimplify a complex psychiatric issue and draw an illogical and ill-informed conclusion that has no basis in evidence.

11. Contrary to Defendants' experts' opinion, the medical definition of a "delusion" is not merely "a fixed, false belief which is held despite clear evidence to the contrary." (Josephson ¶ 42; Van Meter ¶ 50). As the DSM-5 notes, a delusion is a fixed belief not amenable to change in light of conflicting evidence, which is associated with certain psychotic disorders and generally characterized by persecutory, religious or other grandiose themes (DSM-5, pp. 819-820). Delusional ideas or beliefs are "held despite what almost everyone else believes and despite what constitutes incontrovertible and obvious proof or evidence to the contrary" (DSM-5, p. 819). Delusions are generally treated with antipsychotic medication.

12. By contrast, transgender people have a very clear understanding of the reality that their body does not align with their gender identity. If you asked a transgender woman, prior to her transition, whether she has male genitals, is perceived by others who look at her body to be a man, or whether her birth certificate labels her a male, she is acutely aware of these realities. It is precisely the accurate understanding of these realities coupled with the incongruence between experienced gender identity and objectively observable bodily realities that leads to psychological distress and the diagnosis of Gender Dysphoria. Patients with Gender Dysphoria harbor no delusions whatsoever about "external reality" and to categorize these patients as delusional is not only inaccurate, but completely out of step with modern, mainstream, medical thinking.

The Suggestion That the Only Appropriate Treatment for Gender Dysphoria is to Align Gender Identity with Birth Sex

13. The WPATH Standards of Care emphasize the importance of the social transition for transgender people with Gender Dysphoria. Defendants' expert witnesses seem to suggest that rather than follow these professional standards, clinicians who see such patients should try to help them change their gender identity to align with their birth-assigned sex. As I noted in my June 20 declaration, attempts to do this have been found to be ineffective and are recognized as

potentially harmful by professional associations. The only treatment approaches for Gender Dysphoria in adolescents and adults that is supported by evidence and, thus, represents the medical consensus, is the gender-affirming protocols set forth in the WPATH Standards of Care and in the Endocrine Society's guidelines as applied to the hormonal aspects of multimodal treatment for this condition. I note that two of Defendant's experts are members of the Endocrine Society (Drs. Van Meter and Hruz), but their statements about Gender Dysphoria place them completely out of step with their own professional Society in this regard.

14. Evidence cited by Defendants' expert, Dr. Mayer, supports the conclusion that gender identity is real, fixed, and not generally malleable based on external interventions. Dr. Mayer cites the case of David Reimer, who was reported to have been assigned male at birth with no sign of any intersex condition but whose penis was severely damaged in a botched circumcision. According to the sources cited by Dr. Mayer, David's parents, in an effort to grapple with the consequences of the circumcision, opted for additional surgical and hormonal interventions and raised David as a girl ("Brenda"), concealing his history. These decisions were made after consultation with experts at Johns Hopkins. Notwithstanding this alteration to the external sex characteristics and hormones, as well as consistent social inputs affirming that David was a girl, David's gender identity remained fixed as male, and he suffered psychological distress as a result of the divergence between his male gender identity on the one hand and his female social identity, hormones, and external feminized sexual characteristics on the other hand. David lived the last 20 years of his life (from age 18-38) as a male, consistent with his gender identity. This evidence, offered by Defendants' expert, illustrates well the stability of gender identity in the face of overwhelming external interventions, and not the contrary.

The Erroneous Lumping Together of Pre-Pubertal Children, Adolescents, and Adults

15. Defendants' expert witnesses erroneously generalize about the appropriate course of treatment for Gender Dysphoria in adults or adolescents based on data about pre-pubertal children. The DSM-5 recognizes separate criteria for diagnosing Gender Dysphoria in children, on the one hand, and adults and adolescents on the other. The WPATH Standards of Care have distinct standards of care for pre-pubertal children (generally up to about age 10), adolescents and adults.

16. Defendants' experts point to the fact that some professionals do not favor social transition in pre-pubertal children based on data showing high rates of young gender incongruent children ceasing to experience gender incongruence by adulthood. They erroneously suggest that this applies to adolescents and adults as well. It does not. Gender Dysphoria in postpubertal adolescents and adults is very unlikely to "disappear." For example, in one follow-up study of adolescents treated at a gender clinic, 100% of the 70 individuals treated ultimately underwent hormone therapy and continued to identify with a gender different than the one assigned to them at birth. (de Vries, Steensma, Doreleijers, & Cohen-Kettenis, 2010). In my personal experience, I have had no adult or late adolescent patients with Gender Dysphoria have a resolution of these clinical symptoms without one or more interventions.

Misunderstanding the Evidentiary Basis for the Accepted Treatment Protocols

17. Defendants' expert witnesses assert that there is a lack of evidence demonstrating the effectiveness of the accepted protocols for the treatment of Gender Dysphoria. Dr. Hruz argues that there is a need for clinical research trials on treatments. (Hruz ¶ 33). Dr. Mayer specifically criticizes studies demonstrating positive effect, arguing that they lack a matched

control group. (Mayer ¶ 85). Dr. Josephson also criticizes the absence of controlled studies on youth and adolescents. (Josephson ¶ 34).

18. But these kinds of studies are not the only type of evidence scientists and doctors rely on. Studies demonstrating that patients' conditions improved after treatment can be very informative, whether or not there are matched control groups. (Manieri, Castellano, Crespi, et al., 2014). Moreover, Defendants' experts ignore another critically important source of evidence—the clinical experience of generations of doctors who have treated patients with Gender Dysphoria. There is abundant clinical experience going back 50 years establishing the effectiveness of social transition, hormone therapy and surgeries as treatment for Gender Dysphoria.

19. Medical professionals every day make choices about treatment protocols that are not based on matched control group studies or randomized control trials. For example, many aspects of the treatment protocols for common psychiatric conditions such as bipolar disorder, depression, and schizophrenia (the bulk of patients seen in outpatient psychiatric clinics) are not matched with control group studies or double blind clinical trials, but rather have been accepted by the profession as the standard of care based on clinical experience, limited published data, case series, or other types of evidence available. Another common example is a doctor's decision to select one drug over another in treating a particular condition. In many cases, the decision to select drug A over drug B or drug C is not validated by a control group study demonstrating that drug A produces results superior to drug B or drug C. Instead, the doctor makes a decision among available drugs based on clinical experience and his or her overall assessment of a patient's situation. That decision does not lack an evidentiary basis simply because there is not a matched control group study to support it.

20. I personally would never hold myself up as an expert in a clinical psychological condition without having not just some clinical experience but substantial clinical experience. Clinical experience is particularly important in the specialty area of transgender health. Reviewing relevant literature is not a sufficient basis for developing expertise on these subjects. To draw valid conclusions, one must integrate knowledge of the literature with personally obtained clinical information, up-to-date presentations at conferences, consultation with colleagues who work with similar patients, interviewing family members, and other sources of important clinical information. I am hard-pressed to see evidence of relevant clinical experience with gender dysphoric children, adolescents or adults among the Defendants' experts (or in the case of Dr. Mayer, *any* clinical experience).

The Asserted Definition of Sex

21. To the extent that Defendants' experts define sex based on the ability to procreate or engage in reproduction, they are relying on outdated sources that do not reflect the current medical consensus. As I noted in my June 20 declaration, with citations to the relevant sources reflecting the current consensus view, "biological sex" is a broad and complex concept that consists of a number of variables, including gender identity, genital anatomy (internal and externally visible), secondary sexual characteristics, brain anatomy, hormonal levels in the brain and body, and chromosomal complement. Failure to account for these aspects of sex that extend beyond reproductive systems reflects an incomplete and ill-informed understanding of "sex." Defendants' experts limited definition of "sex" does not account for the many humans who have no ability to procreate and may not or cannot engage in reproduction.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct.

Executed on this 14th day of September, 2016.

By: _____
George R. Brown, MD, DFAPA

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UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF NORTH CAROLINA

JOAQUÍN CARCAÑO *et al.*, Plaintiffs, *v.* PATRICK MCCRORY *et al.*, Defendants	CASE NO. 1:16-CV-00236-TDS-JEP
UNITED STATES OF AMERICA, Plaintiff, *v.* STATE OF NORTH CAROLINA *et al.*, Defendants	CASE NO. 1:16-CV-00425-TDS-JEP

EXPERT DECLARATION OF Paul W Hruz, M.D., Ph.D

1. I have been retained by counsel for Defendants as an expert in connection with the above-captioned litigation. I have actual knowledge of the matters stated in this declaration. My professional background, experience, and publications are detailed in my curriculum vitae, a true and accurate copy which is attached as Exhibit A to this declaration. I received my doctor of philosophy degree from the Medical College of Wisconsin in 1993. I received my medical degree from the Medical College of Wisconsin in 1994. I am currently the Director of the Division of Pediatric Endocrinology and Diabetes at Washington University School of Medicine.

I served as the Director of the Pediatric Endocrinology Fellowship Program at Washington University from 2008-2016.

2. I am board certified in Pediatrics and Pediatric Endocrinology. I have been licensed to practice medicine in Missouri since 2000.

3. My professional memberships include the American Academy of Pediatrics, the Pediatric Endocrine Society, the Endocrine Society, and the American Association for Biochemistry and Molecular Biology.

4. I have extensive experience in treating infants and children with disorders of sexual development and am an active member of the multidisciplinary Disorders of Sexual Development (DSD) program at Washington University. The DSD Team at Washington University is part of the DSD-Translational Research Network, a national multi-institutional research network that investigates the genetic causes and the psychologic consequences of DSD.

5. In the nearly 20 years that I have been in clinical practice I have participated in the care of hundreds of children with disorders of sexual development including but not limited to congenital adrenal hyperplasia, 3β-hydroxysteroid dehydrogenase deficiency, partial and complete androgen insensitivity, 17-hydroxysteroid dehydrogenase deficiency, cloacal extrophy, aphallia, and Turner syndrome.

6. In my role as the director of the Division of Pediatric Endocrinology at Washington University, I have extensively studied the existing literature related to the incidence, potential etiology and treatment of gender dysphoria as efforts were made to develop a Transgender clinic at Saint Louis Children's Hospital. I have also participated in local and national meetings where the endocrine care of children with gender dysphoria has been discussed and debated. Pediatric patients referred to our practice for the evaluation and treatment of gender dysphoria are cared

for by an interdisciplinary team of providers that includes a psychologist and pediatric endocrinologist who have been specifically chosen for this role based upon a special interest in this rare patient population. Due to serious concerns regarding the safety, efficacy, and ethics of the current treatment paradigm, I have not directly engaged in hormonal treatment of patients with gender dysphoria.

7. My opinions as detailed in this declaration are based upon my knowledge and direct professional experience in the subject matters discussed. The materials that I have relied upon are the same types of materials that other experts in my field of clinical practice rely upon when forming opinions on the subject. A list of the sources I have relied on is attached as Exhibit B to this declaration.

8. Over my career, I have provided expert medical record review and testified at deposition in less than a dozen cases. I have never testified at trial and I have not been involved in any depositions in the past four years.

9. I am being compensated at an hourly rate for actual time devoted, at the rate of $350 per hour. My compensation does not depend on the outcome of this litigation, the opinions I express, or the testimony I provide.

Basic Terminology

10. Biological sex is a term that specifically refers to a member of a species in relation to the member's capacity to either donate (male) or receive (female) genetic material for the purpose of reproduction. This remains the standard definition that has been accepted and used by scientists, medical personnel, and society in general.

11. Gender, a term that had traditionally been reserved for grammatical purposes, is currently used to describe the psychologic and cultural characteristics of a person in relation to biological sex. Gender therefore exists in reference to societal perceptions, not biology.

12. Gender identity refers to a person's individual perception of being male or female.

13. Sexual orientation refers to a person's arousal and desire for sexual intimacy with members of the male or female sex.

Human sexuality in relation to fundamental biology and observed variations

14. Sex is genetically encoded at the moment of conception due to the presence of specific DNA sequences (i.e. genes) that direct the production of signals that influence the formation of the gonad to develop either into a testis or ovary. This genetic information is normally present on X and Y chromosomes. Chromosomal sex refers to the normal complement of X and Y chromosomes (i.e. normal human males have one X and one Y chromosome whereas normal human females have two X chromosomes). Genetic signals are mediated through the activation or deactivation of other genes and through programmed signaling of hormones and cellular transcription factors. The default pattern of development in the absence of external signaling is female. The development of the male appearance (phenotype) depends upon active signaling processes.

15. For members of the human species, sex is normatively aligned in a binary fashion (i.e., either male or female) in relation to biologic purpose. Medical designation of an individual as male or female is typically made at birth according to external phenotypic expression of primary sexual traits (i.e., presence of a penis for males and presence of labia and vagina for females).

16. Due to genetic and hormonal variation in the developing fetus, normative development of the external genitalia in any individual differs with respect to size and appearance while maintaining an ability to function with respect to biologic purpose (i.e. reproduction). Internal structures (e.g. gonad, uterus, vas deferens) normatively align with external genitalia.

17. Reliance upon external phenotypic expression of primary sexual traits is a highly accurate means to assign biologic sex. In over 99.9% of cases, this designation will correlate with internal sexual traits and capacity for normal biologic sexual function.

18. Due the complexity of signals that are involved in normal sexual development, it is not surprising that a small number of individuals are born with defects in this process. Defects can occur either through inherited or de novo mutations in genes that are involved in sexual determination or through environmental insults during critical states of sexual development. Persons who are born with such abnormalities are considered to have a disorder of sexual development (DSD). Most often, this is first detected as ambiguity in the appearance of the external genitalia.

19. Normal variation in external genital appearance (e.g. phallic size) does not alter the basic biologic nature of sex as a binary trait. "Intersex" conditions represent disorders of normal development, not a third sex.

20. Medical care of persons with DSDs is primarily directed toward identification of the etiology of the defect and treatment of any associated complications. Similar to other diseases, tools such as the Prader scale are used to stage the severity of the deviation from normal. In children with DSDs, characterization based upon phenotype alone does not reliably predict chromosomal sex nor does it necessarily correlate with potential for biological sexual function.

Decisions on initial sex assignment in these rare cases require detailed assessment by a team of expert medical providers.

21. Standard medical practice in the treatment of persons with DSDs has evolved with growing understanding of the physical and psychologic needs and outcomes for affected individuals. Previously, it was felt that a definitive sex assignment was necessary shortly after birth with the belief that this would allow patients with DSDs to best conform to the assigned sex. Current practice is to defer sex assignment until the etiology of the disorder is determined and, if possible, a prediction can be made on likely biologic and psychologic outcomes. When this cannot be done with confidence, a presumptive sex assignment is made. Factors used in making such decisions include chromosomal sex, phenotypic appearance of the external genitalia, and parental desires. The availability of new information can in rare circumstances lead to sex reassignment. Decisions on whether to surgically alter the external genitalia to align with sex are generally deferred until the patient is able to provide consent.

Gender Dysphoria in relation to Biological Sex

22. Although gender usually aligns with biological sex, some individuals experience discordance in these distinct traits. Specifically, biologic females may identify as males and biologic males may identify as females. As gender by definition is distinct from biological sex, one's gender identity does not change a person's biological sex.

23. Individuals who experience significant distress due to discordance between gender identity and sex are considered to have "gender dysphoria". Although the prevalence of gender dysphoria has not been established by rigorous scientific analysis, estimates reported in in the DSM-V are between 0.005% to 0.014% for adult males and 0.002% to 0.003% for adult females.

Thus, gender dysphoria is a rare condition. It is currently unknown whether these estimates are falsely low due to under-reporting, or if changing societal acceptance of transgenderism and the growing number of medical centers providing medical intervention for gender dysphoria affects the number of persons who identify as transgender. Recent data suggests that the number of people seeking care for gender dysphoria is increasing with some estimates as high as 4-fold.

24. Most people with gender dysphoria have normally formed and functional sexual organs. The etiology of gender dysphoria in these persons remains to be identified. Theories include prenatal hormone exposure, genetic variation, and postnatal environmental influences. Based upon the currently available but incomplete dataset, it is likely that gender dysphoria is multifactorial with differing qualitative and quantitative influences in any given individual. There is strong evidence against the theory that gender identity is determined at or before birth and is unchangeable. This comes from identical twin studies where siblings share genetic complements and prenatal environmental exposure but have differing gender identities.

25. Further evidence that gender identity is not fixed comes from well established peer reviewed literature demonstrating that the vast majority (80-95%) of children who express gender dysphoria revert to a gender identity concordant with their biological sex by late adolescence. It is not known whether individuals with gender dysphoria persistence have differing etiologies or severity of precipitating factors compared to desisting individuals.

26. The limited emerging data has suggested structural and functional differences between brains from normal and transgender individuals. These data do not establish whether these differences are innate and fixed or acquired and malleable. The remarkable neuronal plasticity of the brain is known and has been studied extensively in gender-independent contexts related to health and disease, learning and behavior.

Gender Ideology

27. The modern attempt to equate gender identity with sex is not based upon sound scientific principles but rather is based upon ideology fueled by advocacy. Although worldviews among scientists and physicians, similar to society at large, differ, science is firmly grounded in physical reality not perception. The inherent link between human sexual biology and teleology is self-evident and fixed.

28. The claims of proponents of transgenderism, which include opinions such as "Gender defines who one is at his/her core" and "Gender is the only true determinant of sex" must be viewed in their proper philosophical context. There is no scientific basis for redefining sex on the basis of a person's psychological sense of 'gender'. It is erroneous and potentially damaging to equate these opinions as established medical fact.

29. The prevailing, constant and accurate designation of sex as a biological trait grounded in the inherent purpose of male and female anatomy and as manifested in the appearance of external genitalia at birth remains the proper scientific and medical standard. Redefinition of what is normal based upon pathologic variation is not established medical fact.

Potential Harm Related to Gender Dysphoria Treatments

30. The fundamental purpose of the practice of medicine is to treat disease and alleviate suffering. An essential tenet of medical practice is to avoid doing harm in the process. Due to the frequent lack of clear and definitive evidence on how to best accomplish this goal, treatment approaches can and do frequently differ among highly knowledgeable, competent, and caring physicians.

31. Persons with gender dysphoria as delineated in the DSM-V experience significant psychological distress related to their condition with elevated risk of depression, suicide, and other morbidities. Thus, attempts to provide effective medical care to affected persons are clearly warranted.

32. Efforts to effectively treat persons with gender dysphoria require respect for the inherent dignity of those affected, sensitivity to their suffering, and maintenance of objectivity in assessing etiologies and long-term outcomes. Desistance (i.e. reversion to gender identity concordant with sex) provides the greatest lifelong benefit and is the outcome in the majority of patients and should be maintained as a desired goal. Any intervention that interferes with the likelihood of resolution is unwarranted and potentially harmful.

33. There is an urgent need for high quality controlled clinical research trials to determine ways to develop supportive dignity affirming social environments that maintain affirmation of biological reality.

34. The Endocrine Society published in 2009 clinical guidelines for the treatment of gender dysphoric patients which include temporary suppression of pubertal development of children with GnRH agonists (hormone blockers normally used for children experiencing precocious puberty) followed by hormonal treatments to induce the development of secondary sexual traits consistent with one's gender identity. This guideline was developed using the GRADE (Recommendations, Assessment, Development, and Evaluation) system for rating clinical guidelines. As directly stated in the Endocrine Society publication, "the strength of recommendations and the quality of evidence was low or very low." According to the GRADE system, low recommendations indicate "Further research is very likely to have an important

impact on our confidence in the estimate of effect and is likely to change the estimate". Very low recommendations mean that "any estimate of effect is very uncertain".

35. There is little or no data to support pubertal suppression as a safe or effective treatment for gender dysphoria in children or adolescents. As noted, it is well established that 80-95% of children with gender dysphoria will resolve by the end of puberty without direct intervention to affirm transgender identity. Unfavorable long-term psychiatric outcomes for transgender adults point to gender resolution following puberty as the best hope for gender dysphoric children and adolescents.

36. In addition, treatment of gender dysphoric children with hormonal treatment (pubertal suppression and cross-hormone therapy) carries significant risk. It is generally accepted, even by advocates of transgender hormone therapy, that hormonal treatment results in sterility which in many cases is irreversible. Emerging data also show that treated patients have lower bone density which may lead to increased fracture risk later in life. Other potential adverse effects include disfiguring acne, high blood pressure, weight gain, abnormal glucose tolerance, breast cancer, liver disease, thrombosis, and cardiovascular disease.

37. Since strategies for the treatment of transgendered children as summarized by the Endocrine Society guidelines are relatively new, long-term outcomes are unknown. Evidence presented as support for short term reductions in psychological distress following social transition in a "gender affirming" environment remains inconclusive. When considered apart from advocacy based agendas, multiple potential confounders are evident. The most extensive long-term data on this question comes from the Dutch experience. Although appropriate caution is warranted in extrapolating these outcomes with current treatments, adults who have undergone

social transition with or without surgical modification of external genitalia continue to have rates of depression and suicide far above the background population.

38. With regard to public restrooms and other intimate facilities, there is no evidence to support social measures that promote or encourage gender transition as a medically necessary or effective treatment for gender dysphoria. If anything, one might expect that such social affirmation measures would interfere with known rates of gender resolution. Any activity that encourages or perpetuates transgender persistence for those who would otherwise desist can cause significant harm, including permanent sterility, to these persons. This is particularly concerning given that children are likely incapable of making informed consent to castrating treatments.

39. There remains a significant and unmet need to better understand both the biological, psychological, and environmental basis for the manifestation of discordance of gender identity in affected individuals together with rigorous controlled investigation of long-term outcomes including adverse consequences of attempted intervention. Uncontrolled social experimentation including the forced acceptance of altered norms for distinguishing persons according to biological sex is a potentially harmful and unscientific approach to dealing with this serious condition.

Pursuant to 28 U.S.C § 1746, I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Date: 08/09/2016

Signed: Paul W Hruz

Paul W. Hruz, M.D., Ph.D

Exhibit B

Hruz Sources

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Curriculum Vitae

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Present Position

Associate Professor of Cell Biology and Physiology
Associate Professor of Pediatrics
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Education and Training

1987	B.S., Chemistry, Marquette University, Milwaukee, WI
1993	Ph.D., Biology and Physiology, Medical College of Wisconsin, Milwaukee, WI
1994	M.D., Medicine, Medical College of Wisconsin, Milwaukee, WI
1994 - 1997	Pediatric Residency, University of Washington - Pediatric , Seattle, Washington
1997 - 2000	Pediatric Endocrinology Fellowship, Washington University - Pediatric Endocrinology , Saint Louis, MO

Academic Positions and Employment

1996 - 1997	Locum Tenens Physician, Group Health of Puget Sound Eastside Hospital, Group Health of Puget Sound Eastside Hospital, Seattle , WA
2000 - 2003	Instructor of Pediatrics, Washington University, St. Louis, MO
2003 - 2011	Assistant Professor of Pediatrics, Washington University, St. Louis, MO

2004 - 2011	Assistant Professor of Cell Biology and Physiology, Washington University, St. Louis, MO
2011 - Pres	Associate Professor of Pediatrics, Washington University, St. Louis, MO
2011 - Pres	Associate Professor of Cell Biology and Physiology, Washington University, St. Louis, MO
2012 - Pres	Division Director, Pediatric Endocrinology and Diabetes, Washington University, St. Louis, MO

Appointments and Committees

NIH Study Sections:

2005	NIH- NIDDK Special Emphasis Panel ZDK1 GRB-6 (Non-Standing Member)
2009	NIH- ACE Competitive Revisions ZRG1 AARR-H (95) S (Non-Standing Member)
2009	NIH- AIDS and AIDS Related Research IRG (Standing Member)
2011	NIH- Pediatric Endocrinologist K12 ZDK1 GRB-C (Non-Standing Member)
2014	NIH- Special Emphasis Panel ZRG1 BBBPY 58 (Non-Standing Member)
2014	NIH- AIDS and AIDS Related Research IRG (Standing Member)
2015	NIH- Cardiovascular and Respiratory Sciences Special Emphasis Panel ZDK1 GRB-J (02) (Non-Standing Member)
2015	NIH- NIDDK Special Emphasis Panel ZRG1 CVRS-Q (80) (Non-Standing Member)

University Affiliations:

2008 - Pres	Director, Pediatric Endocrinology & Diabetes Fellowship Program
2010 - Pres	Pediatric Computing Facility Advisory Committee
2012 - Pres	Disorders of Sexual Development Interdisciplinary Care Program
2012 - Pres	Director, Division of Pediatric Endocrinology & Diabetes
2014 - Pres	Research Consultant, ICTS Research Forum - Child Health
2014 - Pres	Director, Pediatric Diabetes Research Consortium

Hospital Affiliations:

2000 - Pres	Attending Physician, St. Louis Children's Hospital

Thesis Committees (* Chair)		Advisor
2008 - 2011	Kelly Diggs-Andrews	Simon Fisher
2008 - 2010	Irwin Puentes	Simon Fisher
2008 - 2010	Tony Frovola	Kelle Moley
2009 - 2010	Lauren Flessner	Kelle Moley
2010 - 2012	Katie Boehle	Kelle Moley
2010 - 2013	Candace Reno*	Simon Fisher
2011 -Pres	Thomas Kraft	Paul Hruz
2013 - 2015	Chi Lun Pui	Audrey Odom
2013 -Pres	Leah Imlay	Audrey Odom
2014 -Pres	Anne Robinson	Katie Henzler-Wildman

2015 -Pres Allyson Mayer Brian DeBosch

Scholarship Oversight Committees
2013 -Pres Brittany Knipsein (Advisor: David Rudnick)

Licensure and Certifications

1997 - 2016 Board Certified in General Pediatrics
2000 - 2014 MO State License #2000155004
2001 - Pres Board Certified in Pediatric Endocrinology & Metabolism

Honors and Awards

1987 National Institute of Chemists Research and Recognition Award
1987 Phi Beta Kappa
1987 Phi Lambda Upsilon (Honorary Chemical Society)
1988 American Heart Association Predoctoral Fellowship Award
1994 Alpha Omega Alpha
1994 Armond J. Quick Award for Excellence in Biochemistry
1994 NIDDK/Diabetes Branch Most Outstanding Resident
1998 Pfizer Postdoctoral Fellowship Award
2002 Scholar, Child Health Research Center of Excellence in Developmental Biology at Washington University
2013 Julio V Santiago, M.D. Scholar in Pediatrics

Editorial Responsibilities

Editorial Boards:
2014 - Pres Endocrinology and Metabolism Clinics of North America

Ad Hoc Reviewer:
AIDS
AIDS Research and Human Retroviruses
American Journal of Pathology
American Journal of Physiology
British Journal of Pharmacology
Circulation Research
Clinical Pharmacology & Therapeutics
Comparative Biochemistry and Physiology
Diabetes
Experimental Biology and Medicine
Future Virology
Journal of Antimicrobial Chemotherapy
Journal of Biological Chemistry
Journal of Clinical Endocrinology & Metabolism
Journal of Molecular and Cellular Cardiology
Obesity Research

Professional Societies and Organizations

1992 - 2004	American Medical Association
1994 - 2005	American Academy of Pediatrics
1995 - 2014	American Association for the Advancement of Science
1998 - Pres	American Diabetes Association
1998 - Pres	Endocrine Society
1999 - Pres	Pediatric Endocrine Society
2004 - Pres	American Society for Biochemistry and Molecular Biology
2004 - Pres	Society for Pediatric Research
2004 - 2007	American Chemical Society
2005 - Pres	Full Fellow of the American Academy of Pediatrics
2013 - Pres	International Society for Pediatric and Adolescent Diabetes

Major Invited Professorships and Lectures

2002	St. Louis Children's Hospital, Pediatric Grand Rounds, St. Louis, MO
2004	National Disease Research Interchange, Human Islet Cell Research Conference, Philadelphia, PA
2004	NIDA-NIH Sponsored National Meeting on Hormones, Drug Abuse and Infections, Bethesda, MD
2005	The Collaborative Institute of Virology, Complications Committee Meeting, Boston, MA
2005	University of Indiana, Endocrine Grand Rounds, Indianapolis, IN
2006	Metabolic Syndrome Advisory Board Meeting, Bristol-Meyers Squibb, Pennington, NJ
2007	American Heart Association and American Academy of HIV Medicine State of the Science Conference: Initiative to Decrease Cardiovascular Risk and Increase Quality of Care for Patients Living with HIV/AIDS, Chicago, IL
2007	Medical College of Wisconsin, MSTP Annual Visiting Alumnus Lecture, Milwaukee, WI
2007	St Louis Children's Hospital, Pediatric Grand Rounds, St Louis, MO
2007	University of Arizona, Minority Access to Research Careers Seminar, Tucson AZ
2008	Boston University, Division of Endocrinology, Diabetes and Nutrition, Boston, MA
2009	St Louis Children's Hospital, Pediatric Grand Rounds, St Louis, MO
2010	American Diabetes Association Scientific Sessions, Symposium Lecture Orlando, FL
2010	University of Missouri Kansas City, School of Biological Sciences, Kansas City, MO
2011	Life Cycle Management Advisory Board Meeting, Bristol-Myers Squibb, Chicago, IL
2013	St Louis Children's Hospital, Pediatric Grand Rounds, St Louis MO
2013	St Louis Children's Hospital CPU Lecture, St Louis MO

2014 Pediatric Academic Societies Meeting, Vancouver, Canada, May 5, 2014
2014 American Diabetes Association 74th Scientific Sessions, San Francisco, CA, June 13, 2014

Consulting Relationships and Board Memberships

1996 - 2012 Consultant, Bristol Myers Squibb
1997 - 2012 Consultant, Gilead Sciences

Research Support

Governmental Support
R01 (Hruz) 9/20/2009 - 5/31/2014 (NCE)
NIH
Direct Effects of Antiretroviral Therapy on Cardiac Energy Homeostasis
The goal of this project is to characterize the influence of antiretroviral therapies on myocardial energy homeostasis and to elucidate how these changes in substrate delivery adversely affect cardiac function in the stressed heart.
Role: Principal Investigator

R01 (Hruz) 4/1/2007 - 1/31/2012 (NCE)
NIH
Mechanisms for Altered Glucose Homeostasis During HAART
The goal of this project is to identify the cellular targets of HIV protease inhibitors that lead to peripheral insulin resistance, impaired beta-cell function, and alterations in hepatic glucose production and to elucidate the molecular mechanisms of these effects.
Role: Principal Investigator

Non-Governmental Support
Research Program (Hruz) 6/1/2009 - 5/31/2012 (NCE)
MOD
Regulation of GLUT4 Intrinsic Activity
The major goals of this project are to investigate the ability of the GLUT4 tethering protein TUG and an UBL-domain containing N-terminal fragment of this protein to alter the intrinsic activity of the insulin responsive facilitative glucose transporter, to determine whether protein ubiquitination influences this association, and to characterize the role of the GLUT4 binding site on the modulation of glucose transport.
Role: Principal Investigator

(Hruz) 3/9/2010 - 6/8/2011 (NCE)
Bristol-Myers Squibb
Protective Effect of Saxagliptin on a Progressive Deterioration of Cardiovascular Function
Role: Principal Investigator

(Hruz)
Gilead Pharma

Novel HIV Protease Inhibitors and GLUT4
Role: Principal Investigator

II (Hruz) 2/1/2008 - 1/31/2011 (NCE)
CDI
Insulin Resistance and Myocardial Glucose Metabolism in Pediatric Heart Failure
Role: Co-Principal Investigator

Completed Support
R01 Student Supp (Hruz) 6/10/2009 - 8/31/2011
NIH
Mechanisms for Altered Glucose Homeostasis During HAART

II (Hruz) 2/1/2012 - 1/31/2015
CDI
Solution-State NMR Structure and Dynamics of Facilitative Glucose Transport Proteins

Past Trainees

2002 - 2002 Nishant Raj- Undergraduate Student (Other)
Study area: Research

2003 - 2004 Johann Hertel (Medical Student)
Study area: Research
Present position: Assistant Professor, University of North Carolina, Chapel Hill, NC

2003 John Paul Shen (Medical Student)
Study area: Research

2004 - 2005 Carl Cassel- High School Student (Other)
Study area: Research

2004 - 2004 Christopher Hawkins- Undergraduate Student (Other)
Study area: Research

2004 - 2004 Kaiming Wu- High School Student (Other)
Study area: Research

2005 Helena Johnson (Graduate Student)

2005 Jeremy Etzkorn (Medical Student)
Study area: Research
Present position: Assistant Professor, University of Pennsylvania

2006 Ramon Jin (Graduate Student)
Study area: Research

2006 Taekyung Kim (Graduate Student)
Study area: Research

2007 - 2008 Kai-Chien Yang (Graduate Student)
Study area: Research
Present position: Postdoctoral Research Associate, University of Chicago

2007 Paul Buske (Graduate Student)
Study area: Research
Present position: Postdoctoral Fellow, UCSF, San Francisco CA

2007	Randy Colvin (Medical Student) Study area: Research
2007 - 2007	Jan Freiss- Undergraduate Student (Other) Study area: Research
2008 - 2011	Arpita Vyas, MD (Clinical Fellow) Study area: Research Present position: Assistant Professor, Michigan State University, Lansing MI
2008 - 2009	Candace Reno (Graduate Student) Study area: Research Present position: Research Associate, University of Utah
2008	Temitope Aiyejorun (Grad Student) Study area: Research
2008 - 2012	Dennis Woo- Undergraduate Student (Other) Study area: Research Present position: MSTP Student, USC, Los Angeles CA
2009	Stephanie Scherer (Grad Student) Study area: Research
2009	Anne-Sophie Stolle- Undergraduate Student (Other) Study area: Research
2009 - 2009	Matthew Hruz- High School Student (Other) Study area: Research Present position: Computer Programmer, Consumer Affairs, Tulsa OK
2010	Constance Haufe- Undergraduate Student (Other) Study area: Research
2010 - 2011	Corinna Wilde- Undergraduate Student (Other) Study area: Researcher
2010 - 2010	Samuel Lite- High School Student (Other) Study area: Research
2011 - 2011	Amanda Koenig- High School Student (Other) Study area: Research
2011 - 2012	Lisa Becker- Undergraduate Student (Other)
2011 - 2011	Melissa Al-Jaoude- High School Students (Other)
2002 - 2010	Joseph Koster, PhD (Postdoc Fellow) Study area: Research
2005	Dominic Doran, DSc (Postdoctoral Fellow) Study area: HIV Protease Inhibitor Effects on Exercise Tolerance Present position: Faculty of Science, Liverpool John Moores Institute
2014 - 2014	David Hannibal (Clinical Research Trainee)
2010 - 2014	Lauren Flessner, PhD (Postdoctoral Fellow) Present position: Instructor, Syracuse University
2011 - 2016	Thomas Kraft (Graduate Student) Study Area: Glucose transporter structure/function Present position: Postdoctoral Fellow, Roche, Penzberg, Germany

Clinical Responsibilities

General Pediatrician, General Pediatric Ward Attending: 2-4 weeks per year, St. Louis Children's Hospital
Pediatric Endocrinologist, Endocrinology Night Telephone Consult Service: Average of 2-6 weeks/per year, St. Louis Children's Hospital
Pediatric Endocrinologist, Inpatient Endocrinology Consult Service: 4-6 weeks per year, St. Louis Children's Hospital
Pediatric Endocrinologist, Outpatient Endocrinology Clinic: Approximately 50 patient visits per month, St. Louis Children's Hospital

Teaching Responsibilities

Facilitator, Biology 5011- Ethics and Research Science, 6 hours/year
Facilitator, Cell Biology Graduate Student Journal Club, 4 hour/year
Facilitator, Discussion: Pituitary, Growth & Gonadal Cases, 2 hours/year
Facilitator, Medical Student Endocrinology and Metabolism Course, Small group
Lecturer, Cell Signaling Course, Diabetes module, 3 hours/year
Lecturer, Markey Course-Diabetes Module
Lecturer, Medical Student Growth Lecture (Women and Children's Health Rotation): Variable
Lecturer, Metabolism Clinical Rounds/Research Seminar: Presentations twice yearly
Lecturer, Pediatric Endocrinology Journal Club: Presentations yearly

Publications

1. Hruz, P. W., Narasimhan, C., Miziorko, H. M. (1992). 3-Hydroxy-3-methylglutaryl coenzyme A lyase: affinity labeling of the Pseudomonas mevalonii enzyme and assignment of cysteine-237 to the active site. *Biochemistry*, 31 (29), 6842-7 PubMed: 1637819.
2. Hruz, P. W., Miziorko, H. M. (1992). Avian 3-hydroxy-3-methylglutaryl-CoA lyase: sensitivity of enzyme activity to thiol/disulfide exchange and identification of proximal reactive cysteines. *Protein Sci*, 1 (9), 1144-53. PMCID: PMC2142181 PubMed: 1304393.
3. Mitchell, G. A., Robert, M. F., Hruz, P. W., Wang, S., Fontaine, G., Behnke, C. E., Mende-Mueller, L. M., Schappert, K., Lee, C., Gibson, K. M., Miziorko, H. M. (1993). 3-Hydroxy-3-methylglutaryl coenzyme A lyase (HL). Cloning of human and chicken liver HL cDNAs and characterization of a mutation causing human HL deficiency. *J Biol Chem*, 268 (6), 4376-81 PubMed: 8440722.
4. Hruz, P. W., Anderson, V. E., Miziorko, H. M. (1993). 3-Hydroxy-3-methylglutaryldithio-CoA: utility of an alternative substrate in elucidation of a role for HMG-CoA lyase's cation activator. *Biochim Biophys Acta*, 1162 (1-2), 149-54 PubMed: 8095409.
5. Roberts, J. R., Narasimhan, C., Hruz, P. W., Mitchell, G. A., Miziorko, H. M. (1994). 3-Hydroxy-3-methylglutaryl-CoA lyase: expression and isolation of the recombinant

human enzyme and investigation of a mechanism for regulation of enzyme activity. *J Biol Chem*, 269 (27), 17841-6 PubMed: 8027038.

6. Hruz, P. W., Mueckler, M. M. (1999). Cysteine-scanning mutagenesis of transmembrane segment 7 of the GLUT1 glucose transporter. *J Biol Chem*, 274 (51), 36176-80 PubMed: 10593902.
7. Murata, H., Hruz, P. W., Mueckler, M. (2000). The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *J Biol Chem*, 275 (27), 20251-4 PubMed: 10806189.
8. Hruz, P. W., Mueckler, M. M. (2000). Cysteine-scanning mutagenesis of transmembrane segment 11 of the GLUT1 facilitative glucose transporter. *Biochemistry*, 39 (31), 9367-72 PubMed: 10924131.
9. Hruz, P. W., Mueckler, M. M. (2001). Structural analysis of the GLUT1 facilitative glucose transporter (review). *Mol Membr Biol*, 18 (3), 183-93 PubMed: 11681785.
10. Hruz, P. W., Murata, H., Mueckler, M. (2001). Adverse metabolic consequences of HIV protease inhibitor therapy: the search for a central mechanism. *Am J Physiol Endocrinol Metab*, 280 (4), E549-53 PubMed: 11254460.
11. Murata, H., Hruz, P. W., Mueckler, M. (2002). Investigating the cellular targets of HIV protease inhibitors: implications for metabolic disorders and improvements in drug therapy. *Curr Drug Targets Infect Disord*, 2 (1), 1-8 PubMed: 12462148.
12. Hruz, P. W., Murata, H., Qiu, H., Mueckler, M. (2002). Indinavir induces acute and reversible peripheral insulin resistance in rats. *Diabetes*, 51 (4), 937-42 PubMed: 11916910.
13. Murata, H., Hruz, P. W., Mueckler, M. (2002). Indinavir inhibits the glucose transporter isoform Glut4 at physiologic concentrations. *AIDS*, 16 (6), 859-63 PubMed: 11919487.
14. Koster, J. C., Remedi, M. S., Qiu, H., Nichols, C. G., Hruz, P. W. (2003). HIV protease inhibitors acutely impair glucose-stimulated insulin release. *Diabetes*, 52 (7), 1695-700. PMCID: PMC1403824 PubMed: 12829635.
15. Liao, Y., Shikapwashya, O. N., Shteyer, E., Dieckgraefe, B. K., Hruz, P. W., Rudnick, D. A. (2004). Delayed hepatocellular mitotic progression and impaired liver regeneration in early growth response-1-deficient mice. *J Biol Chem*, 279 (41), 43107-16 PubMed: 15265859.
16. Shteyer, E., Liao, Y., Muglia, L. J., Hruz, P. W., Rudnick, D. A. (2004). Disruption of hepatic adipogenesis is associated with impaired liver regeneration in mice. *Hepatology*, 40 (6), 1322-32 PubMed: 15565660.
17. Hertel, J., Struthers, H., Horj, C. B., Hruz, P. W. (2004). A structural basis for the acute effects of HIV protease inhibitors on GLUT4 intrinsic activity. *J Biol Chem*, 279 (53), 55147-52. PMCID: PMC1403823 PubMed: 15496402.
18. Yan, Q., Hruz, P. W. (2005). Direct comparison of the acute in vivo effects of HIV protease inhibitors on peripheral glucose disposal. *J Acquir Immune Defic Syndr*, 40 (4), 398-403. PMCID: PMC1360159 PubMed: 16280693.
19. Hruz, P. W. (2006). Molecular Mechanisms for Altered Glucose Homeostasis in HIV Infection. *Am J Infect Dis*, 2 (3), 187-192. PMCID: PMC1716153 PubMed: 17186064.
20. Turmelle, Y. P., Shikapwashya, O., Tu, S., Hruz, P. W., Yan, Q., Rudnick, D. A. (2006). Rosiglitazone inhibits mouse liver regeneration. *FASEB J*, 20 (14), 2609-11 PubMed: 17077279.

21. Hruz, P. W., Yan, Q. (2006). Tipranavir without ritonavir does not acutely induce peripheral insulin resistance in a rodent model. *J Acquir Immune Defic Syndr*, 43 (5), 624-5 PubMed: 17133213.
22. Hruz, P. W., Yan, Q., Struthers, H., Jay, P. Y. (2008). HIV protease inhibitors that block GLUT4 precipitate acute, decompensated heart failure in a mouse model of dilated cardiomyopathy. *FASEB J*, 22 (7), 2161-7 PubMed: 18256305.
23. Hruz, P. W. (2008). HIV protease inhibitors and insulin resistance: lessons from in-vitro, rodent and healthy human volunteer models. *Curr Opin HIV AIDS*, 3 (6), 660-5. PMCID: PMC2680222 PubMed: 19373039.
24. Flint, O. P., Noor, M. A., Hruz, P. W., Hylemon, P. B., Yarasheski, K., Kotler, D. P., Parker, R. A., Bellamine, A. (2009). The role of protease inhibitors in the pathogenesis of HIV-associated lipodystrophy: cellular mechanisms and clinical implications. *Toxicol Pathol*, 37 (1), 65-77. PMCID: PMC3170409 PubMed: 19171928.
25. Tu, P., Bhasin, S., Hruz, P. W., Herbst, K. L., Castellani, L. W., Hua, N., Hamilton, J. A., Guo, W. (2009). Genetic disruption of myostatin reduces the development of proatherogenic dyslipidemia and atherogenic lesions in Ldlr null mice. *Diabetes*, 58 (8), 1739-48. PMCID: PMC2712781 PubMed: 19509018.
26. Guo, W., Wong, S., Pudney, J., Jasuja, R., Hua, N., Jiang, L., Miller, A., Hruz, P. W., Hamilton, J. A., Bhasin, S. (2009). Acipimox, an inhibitor of lipolysis, attenuates atherogenesis in LDLR-null mice treated with HIV protease inhibitor ritonavir. *Arterioscler Thromb Vasc Biol*, 29 (12), 2028-32. PMCID: PMC2783673 PubMed: 19762785.
27. Vyas, A. K., Koster, J. C., Tzekov, A., Hruz, P. W. (2010). Effects of the HIV protease inhibitor ritonavir on GLUT4 knock-out mice. *J Biol Chem*, 285 (47), 36395-400. PMCID: PMC2978568 PubMed: 20864532.
28. Gazit, V., Weymann, A., Hartman, E., Finck, B. N., Hruz, P. W., Tzekov, A., Rudnick, D. A. (2010). Liver regeneration is impaired in lipodystrophic fatty liver dystrophy mice. *Hepatology*, 52 (6), 2109-17. PMCID: PMC2991544 PubMed: 20967828.
29. Hresko, R. C., Hruz, P. W. (2011). HIV protease inhibitors act as competitive inhibitors of the cytoplasmic glucose binding site of GLUTs with differing affinities for GLUT1 and GLUT4. *PLoS One*, 6 (9), e25237. PMCID: PMC3179492 PubMed: 21966466.
30. Vyas, A. K., Yang, K. C., Woo, D., Tzekov, A., Kovacs, A., Jay, P. Y., Hruz, P. W. (2011). Exenatide improves glucose homeostasis and prolongs survival in a murine model of dilated cardiomyopathy. *PLoS One*, 6 (2), e17178. PMCID: PMC3040766 PubMed: 21359201.
31. Hruz, P. W., Yan, Q., Tsai, L., Koster, J., Xu, L., Cihlar, T., Callebaut, C. (2011). GS-8374, a novel HIV protease inhibitor, does not alter glucose homeostasis in cultured adipocytes or in a healthy-rodent model system. *Antimicrob Agents Chemother*, 55 (4), 1377-82. PMCID: PMC3067185 PubMed: 21245443.
32. Hruz, P. W. (2011). Molecular mechanisms for insulin resistance in treated HIV-infection. *Best Pract Res Clin Endocrinol Metab*, 25 (3), 459-68. PMCID: PMC3115529 PubMed: 21663839.
33. Remedi, M. S., Agapova, S. E., Vyas, A. K., Hruz, P. W., Nichols, C. G. (2011). Acute sulfonylurea therapy at disease onset can cause permanent remission of KATP-induced diabetes. *Diabetes*, 60 (10), 2515-22. PMCID: PMC3178299

PubMed: 21813803.
34. Aerni-Flessner, L., Abi-Jaoude, M., Koenig, A., Payne, M., Hruz, P. W. (2012). GLUT4, GLUT1, and GLUT8 are the dominant GLUT transcripts expressed in the murine left ventricle. *Cardiovasc Diabetol*, 11, 63. PMCID: PMC3416696 PubMed: 22681646.
35. Vyas, A. K., Aerni-Flessner, L. B., Payne, M. A., Kovacs, A., Jay, P. Y., Hruz, P. W. (2012). Saxagliptin Improves Glucose Tolerance but not Survival in a Murine Model of Dilated Cardiomyopathy. *Cardiovasc Endocrinol*, 1 (4), 74-82. PMCID: PMC3686315 PubMed: 23795310.
36. Hresko, R. C., Kraft, T. E., Tzekov, A., Wildman, S. A., Hruz, P. W. (2014). Isoform-selective Inhibition of Facilitative Glucose Transporters: Elucidation of the Molecular Mechanism of HIV Protease Inhibitor Binding. *J Biol Chem*, 289 (23), 16100-16113. PMCID: PMC4047383 PubMed: 24706759.
37. Mishra, R. K., Wei, C., Hresko, R. C., Bajpai, R., Heitmeier, M., Matulis, S. M., Nooka, A. K., Rosen, S. T., Hruz, P. W., Schiltz, G. E., Shanmugam, M. (2015). In Silico Modeling-based Identification of Glucose Transporter 4 (GLUT4)-selective Inhibitors for Cancer Therapy. *J Biol Chem*, 290 (23), 14441-53 PubMed: 25847249.
38. Kraft, T. E., Hresko, R. C., Hruz, P. W. (2015). Expression, purification, and functional characterization of the insulin-responsive facilitative glucose transporter GLUT4. *Protein Sci* PubMed: 26402434.
39. Kraft, T. E., Armstrong, C., Heitmeier, M. R., Odom, A. R., Hruz, P. W. (2015). The Glucose Transporter PfHT1 Is an Antimalarial Target of the HIV Protease Inhibitor Lopinavir. *Antimicrob Agents Chemother*, 59 (10), 6203-9. PMCID: PMC4576095 PubMed: 26248369.
40. DeBosch, B. J., Heitmeier, M. R., Mayer, A. L., Higgins, C. B., Crowley, J. R., Kraft, T. E., Chi, M., Newberry, E. P., Chen, Z., Finck, B. N., Davidson, N. O., Yarasheski, K. E., Hruz, P. W., Moley, K. H. (2016). Trehalose inhibits solute carrier 2A (SLC2A) proteins to induce autophagy and prevent hepatic steatosis. *Sci Signal*, 9 (416), ra21 PubMed: 26905426.
41. Hresko, R. C., Kraft, T. E., Quigley, A., Carpenter, E. P., Hruz, P. W. (2016) Mammalian glucose transporter activity is dependent upon anionic and conical phospholipids. *J Biol Chem*, 2016 Jun 14. PubMed: 27302065.

Invited Publications

1. Hruz, P. W., Mueckler, M. M. (2001). Structural analysis of the GLUT1 facilitative glucose transporter (review). *Mol Membr Biol*, 18 (3), 183-93 PubMed: 11681785.
2. Hruz, P. W., Murata, H., Mueckler, M. (2001). Adverse metabolic consequences of HIV protease inhibitor therapy: the search for a central mechanism. *Am J Physiol Endocrinol Metab*, 280 (4), E549-53 PubMed: 11254460.
3. Murata, H., Hruz, P. W., Mueckler, M. (2002). Investigating the cellular targets of HIV protease inhibitors: implications for metabolic disorders and improvements in drug therapy. *Curr Drug Targets Infect Disord*, 2 (1), 1-8 PubMed: 12462148.
4. Hruz, P. W. (2006). Molecular Mechanisms for Altered Glucose Homeostasis in HIV Infection. *Am J Infect Dis*, 2 (3), 187-192. PMCID: PMC1716153 PubMed: 17186064.
5. Grunfeld, C., Kotler, D. P., Arnett, D. K., Falutz, J. M., Haffner, S. M., Hruz, P.,

Masur, H., Meigs, J. B., Mulligan, K., Reiss, P., Samaras, K., Working, Group 1 (2008). Contribution of metabolic and anthropometric abnormalities to cardiovascular disease risk factors. *Circulation*, 118 (2), e20-8. PMCID: PMC3170411 PubMed: 18566314.

6. Hruz, P. W. (2008). HIV protease inhibitors and insulin resistance: lessons from in-vitro, rodent and healthy human volunteer models. *Curr Opin HIV AIDS*, 3 (6), 660-5. PMCID: PMC2680222 PubMed: 19373039.
7. Flint, O. P., Noor, M. A., Hruz, P. W., Hylemon, P. B., Yarasheski, K., Kotler, D. P., Parker, R. A., Bellamine, A. (2009). The role of protease inhibitors in the pathogenesis of HIV-associated lipodystrophy: cellular mechanisms and clinical implications. *Toxicol Pathol*, 37 (1), 65-77. PMCID: PMC3170409 PubMed: 19171928.
8. Hruz, P. W. (2011). Molecular mechanisms for insulin resistance in treated HIV-infection. *Best Pract Res Clin Endocrinol Metab*, 25 (3), 459-68. PMCID: PMC3115529 PubMed: 21663839.
9. Hruz, P.W. (2014). HIV and endocrine disorders. *Endocrinol Metab Clin North Am*, 43 (3), xvii–xviii PubMed: 25169571.

Book Chapters (most recent editions)

1. Henderson KE, Baranski TJ, Bickel PE, Clutter PE, Clutter WE, McGill JB "Endocrine Disorders in HIV/AIDS ." *The Washington Manual Endocrinology Subspecialty Consult*. Philadelphia, PA: Lippincott Williams and Wilkins, 2008. 321-328.

Gender Development and Sexuality in Disorders of Sex Development

Authors S. A. Berenbaum[1], H. F. L. Meyer-Bahlburg[2]

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Key words
- gendered activities
- gender roles
- gender identity
- gender dysphoria
- sexual orientation
- sex hormones

Abstract

Understanding psychological development in individuals with disorders of sex development (DSD) is important for optimizing their clinical care and for identifying paths to competence and health in all individuals. In this paper, we focus on psychological outcomes likely to be influenced by processes of physical sexual differentiation that may be atypical in DSD, particularly characteristics related to being male or female (those that show sex differences in the general population, gender identity, and sexuality). We review evidence suggesting that (a) early androgens facilitate several aspects of male-typed behavior, with large effects on activity interests, and moderate effects on some social and personal behaviors (including sexual orientation) and spatial ability; (b) gender dysphoria and gender change occur more frequently in individuals with DSD than in the general population, with rates varying in relation to syndrome, initial gender assignment, and medical treatment; and (c) sexual behavior may be affected by DSD through several paths related to the condition and treatment, including reduced fertility, physical problems associated with genital ambiguity, social stigmatization, and hormonal variations. We also consider limitations to current work and challenges to studying gender and sexuality in DSD. We conclude with suggestions for a research agenda and a proposed research framework.

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Bibliography
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Gender Development and Sexuality in DSD

Psychological development in individuals with disorders of sex development (DSD) is influenced by many factors. Such disorders, by definition, affect processes of physical sexual differentiation, so much of the work on psychological development in DSD has focused on influences related to those processes (particularly sex chromosome genes and sex hormones) and on characteristics related to being male or female (those that show sex differences in the general population, gender identity, and sexuality). In this paper, we discuss outcomes of gender development and sexuality in individuals with DSD, with a particular focus on (a) the evidence regarding the nature and causes of outcome, (b) the challenges involved in obtaining this information, and (c) suggestions for a research agenda for the future. (Given space constraints, citations are generally to review papers.)

Background

Studies in non-human animals provide important information to help us understand human psychosexual differentiation and outcomes in individuals with disorders of sex development (DSD). The main processes that produce physical sexual differentiation – genes and sex hormones – have been studied for their effects on behavioral sexual differentiation as well. Evidence from many species unequivocally shows that sex hormones during multiple developmental periods affect a variety of behaviors, including sexual behavior, aggression, infant care, and spatial abilities; limited evidence suggests that sex chromosome genes contribute to some aspects of behavior, including aggression [1].

Sex hormones influence behavior in 2 main ways: by causing permanent changes to the brain that have long-lasting effects on behavior (organizational effects) and by producing temporary changes to the brain that affect behavior only when the hormones are present (activational effects). Organizational effects occur primarily

during early (especially prenatal) development, although there is increasing evidence that there may be additional effects during puberty/adolescence [1,2]. Activational effects refer to temporary changes to the brain (and behavior) produced by circulating hormones at the time; hormones activate neural structures that were organized early in development. The main distinctions between organizational and activational effects concern timing and permanence, although these distinctions are somewhat simplified and not absolute [3].

Individuals with DSD have been studied as natural experiments to understand sex hormone effects on human behavior. Those studies are translational, providing basic science information about influences on psychological development, and clinical information about psychological outcomes in DSD, often in relation to aspects of the condition. Most work has been done in females with congenital adrenal hyperplasia (CAH) because it is the most common DSD, but additional data come from people with other DSD and from typical individuals, that is, those without DSD. Other DSD include partial and complete androgen insensitivity syndrome (AIS) and 5α-reductase-2 deficiency (5αR2D). Data from typical individuals include studies linking amniotic hormones to childhood behavior. As reviewed below, converging evidence shows that sex hormones also influence human psychological development – but not in a simple way. High levels of prenatal androgens facilitate male-typed and inhibit female-typed behaviors, with androgens influencing some behaviors more than others.

Gendered Development in DSD: Evidence and Challenges

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Psychological studies of DSD have focused on characteristics that show sex differences in the general population, and on general psychological adjustment or quality of life (QoL). We focus on the former; the latter is discussed elsewhere in this issue [4]. The gender-related outcomes most often studied range across a variety of domains, as shown in ○ **Table 1**.

Table 1 Gender-related psychological domains typically studied in DSD.

- **Activities and Interests**
  - Toy preferences
  - Play activities
  - Hobbies and leisure interests
  - Occupational interests and occupational choices
- **Personality**
  - Aggression
  - Empathy
- **Social Behaviors**
  - Interest in babies
- **Cognitive Abilities**
  - Spatial abilities
  - Motor abilities
  - Verbal abilities
- **Gender Identity**
- **Sexuality**
  - Sexual orientation
  - Sexual behavior

Gendered Activities and Interests

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Childhood play is strongly sex-typed: on average, boys and girls play with different toys. Sex differences in activities continue later in development, so that adolescent and adult females and males, on average, prefer and engage in different activities, including occupations. These interests are influenced by social factors, such as parent expectations and behavior [5], but they are also strongly influenced by prenatal androgens.

Girls and women with CAH are interested in and engage with male-typed toys in childhood, and male-typed hobbies, leisure activities, and occupations in adolescence and adulthood; effects are seen across measures (e.g., observation, self report, drawings) and countries [2,6]. Individuals with other DSD also engage in male-typed activities in relation to their prenatal androgen exposure and not sex chromosomes or sex of rearing [7].

A key concern has been that male-typed behavior in individuals with DSD reflects parent responses to the atypical genitalia or other aspects of the condition (e.g., postnatal androgen excess in poorly-treated CAH). But, there is little evidence that this is the case. For example, male-typed interests in females with CAH are associated with degree of prenatal androgen exposure, not postnatal androgen excess or social responses to girls' virilized genitalia [reviewed in [2,6]].

Gendered Personality and Social Behavior

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Aspects of social behavior and personality have also been seen to differ in individuals with DSD compared to typical individuals, presumably in relation to prenatal androgens [2]. But these characteristics have not been as well studied as have activities, and androgen effects on them appear to be smaller. For example, compared to their sisters, females with CAH are less interested in babies, and more aggressive. Little is known about these characteristics in other DSD.

Cognition

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The sexes do not differ in general intelligence, but they do differ in pattern of cognitive abilities, with boys and men superior on spatial and mathematical abilities, and girls and women superior on some verbal abilities (especially fluency), memory, and processing speed [5]. There is some evidence that girls and women with CAH have better spatial and mechanical abilities than their unaffected sisters, consistent with other data for effects of prenatal androgens on these abilities (for review and data, see [8]). This topic has not been well-studied in other DSD.

Gender Identity

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The basic structure of virtually all societies is a binary system of gender, and gender assignment is typically associated with the corresponding identity later, so the gender assignment of a newborn is a crucial decision with lifelong implications for the individual and family. Most newborns have genitalia that are clearly male or female, so gender assignment is simple, based on genital appearance. But atypical genitalia in newborns make the decision difficult. Gender assignment in such cases has been based on criteria that have changed over time and are influenced by

societal gender preferences [9]; policy has been influenced by clinicians' growing awareness of patients whose gender assignment does not match their identified gender (gender dysphoria), and who initiate gender change later in development.

Gender dysphoria and gender change occur more frequently in individuals with DSD than in the general population, but specific rates vary widely as a function of syndrome, syndrome severity, initial gender assignment, and medical treatment [9]. In classical CAH, girls and women generally maintain a female gender identity, even in the presence of highly masculinized behavior [10]. In 46,XY DSD, adults raised in both genders retrospectively report gender uncertainty early in development, but most resolve it and maintain their assigned gender without gender dysphoria [11]. Rates of gender change appear to be higher in conditions with continued postnatal exposure to androgens, such as 5αR2D [9].

Key questions relate to the prediction of gender identity, particularly its relation to prenatal androgen exposure or other aspects of sexual differentiation, and to gendered behaviors. Available evidence strongly suggests that biological and psychosocial factors contribute to gender identity development, and that gender identity is not simply predictable from other gendered psychological characteristics [9]. Clear conclusions are impeded because of methodological differences across studies. Nevertheless, the limited evidence available has prompted revisions of earlier clinical guidelines, for example, female assignment of 46,XY newborns with genital ambiguity due to non-hormonal causes in the presence of effective high prenatal androgen levels, such as cloacal exstrophy and penile agenesis [12].

Recent policies have increased acceptance of variations in gender and sexual orientation, at least in industrialized societies. Laws in some countries now accommodate identity as a third gender (e.g., India, Australia), or eliminate the need to declare sex on the birth certificate of a child with DSD (e.g., Germany) [13]. A dramatic recent increase in referrals related to gender problems to centers that specialize in LGBT care [14] appears to reflect diversification of the transgender spectrum [15]. These changes to gender boundaries may affect people with DSD, for example, some individuals with DSD have identified publicly as intersex rather than as male or female, and some with marked gender-atypical behavior report reduced confidence in identifying as male or female [16]; the frequency of such identifications and their impact on other aspects of quality of life should be studied. Such studies should focus on understanding both the biological contributors to gender identity and the psychological and social contexts in which gender atypical behavior yields distress and gender change. Improvements in predicting gender identity have clear implications for initial gender assignment and should lead to fewer future patient-initiated gender reassignment and associated adverse consequences (including psychological toll and genital surgery that is inconsistent with ultimate gender identity).

Sexuality in DSD: Evidence and Challenges

Several aspects of sexuality may be affected in DSD as a result of features of the conditions (e.g., atypical hormone exposure) or treatment (e.g., genital surgery). We focus here on sexual orientation, that is, the gender of the target of romantic and erotic attraction and love, and sexual function and satisfaction.

Sexual Orientation

Most evidence on sexual orientation in DSD comes from women with CAH, who are less likely than typical women to be exclusively heterosexual, that is, they have increased gynecophilia or attraction to females. But the majority of women with CAH are heterosexual, and attraction to females correlates moderately with degree of prenatal androgen excess [17]. As with other characteristics, systematic data on sexual orientation in individuals with other DSD are limited, but also suggest increased development of non-heterosexuality in 46,XY individuals raised female with some degree of effective prenatal androgen exposure, such as partial AIS or mixed gonadal dysgenesis. By contrast, 46,XY individuals raised female with very low prenatal exposure to effective androgens, as is characteristic of complete AIS or complete gonadal dysgenesis, are typically androphilic, that is, attracted to males [18]. The few studies in this area are mostly descriptive; there is a need for evidence on the development of sexual orientation and of the potential contribution of various biological and experiential factors and social contexts as proposed for typical individuals, e.g., [19]. Important related questions concern the ways in which DSD affect patterns of sexual arousal (given that typical men show stronger specificity of arousal to one sex than do typical women) [20] and fluidity of sexual orientation (given that typical women are more fluid than typical men) [21].

Sexual Behavior

Sexual behavior may be affected by DSD through several paths related to the condition and treatment. Fertility may be reduced. Genital ambiguity may cause physical problems, including urinary problems, impairment of menstrual flow, and difficulties with peno-vaginal intercourse. It may also elicit pervasive social stigmatization, undermining self-esteem and leading to avoidance of nudity, sexual relations, and dating. Thus, genital ambiguity is not simply a "cosmetic" problem [22]. Corrective surgery, however, comes with its own risks, for both anatomy (esthetic appearance) and sexual function, especially if done by surgeons with insufficient experience with DSD.

Sex hormones may also affect sexuality through effects on sexual motivation ("drive") and other aspects of sexual functioning. Variations in hormones may result from the condition itself (e.g., low effective androgens in complete AIS) or in treatments used to initiate puberty and maintain secondary sex characteristics, and, for classical CAH, glucocorticoid replacement therapy, which modulates sex hormone levels.

Outcome data on sexual behavior and sexual functioning are again primarily available on individuals with 46,XX CAH, most of whom have undergone genital surgery(ies) [13]. Women with classical CAH are more likely than typical women to delay sexual initiation, to lack coital experience, and to live without a sexual partner. Those who are sexually active (particularly those with severe CAH) show, on average, decreased sexual desire, decreased arousability, decreased erotic sensitivity, increased genital pain during coitus, decreased orgasmic capacity, and increased rates of overall dissatisfaction with their sex lives in comparison to non-CAH control women. The limited data on 46,XY individuals with DSD show analogous sexual-function problems [23]. But, there is considerable variability in such out-

comes for reasons that are not well understood. Furthermore, existing follow-up studies do not yet include women who have undergone genital surgery with recently improved techniques that may improve functional outcomes.

A key question concerns the best age for genital surgery. Practice for the past 60 years has been to perform gender-confirming surgery in infancy or early childhood, with the assumption that this minimizes caretakers' doubts about gender assignment and stigmatization by others in the social environment. In view of the variable outcomes, there have been calls by both DSD activists and ethicists to delay surgery until the age of consent. But, surveys of individuals with DSD (mostly women with CAH), most of whom had undergone genital surgery, showed that most supported genital surgery at an early age; and women with CAH reported more satisfaction with clitoral function with early than with late surgery in the one study that examined the issue [13].

Neural Substrates of Behavior in DSD

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Sex differences in brain anatomy and activity have been documented in many ways in humans and non-human animals, and studies in the latter show influences of sex hormones and of genes located on the sex chromosomes [1, 24, 25]. This has led to the expectation that individuals with DSD can be differentiated from typical individuals on the basis of brain structure or function assessed with contemporary neuroimaging techniques, such as magnetic resonance imaging. Moreover, it might be important to understand what happens to the areas of the cortex that usually represent genital structures, when those structures are atypical or not fully developed. This is a new area of research, and studies to date are limited in scope and findings. For example, a study of individuals with CAH revealed a reduced volume of the amygdala in both boys and girls [26] that is difficult to interpret within the framework of sexual differentiation and may partly reflect effects of the disease or its treatment [25]. Studies of transsexualism [27] suggest that relevant brain differences might be more noticeable in connections among neural regions (investigated by diffusion tensor imaging) than in overall brain morphology.

Nevertheless, it is unlikely that brain anatomy or activity will provide a newborn marker of any gendered characteristic. Sex differences observed to date are not large, and there is considerable overlap among typical males and females [25]. Furthermore, the brain is plastic, so that both structure and function reflect genes, physiological processes (including hormones), and experiences. For example, differences in the brains of transgendered individuals might contribute to their atypical identity development and/or result from it.

Challenges across Domains

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We have identified above specific challenges in studying specific psychological domains in DSD. There are also a number of challenges that apply to all domains, and have limited our understanding of psychological development in DSD.

Perhaps the main issue has been the limited attention paid to developmental processes. Most work has focused on outcomes at different developmental periods, and the extent to which they reflect specific broad influences, particularly effects of early sex hormones and rearing sex. But, outcomes do not emerge fully formed at any age, and it is important to study the processes whereby outcomes develop from the joint effects of genes, hormones, and multiple aspects of the social environment (e.g., parents, extended family, cultural group, context).

Methodological issues make studies of DSD very challenging. The first problem concerns recruitment of participants. DSD is not very common; CAH is the most common, occurring in approximately 1:15 000 live births. It is difficult to accrue a sufficient study sample from any individual clinic, especially in the United States; in other countries, centralized health care and medical registries make such studies easier to implement, although populations are generally smaller than in the US. Even when sufficient participants are accrued, they may not be representative of the population of patients, with particular concern that participants differ in outcomes from those who cannot be located or elect not to participate. Research regulations generally make it difficult to evaluate any bias, because it is not ethical to examine any information (e.g., from medical records) on patients who do not participate. A related issue concerns the comparison group: Many studies involve comparison participants from the general population, but better comparisons are siblings without DSD who provide a control for general genetic and environmental (especially family) background, and individuals with other medical or surgical conditions that have some parallel to DSD (e.g., chronic diseases, conditions that affect appearance and involve corrective surgery); the comparison group should be selected for relevance to the outcome studied (e.g., for sexual function related to genital surgery in DSD, people with non-genital surgeries are not a good comparison).

A second methodological issue relates to measurement of key constructs. It is typical for studies to focus on self-reported outcomes assessed with short and limited questions, but it is important to assess psychological characteristics with multiple methods (e.g., observation, structured interviews) and to obtain information from multiple sources (e.g., parents, teachers, peers). Furthermore, it is essential to differentiate aspects of gendered behavior, for example, expressed interests vs. public presentation of gender roles vs. internal gender identity.

Key Questions

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We summarize here some of the questions regarding gender development and sexuality in DSD. Some questions reflect the complete lack of data, whereas others reflect the need to elaborate the existing evidence. These questions address basic questions about psychological development and have considerable implications for clinical care of DSD. Note that the questions are not mutually exclusive.

- What accounts for variations in outcome? This includes variations across behavior (e.g., why do androgens affect activity interests more than gender identity?), diagnoses (e.g., why is gender change more common in 5αR2D than in CAH?), and individuals (e.g., why are some women with CAH non-heterosexual but most are exclusively heterosexual?). As an example with clinical application, how can we identify and validate predictors of gender dysphoria and patient-initiated gender change and use them to optimize initial gender assignment?
- What are the psychological effects of other processes of physical sexual differentiation beyond prenatal androgens? It is

important to consider effects of genes, early postnatal hormones ("minipuberty") and pubertal hormones. Such factors might contribute to some of the variations noted above that need to be explained.

- How do genetic and hormonal processes transact with aspects of a child's social environment to produce behavior? Again, answers to this question might contribute to understanding variations noted above. This question is crucial to understanding gender identity outcome.
- How do gendered characteristics affect other aspects of QoL? Although QoL may be compromised in DSD [4], little is known about how this is affected by gender-atypical characteristics.
- How is gender represented in the brain? For example, how are specific brain structures and activations affected by sex chromosome genes and sex hormones during different developmental periods? Is it reasonable to expect neuroanatomical markers of gender identity that can facilitate decisions about gender assignment and treatment?
- How does gender development occur? Most research has focused on describing, predicting, and explaining gendered outcomes at specific ages. But behavior changes across time as a function of the individual, his/her genes, and the context in which he/she is embedded. There is a large and rich literature on psychological development that could be used as a model for DSD.

Research Framework Needed

Answers to these questions will most likely come from multisite studies, given the low incidence of DSD; it would be particularly helpful to establish registries. There are some efforts in this regard [28–30], but they have experienced challenges, for example, navigating ownership of data, accrual of participants, and comparability of measures in different languages.

Such studies should include psychometrically sound measures of psychological outcomes and of potential predictors, and appropriate comparison groups (which may differ for different outcomes). Ideally, work should include long-term prospective follow-up studies. The focus to date has been on genetic and hormonal predictors of outcome, but there is need for detailed assessment of the social environment, including, for example, cutting-edge measures of parenting, pressures for gender conformity, supports and barriers to patient-initiated gender change. The time is right to extend our study of gender development and sexuality in individuals with DSD. Understanding developmental processes and psychological outcomes in individuals with DSD will facilitate optimal treatment for those individuals and tell us about human psychological development in general.

Conflict of Interest

The authors declare no conflict of interest.

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Title: Sex and Gender are Different: Sexual Identity and Gender Identity are Different

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Abstract

This paper attempts to enhance understanding and communication about different sexual issues. It starts by offering definitions to common terms like sex, gender, gender identity, and sexual identity. Alternate ways to discuss one's sexual attractions are also presented. Terms are defined or redefined and examples given of their preferred use in different clinical situations including those associated with children. Adherence to the usage advocated here is proposed as helpful in theory formulation and discussion as well as in clinical practice. When reference is made to individuals of various sexual-minority groups such as transsexual or intersexual persons, the distinctions offered are particularly advocated.

Key Words

Sexual identity, gender identity, sexual orientation, transsexuality, intersexuality, transvestite, transgender, ambiguous genitalia

Introduction

For the last several decades the term *gender* has come into common usage particularly as a synonym for *sex*. The term has proved useful in many ways although distinctions between the two words, *sex* and *gender*, when one might be more appropriate than the other, has not been firmly established. In most instances, particularly in casual conversation, the words gender and sex are used interchangeably and it seems to make little difference. If there is room for doubt the context generally makes the meaning clear. However, in scientific, medical, legal or

political and even religious discourse the discrepant use of the terms can lead to confusion and a lack of understanding.

Here is a quote from a recent report (Schmidt 2001): "the findings [of a second gene related to sex determination] offer new hope for parents whose babies are born with this [ambiguous genital] condition - as well as valuable information to help physicians more accurately and quickly diagnose the newborn's gender." Knowing the genetics of a child's sex in cases with ambiguous genitalia is not always helpful in knowing what a child's genitals would look like and certainly rarely helpful in predicting a child's gender. The term *sex* is related to anatomical structure, the term *gender* is related to an imposed or adopted social and psychological condition. Explaining the difference to anguished parents and confused physicians occupies a good part of my time. Both parents and many professionals assume that knowing sex infers gender but this is not always the case.

Maintenance of clear conceptual distinctions between the two words *sex* and *gender* and associated concepts is particularly helpful for the psychological understanding of identity. This paper attempts to show that, in certain contexts -- particularly those involving transsexuality and intersexuality but in other instances as well-- it is most useful to recognize and encourage the distinction.

The term *sex*, since classical times, has been used to designate matters related to biology and medicine when male, female or bisexual were in context. Thus animals, including humans, are categorized dependent upon whether they either produce gametes as, or similar to, spermatozoa (*males*) or ova (*females*), or have parts of the reproductive system appropriate to the development of and delivery or reception of such gametes. Among non-human animals bisexuality covers those cases where both male and female reproductive components are present.[1] Among animals the term bisexuality, unless specifically so-stated, usually refers to anatomy and not to sexual behavior. Classically, for humans, those individuals that had both male and female characteristics were called hermaphrodites. Presently the term intersex is preferred (Kessler 1998).[2]

The term *gender* has generally been used in social or cultural contexts, in distinction from biological ones. This was particularly associated with language. The first known use of the word gender was listed as 1387 CE when T. Usk wrote "No mo genders been there but masculine and femynyne, all the remnaunte been no genders but of grace, in faculte of grammar (Simpson and Weiner 1989)."[3] This context for gender has been expanded so that since the 1960s or 1970s the word is often used as a euphemism for the sex of a human being but the intended emphasis remains on the social and cultural, as opposed to the biological. United States Supreme Court Justice Anthony Scalia, in an attempt to clarify usage of the terms has written (J.E.B. 1994) "The word gender has acquired the new and useful connotation of cultural or attitudinal characteristics (as opposed to physical characteristics) distinctive to the sexes. That is to say, gender is to sex as feminine is to female and masculine is to male," According to U.S. Supreme Court Justice Ruth Bader Ginsburg, however, the words are interchangeable. She relates that she used them in composing her legal briefs about sex/gender related matters so the word

sex would not appear on every page. Supposedly her secretary encouraged this saying: "Don't you know those nine men [on the Supreme Court, when] they hear that word their first association is not the way you want them to be thinking (Case 1995)."

With these distinctions in mind, contemporary use of the terms often maintains these discriminations but frequently does not. Much seems to depend upon the proximity of the speaker/writer to a background or reference related to biology or medicine or to philosophical, social or anthropological studies. For most of those persons, who are biologically or medically attuned, sex appears fixed. The gonads determine sex or it is diagnosed by the gametes that the individual possesses or would be expected to possess on the basis of some other biological feature such as chromosomes.[4] Human males and females, as biological entities, are also categorized as male or female or intersexed (having biological features of both a typical male and female). As social entities, however, *men* and *women*, by virtue of the multitude of different roles they play in diversified societies, and by virtue of the many individual decisions they make in their own lives, are not so easily distinguished. Males can certainly live, work, or play, as girls or woman appropriate or not to their society, and females can equally live, work, or play, as boys or men. This mutable aspect of their lives is their *gender*.[5]

Roles and Identity

Most usually the roles that one enacts are sex-linked. The term *role* is used to indicate that the behavior patterns exhibited are learned or acted as if according to some sort of social script (Gagnon and Simon 1973). Men and men's roles are typically associated with strength and dangerous occupations while woman and women's roles are more often associated with child rearing and nurturing pursuits. But even so, these distinctions are increasingly being blurred. What was seen as a man's job at one time came to be seen as a woman's job and now anyone's job today (e.g., telephone operator). Since these aspects of life are seen to vary in different cultures and to be changing at different rates the society and learning-bound nature of culture is acknowledged.

Many of the cultural and social differences in behavior patterns associated with the two genders, man and woman, have came to be accepted and recognized as societal constructs -notions or abstractions which carry with them certain expectations and classifications. *Man* in a technological Western society means different things than does man in a non-technological African society. *Woman* in both types of societies also brings to mind different things. It is particularly this cultural flexibility that is central to the arguments of writers like Michel Foucault (Foucault 1980). To Foucault gender, unlike sex, should be recognized and accepted as a fluid variable that shifts and changes in different contexts and times.[6]

For transsexuals and intersexuals the distinction between sex and gender, as presented here, can become central to their being. The values each group or individual transsexual or intersexual person assigns to sex and gender, however, might be quite different. It is also suggested that to psychologists, philosophers and

others it is also of benefit to clarify the differences between the two concepts. To best understand these distinctions one other set of definitions should first be made clear. These terms are related to the concept of *identity*.

Identity is a term that has usage in psychology but is also a term used in everyday conversation. Commonly, people 'identify" themselves as homosexual or see their 'identity" as heterosexual. Individuals may identify, recognize themselves, as transsexual or intersexed without being specific as to what the term means. This usage of the terms is in an affiliative sense. It is as if one might identify as a Conservative, a Unitarian or a mechanic.

The following terms are defined as some others and I use them. While they might be considered somewhat idiosyncratic, I find them useful (e.g., Diamond 1976; 1979; 1994; 1995) and so have others.

Sexual identity[7] speaks to the way one views him or her self as a male or female. This inner conviction of identification usually mirrors one's outward physical appearance and the typically sex-linked role one develops and prefers or society attempts to impose. *Gender identity* is recognition of the perceived social gender attributed to a person. Typically a male is perceived as a boy or a man where boy and man are social terms with associated cultural expectations attached. Similarly, a female is perceived as a girl or woman. The distinctions made between boy and girl and man and woman are of age and usually again represent differences in societal expectations that go along with increases in maturity.

Gender and *gender role* refers to society's idea of how boys or girls or men and women are expected to behave and should be treated. A display of gender, as with a gender role, represents a public manifestation of gender identity. It can be said that one is a sex and one does gender; that sex typically, but not always, represents what is between one's legs while gender represents what is between one's ears. A sex role usually involves the acting out of one's biological predisposition. In young males this is associated typically with their greater aggressive, combative, and competitive nature than is usual with young females. In young females their sex roles are usually manifest by nurturing and compromising behavior, less frequently seen in boys. These might actually better be called sex-typical (*male-typical*; *female-typical*) behaviors. *Gender* roles are those behaviors imposed overtly or covertly by society. As described by Gagnon and Simon (Gagnon and Simon 1973) gender roles are behaviors that can be considered "scripted" by society. Examples of this is how girls learn to keep their knees together or adjust their dresses and apply cosmetics while boys actively memorize the rules of sports and games. Gender has everything to do with the society, in which one lives and may or may not have much to do with biology (Gagnon and Simon 1973).

This usage and terminology presented is somewhat different from that used by John Money and Anke Ehrhardt (1972). These investigators do not use the term *sexual identity* and have generally conflated the meanings above under the terms *gender identity/role* and offer, in addition, their own definitions: "Gender identity is the private experience of gender role; and gender role is the public manifestation of gender identity . . .'gender identity' can be read to mean 'gender identity/role.

(Page 146)." But here again the terminology has not been consistent with that used by others. Stoller (1968), for example, called this inner realization of self-identity as a male or female "core gender identity."[8]

Intersexual Child

Let us see how these terms and concepts might involve a developing child.9 A mother of an 8-year-old chromosomal XY male with ambiguous genitalia said to me:

"My child has questions on her gender. Oddly enough, we have raised her as a complete female child, to date...she does not know of her condition. We thought best to wait, as a young child would never understand. ...Increasingly over the years she has said things like ' I'm not a girl...I'm a boy'...clothing desired is neutral...teachers' complaints (they are unaware) is that she is very tomboyish.... all her friends are boys. At home it is her brothers she hangs out with. And her strength...wow!"

The mother, at the child's birth, had been advised by her physician to raise the child as a girl due to its lack of a penis. This was a standard recommendation until just several years ago (Diamond and Sigmundson 1997a; b; Diamond 1998; Kipnis and Diamond 1998; Diamond 1999). The child's sex is male but it had an imposed gender of girl. It had been raised since birth as a girl. Obviously here is a case where sex and gender are not in agreement.

The child knows it is being raised as a girl and encouraged by its parents and physicians to live as one. The child recognizes it is being seen and reacted to as a social girl. It is, thus, aware of its (social) *gender* identity. Yet, although raised as a girl, the child manifests gender roles more typical of a boy. Further, despite its rearing and ignorance of its biology, the child has developed the (inner) *sexual* identity of a boy; i.e. the child feels at his core that he is a boy or should be a boy. This realization comes about by comparing his feelings, interests, attitudes and preferences with those of male and female peers and judging that his living as a boy is a better "fit" with the reality he sees and comes to know (Diamond, 1999).

The child has male chromosomes (is an intersexed male pseudohermaphrodite) with the imposed gender of a girl. When the child matures and becomes more aware of his history I predict he will likely come to live as a man or in as close to a neuter gender as possible. He will come to recognize that he is intersexed and might or might not openly identify as such.

The mother asked if I thought it would be better to allow the child to switch to live as a boy or proceed with the prepubertal feminizing hormone administration advised by her physicians. My advice was to allow the child to live as a boy and foster typical male development. Despite the genital ambiguity such management would allow gender and sex to be better matched than is presently so. Genital reconstruction can occur later if desired.

Potential Transsexuality

In communicating about or describing transsexuals the distinctions in definitions are also helpful. In the real world, the potential transsexual, no different from others, is reared in accordance with custom, boy or girl, as society views his or her genitals. Unlike many intersexed individuals, there is no way to identify those who will develop as a transsexual.

The term *transsexual* is best reserved for those adult individuals who manifest the diagnostic criteria for gender dysphoria or Gender Identity Disorder (GID) and not used for children. In the DSM-IV there are separate criteria for GID of children (302.6) and GID of adolescents and adults (302.85) (Frances, 1994). A child or adolescent with GID is generally not considered a transsexual until he or she is an adult. In some circles distinctions are made between preoperative transsexuals and postoperative transsexuals.

Some clinicians such as Issay (1997) and Menvielle (1998) have argued that childhood GID should not be in the DSM because it appears to be a symptom of homosexual orientation. Cohen-Kettenis (2001) and Zucker (2001) find of value its consideration as a distinct entity so its treatment may be appropriately managed.

A child might have a gender identity conflict but such conflicts, more often than not, have been reported by Green, (1987), Zucker and Bradley (1995), and Zucker, (2001) to resolve themselves to a homosexual or typical condition. Cohen-Kettenis (2001) finds this also, however, she finds a large percentage of those children who manifest GID as children (17 of 74), as adolescents continue to exhibit gender dysphoric behaviors and have requested sex reassignment surgery).[10]

If a designation of transsexualism is to obtain, as the individual matures, the self-image (sexual identity) he or she has of himself or herself solidifies as that of the sex opposite to their anatomical sex. The mirror image is in conflict with the mind's image (Benjamin 1966; Green and Money 1969; Bolin 1987; Docter 1990). The developing male, for instance, knows he is being raised as a boy but thinks it more appropriate that rearing and treatment ought to be that accorded to a girl. The transsexual male thinks he is actually a female or should be a female or aspires to be a female. Gender identity conflict can start quite young and is illustrated by the following portion of a recorded dialogue between a therapist (Interviewer =I) and a 4 year old boy (Zucker, Bradley et al. 1992):

Interview with child:

I: Are you a girl?

C: Yes

I: When you grow up, will you be a Mommy or a Daddy?

C: Mommy.

I: Could you grow up to be a daddy?

C: No.

I: Are there any good things about being a boy?

C: No.

I: Are there things that you don't like about being a boy?

C: Yes.

I: Tell me some of the things that you don't like about being a boy?

C: Because I hate it. 'cause we get to do stupid, sitting down.

I: Do you think it is better to be a boy or a girl?

C: Girl.

I: Why?

C: Because it's fun - they sit around and talk.

I: In your mind, do you ever think that you would like to be a girl?

C: Yes.

This child is aware of being raised as a boy but thinks of himself as a girl. This awareness of how he is living and is expected to live in society is his gender identity. The child's core view of self is "her" sexual identity. This gender identity and sexual identity disparity diagnosed as *gender identity disorder*, may or may not persist into adulthood. If it does persist this child can then be diagnosed as a transsexual. If he is typical, he will then eventually attempt to arrange endocrine therapy and or surgery or both to have his features changed sufficient that he be seen as a woman. Changing his anatomy to that resembling a woman's will facilitate social acceptance and life as a woman. His gender identity and sexual identity will thus be brought into concert.[11]

The processes through which the transsexual passes in getting to his or her physical transformation might be tortuous and conflict laden. It can involve a prolonged process of introspection, and often psychotherapy and counseling. Not a few undergo an extensive set of self-tests in attempts to prove to themselves if they are male or female, should they live as man or woman (Diamond 1996). For others, however, the inner processes are fairly straightforward with the individual harboring little doubt of the correctness of the decision to switch gender. In general, however, the transsexual's final mantra becomes "change my body, not my mind." Socially he becomes she and she becomes he. The transsexual's sexual identity is immutable.

Intersex

An *intersexed* individual is one born with physical characteristics that are both male and female. For instance an individual can be XX in chromosomal configuration but have a male-like phallus; another individual might be XY in

chromosomal make-up and not have a penis but have a vagina instead. The intersex person might have genitals that are ambiguous in character or they might appear typical.

Intersexed men and women might identify as female, male or intersexed and they might live ostensibly as women or men or in some sort of neuter manner (Diamond, 1999). Intersexed children, while not aware of their condition, might nevertheless manifest this neuter status in choice of dress, hairstyle and comportment.

The variety of intersex conditions is so large that only broad generalizations can be made as to how any single individual's sexual identity and gender identity might compare. While some intersexed individuals can easily meld their biological incongruities with the way they are raised and with the life they lead, others find great difficulty in reconciling the disparities they see and feel with the social input that is thrust upon them. Even within a single category of intersex there is a great variation. It is for this reason that I believe it best that the child itself, particularly after puberty, have the final say in how he or she is allowed to live (Diamond and Sigmundson 1997b).

Before leaving this topic let me emphasize that at issue here is not whether a person, male for example, thinks he is masculine looking "enough" or macho behaving "enough" to satisfy his ego or some social stereotype. Most men wish that they could increase some aspect of their male selves. And the same can be said similarly for females. Most women would relish the ability to enhance some aspect of their feminine looks and modify some aspect of their behavior. But for the typical person there is little doubt of his or her basic male or female self and sexual identity despite any lack in wished for socially preferred gender feature.

Sexual Orientation

One's sexual identity, gender identity, and gender roles are aspects of life tangentially related to a person's *sexual orientation*. *Sexual orientation* refers to the sex of the erotic/love/affectionate partner a person prefers. Does the individual seek a mate who is male or female; does the desired person live as a woman or man? Most often, to describe orientation, the term's *heterosexual*, *homosexual*, and *bisexual* are used. Scientifically it would be better if these terms were used as adjectives, not nouns and better applied to behaviors not people. In lay usage, however, one often speaks of a person as a homosexual or heterosexual. Indeed, people often refer to themselves the same way. Unfortunately such causal usage often links together those whose regular sexual partners are of the same sex with those whose same-sex encounters are only occasional in comparison with heterosexual contacts. The term *homosexual* is best reserved for those whose sexual activities are exclusively or almost exclusively with members of the same sex, the term *heterosexual* for those whose erotic companions are always or almost always with the opposite sex, and the term *bisexual* for those with more or less regular sexual activities with members of either sex (Diamond 1993). Lately it is advocated that the terms *androphilic*, *gynecophilic*, and *ambiphilic* are used to describe the sexual/erotic partners one prefers (andro = male; gyneco = female; ambi = both;

philic = to love) (Diamond 1997). The use of such terms obviates the need to define specifically the sex or gender of the person referred to and focuses solely on the sex of the desired partner. Again, this clarity of usage is particularly advantageous when discussing transsexuals or intersexed individuals. For instance, what would be homosexual or heterosexual for an intersexed person? And there is often confusion when discussing transsexuals as to whether a designation of homosexual refers to a pre or post surgery situation. These latter terms also do not carry the social weight or taboos of the former ones.[12]

Before leaving this topic it should be mentioned that individuals that engage in same-sex behaviors do not necessarily exhibit any particular concomitant sexual identity or gender identity. Males that engage in homosexual behaviors, for instance, can be comfortable in their male bodies and have no gender atypical behavior patterns. The same for lesbians; they can be quite pleased with their sex and gender roles.

For most people their identity, orientation and gender are in concert. The typical male sees himself as such, acts in a masculine manner-a combination of biologically and socially determined gender behavior patterns-is treated as a male by society, and prefers to have sexual interactions with females. The typical female sees herself as such, acts in a feminine manner-also a combination of biologically and socially determined behaviors-is treated as a female by society, and prefers to have sexual interactions with males. For the usual person there is no conflict between sexual and gender identity and it makes no difference that the terms involved refer to different things.

Now consider the atypical person. When variations occur, such as when individuals want to live in the gender opposite to the one in which they were reared, for any of several reasons, the distinct meanings of the terms, and their usefulness, becomes clear. So too do the separate terms offer clarity for cases when an individual chooses to be atypically flexible in manifestation of gender.

It is useful to note that our discussion has covered three of five central aspects of life I use to register a sexual profile for an individual. In addition to the three mentioned already, gender role Patterns, sexual Identity, and sexual Orientation, I find it advantageous to specify aspects of sexual Mechanisms and Reproduction. *Mechanisms* refer to those processes usually associated with sexual activities. They include, for example, erection, nocturnal emission and ejaculation for men and lubrication, pregnancy, and lactation for women. Reproductive history, functioning and attitudes are also significant. Regarding *reproduction* we are interested in pregnancies, live births, miscarriages, abortions, fertility or infertility, if they did or didn't occur and one's attitudes toward these processes. Used together I find these five parameters offer a rather broad yet full picture. The acronym **PRIMO** serves as a mnemonic to keep these five features in mind (Diamond 1995). (A diagrammatic representation of Sexual Development utilizing the PRIMO components is seen in Figure 1).

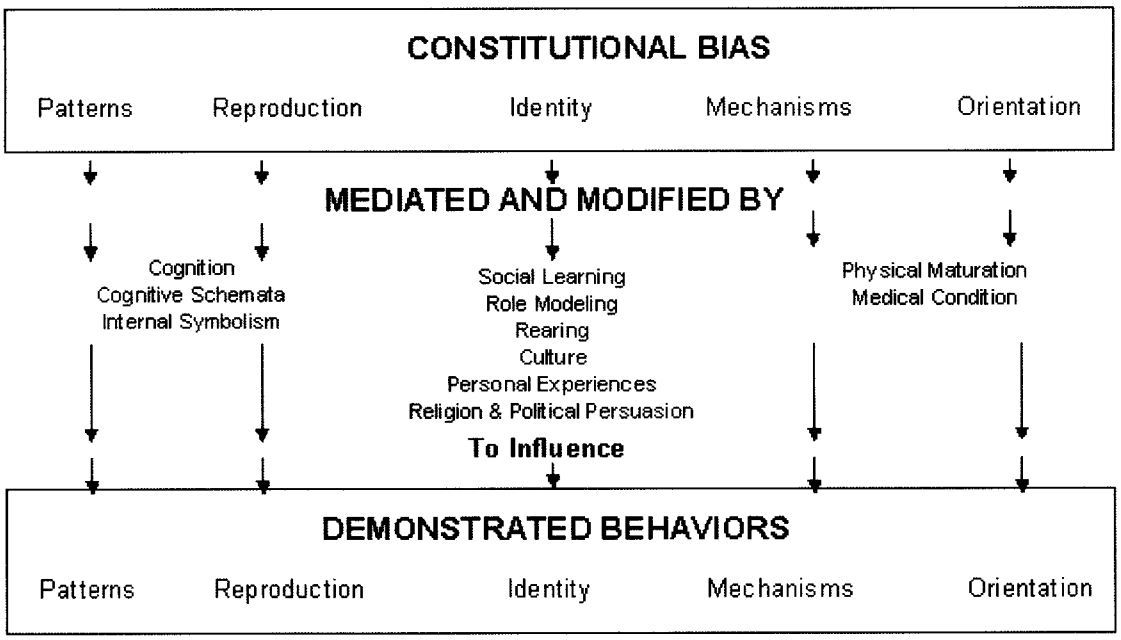

Figure 1

Examples

The following examples will present some instances of how the terms might be appropriately applied. The quotes are relatively typical and, with minimal modification, taken from relevant testimonies. In actual life, the intensity of the feelings of identity might vary among individuals and along one's life course. There may be periods of doubt and conflict or never any hint of them.

Typical female or male:

"My parents wanted to be up-to-date in the way they raised my siblings and myself and sort of let us do what we wanted. I was very much a tomboy. Regardless of all that room in which to express myself I never had any doubt as to what I was nor how I preferred to live."

The average woman or man, while perhaps questioning his or her degree of masculinity or femininity, never or rarely questions if he or she is male or female. Sexual identity conforms to *sexual anatomy* and *gender identity* follows along the same lines. [13]

Transsexual (male to female):

"My dad very much wanted me to grow up and paddle and fish with him, and follow in his footsteps. But that was not me. Since I was about six or seven, or maybe even earlier, I wanted to grow my hair long, paint my fingernails, wear pretty clothes and hang out with the queens downtown."

Here the individual is obviously aware of his sex as a male but yearns to live as a woman. Although he is aware he is a male, his *sexual identity* is female. And he knows his *gender identity*, as male, the way he had been perceived by others in his

community, was not in keeping with the person he imagined himself to be. His present condition at this time, before transsexual surgery, is as a woman. After male-to-female surgery his gender identity and sexual identity will match. By altering his body, in his mind and to the world, *he* will become *she*.

Transsexual (female to male):

"When we were having sex things never seemed right. I had always felt masculine but in erotic situations in particular, I thought I should have a penis instead of what I had. While I had felt that way for many years, I always saw myself as a man even more strongly in these situations. And even though, for several years I had considered myself a butch lesbian that was very masculine, I came to realize that was not sufficient for me. That life didn't feel right. After sex reassignment surgery things felt right. Being a man solved those problems."

This female has a male *sexual identity*. She knows, however, that the world was recognizing her as a woman and she uncomfortably recognized herself in that role. Her gynecophilia was not a major factor in the desire to transition although it did seem to make things easier. Her societal *gender identity* was that of a woman yet she saw herself as a male. Her sex reassignment surgery brought her gender identity into agreement with her sexual identity; her body was reshaped to conform to her mind's image.

Before leaving this topic of transsexualism it is illuminating to consider what one highly educated male-to-female transsexual said to me when she heard how I was trying to understand the motive or drive for sex change. It illustrates that these are questions of the investigator and clinician and may have nothing to do with the interest of the transsexual. "If there is anything I want to shout from the rooftops, it is that some of us want to change our bodies for reasons that have little or nothing to do with facilitating our acceptance as social women. We want to change our bodies because we want to change them. Sometimes we decide to change them even though we know we won't be accepted as women, and wouldn't want to be accepted anyway." An intersexed person who wants to change his or her life for reasons that are personal and not necessarily available or amenable for investigation can say the same.

Intersexual (content with rearing):

"When I was first confronted with the diagnosis I was freaked out and almost had a break down. Now I have accepted it and move on with life. I have always felt to be a female and a feminist and I feel comfortable living as a woman."

This person, having XY chromosomes and testes, until the diagnosis, had no doubts as to her sexual identity as a woman. She had always considered herself to be a female and accepts living as a woman. She accepts her *gender identity* as a woman and, despite concerns with infertility and other features common to her intersex condition, confidentially presents herself to the world.[14]

Intersexual (not content with rearing):

"I had been living with doubts as to who and what I was ever since I was small. I had always felt myself to be a female rather than as the male I was being raised." When I found out that I had both male and female chromosomes, with XXY, I figured I could and should and would more comfortably live as the woman I felt myself to be."

This woman, while quite young, as many individuals who will eventually switch their gender, had developed a *sexual identity* other than in accordance with how she was being raised. Thus, despite her upbringing as a male and her having a penis, she envisioned herself growing up to be a woman. As a woman in society her *gender identity* conforms to her sexual identity. She had genital surgery and breast implants to satisfy her needs.

Lately, along with greater freedom in many social areas, in the West it is becoming more common for intersexed individuals to accept their condition and identify as intersexed persons rather than considering themselves either male or female. While this might solve some psychic considerations, this stance is not without its social cost and legal repercussions. Difficulties can occur with driver's license identification, marriage license or passport acquisition, and birth certificate verification. Intersex identification can make it difficult for family and potential partners.

Male, Sex Reassigned due to genital trauma:

"Even though I was being brought up as a girl, I suspected I was a boy since the second grade. At about the age of 14 I decided I had to either live as a boy or I would kill myself."

This statement clearly shows an individual with the sexual identity of a male strongly expressing his move to live as one. He saw the overwhelming need for his *gender identity* to match his *sexual identity*. Once making the shift, he was accepted well in his new social role.

Drag Queen:

"This is the way I see myself. I love parading [in woman's clothing and heels] as I do. Sure, I get a lot of grief from the *straights* around the neighborhood, but I have no doubt as to who and what I am."

This male accepts that he is confronting strong social conventions against his behavior. He maintains a male *sexual identity* and does not want to lose his penis. He does not see its presence as incongruent with a woman's *gender identity* or *gender role*. To the Western world in which he lives, his gender is that of a woman while his sex is male. He is willing to accept the incongruity for perceived real and potential gains. Except for the exceptional stage cross-dresser, drag queens are androphilic.[15]

Transvestite:

As many of the terms presented, this noun has a long and varied history. First coined by Magnus Hirschfeld (1910/1991) this word referred to individuals, usually men that sought and received erotic pleasure by wearing the clothes of the opposite sex. While Hirschfeld used the term for individuals who might engage in heterosexual as well as homosexual or bisexual behaviors, he also described individuals who cross-dressed solely for autoerotic pleasure. Presently, many that cross-dress dismiss the allegation that it is related to autoeroticism and contend it is basically to satisfy a feature of their personality not otherwise expressed. In the general press or everyday speech the term might be applied to any one who cross-dresses. Among the majority of sexologists, however, the term *transvestite* usually refers to men who are gynecophilic in orientation. "The Society for the Second Self" (SSS)[16] is basically an organization founded for heterosexual men and their wives and, in the United States, is the largest organization of its kind.

Transgender:

To our lexicon a relatively new term has come into use, *transgender*. An individual exhibiting transgender behavior is one that sees gender as being either constructed or inborn but nevertheless open in manifestation. The term has taken on a very fluid meaning adopted by individuals and for individuals who might otherwise be identified as transsexual, intersexed or even homosexual or bisexual; anyone who simultaneously exhibits traits or characteristics of both men and women. Actually the word transgender has been, in a continuous state of flux since its having been coined by Virginia Prince in the late 1960s (Denny 2000). Prince, considered by many the first modern public transvestite, found the term *transgender* useful to describe individuals like herself that had no difficulty accepting that they were male but who wanted to live as women, at least partially or part time. She also saw the term extending to females that manifest male characteristics. In her use of the term *transgender*, it excluded transsexuals.

Individuals that exhibit transgender behaviors don't necessarily want to change their sex but do want to change aspects of their gender (Bullough, Bullough et al. 1997).[17] Many such persons eschew any strict dichotomy in male and female gender roles. In their own lives, they mix characteristics that are most often considered both male and female.

Lately the word transgender has become quite inclusive to cover transsexuals, transvestites, drag queens and others that bend society's usual gender boundaries. Some welcome the term transgender due to its inclusiveness and others abhor it for the same reason. The individual exhibiting transgender behaviors does not attempt to pass as anything he or she is not. Transgender individuals feel they are expressing aspects of themselves that can not be manifest any other way. As Anne Bolin has written (Bolin 1997): "The formation of a transgender community denotes a newfound kinship which supplants the dichotomy of transsexual and transvestite with a concept of continuity. "[18]

Comment

Earlier I remarked that the terms heterosexual, homosexual and bisexual might better be used as adjectives rather than nouns since the terms too often label individuals as if that is the total aspect of their character rather than just representing one facet of their personality and life. I think that caveat might also be extended to all the other terms often used as labels for people. One is not simply a lesbian, or transvestite or transsexual any more than one is simply a teenager, a Jew, a political Green or plumber. Life and character are complicated and it is clinically and socially better and wiser to acknowledge this diversity. Clients, children as well as adults, will appreciate this recognition. Similarly, when labels such as *victim* or *perpetrator* are used, the persons referred to are denied recognition for other, and probably better characteristics. The danger is that individuals so labeled might, themselves, come to see only that facet of self and limit or deprive their life of other aspects of meaningful expression. Or they might think they then have to conform to some model of group stereotyped behavior. Particularly for children and adolescents, allowing, recognizing and supporting multiple aspects of an individual's personality is usually a welcome clinical practice.

Summary

This paper has attempted to enhance clarity in understanding and communicating with different terms. In particular, emphasis was placed on the terms: sex, gender, sexual identity, and gender identity. The value in doing so is particularly seen when reference is made to individuals of various minority groups such as transsexuals, intersexuals or others. Standardization of these widely used terms, it is hoped, will help in theory formulation and discussion. It also allows for a more precise way to document an individual's clinical ontogenetic path especially if he or she exhibits an atypical life. A warning is also given not to use these terms as all encompassing labels.

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END NOTES

[1] Plants too are sexually organized. In their case, however, the term perfect is used to describe plants that have both male and female reproductive characteristics.

[2] *Androgyne* is a term also used, but less frequently, to mean an intersex person.

[3] Why some languages assign nouns as masculine or feminine or neuter and others don't see any value to this is still an issue that puzzles linguists.

[4] In some species, as in many types of fish, the individual might be male, producing sperm at one moment, and female, producing eggs, at another or in a transition stage going from one sex to the other. Typically these species do not have sex chromosomes.

[5] For the biologist and many others, non-human animals and plants, not having a culture, do not have a gender.

[6] There are many additional ways to view gender. Richard Ekins and Dave King, for example (1999, 2001), pursue different forms of the term ungendering. These are processes some persons utilize to dramatically change gender distinctions. This

might involve attempts by individuals to "negate," "transcend," "migrate from," "erase," or "deny" gender attributes. These authors also utilize new terminology such as "male femaling," "female maling," "transgendering," and "oscillating." All these words refer to different techniques people use to alter aspects of their sex, gender and eroticism.

[7] In some contexts, such as in lesbian or gay readings, one's *sexual identity* refers to whether the individual considers him/herself either heterosexual, homosexual, or bisexual. Among sexologists, however, one's relation to a sexual partner is called *sexual orientation* or *sexual preference*.

[8] It is possible that Money and Ehrhardt (1972) did not separate the concept of sexual and gender identity since they believed that one's social status, one's assigned gender, would lead to a concordant identity.

[9] This is an actual case that came to me at the time of this writing and the quotes are exact.

[10] These are the results of follow-up studies of those exhibiting GID as children and who have received treatment. However, these studies do not include review of children with GID who did not receive treatment. Without untreated controls, for comparison, the value of treatment is still unclear.

[11] An ongoing debate exists as to how best to manage such children. Clinicians such as Zucker (1990, 2001), Rekers, Kilgus and Rosen, (1990), and Cohen-Kettenis (2001) think it best to actively treat such children to prevent anticipated peer rejection, depression, associated psychopathologies and potential transsexualism. Others such as Coleman (1986) question the ethics or necessity of such intervention. Long term studies are not common but treatment proponents claim the treatments do seem to help reduce the child's problems.

[12] There are many individuals that have sex with members of their own sex but do not consider themselves homosexual or associate with the gay scene. For this reason, as well as others, those involved with AIDS research, for example, instead of referring to homosexual behaviors use the designation "males that have sex with men" (MSM).

[13] Discussion of a so-called "true sex" developed in the 18th Century when physicians and scientists tried to understand the phenomena of intersexuality. The debate still continues to some extent when different biological and social characteristics are in obvious conflict. For the typical individual, however, this issue does not develop since all basic characteristics of sex and gender are concordant. For an historical view of the topic see Dreger, A. D. (1998). Hermaphrodites and the Medical Invention of Sex. Cambridge, Mass, Harvard University Press.

[14] While this woman accepts her androgen insensitivity (AIS) that does not mean there have been no conflicts along the way. However, she deals with her

situation with its negative aspects and makes the most of it, as would other persons with their own particular life difficulties.

[15] Drag Kings also exist but are much less common. Their activities and thinking patterns are similar to that of Drag Queens except Drag Kings prefer life in the male gender and are gynecophilic.

[16] The organization's headquarters is located at 8880 Bellaire Blvd., B2, Suite 104, Houston, Texas 77036-4621 USA.

[17] Recently in the United Kingdom the term 3rd G, as in "TS, TV, LGB and 3rd G" has appeared to represent the transgender population or those intersexed individuals that prefer not to be identified as either male or female. In the USA, the term TGV (TransGender Variant) is becoming popular.

[18] The world's largest transgender support group is the British Beaumont Society http://www.beaumontsociety.org.uk 27 Old Glouster St., London WC1N 3XX.

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Title: Sex, Gender, and Identity over the Years: A changing perspective

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History: the 1950s to the 1970s

Freud, in his monumental works, distinguished the anatomic and physiologic sex of self from what we presently know as "gender." He wrote of the effects of the environment and experience that challenged one's biology. The linkage of "sex" and "gender" as terms that reflect identical or closely-related concepts is long standing; we now know that the two expressions and concepts often must be separated for analysis of human behavior. Since the 1960s and 1970s, distinguishing the terms took on a new urgency. This may have been a reflection of increased notice of, and interest in, subjects, such as homosexuality, transsexuality and intersexuality. Clinicians and researchers were scrutinizing these topics with an aim to determine whether they were sicknesses that were amenable to treatment, mental or moral matters, or just unique, yet normal, and to- be-expected variations.

Even today, typical expectations are that the terms "sex" and "gender" reflect each other. Males are expected to be masculine and females are expected to be feminine, regardless of how the terms are defined in any particular society. Intermediate, but less socially threatening, occasional blended-gender roles became more noticeable in the 1960s and gave increased prominence to distinguishing sex from gender [1].

In the United States, the 1950s were a time when homosexuals were denied jobs and were imprisoned for "criminal" behavior. It also was a time when Christine Jorgensen, an ex-G.I., went to Denmark to have a "sex-change" operation and the world began to hear of individuals of one sex who wanted to change their bodies and adapt the gender of the other sex [2]. Also, intersexed individuals began to be better known to the medical community [3]. In the 1960s and 1970s, clinicians and

theorists increasingly attended to sex-gender relationships, mostly to look at differences—rather than similarities—between men and women [4-6].

These challenging situations brought new ways of thinking about behavior. Among these ways were discussions of "identity" and "roles." Stoller [7] coined the term "core gender identity" to reflect a person's "fundamental sense of belonging to one sex [an awareness of being male or female and] an over-all sense of identity." He attributed this to a combination of infant—parent relationships, the child's perception of its external genitalia, and by a biologic force that springs from the biologic variables of sex [7,8] Money and colleagues [9] coined the term "gender role" to "mean all those things [behaviors] that a person says or does to disclose him or herself having the status of boy or man, girl or woman, respectively" [9]. Money and Ehrhardt [10] defined "gender identity" as "the sameness, unity, and persistence of one's individuality as male, female, or ambivalent...the private experience of gender role." This, they said, basically was derived from rearing experiences. Gagnon and Simon [11] introduced the term "sexual identity" to indicate the awareness of an individual as a sexual-erotic agent within a larger "social identity" that was an appreciation of how a person fit into society. They also introduced the concept of "sexual scripts" that are socially imbued ways of acting in different circumstances. The basic ideas are that sex, genes, and hormones establish one's body and physiology, but one's gender is a product of learning, experience, and indoctrination.

These ideas did not go unchallenged. Several animal experiments revealed the power of genetics and endocrines to structure males to show reproductive sex-typical female behaviors and to induce females to display as males [12,13]. For animals, the term "sex-typical behavior" was comparable to gender-appropriate behaviors. Reports on humans also showed that individuals who rejected their sex of rearing and experience were not rare [14,15]. From these studies, a distinction was made between "organizing" forces—usually prenatal—that dictate the direction of future behaviors and "activating" events or forces— usually postnatal—that precipitate behaviors [12,16]. Debate on theoretic grounds also existed [4,17-19] and there were calls for a middle ground where organizing and activating forces—built-in and learned—would interact to mold behavior [18].

An ongoing dispute appeared among psychotherapists, biologists, educators, and others about the forces that are involved in the development of gender and how those forces are influenced by the environment. In contrast, a seemingly unified medical understanding emerged. This medical consensus harkened back to the ideas that sex-atypical gender behaviors were the product of social and environmental forces. Most physicians believed that homosexual, cross-dressing, and transsexual activities were deviant; the treatment for the atypical behaviors seemed to be clear. The subject should be helped to "unlearn" and get rid of whatever misperceptions and negative experiences had engendered these behaviors. Often, the treatments that were applied would be considered abusive today. They ranged from different aversion therapies to castration to electroshock [20,21]. Such treatment was seen as justified. For example, Bancroft [21] wrote "In the absence of unequivocal scientific criteria of morbidity, behavior may be deemed pathological because it violates social norms." Intersexuality was not seen as

antisocial but it was seen as something to be hidden or disguised; often by surgical intervention [22,23]. It also was seen as a body of conditions that resulted from some medical "error" [24].

The "middle" years: 1970s—1990s

From the 1970s to the 1990s things changed. In the 1970s, the American Psychiatric Association removed homosexuality from its list of disorders and the American Association of Behavioral Therapy questioned the ethics of attempting to change men's or women's sexual orientation. Homosexuality was seen less frequently as a medical disease that required treatment and was seen increasingly as a variation in orientation that only needed medical management when it was ego-dystonic.

The Harry Benjamin International Gender Dysphoria Association (HBIGDA), named after the physician that presented a major human face to transvestism and transsexuality [25] was formed in 1977. This organization dedicated itself to dealing with persons who were diagnosed as transsexuals (persons who have a desire to change sex that persists for at least 2 years). This diagnosis was introduced into the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* as Gender Dysphoria of Adulthood. Gender Identity Disorder of Adolescence was introduced as a separate category. In 1994, the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) listed Gender Identity Disorder of Childhood, Adolescence, or Adulthood. Initially, HBIGDA clearly considered transsexualism to be a mental disorder that could benefit from counseling, hormone therapy, and surgery. In *Standards of Care* that was published in 2001, however, HBIGDA hedged its bets regarding the "disease" status of transsexualism. In their 2001 guideline booklet, the relevant section was entitled "Are Gender Identity Disorders Mental Disorders"? Without answering their own question they went on to state "To qualify' as a mental disorder, a behavioral pattern must result in a significant adaptive disadvantage to the person and cause personal mental suffering" [26]. Debate occurs because many persons who are diagnosed as transsexuals consider their behaviors to be a significant advantage to their lives. Nevertheless, many transsexuals do manifest signs of emotional distress and recommendations were offered to assist the individual in appropriate transformation when warranted. In the DSM-IV the diagnosis of Transsexualism was replaced by Gender Identity Disorder [27].

The 1970s also saw the increasingly frequent use of the new term "transgender" which was coined by Virginia Prince. The term was meant to describe persons like Prince who were heterosexual males who wanted to live as women, at least part time. The more common term for such people is "transvestite." Prince also intended that the term include females who chose to exhibit male behaviors and dress. In Prince's use, the term "transgender" specifically excluded transsexuals because transgendered persons desired to change only their behaviors, not their sex [28]. The term has been in a constant state of flux, and, can, at present, seemingly cover any gender-bending or gender-blending combination of masculine and feminine [29].

Among the more significant developments of this period was the formation of different support groups for sexual and intersex situations. These primarily were started by parents who sought information and help in understanding intersexuality and to press for further research and improved treatment for their children. Previously, medical management guidelines had not fostered the meeting of such parents or their children with others who were similarly involved. Often, such meetings were actively discouraged and secrecy was encouraged.

The first support groups to form were those for Turner's syndrome in Canada in 1981 and in the United States in 1987; however, others followed soon after. The Klinefelter's syndrome support group in the United States and the Androgen Insensitivity Syndrome group in the United Kingdom were formed in 1989. These groups proved to be popular. In 1993, in the United States, Cheryl Chase, an individual who had an intersex condition, founded the Intersex Society of North America (ISNA). This organization developed into a highly vocal and visible association. Another intersex support group, Bodies Like Ours, has since joined in working on behalf of intersexual persons with any diagnosis. Support groups for lesbians and gays also formed in the 1970s and 1980s.

The current years: the 1990s to the present and intersexuality

It is probably fair to say that intersexuality—until the last 10 years or so—was a comparatively hidden medical condition that was far from the public's consciousness. The general public often had a biased view of people who were then called "hermaphrodites." Their view often was drawn from circus sideshows and their displays of women who had beards and men who had breasts. Physicians—when they met with intersexed patients in their practice—often recalled their uniqueness in later casual discussions. Without asking the patient's permission, residents and medical students were brought in frequently to observe the most private of examinations. Without necessarily using the words, clinicians often told these patients that they were oddities and so rare they would never meet another person like themselves—worse, the patients were told not to try. Over the last several years, in addition to media exposure, several books [23,30,31] and popular writings [32—34] have brought the phenomenon out of the closet and more intersexed individuals to the awareness of physicians.

Intersexed persons have a biologic/medical condition that is not uncommon. It is a diagnosis that is shared by as many as 1% of the population.[1] It has been estimated that in the United States, the incidence of intersex conditions with ambiguous genitalia is about 1 in 2000; overall, when including those who have typical looking genitalia the incidence approximates 1 in 100 [30]. Only those conditions that are accompanied by ambiguous genitalia are detected routinely at birth.

Increased medical attention toward intersexuality started to shift in 1997. Until then, the attitudes regarding intersex situations and the standards of care for the management and treatment of individuals who had the conditions were different

from those that are available today. Drawing on the theory that psychosexual development largely was a product of upbringing and genitalia that were typical, those who cared for infants who had ambiguous genitalia tried to benefit those children by "normalizing" their genitalia. Surgeons reduced enlarged clitorides in infants who were assigned as females and because of the technical difficulty of creating a functional and cosmetically believable set of male genitals, refashioned the genitalia as female. This practice was standard and was sanctioned by the American Academy of Pediatrics [35].

Since 1997, many of the issues that are associated with medical concerns of the genitalia and the treatment of intersexuals have come under review and management techniques have been altered. It is likely that facets of intersex management will continue to occupy the attention of health care workers for years to come.

Significance of John/Joan: the debate

Intersexuality and its management were brought into focus, not by a case of intersexuality, but by a circumcision accident and its follow-up. This story is now known by the pseudonyms John/Joan [34,36].

John's penis was burned off accidentally in a circumcision that was done by cautery. Following the accident, the decision was made to rear the child as a girl, Joan. The decision was based on the belief that in the absence of a functioning and adequate penis, normal male development was impossible. Furthermore, it was believed that an individual was psychosexually neutral at birth and a gender would be determined by rearing [9,37,38].

Following John's sex reassignment, it was reported that the switch to life as a girl was successful [10]. For physicians, this report was significant. On the belief that sex reassignment was possible for a typical child, clinicians reasoned that it could be suitable for the numerous individuals whose genitalia were ambiguous. Physicians were advised "... an intersexed baby with female-appearing genitals should always be assigned as female" and "in the case of a genetic male baby born with no penis at all ... or with major hyperplasia of the penis, the baby should be assigned as a girl" [39]. Aside from the theoretical view that psychosexual development would be structured by rearing, there was the practically appealing matter that it is easy to create a vagina if one is absent, but it is not possible to create a satisfactory penis if the phallus is absent or rudimentary. "The decision to raise the child as a male centers around the potential for the phallus to function adequately in later sexual relations" [40]. Pronouncements such as these essentially established that, regardless of karyotype and prenatal endocrine exposure and particular medical diagnosis, all intersex conditions could be managed by cosmetic attention to the genitals and gender assignment that usually was female.

Things changed in 1997 when an article appeared that detailed a follow-up to the John/Joan case [36]. Instead of supporting the original claims that a typical boy could have his gender successfully reassigned to that of a girl, the new report documented the opposite. At the age of 14 years, despite being reared as a girl and

undergoing psychiatric counseling and an estrogen regimen to reinforce a female identity, Joan reassigned himself to live as a boy. He never had accepted his original gender reassignment. Other cases where the sex reassignment of intersexed children was rejected also were reported [41,42]. These new findings, with their implications for general and typical gender development, were reported immediately on the front page of the *New York Times* and in the pages of other major popular and medical media.[2]

This case seemed to indicate that people were psychosexually biased and predisposed at birth. The belief that one's sexual identity could be modified easily by rearing and that individuals were psychosexually neutral at birth lost its footing and a dramatic shift in thinking about the management of intersex conditions gained momentum. New principles of management for intersex conditions were provided [43].

The most basic recommendation was that intersexed infants should be assigned a gender that is not based on the appearance of the genitalia and chance of good cosmetic surgery, but on a specific diagnosis of the exact condition and the best prediction of the child's future choice of identity. These new principles of management for intersex conditions also recommended that any cosmetic, non-medically-essential surgery should be postponed and that intersexed children and adolescents should be allowed to make their own decisions as to how they want to live and be treated. Other recommendations were that male infants who had a micropenis should be reared as boys, unless evidence for managing them otherwise was presented. This had been successful in the past [44] and subsequently was found to be successful. The secrecy that most often was recommended to accompany genital surgery and sex reassignment was rejected. Honesty and information was to be provided and it also was recommended that, whenever possible, intersexed persons are put into contact with others who have the same condition. It also was recommended that the child and parents be given ongoing counseling.

In 1998, at the national meeting of the American Association of Pediatrics (AAP), evidence was offered that their standards of care for intersex management were on shaky ground; three strong recommendations were offered [46,47]. These recommendations are applicable to psychiatrists as well as to pediatricians.

Recommendation 1

"There should be a general moratorium on sex assignment cosmetic surgery when it is done without the consent of the patient."

This recommendation did not infer that such surgery had no application; however, no evidence had been presented that the surgery was beneficial. The application for such surgery was based on anecdotes and some case reports, not evidence-based medicine. Because there was no reported evidence for the practice, and such evidence still remains elusive, the golden rule of medicine seemed appropriate "First do no harm — Primum non nocere."

Recommendation 2

"This moratorium should not be lifted unless and until complete and comprehensive retrospective studies are done and it is found that the outcomes of past interventions have been positive."

Because long-term follow-up studies on the old protocols were lacking, evidence must be gathered to justify the practices. Because so many procedures had been done over the years, at least the records of those physicians and surgeons who were still active should be examined. Part of the difficulty stems from the fact that children do not become erotically active within the 6 months or 1 year follow-up period that might follow infant surgery; erotic sexual activities might not occur until puberty, adolescence, or later. Research must inquire in detail about sensuality, orgasmic thresholds, identity and the like. Simply asking if one is sexually active or sexually experienced—whatever that could mean—or if one is dating or married is insufficient.

Future research may find that such operations and procedures are appropriate; however, not having the evidence lends uncertainty to life features of dramatic importance. These can range for one opting or being forced to live as a man or woman, and surgery can preclude males from being fertile and procreating. Such procedures can alter future medical conditions and situations. The negative cost of ill-advised surgeries and sex reassignments can be high. It recently was determined, for instance, that infant clitoral and vaginal surgery is ill-advised. Among adolescent women who were studied who had these procedures, 41% felt that the cosmetic result was poor and 98% needed further treatment to their genitals [48]. In a separate study, women who had clitoral surgery for an intersex condition reported associated sexual problems. These were characterized as "difficulties with sensuality," "communication difficulties," "avoidance," and lack of orgasm. This was in significant distinction from comparable women who did not have such surgeries [49]. Creighton et al [50] reported that "Most vaginal surgery can be deferred ... Repeated clitoral surgery may be more damaging to sexual function than a single procedure .... and that children with mild clitoromegaly should have surgery deferred until they are old enough to be involved in the decision."

Recommendation 3

"Efforts should be made to undo the effects of past physician deception and secrecy."

Often, parents and physicians had concealed aspects of surgery and treatment from the child and excluded maturing children from medical management decisions. Furthermore, secrecy had kept intersexed individuals isolated from honest contact with their families, physicians, and others who had a similar diagnosis. Typically, patients discover their condition from an inadvertent family slip, community gossip, personal investigation into puzzling aspects of their lives, or mix-ups at the doctor's office; it is better for the physician to initiate disclosure. Without openness, the patient discovers that his or her condition is shameful in the minds of parents and doctors. They wonder why they were not accepted and loved

as they were and on what grounds it was decided that they could not manage the information. Also, the patient learns that s/he has been deceived since childhood by the people who should have been the most trustworthy—parents and physicians. All of this is damaging. To the extent that these children are misled, as they mature to adulthood they cannot act rationally from a realistic appraisal of their medical condition.[3]

Following the San Francisco meeting of the AAP, matters regarding intersexuality moved quickly. Many physicians have changed their practices. For others, skepticism of the new ideas remained and surgery still was advocated [52]; subsequently, caution and awareness of potential problems was recognized [53]. Sheldon [54] wrote "Surprisingly little has been written on the psychosocial outcome... We must completely inform the parents of such children regarding not only the physical risks of surgery, but the psychosocial risks as well... While I strongly disagree that a moratorium on childhood genital reconstruction is in order ... we should present this as an option, continue to listen carefully to our patients, make a meaningful attempt to study psychosocial adaptation and then alter our management accordingly." Others quickly argued for rethinking the old protocols [55,56].

The year 1998 was important for the study of intersexuality for other reasons. Two significant publications appeared: Kessler's [23] *Lessons from the Intersexed* and a special issue of the *Journal of Clinical Ethics* organized by Alice Dreger [57]. Kessler argued that the medical community was subjugating the intersexed child's needs, not to evidence but to maintaining existing practices and to their social and cultural beliefs of gender. The *Journal of Clinical Ethics* issue was devoted to ethical matters that are related to intersexuality. This issue also contained testimonies of intersexed persons who declared that they wanted to be allowed to develop without surgery and to participate in any medical decisions.

A 1998 report challenged the findings of the John/Joan case. Bradley et al [58] reported on a case in which, like David, a circumcision accident resulted in a normal boy losing his penis; like David, this boy was raised as a girl. When questioned as an adult, this individual claimed to see herself as a woman. She admitted that she was a tomboy as an adolescent and presently is predominantly gynecophilic and considers herself ambisexual [59]. Other cases, however, have reinforced the John/Joan findings [47,60].

The Texas Conference

One rapid result following the publication of the follow-up to the John/Joan case and the presentation to the pediatricians was a call for a conference to consider the implications of the findings and the subsequent three recommendations. The conference was held in Dallas, Texas in the spring of 1999.

From the Texas conference [61], two themes were reinforced: (1) more research with long-term studies are needed and (2) patients should be as informed as soon as possible as to their condition. A third theme re-emerged: the brain has to be recognized as a sexual organ [62] and "Since the human brain is sexually

dimorphic, it is not always possible to predict whether the adult will be happy with their gender 20 or 30 years after such a critical decision has been made in the first days of life" [63]. A moratorium on infant surgery was considered unrealistic, however; mostly because it was hypothesized that it would not be accepted by parents [53].

Shift in stigma: atypical versus disorder

Intersex conditions are no longer seen universally as disorders or errors of development but are increasingly being seen as "variations" of life. This change occurred rapidly among intersexuals themselves but is ongoing among the medical community. It is advocated that intersexuality be considered and labeled with a more neutral term and seen as a condition without stigma rather than as a disorder [43]. Humiliation and shame need not accompany and taint the medical or social circumstances; humiliation and shame often have followed from intersexed persons being treated as bizarre and with mendacity. This led many to seek psychiatric care. Seeing intersexuality as a typical variation—rather than as a stigmatizing condition —is an ongoing process but one that should prove easy for clinicians to eventually adopt and foster.

Change in medical practices: standards

Standards of care for intersex conditions have changed markedly. In 2000, the American Academy of Pediatrics modified their standards in recognition of the new evidence [64]. Similarly, in 2001 the British Association of Pediatric Surgeons modified their standard of care for intersexed children [65]. In these new guidelines, some concessions were made to the three recommendations; however, neither the US nor the British group accepted the idea of a surgical moratorium and neither group spoke to the recommendation for call back to those families or individuals that had previous treatment. Both groups recognized the need for more research on the topic and greater candor and honesty when dealing with families and patients. The recommendations from the United States and the United Kingdom pediatric associations are not identical; they differ in some important ways. The following are noteworthy differences:

- The identification of ambiguous genitalia should alert the staff that this is a social emergency (US); "While there is likely to be continuing pressure from parents for early corrective surgery, fully informed consent for such procedures would require them to be aware of the possibility of non-operative management with psychological support for the child and family" (UK).

- All females who are virilized because of congenital adrenal hyperplasia (CAH) or matemal androgens should, because of their retained fertility, be raised as girls (US); "Assignment of gender has to be on an individual basis, and the decision may need to include cultural considerations" (UK).

- Infants who are raised as girls "will usually require clitoral reduction" (US); "There is a strong case for no clitoral surgery in lesser degrees of clitoromegaly" (UK).

- Boys who have partial androgen insensitivity syndrome (AIS) "in whom a very small phallus mandates a female sex of rearing" should have their testes removed (US). The risk of malignant testicular changes in AIS is small (UK).

Both groups recognized that the potential role of prenatal influences on subsequent behavior need to be taken into account. They also caution that the sex of rearing should differ from the chromosomal sex only after careful individual consideration. What this means in practice is not stated.

Although in some ways these guidelines might be the current recommendations, a host of publications and events have already appeared that will modify their application. These publications and events are within and outside of medicine. Developments in law, for instance, are moving quickly and probably will have an influence on future management [66,67].

Legal considerations: recent developments

In 1998, the Constitutional Court of Colombia, South America ruled that sex reassignment of children would no longer be legal in that country. The Court's purported goal was "forcing parents to put the child's best interest ahead of their own fears and concerns about sexual ambiguity" [68]. The Constitution guarantees free development of one's own personality, which implies a right to define one's own sexual identity.

Early in 2000, a North American Task Force on Intersex was formed. With a broad interdisciplinary board as consultants, their goal is to gather follow-up data from clinics and physicians about their treatments and results regarding intersex management [69]. In 2002, a meeting that was similar to the one held in Dallas, Texas was held in Tempe, Arizona with hopes that sufficient new data might be reported. Some new findings were gathered and presented; however, it was acknowledged that anecdotal reports were still the norm.[4]

New data and good research have been slow to develop. Cases of individuals who change gender have continued to appear in the literature [56,70,71]. At the Phoenix meeting, the presentation by law professor, Julia Greenberg, drew the most attention [72]. Her talk was on the legal aspects of gender assignment and the problems that were attendant with then current practice. She indicated that physicians might face legal liability if they continued as before; truly informed consent is not yet possible and the needed research has not been done [66,72]. Another potential problem might occur as a result of sexual discrimination when XX and XY children are treated differently.

Findings about intersexuality of the last several years that are of psychiatric relevance include (in rough chronologic order):

- Slijper et al [73] reported cases of general psychopathology, excluding problems with gender, in 39% of the intersex cases that they reviewed. They specifically found that 13% of girls exhibited gender disorder of childhood "with intense sadness and dissatisfaction with the assigned sex and a

16. Due to genetic and hormonal variation in the developing fetus, normative development of the external genitalia in any individual differs with respect to size and appearance while maintaining an ability to function with respect to biologic purpose (i.e. reproduction). Internal structures (e.g. gonad, uterus, vas deferens) normatively align with external genitalia.

17. Reliance upon external phenotypic expression of primary sexual traits is a highly accurate means to assign biologic sex. In over 99.9% of cases, this designation will correlate with internal sexual traits and capacity for normal biologic sexual function.

18. Due the complexity of signals that are involved in normal sexual development, it is not surprising that a small number of individuals are born with defects in this process. Defects can occur either through inherited or de novo mutations in genes that are involved in sexual determination or through environmental insults during critical states of sexual development. Persons who are born with such abnormalities are considered to have a disorder of sexual development (DSD). Most often, this is first detected as ambiguity in the appearance of the external genitalia.

19. Normal variation in external genital appearance (e.g. phallic size) does not alter the basic biologic nature of sex as a binary trait. "Intersex" conditions represent disorders of normal development, not a third sex.

20. Medical care of persons with DSDs is primarily directed toward identification of the etiology of the defect and treatment of any associated complications. Similar to other diseases, tools such as the Prader scale are used to stage the severity of the deviation from normal. In children with DSDs, characterization based upon phenotype alone does not reliably predict chromosomal sex nor does it necessarily correlate with potential for biological sexual function.

Decisions on initial sex assignment in these rare cases require detailed assessment by a team of expert medical providers.

21. Standard medical practice in the treatment of persons with DSDs has evolved with growing understanding of the physical and psychologic needs and outcomes for affected individuals. Previously, it was felt that a definitive sex assignment was necessary shortly after birth with the belief that this would allow patients with DSDs to best conform to the assigned sex. Current practice is to defer sex assignment until the etiology of the disorder is determined and, if possible, a prediction can be made on likely biologic and psychologic outcomes. When this cannot be done with confidence, a presumptive sex assignment is made. Factors used in making such decisions include chromosomal sex, phenotypic appearance of the external genitalia, and parental desires. The availability of new information can in rare circumstances lead to sex reassignment. Decisions on whether to surgically alter the external genitalia to align with sex are generally deferred until the patient is able to provide consent.

Gender Dysphoria in relation to Biological Sex

22. Although gender usually aligns with biological sex, some individuals experience discordance in these distinct traits. Specifically, biologic females may identify as males and biologic males may identify as females. As gender by definition is distinct from biological sex, one's gender identity does not change a person's biological sex.

23. Individuals who experience significant distress due to discordance between gender identity and sex are considered to have "gender dysphoria". Although the prevalence of gender dysphoria has not been established by rigorous scientific analysis, estimates reported in in the DSM-V are between 0.005% to 0.014% for adult males and 0.002% to 0.003% for adult females.

Thus, gender dysphoria is a rare condition. It is currently unknown whether these estimates are falsely low due to under-reporting, or if changing societal acceptance of transgenderism and the growing number of medical centers providing medical intervention for gender dysphoria affects the number of persons who identify as transgender. Recent data suggests that the number of people seeking care for gender dysphoria is increasing with some estimates as high as 4-fold.

24. Most people with gender dysphoria have normally formed and functional sexual organs. The etiology of gender dysphoria in these persons remains to be identified. Theories include prenatal hormone exposure, genetic variation, and postnatal environmental influences. Based upon the currently available but incomplete dataset, it is likely that gender dysphoria is multifactorial with differing qualitative and quantitative influences in any given individual. There is strong evidence against the theory that gender identity is determined at or before birth and is unchangeable. This comes from identical twin studies where siblings share genetic complements and prenatal environmental exposure but have differing gender identities.

25. Further evidence that gender identity is not fixed comes from well established peer reviewed literature demonstrating that the vast majority (80-95%) of children who express gender dysphoria revert to a gender identity concordant with their biological sex by late adolescence. It is not known whether individuals with gender dysphoria persistence have differing etiologies or severity of precipitating factors compared to desisting individuals.

26. The limited emerging data has suggested structural and functional differences between brains from normal and transgender individuals. These data do not establish whether these differences are innate and fixed or acquired and malleable. The remarkable neuronal plasticity of the brain is known and has been studied extensively in gender-independent contexts related to health and disease, learning and behavior.

Gender Ideology

27. The modern attempt to equate gender identity with sex is not based upon sound scientific principles but rather is based upon ideology fueled by advocacy. Although worldviews among scientists and physicians, similar to society at large, differ, science is firmly grounded in physical reality not perception. The inherent link between human sexual biology and teleology is self-evident and fixed.

28. The claims of proponents of transgenderism, which include opinions such as "Gender defines who one is at his/her core" and "Gender is the only true determinant of sex" must be viewed in their proper philosophical context. There is no scientific basis for redefining sex on the basis of a person's psychological sense of 'gender'. It is erroneous and potentially damaging to equate these opinions as established medical fact.

29. The prevailing, constant and accurate designation of sex as a biological trait grounded in the inherent purpose of male and female anatomy and as manifested in the appearance of external genitalia at birth remains the proper scientific and medical standard. Redefinition of what is normal based upon pathologic variation is not established medical fact.

Potential Harm Related to Gender Dysphoria Treatments

30. The fundamental purpose of the practice of medicine is to treat disease and alleviate suffering. An essential tenet of medical practice is to avoid doing harm in the process. Due to the frequent lack of clear and definitive evidence on how to best accomplish this goal, treatment approaches can and do frequently differ among highly knowledgeable, competent, and caring physicians.

31. Persons with gender dysphoria as delineated in the DSM-V experience significant psychological distress related to their condition with elevated risk of depression, suicide, and other morbidities. Thus, attempts to provide effective medical care to affected persons are clearly warranted.

32. Efforts to effectively treat persons with gender dysphoria require respect for the inherent dignity of those affected, sensitivity to their suffering, and maintenance of objectivity in assessing etiologies and long-term outcomes. Desistance (i.e. reversion to gender identity concordant with sex) provides the greatest lifelong benefit and is the outcome in the majority of patients and should be maintained as a desired goal. Any intervention that interferes with the likelihood of resolution is unwarranted and potentially harmful.

33. There is an urgent need for high quality controlled clinical research trials to determine ways to develop supportive dignity affirming social environments that maintain affirmation of biological reality.

34. The Endocrine Society published in 2009 clinical guidelines for the treatment of gender dysphoric patients which include temporary suppression of pubertal development of children with GnRH agonists (hormone blockers normally used for children experiencing precocious puberty) followed by hormonal treatments to induce the development of secondary sexual traits consistent with one's gender identity. This guideline was developed using the GRADE (Recommendations, Assessment, Development, and Evaluation) system for rating clinical guidelines. As directly stated in the Endocrine Society publication, "the strength of recommendations and the quality of evidence was low or very low." According to the GRADE system, low recommendations indicate "Further research is very likely to have an important

impact on our confidence in the estimate of effect and is likely to change the estimate". Very low recommendations mean that "any estimate of effect is very uncertain".

35. There is little or no data to support pubertal suppression as a safe or effective treatment for gender dysphoria in children or adolescents. As noted, it is well established that 80-95% of children with gender dysphoria will resolve by the end of puberty without direct intervention to affirm transgender identity. Unfavorable long-term psychiatric outcomes for transgender adults point to gender resolution following puberty as the best hope for gender dysphoric children and adolescents.

36. In addition, treatment of gender dysphoric children with hormonal treatment (pubertal suppression and cross-hormone therapy) carries significant risk. It is generally accepted, even by advocates of transgender hormone therapy, that hormonal treatment results in sterility which in many cases is irreversible. Emerging data also show that treated patients have lower bone density which may lead to increased fracture risk later in life. Other potential adverse effects include disfiguring acne, high blood pressure, weight gain, abnormal glucose tolerance, breast cancer, liver disease, thrombosis, and cardiovascular disease.

37. Since strategies for the treatment of transgendered children as summarized by the Endocrine Society guidelines are relatively new, long-term outcomes are unknown. Evidence presented as support for short term reductions in psychological distress following social transition in a "gender affirming" environment remains inconclusive. When considered apart from advocacy based agendas, multiple potential confounders are evident. The most extensive long-term data on this question comes from the Dutch experience. Although appropriate caution is warranted in extrapolating these outcomes with current treatments, adults who have undergone

social transition with or without surgical modification of external genitalia continue to have rates of depression and suicide far above the background population.

38. With regard to public restrooms and other intimate facilities, there is no evidence to support social measures that promote or encourage gender transition as a medically necessary or effective treatment for gender dysphoria. If anything, one might expect that such social affirmation measures would interfere with known rates of gender resolution. Any activity that encourages or perpetuates transgender persistence for those who would otherwise desist can cause significant harm, including permanent sterility, to these persons. This is particularly concerning given that children are likely incapable of making informed consent to castrating treatments.

39. There remains a significant and unmet need to better understand both the biological, psychological, and environmental basis for the manifestation of discordance of gender identity in affected individuals together with rigorous controlled investigation of long-term outcomes including adverse consequences of attempted intervention. Uncontrolled social experimentation including the forced acceptance of altered norms for distinguishing persons according to biological sex is a potentially harmful and unscientific approach to dealing with this serious condition.

Pursuant to 28 U.S.C § 1746, I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Date: 08/09/2016

Signed: Paul W Hruz

Paul W. Hruz, M.D., Ph.D

Exhibit B

Hruz Sources

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Curriculum Vitae

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Education and Training

1987	B.S., Chemistry, Marquette University, Milwaukee, WI
1993	Ph.D., Biology and Physiology, Medical College of Wisconsin, Milwaukee, WI
1994	M.D., Medicine, Medical College of Wisconsin, Milwaukee, WI
1994 - 1997	Pediatric Residency, University of Washington - Pediatric , Seattle, Washington
1997 - 2000	Pediatric Endocrinology Fellowship, Washington University - Pediatric Endocrinology , Saint Louis, MO

Academic Positions and Employment

1996 - 1997	Locum Tenens Physician, Group Health of Puget Sound Eastside Hospital, Group Health of Puget Sound Eastside Hospital, Seattle , WA
2000 - 2003	Instructor of Pediatrics, Washington University, St. Louis, MO
2003 - 2011	Assistant Professor of Pediatrics, Washington University, St. Louis, MO

2004 - 2011	Assistant Professor of Cell Biology and Physiology, Washington University, St. Louis, MO
2011 - Pres	Associate Professor of Pediatrics, Washington University, St. Louis, MO
2011 - Pres	Associate Professor of Cell Biology and Physiology, Washington University, St. Louis, MO
2012 - Pres	Division Director, Pediatric Endocrinology and Diabetes, Washington University, St. Louis, MO

Appointments and Committees

NIH Study Sections:

2005	NIH- NIDDK Special Emphasis Panel ZDK1 GRB-6 (Non-Standing Member)
2009	NIH- ACE Competitive Revisions ZRG1 AARR-H (95) S (Non-Standing Member)
2009	NIH- AIDS and AIDS Related Research IRG (Standing Member)
2011	NIH- Pediatric Endocrinologist K12 ZDK1 GRB-C (Non-Standing Member)
2014	NIH- Special Emphasis Panel ZRG1 BBBPY 58 (Non-Standing Member)
2014	NIH- AIDS and AIDS Related Research IRG (Standing Member)
2015	NIH- Cardiovascular and Respiratory Sciences Special Emphasis Panel ZDK1 GRB-J (02) (Non-Standing Member)
2015	NIH- NIDDK Special Emphasis Panel ZRG1 CVRS-Q (80) (Non-Standing Member)

University Affiliations:

2008 - Pres	Director, Pediatric Endocrinology & Diabetes Fellowship Program
2010 - Pres	Pediatric Computing Facility Advisory Committee
2012 - Pres	Disorders of Sexual Development Interdisciplinary Care Program
2012 - Pres	Director, Division of Pediatric Endocrinology & Diabetes
2014 - Pres	Research Consultant, ICTS Research Forum - Child Health
2014 - Pres	Director, Pediatric Diabetes Research Consortium

Hospital Affiliations:

2000 - Pres	Attending Physician, St. Louis Children's Hospital

Thesis Committees (* Chair)		Advisor
2008 - 2011	Kelly Diggs-Andrews	Simon Fisher
2008 - 2010	Irwin Puentes	Simon Fisher
2008 - 2010	Tony Frovola	Kelle Moley
2009 - 2010	Lauren Flessner	Kelle Moley
2010 - 2012	Katie Boehle	Kelle Moley
2010 - 2013	Candace Reno*	Simon Fisher
2011 -Pres	Thomas Kraft	Paul Hruz
2013 - 2015	Chi Lun Pui	Audrey Odom
2013 -Pres	Leah Imlay	Audrey Odom
2014 -Pres	Anne Robinson	Katie Henzler-Wildman

2015 -Pres Allyson Mayer Brian DeBosch

Scholarship Oversight Committees
2013 -Pres Brittany Knipsein (Advisor: David Rudnick)

Licensure and Certifications

1997 - 2016 Board Certified in General Pediatrics
2000 - 2014 MO State License #2000155004
2001 - Pres Board Certified in Pediatric Endocrinology & Metabolism

Honors and Awards

1987 National Institute of Chemists Research and Recognition Award
1987 Phi Beta Kappa
1987 Phi Lambda Upsilon (Honorary Chemical Society)
1988 American Heart Association Predoctoral Fellowship Award
1994 Alpha Omega Alpha
1994 Armond J. Quick Award for Excellence in Biochemistry
1994 NIDDK/Diabetes Branch Most Outstanding Resident
1998 Pfizer Postdoctoral Fellowship Award
2002 Scholar, Child Health Research Center of Excellence in Developmental Biology at Washington University
2013 Julio V Santiago, M.D. Scholar in Pediatrics

Editorial Responsibilities

Editorial Boards:
2014 - Pres Endocrinology and Metabolism Clinics of North America

Ad Hoc Reviewer:
AIDS
AIDS Research and Human Retroviruses
American Journal of Pathology
American Journal of Physiology
British Journal of Pharmacology
Circulation Research
Clinical Pharmacology & Therapeutics
Comparative Biochemistry and Physiology
Diabetes
Experimental Biology and Medicine
Future Virology
Journal of Antimicrobial Chemotherapy
Journal of Biological Chemistry
Journal of Clinical Endocrinology & Metabolism
Journal of Molecular and Cellular Cardiology
Obesity Research

Professional Societies and Organizations

1992 - 2004	American Medical Association
1994 - 2005	American Academy of Pediatrics
1995 - 2014	American Association for the Advancement of Science
1998 - Pres	American Diabetes Association
1998 - Pres	Endocrine Society
1999 - Pres	Pediatric Endocrine Society
2004 - Pres	American Society for Biochemistry and Molecular Biology
2004 - Pres	Society for Pediatric Research
2004 - 2007	American Chemical Society
2005 - Pres	Full Fellow of the American Academy of Pediatrics
2013 - Pres	International Society for Pediatric and Adolescent Diabetes

Major Invited Professorships and Lectures

2002	St. Louis Children's Hospital, Pediatric Grand Rounds, St. Louis, MO
2004	National Disease Research Interchange, Human Islet Cell Research Conference, Philadelphia, PA
2004	NIDA-NIH Sponsored National Meeting on Hormones, Drug Abuse and Infections, Bethesda, MD
2005	The Collaborative Institute of Virology, Complications Committee Meeting, Boston, MA
2005	University of Indiana, Endocrine Grand Rounds, Indianapolis, IN
2006	Metabolic Syndrome Advisory Board Meeting, Bristol-Meyers Squibb, Pennington, NJ
2007	American Heart Association and American Academy of HIV Medicine State of the Science Conference: Initiative to Decrease Cardiovascular Risk and Increase Quality of Care for Patients Living with HIV/AIDS, Chicago, IL
2007	Medical College of Wisconsin, MSTP Annual Visiting Alumnus Lecture, Milwaukee, WI
2007	St Louis Children's Hospital, Pediatric Grand Rounds, St Louis, MO
2007	University of Arizona, Minority Access to Research Careers Seminar, Tucson AZ
2008	Boston University, Division of Endocrinology, Diabetes and Nutrition, Boston, MA
2009	St Louis Children's Hospital, Pediatric Grand Rounds, St Louis, MO
2010	American Diabetes Association Scientific Sessions, Symposium Lecture Orlando, FL
2010	University of Missouri Kansas City, School of Biological Sciences, Kansas City, MO
2011	Life Cycle Management Advisory Board Meeting, Bristol-Myers Squibb, Chicago, IL
2013	St Louis Children's Hospital, Pediatric Grand Rounds, St Louis MO
2013	St Louis Children's Hospital CPU Lecture, St Louis MO

2014 Pediatric Academic Societies Meeting, Vancouver, Canada, May 5, 2014
2014 American Diabetes Association 74th Scientific Sessions, San Francisco, CA, June 13, 2014

Consulting Relationships and Board Memberships

1996 - 2012 Consultant, Bristol Myers Squibb
1997 - 2012 Consultant, Gilead Sciences

Research Support

Governmental Support
R01 (Hruz) 9/20/2009 - 5/31/2014 (NCE)
NIH
Direct Effects of Antiretroviral Therapy on Cardiac Energy Homeostasis
The goal of this project is to characterize the influence of antiretroviral therapies on myocardial energy homeostasis and to elucidate how these changes in substrate delivery adversely affect cardiac function in the stressed heart.
Role: Principal Investigator

R01 (Hruz) 4/1/2007 - 1/31/2012 (NCE)
NIH
Mechanisms for Altered Glucose Homeostasis During HAART
The goal of this project is to identify the cellular targets of HIV protease inhibitors that lead to peripheral insulin resistance, impaired beta-cell function, and alterations in hepatic glucose production and to elucidate the molecular mechanisms of these effects.
Role: Principal Investigator

Non-Governmental Support
Research Program (Hruz) 6/1/2009 - 5/31/2012 (NCE)
MOD
Regulation of GLUT4 Intrinsic Activity
The major goals of this project are to investigate the ability of the GLUT4 tethering protein TUG and an UBL-domain containing N-terminal fragment of this protein to alter the intrinsic activity of the insulin responsive facilitative glucose transporter, to determine whether protein ubiquitination influences this association, and to characterize the role of the GLUT4 binding site on the modulation of glucose transport.
Role: Principal Investigator

(Hruz) 3/9/2010 - 6/8/2011 (NCE)
Bristol-Myers Squibb
Protective Effect of Saxagliptin on a Progressive Deterioration of Cardiovascular Function
Role: Principal Investigator

(Hruz)
Gilead Pharma

Novel HIV Protease Inhibitors and GLUT4
Role: Principal Investigator

II (Hruz) 2/1/2008 - 1/31/2011 (NCE)
CDI
Insulin Resistance and Myocardial Glucose Metabolism in Pediatric Heart Failure
Role: Co-Principal Investigator

Completed Support
R01 Student Supp (Hruz) 6/10/2009 - 8/31/2011
NIH
Mechanisms for Altered Glucose Homeostasis During HAART

II (Hruz) 2/1/2012 - 1/31/2015
CDI
Solution-State NMR Structure and Dynamics of Facilitative Glucose Transport Proteins

Past Trainees

2002 - 2002 Nishant Raj- Undergraduate Student (Other)
Study area: Research

2003 - 2004 Johann Hertel (Medical Student)
Study area: Research
Present position: Assistant Professor, University of North Carolina, Chapel Hill, NC

2003 John Paul Shen (Medical Student)
Study area: Research

2004 - 2005 Carl Cassel- High School Student (Other)
Study area: Research

2004 - 2004 Christopher Hawkins- Undergraduate Student (Other)
Study area: Research

2004 - 2004 Kaiming Wu- High School Student (Other)
Study area: Research

2005 Helena Johnson (Graduate Student)

2005 Jeremy Etzkorn (Medical Student)
Study area: Research
Present position: Assistant Professor, University of Pennsylvania

2006 Ramon Jin (Graduate Student)
Study area: Research

2006 Taekyung Kim (Graduate Student)
Study area: Research

2007 - 2008 Kai-Chien Yang (Graduate Student)
Study area: Research
Present position: Postdoctoral Research Associate, University of Chicago

2007 Paul Buske (Graduate Student)
Study area: Research
Present position: Postdoctoral Fellow, UCSF, San Francisco CA

2007	Randy Colvin (Medical Student) Study area: Research
2007 - 2007	Jan Freiss- Undergraduate Student (Other) Study area: Research
2008 - 2011	Arpita Vyas, MD (Clinical Fellow) Study area: Research Present position: Assistant Professor, Michigan State University, Lansing MI
2008 - 2009	Candace Reno (Graduate Student) Study area: Research Present position: Research Associate, University of Utah
2008	Temitope Aiyejorun (Grad Student) Study area: Research
2008 - 2012	Dennis Woo- Undergraduate Student (Other) Study area: Research Present position: MSTP Student, USC, Los Angeles CA
2009	Stephanie Scherer (Grad Student) Study area: Research
2009	Anne-Sophie Stolle- Undergraduate Student (Other) Study area: Research
2009 - 2009	Matthew Hruz- High School Student (Other) Study area: Research Present position: Computer Programmer, Consumer Affairs, Tulsa OK
2010	Constance Haufe- Undergraduate Student (Other) Study area: Research
2010 - 2011	Corinna Wilde- Undergraduate Student (Other) Study area: Researcher
2010 - 2010	Samuel Lite- High School Student (Other) Study area: Research
2011 - 2011	Amanda Koenig- High School Student (Other) Study area: Research
2011 - 2012	Lisa Becker- Undergraduate Student (Other)
2011 - 2011	Melissa Al-Jaoude- High School Students (Other)
2002 - 2010	Joseph Koster, PhD (Postdoc Fellow) Study area: Research
2005	Dominic Doran, DSc (Postdoctoral Fellow) Study area: HIV Protease Inhibitor Effects on Exercise Tolerance Present position: Faculty of Science, Liverpool John Moores Institute
2014 - 2014	David Hannibal (Clinical Research Trainee)
2010 - 2014	Lauren Flessner, PhD (Postdoctoral Fellow) Present position: Instructor, Syracuse University
2011 - 2016	Thomas Kraft (Graduate Student) Study Area: Glucose transporter structure/function Present position: Postdoctoral Fellow, Roche, Penzberg, Germany

Clinical Responsibilities

General Pediatrician, General Pediatric Ward Attending: 2-4 weeks per year, St. Louis Children's Hospital
Pediatric Endocrinologist, Endocrinology Night Telephone Consult Service: Average of 2-6 weeks/per year, St. Louis Children's Hospital
Pediatric Endocrinologist, Inpatient Endocrinology Consult Service: 4-6 weeks per year, St. Louis Children's Hospital
Pediatric Endocrinologist, Outpatient Endocrinology Clinic: Approximately 50 patient visits per month, St. Louis Children's Hospital

Teaching Responsibilities

Facilitator, Biology 5011- Ethics and Research Science, 6 hours/year
Facilitator, Cell Biology Graduate Student Journal Club, 4 hour/year
Facilitator, Discussion: Pituitary, Growth & Gonadal Cases, 2 hours/year
Facilitator, Medical Student Endocrinology and Metabolism Course, Small group
Lecturer, Cell Signaling Course, Diabetes module, 3 hours/year
Lecturer, Markey Course-Diabetes Module
Lecturer, Medical Student Growth Lecture (Women and Children's Health Rotation): Variable
Lecturer, Metabolism Clinical Rounds/Research Seminar: Presentations twice yearly
Lecturer, Pediatric Endocrinology Journal Club: Presentations yearly

Publications

1. Hruz, P. W., Narasimhan, C., Miziorko, H. M. (1992). 3-Hydroxy-3-methylglutaryl coenzyme A lyase: affinity labeling of the Pseudomonas mevalonii enzyme and assignment of cysteine-237 to the active site. *Biochemistry*, 31 (29), 6842-7 PubMed: 1637819.
2. Hruz, P. W., Miziorko, H. M. (1992). Avian 3-hydroxy-3-methylglutaryl-CoA lyase: sensitivity of enzyme activity to thiol/disulfide exchange and identification of proximal reactive cysteines. *Protein Sci*, 1 (9), 1144-53. PMCID: PMC2142181 PubMed: 1304393.
3. Mitchell, G. A., Robert, M. F., Hruz, P. W., Wang, S., Fontaine, G., Behnke, C. E., Mende-Mueller, L. M., Schappert, K., Lee, C., Gibson, K. M., Miziorko, H. M. (1993). 3-Hydroxy-3-methylglutaryl coenzyme A lyase (HL). Cloning of human and chicken liver HL cDNAs and characterization of a mutation causing human HL deficiency. *J Biol Chem*, 268 (6), 4376-81 PubMed: 8440722.
4. Hruz, P. W., Anderson, V. E., Miziorko, H. M. (1993). 3-Hydroxy-3-methylglutaryldithio-CoA: utility of an alternative substrate in elucidation of a role for HMG-CoA lyase's cation activator. *Biochim Biophys Acta*, 1162 (1-2), 149-54 PubMed: 8095409.
5. Roberts, J. R., Narasimhan, C., Hruz, P. W., Mitchell, G. A., Miziorko, H. M. (1994). 3-Hydroxy-3-methylglutaryl-CoA lyase: expression and isolation of the recombinant

human enzyme and investigation of a mechanism for regulation of enzyme activity. *J Biol Chem*, 269 (27), 17841-6 PubMed: 8027038.

6. Hruz, P. W., Mueckler, M. M. (1999). Cysteine-scanning mutagenesis of transmembrane segment 7 of the GLUT1 glucose transporter. *J Biol Chem*, 274 (51), 36176-80 PubMed: 10593902.
7. Murata, H., Hruz, P. W., Mueckler, M. (2000). The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *J Biol Chem*, 275 (27), 20251-4 PubMed: 10806189.
8. Hruz, P. W., Mueckler, M. M. (2000). Cysteine-scanning mutagenesis of transmembrane segment 11 of the GLUT1 facilitative glucose transporter. *Biochemistry*, 39 (31), 9367-72 PubMed: 10924131.
9. Hruz, P. W., Mueckler, M. M. (2001). Structural analysis of the GLUT1 facilitative glucose transporter (review). *Mol Membr Biol*, 18 (3), 183-93 PubMed: 11681785.
10. Hruz, P. W., Murata, H., Mueckler, M. (2001). Adverse metabolic consequences of HIV protease inhibitor therapy: the search for a central mechanism. *Am J Physiol Endocrinol Metab*, 280 (4), E549-53 PubMed: 11254460.
11. Murata, H., Hruz, P. W., Mueckler, M. (2002). Investigating the cellular targets of HIV protease inhibitors: implications for metabolic disorders and improvements in drug therapy. *Curr Drug Targets Infect Disord*, 2 (1), 1-8 PubMed: 12462148.
12. Hruz, P. W., Murata, H., Qiu, H., Mueckler, M. (2002). Indinavir induces acute and reversible peripheral insulin resistance in rats. *Diabetes*, 51 (4), 937-42 PubMed: 11916910.
13. Murata, H., Hruz, P. W., Mueckler, M. (2002). Indinavir inhibits the glucose transporter isoform Glut4 at physiologic concentrations. *AIDS*, 16 (6), 859-63 PubMed: 11919487.
14. Koster, J. C., Remedi, M. S., Qiu, H., Nichols, C. G., Hruz, P. W. (2003). HIV protease inhibitors acutely impair glucose-stimulated insulin release. *Diabetes*, 52 (7), 1695-700. PMCID: PMC1403824 PubMed: 12829635.
15. Liao, Y., Shikapwashya, O. N., Shteyer, E., Dieckgraefe, B. K., Hruz, P. W., Rudnick, D. A. (2004). Delayed hepatocellular mitotic progression and impaired liver regeneration in early growth response-1-deficient mice. *J Biol Chem*, 279 (41), 43107-16 PubMed: 15265859.
16. Shteyer, E., Liao, Y., Muglia, L. J., Hruz, P. W., Rudnick, D. A. (2004). Disruption of hepatic adipogenesis is associated with impaired liver regeneration in mice. *Hepatology*, 40 (6), 1322-32 PubMed: 15565660.
17. Hertel, J., Struthers, H., Horj, C. B., Hruz, P. W. (2004). A structural basis for the acute effects of HIV protease inhibitors on GLUT4 intrinsic activity. *J Biol Chem*, 279 (53), 55147-52. PMCID: PMC1403823 PubMed: 15496402.
18. Yan, Q., Hruz, P. W. (2005). Direct comparison of the acute in vivo effects of HIV protease inhibitors on peripheral glucose disposal. *J Acquir Immune Defic Syndr*, 40 (4), 398-403. PMCID: PMC1360159 PubMed: 16280693.
19. Hruz, P. W. (2006). Molecular Mechanisms for Altered Glucose Homeostasis in HIV Infection. *Am J Infect Dis*, 2 (3), 187-192. PMCID: PMC1716153 PubMed: 17186064.
20. Turmelle, Y. P., Shikapwashya, O., Tu, S., Hruz, P. W., Yan, Q., Rudnick, D. A. (2006). Rosiglitazone inhibits mouse liver regeneration. *FASEB J*, 20 (14), 2609-11 PubMed: 17077279.

21. Hruz, P. W., Yan, Q. (2006). Tipranavir without ritonavir does not acutely induce peripheral insulin resistance in a rodent model. *J Acquir Immune Defic Syndr*, 43 (5), 624-5 PubMed: 17133213.
22. Hruz, P. W., Yan, Q., Struthers, H., Jay, P. Y. (2008). HIV protease inhibitors that block GLUT4 precipitate acute, decompensated heart failure in a mouse model of dilated cardiomyopathy. *FASEB J*, 22 (7), 2161-7 PubMed: 18256305.
23. Hruz, P. W. (2008). HIV protease inhibitors and insulin resistance: lessons from in-vitro, rodent and healthy human volunteer models. *Curr Opin HIV AIDS*, 3 (6), 660-5. PMCID: PMC2680222 PubMed: 19373039.
24. Flint, O. P., Noor, M. A., Hruz, P. W., Hylemon, P. B., Yarasheski, K., Kotler, D. P., Parker, R. A., Bellamine, A. (2009). The role of protease inhibitors in the pathogenesis of HIV-associated lipodystrophy: cellular mechanisms and clinical implications. *Toxicol Pathol*, 37 (1), 65-77. PMCID: PMC3170409 PubMed: 19171928.
25. Tu, P., Bhasin, S., Hruz, P. W., Herbst, K. L., Castellani, L. W., Hua, N., Hamilton, J. A., Guo, W. (2009). Genetic disruption of myostatin reduces the development of proatherogenic dyslipidemia and atherogenic lesions in Ldlr null mice. *Diabetes*, 58 (8), 1739-48. PMCID: PMC2712781 PubMed: 19509018.
26. Guo, W., Wong, S., Pudney, J., Jasuja, R., Hua, N., Jiang, L., Miller, A., Hruz, P. W., Hamilton, J. A., Bhasin, S. (2009). Acipimox, an inhibitor of lipolysis, attenuates atherogenesis in LDLR-null mice treated with HIV protease inhibitor ritonavir. *Arterioscler Thromb Vasc Biol*, 29 (12), 2028-32. PMCID: PMC2783673 PubMed: 19762785.
27. Vyas, A. K., Koster, J. C., Tzekov, A., Hruz, P. W. (2010). Effects of the HIV protease inhibitor ritonavir on GLUT4 knock-out mice. *J Biol Chem*, 285 (47), 36395-400. PMCID: PMC2978568 PubMed: 20864532.
28. Gazit, V., Weymann, A., Hartman, E., Finck, B. N., Hruz, P. W., Tzekov, A., Rudnick, D. A. (2010). Liver regeneration is impaired in lipodystrophic fatty liver dystrophy mice. *Hepatology*, 52 (6), 2109-17. PMCID: PMC2991544 PubMed: 20967828.
29. Hresko, R. C., Hruz, P. W. (2011). HIV protease inhibitors act as competitive inhibitors of the cytoplasmic glucose binding site of GLUTs with differing affinities for GLUT1 and GLUT4. *PLoS One*, 6 (9), e25237. PMCID: PMC3179492 PubMed: 21966466.
30. Vyas, A. K., Yang, K. C., Woo, D., Tzekov, A., Kovacs, A., Jay, P. Y., Hruz, P. W. (2011). Exenatide improves glucose homeostasis and prolongs survival in a murine model of dilated cardiomyopathy. *PLoS One*, 6 (2), e17178. PMCID: PMC3040766 PubMed: 21359201.
31. Hruz, P. W., Yan, Q., Tsai, L., Koster, J., Xu, L., Cihlar, T., Callebaut, C. (2011). GS-8374, a novel HIV protease inhibitor, does not alter glucose homeostasis in cultured adipocytes or in a healthy-rodent model system. *Antimicrob Agents Chemother*, 55 (4), 1377-82. PMCID: PMC3067185 PubMed: 21245443.
32. Hruz, P. W. (2011). Molecular mechanisms for insulin resistance in treated HIV-infection. *Best Pract Res Clin Endocrinol Metab*, 25 (3), 459-68. PMCID: PMC3115529 PubMed: 21663839.
33. Remedi, M. S., Agapova, S. E., Vyas, A. K., Hruz, P. W., Nichols, C. G. (2011). Acute sulfonylurea therapy at disease onset can cause permanent remission of KATP-induced diabetes. *Diabetes*, 60 (10), 2515-22. PMCID: PMC3178299

PubMed: 21813803.
34. Aerni-Flessner, L., Abi-Jaoude, M., Koenig, A., Payne, M., Hruz, P. W. (2012). GLUT4, GLUT1, and GLUT8 are the dominant GLUT transcripts expressed in the murine left ventricle. *Cardiovasc Diabetol*, 11, 63. PMCID: PMC3416696 PubMed: 22681646.
35. Vyas, A. K., Aerni-Flessner, L. B., Payne, M. A., Kovacs, A., Jay, P. Y., Hruz, P. W. (2012). Saxagliptin Improves Glucose Tolerance but not Survival in a Murine Model of Dilated Cardiomyopathy. *Cardiovasc Endocrinol*, 1 (4), 74-82. PMCID: PMC3686315 PubMed: 23795310.
36. Hresko, R. C., Kraft, T. E., Tzekov, A., Wildman, S. A., Hruz, P. W. (2014). Isoform-selective Inhibition of Facilitative Glucose Transporters: Elucidation of the Molecular Mechanism of HIV Protease Inhibitor Binding. *J Biol Chem*, 289 (23), 16100-16113. PMCID: PMC4047383 PubMed: 24706759.
37. Mishra, R. K., Wei, C., Hresko, R. C., Bajpai, R., Heitmeier, M., Matulis, S. M., Nooka, A. K., Rosen, S. T., Hruz, P. W., Schiltz, G. E., Shanmugam, M. (2015). In Silico Modeling-based Identification of Glucose Transporter 4 (GLUT4)-selective Inhibitors for Cancer Therapy. *J Biol Chem*, 290 (23), 14441-53 PubMed: 25847249.
38. Kraft, T. E., Hresko, R. C., Hruz, P. W. (2015). Expression, purification, and functional characterization of the insulin-responsive facilitative glucose transporter GLUT4. *Protein Sci* PubMed: 26402434.
39. Kraft, T. E., Armstrong, C., Heitmeier, M. R., Odom, A. R., Hruz, P. W. (2015). The Glucose Transporter PfHT1 Is an Antimalarial Target of the HIV Protease Inhibitor Lopinavir. *Antimicrob Agents Chemother*, 59 (10), 6203-9. PMCID: PMC4576095 PubMed: 26248369.
40. DeBosch, B. J., Heitmeier, M. R., Mayer, A. L., Higgins, C. B., Crowley, J. R., Kraft, T. E., Chi, M., Newberry, E. P., Chen, Z., Finck, B. N., Davidson, N. O., Yarasheski, K. E., Hruz, P. W., Moley, K. H. (2016). Trehalose inhibits solute carrier 2A (SLC2A) proteins to induce autophagy and prevent hepatic steatosis. *Sci Signal*, 9 (416), ra21 PubMed: 26905426.
41. Hresko, R. C., Kraft, T. E., Quigley, A., Carpenter, E. P., Hruz, P. W. (2016) Mammalian glucose transporter activity is dependent upon anionic and conical phospholipids. *J Biol Chem*, 2016 Jun 14. PubMed: 27302065.

Invited Publications

1. Hruz, P. W., Mueckler, M. M. (2001). Structural analysis of the GLUT1 facilitative glucose transporter (review). *Mol Membr Biol*, 18 (3), 183-93 PubMed: 11681785.
2. Hruz, P. W., Murata, H., Mueckler, M. (2001). Adverse metabolic consequences of HIV protease inhibitor therapy: the search for a central mechanism. *Am J Physiol Endocrinol Metab*, 280 (4), E549-53 PubMed: 11254460.
3. Murata, H., Hruz, P. W., Mueckler, M. (2002). Investigating the cellular targets of HIV protease inhibitors: implications for metabolic disorders and improvements in drug therapy. *Curr Drug Targets Infect Disord*, 2 (1), 1-8 PubMed: 12462148.
4. Hruz, P. W. (2006). Molecular Mechanisms for Altered Glucose Homeostasis in HIV Infection. *Am J Infect Dis*, 2 (3), 187-192. PMCID: PMC1716153 PubMed: 17186064.
5. Grunfeld, C., Kotler, D. P., Arnett, D. K., Falutz, J. M., Haffner, S. M., Hruz, P.,

Masur, H., Meigs, J. B., Mulligan, K., Reiss, P., Samaras, K., Working, Group 1 (2008). Contribution of metabolic and anthropometric abnormalities to cardiovascular disease risk factors. *Circulation*, 118 (2), e20-8. PMCID: PMC3170411 PubMed: 18566314.

6. Hruz, P. W. (2008). HIV protease inhibitors and insulin resistance: lessons from in-vitro, rodent and healthy human volunteer models. *Curr Opin HIV AIDS*, 3 (6), 660-5. PMCID: PMC2680222 PubMed: 19373039.
7. Flint, O. P., Noor, M. A., Hruz, P. W., Hylemon, P. B., Yarasheski, K., Kotler, D. P., Parker, R. A., Bellamine, A. (2009). The role of protease inhibitors in the pathogenesis of HIV-associated lipodystrophy: cellular mechanisms and clinical implications. *Toxicol Pathol*, 37 (1), 65-77. PMCID: PMC3170409 PubMed: 19171928.
8. Hruz, P. W. (2011). Molecular mechanisms for insulin resistance in treated HIV-infection. *Best Pract Res Clin Endocrinol Metab*, 25 (3), 459-68. PMCID: PMC3115529 PubMed: 21663839.
9. Hruz, P.W. (2014). HIV and endocrine disorders. *Endocrinol Metab Clin North Am*, 43 (3), xvii–xviii PubMed: 25169571.

Book Chapters (most recent editions)

1. Henderson KE, Baranski TJ, Bickel PE, Clutter PE, Clutter WE, McGill JB "Endocrine Disorders in HIV/AIDS ." *The Washington Manual Endocrinology Subspecialty Consult*. Philadelphia, PA: Lippincott Williams and Wilkins, 2008. 321-328.

Gender Development and Sexuality in Disorders of Sex Development

Authors S. A. Berenbaum[1], H. F. L. Meyer-Bahlburg[2]

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Key words
- gendered activities
- gender roles
- gender identity
- gender dysphoria
- sexual orientation
- sex hormones

Abstract

Understanding psychological development in individuals with disorders of sex development (DSD) is important for optimizing their clinical care and for identifying paths to competence and health in all individuals. In this paper, we focus on psychological outcomes likely to be influenced by processes of physical sexual differentiation that may be atypical in DSD, particularly characteristics related to being male or female (those that show sex differences in the general population, gender identity, and sexuality). We review evidence suggesting that (a) early androgens facilitate several aspects of male-typed behavior, with large effects on activity interests, and moderate effects on some social and personal behaviors (including sexual orientation) and spatial ability; (b) gender dysphoria and gender change occur more frequently in individuals with DSD than in the general population, with rates varying in relation to syndrome, initial gender assignment, and medical treatment; and (c) sexual behavior may be affected by DSD through several paths related to the condition and treatment, including reduced fertility, physical problems associated with genital ambiguity, social stigmatization, and hormonal variations. We also consider limitations to current work and challenges to studying gender and sexuality in DSD. We conclude with suggestions for a research agenda and a proposed research framework.

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Bibliography
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Gender Development and Sexuality in DSD

Psychological development in individuals with disorders of sex development (DSD) is influenced by many factors. Such disorders, by definition, affect processes of physical sexual differentiation, so much of the work on psychological development in DSD has focused on influences related to those processes (particularly sex chromosome genes and sex hormones) and on characteristics related to being male or female (those that show sex differences in the general population, gender identity, and sexuality). In this paper, we discuss outcomes of gender development and sexuality in individuals with DSD, with a particular focus on (a) the evidence regarding the nature and causes of outcome, (b) the challenges involved in obtaining this information, and (c) suggestions for a research agenda for the future. (Given space constraints, citations are generally to review papers.)

Background

Studies in non-human animals provide important information to help us understand human psychosexual differentiation and outcomes in individuals with disorders of sex development (DSD). The main processes that produce physical sexual differentiation – genes and sex hormones – have been studied for their effects on behavioral sexual differentiation as well. Evidence from many species unequivocally shows that sex hormones during multiple developmental periods affect a variety of behaviors, including sexual behavior, aggression, infant care, and spatial abilities; limited evidence suggests that sex chromosome genes contribute to some aspects of behavior, including aggression [1].

Sex hormones influence behavior in 2 main ways: by causing permanent changes to the brain that have long-lasting effects on behavior (organizational effects) and by producing temporary changes to the brain that affect behavior only when the hormones are present (activational effects). Organizational effects occur primarily

during early (especially prenatal) development, although there is increasing evidence that there may be additional effects during puberty/adolescence [1,2]. Activational effects refer to temporary changes to the brain (and behavior) produced by circulating hormones at the time; hormones activate neural structures that were organized early in development. The main distinctions between organizational and activational effects concern timing and permanence, although these distinctions are somewhat simplified and not absolute [3].

Individuals with DSD have been studied as natural experiments to understand sex hormone effects on human behavior. Those studies are translational, providing basic science information about influences on psychological development, and clinical information about psychological outcomes in DSD, often in relation to aspects of the condition. Most work has been done in females with congenital adrenal hyperplasia (CAH) because it is the most common DSD, but additional data come from people with other DSD and from typical individuals, that is, those without DSD. Other DSD include partial and complete androgen insensitivity syndrome (AIS) and 5α-reductase-2 deficiency (5αR2D). Data from typical individuals include studies linking amniotic hormones to childhood behavior. As reviewed below, converging evidence shows that sex hormones also influence human psychological development – but not in a simple way. High levels of prenatal androgens facilitate male-typed and inhibit female-typed behaviors, with androgens influencing some behaviors more than others.

Gendered Development in DSD: Evidence and Challenges

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Psychological studies of DSD have focused on characteristics that show sex differences in the general population, and on general psychological adjustment or quality of life (QoL). We focus on the former; the latter is discussed elsewhere in this issue [4]. The gender-related outcomes most often studied range across a variety of domains, as shown in ○ **Table 1**.

Table 1 Gender-related psychological domains typically studied in DSD.

- **Activities and Interests**
  - Toy preferences
  - Play activities
  - Hobbies and leisure interests
  - Occupational interests and occupational choices
- **Personality**
  - Aggression
  - Empathy
- **Social Behaviors**
  - Interest in babies
- **Cognitive Abilities**
  - Spatial abilities
  - Motor abilities
  - Verbal abilities
- **Gender Identity**
- **Sexuality**
  - Sexual orientation
  - Sexual behavior

Gendered Activities and Interests

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Childhood play is strongly sex-typed: on average, boys and girls play with different toys. Sex differences in activities continue later in development, so that adolescent and adult females and males, on average, prefer and engage in different activities, including occupations. These interests are influenced by social factors, such as parent expectations and behavior [5], but they are also strongly influenced by prenatal androgens.

Girls and women with CAH are interested in and engage with male-typed toys in childhood, and male-typed hobbies, leisure activities, and occupations in adolescence and adulthood; effects are seen across measures (e.g., observation, self report, drawings) and countries [2,6]. Individuals with other DSD also engage in male-typed activities in relation to their prenatal androgen exposure and not sex chromosomes or sex of rearing [7].

A key concern has been that male-typed behavior in individuals with DSD reflects parent responses to the atypical genitalia or other aspects of the condition (e.g., postnatal androgen excess in poorly-treated CAH). But, there is little evidence that this is the case. For example, male-typed interests in females with CAH are associated with degree of prenatal androgen exposure, not postnatal androgen excess or social responses to girls' virilized genitalia [reviewed in [2,6]].

Gendered Personality and Social Behavior

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Aspects of social behavior and personality have also been seen to differ in individuals with DSD compared to typical individuals, presumably in relation to prenatal androgens [2]. But these characteristics have not been as well studied as have activities, and androgen effects on them appear to be smaller. For example, compared to their sisters, females with CAH are less interested in babies, and more aggressive. Little is known about these characteristics in other DSD.

Cognition

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The sexes do not differ in general intelligence, but they do differ in pattern of cognitive abilities, with boys and men superior on spatial and mathematical abilities, and girls and women superior on some verbal abilities (especially fluency), memory, and processing speed [5]. There is some evidence that girls and women with CAH have better spatial and mechanical abilities than their unaffected sisters, consistent with other data for effects of prenatal androgens on these abilities (for review and data, see [8]). This topic has not been well-studied in other DSD.

Gender Identity

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The basic structure of virtually all societies is a binary system of gender, and gender assignment is typically associated with the corresponding identity later, so the gender assignment of a newborn is a crucial decision with lifelong implications for the individual and family. Most newborns have genitalia that are clearly male or female, so gender assignment is simple, based on genital appearance. But atypical genitalia in newborns make the decision difficult. Gender assignment in such cases has been based on criteria that have changed over time and are influenced by

societal gender preferences [9]; policy has been influenced by clinicians' growing awareness of patients whose gender assignment does not match their identified gender (gender dysphoria), and who initiate gender change later in development.

Gender dysphoria and gender change occur more frequently in individuals with DSD than in the general population, but specific rates vary widely as a function of syndrome, syndrome severity, initial gender assignment, and medical treatment [9]. In classical CAH, girls and women generally maintain a female gender identity, even in the presence of highly masculinized behavior [10]. In 46,XY DSD, adults raised in both genders retrospectively report gender uncertainty early in development, but most resolve it and maintain their assigned gender without gender dysphoria [11]. Rates of gender change appear to be higher in conditions with continued postnatal exposure to androgens, such as 5αR2D [9].

Key questions relate to the prediction of gender identity, particularly its relation to prenatal androgen exposure or other aspects of sexual differentiation, and to gendered behaviors. Available evidence strongly suggests that biological and psychosocial factors contribute to gender identity development, and that gender identity is not simply predictable from other gendered psychological characteristics [9]. Clear conclusions are impeded because of methodological differences across studies. Nevertheless, the limited evidence available has prompted revisions of earlier clinical guidelines, for example, female assignment of 46,XY newborns with genital ambiguity due to non-hormonal causes in the presence of effective high prenatal androgen levels, such as cloacal exstrophy and penile agenesis [12].

Recent policies have increased acceptance of variations in gender and sexual orientation, at least in industrialized societies. Laws in some countries now accommodate identity as a third gender (e.g., India, Australia), or eliminate the need to declare sex on the birth certificate of a child with DSD (e.g., Germany) [13]. A dramatic recent increase in referrals related to gender problems to centers that specialize in LGBT care [14] appears to reflect diversification of the transgender spectrum [15]. These changes to gender boundaries may affect people with DSD, for example, some individuals with DSD have identified publicly as intersex rather than as male or female, and some with marked gender-atypical behavior report reduced confidence in identifying as male or female [16]; the frequency of such identifications and their impact on other aspects of quality of life should be studied. Such studies should focus on understanding both the biological contributors to gender identity and the psychological and social contexts in which gender atypical behavior yields distress and gender change. Improvements in predicting gender identity have clear implications for initial gender assignment and should lead to fewer future patient-initiated gender reassignment and associated adverse consequences (including psychological toll and genital surgery that is inconsistent with ultimate gender identity).

Sexuality in DSD: Evidence and Challenges

Several aspects of sexuality may be affected in DSD as a result of features of the conditions (e.g., atypical hormone exposure) or treatment (e.g., genital surgery). We focus here on sexual orientation, that is, the gender of the target of romantic and erotic attraction and love, and sexual function and satisfaction.

Sexual Orientation

Most evidence on sexual orientation in DSD comes from women with CAH, who are less likely than typical women to be exclusively heterosexual, that is, they have increased gynecophilia or attraction to females. But the majority of women with CAH are heterosexual, and attraction to females correlates moderately with degree of prenatal androgen excess [17]. As with other characteristics, systematic data on sexual orientation in individuals with other DSD are limited, but also suggest increased development of non-heterosexuality in 46,XY individuals raised female with some degree of effective prenatal androgen exposure, such as partial AIS or mixed gonadal dysgenesis. By contrast, 46,XY individuals raised female with very low prenatal exposure to effective androgens, as is characteristic of complete AIS or complete gonadal dysgenesis, are typically androphilic, that is, attracted to males [18]. The few studies in this area are mostly descriptive; there is a need for evidence on the development of sexual orientation and of the potential contribution of various biological and experiential factors and social contexts as proposed for typical individuals, e.g., [19]. Important related questions concern the ways in which DSD affect patterns of sexual arousal (given that typical men show stronger specificity of arousal to one sex than do typical women) [20] and fluidity of sexual orientation (given that typical women are more fluid than typical men) [21].

Sexual Behavior

Sexual behavior may be affected by DSD through several paths related to the condition and treatment. Fertility may be reduced. Genital ambiguity may cause physical problems, including urinary problems, impairment of menstrual flow, and difficulties with peno-vaginal intercourse. It may also elicit pervasive social stigmatization, undermining self-esteem and leading to avoidance of nudity, sexual relations, and dating. Thus, genital ambiguity is not simply a "cosmetic" problem [22]. Corrective surgery, however, comes with its own risks, for both anatomy (esthetic appearance) and sexual function, especially if done by surgeons with insufficient experience with DSD.

Sex hormones may also affect sexuality through effects on sexual motivation ("drive") and other aspects of sexual functioning. Variations in hormones may result from the condition itself (e.g., low effective androgens in complete AIS) or in treatments used to initiate puberty and maintain secondary sex characteristics, and, for classical CAH, glucocorticoid replacement therapy, which modulates sex hormone levels.

Outcome data on sexual behavior and sexual functioning are again primarily available on individuals with 46,XX CAH, most of whom have undergone genital surgery(ies) [13]. Women with classical CAH are more likely than typical women to delay sexual initiation, to lack coital experience, and to live without a sexual partner. Those who are sexually active (particularly those with severe CAH) show, on average, decreased sexual desire, decreased arousability, decreased erotic sensitivity, increased genital pain during coitus, decreased orgasmic capacity, and increased rates of overall dissatisfaction with their sex lives in comparison to non-CAH control women. The limited data on 46,XY individuals with DSD show analogous sexual-function problems [23]. But, there is considerable variability in such out-

comes for reasons that are not well understood. Furthermore, existing follow-up studies do not yet include women who have undergone genital surgery with recently improved techniques that may improve functional outcomes.

A key question concerns the best age for genital surgery. Practice for the past 60 years has been to perform gender-confirming surgery in infancy or early childhood, with the assumption that this minimizes caretakers' doubts about gender assignment and stigmatization by others in the social environment. In view of the variable outcomes, there have been calls by both DSD activists and ethicists to delay surgery until the age of consent. But, surveys of individuals with DSD (mostly women with CAH), most of whom had undergone genital surgery, showed that most supported genital surgery at an early age; and women with CAH reported more satisfaction with clitoral function with early than with late surgery in the one study that examined the issue [13].

Neural Substrates of Behavior in DSD

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Sex differences in brain anatomy and activity have been documented in many ways in humans and non-human animals, and studies in the latter show influences of sex hormones and of genes located on the sex chromosomes [1, 24, 25]. This has led to the expectation that individuals with DSD can be differentiated from typical individuals on the basis of brain structure or function assessed with contemporary neuroimaging techniques, such as magnetic resonance imaging. Moreover, it might be important to understand what happens to the areas of the cortex that usually represent genital structures, when those structures are atypical or not fully developed. This is a new area of research, and studies to date are limited in scope and findings. For example, a study of individuals with CAH revealed a reduced volume of the amygdala in both boys and girls [26] that is difficult to interpret within the framework of sexual differentiation and may partly reflect effects of the disease or its treatment [25]. Studies of transsexualism [27] suggest that relevant brain differences might be more noticeable in connections among neural regions (investigated by diffusion tensor imaging) than in overall brain morphology.

Nevertheless, it is unlikely that brain anatomy or activity will provide a newborn marker of any gendered characteristic. Sex differences observed to date are not large, and there is considerable overlap among typical males and females [25]. Furthermore, the brain is plastic, so that both structure and function reflect genes, physiological processes (including hormones), and experiences. For example, differences in the brains of transgendered individuals might contribute to their atypical identity development and/or result from it.

Challenges across Domains

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We have identified above specific challenges in studying specific psychological domains in DSD. There are also a number of challenges that apply to all domains, and have limited our understanding of psychological development in DSD.

Perhaps the main issue has been the limited attention paid to developmental processes. Most work has focused on outcomes at different developmental periods, and the extent to which they reflect specific broad influences, particularly effects of early sex hormones and rearing sex. But, outcomes do not emerge fully formed at any age, and it is important to study the processes whereby outcomes develop from the joint effects of genes, hormones, and multiple aspects of the social environment (e.g., parents, extended family, cultural group, context).

Methodological issues make studies of DSD very challenging. The first problem concerns recruitment of participants. DSD is not very common; CAH is the most common, occurring in approximately 1:15 000 live births. It is difficult to accrue a sufficient study sample from any individual clinic, especially in the United States; in other countries, centralized health care and medical registries make such studies easier to implement, although populations are generally smaller than in the US. Even when sufficient participants are accrued, they may not be representative of the population of patients, with particular concern that participants differ in outcomes from those who cannot be located or elect not to participate. Research regulations generally make it difficult to evaluate any bias, because it is not ethical to examine any information (e.g., from medical records) on patients who do not participate. A related issue concerns the comparison group: Many studies involve comparison participants from the general population, but better comparisons are siblings without DSD who provide a control for general genetic and environmental (especially family) background, and individuals with other medical or surgical conditions that have some parallel to DSD (e.g., chronic diseases, conditions that affect appearance and involve corrective surgery); the comparison group should be selected for relevance to the outcome studied (e.g., for sexual function related to genital surgery in DSD, people with non-genital surgeries are not a good comparison).

A second methodological issue relates to measurement of key constructs. It is typical for studies to focus on self-reported outcomes assessed with short and limited questions, but it is important to assess psychological characteristics with multiple methods (e.g., observation, structured interviews) and to obtain information from multiple sources (e.g., parents, teachers, peers). Furthermore, it is essential to differentiate aspects of gendered behavior, for example, expressed interests vs. public presentation of gender roles vs. internal gender identity.

Key Questions

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We summarize here some of the questions regarding gender development and sexuality in DSD. Some questions reflect the complete lack of data, whereas others reflect the need to elaborate the existing evidence. These questions address basic questions about psychological development and have considerable implications for clinical care of DSD. Note that the questions are not mutually exclusive.

- What accounts for variations in outcome? This includes variations across behavior (e.g., why do androgens affect activity interests more than gender identity?), diagnoses (e.g., why is gender change more common in 5αR2D than in CAH?), and individuals (e.g., why are some women with CAH non-heterosexual but most are exclusively heterosexual?). As an example with clinical application, how can we identify and validate predictors of gender dysphoria and patient-initiated gender change and use them to optimize initial gender assignment?
- What are the psychological effects of other processes of physical sexual differentiation beyond prenatal androgens? It is

important to consider effects of genes, early postnatal hormones ("minipuberty") and pubertal hormones. Such factors might contribute to some of the variations noted above that need to be explained.

- How do genetic and hormonal processes transact with aspects of a child's social environment to produce behavior? Again, answers to this question might contribute to understanding variations noted above. This question is crucial to understanding gender identity outcome.
- How do gendered characteristics affect other aspects of QoL? Although QoL may be compromised in DSD [4], little is known about how this is affected by gender-atypical characteristics.
- How is gender represented in the brain? For example, how are specific brain structures and activations affected by sex chromosome genes and sex hormones during different developmental periods? Is it reasonable to expect neuroanatomical markers of gender identity that can facilitate decisions about gender assignment and treatment?
- How does gender development occur? Most research has focused on describing, predicting, and explaining gendered outcomes at specific ages. But behavior changes across time as a function of the individual, his/her genes, and the context in which he/she is embedded. There is a large and rich literature on psychological development that could be used as a model for DSD.

Research Framework Needed

Answers to these questions will most likely come from multisite studies, given the low incidence of DSD; it would be particularly helpful to establish registries. There are some efforts in this regard [28–30], but they have experienced challenges, for example, navigating ownership of data, accrual of participants, and comparability of measures in different languages.

Such studies should include psychometrically sound measures of psychological outcomes and of potential predictors, and appropriate comparison groups (which may differ for different outcomes). Ideally, work should include long-term prospective follow-up studies. The focus to date has been on genetic and hormonal predictors of outcome, but there is need for detailed assessment of the social environment, including, for example, cutting-edge measures of parenting, pressures for gender conformity, supports and barriers to patient-initiated gender change. The time is right to extend our study of gender development and sexuality in individuals with DSD. Understanding developmental processes and psychological outcomes in individuals with DSD will facilitate optimal treatment for those individuals and tell us about human psychological development in general.

Conflict of Interest

The authors declare no conflict of interest.

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Title: Sex and Gender are Different: Sexual Identity and Gender Identity are Different

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Abstract

This paper attempts to enhance understanding and communication about different sexual issues. It starts by offering definitions to common terms like sex, gender, gender identity, and sexual identity. Alternate ways to discuss one's sexual attractions are also presented. Terms are defined or redefined and examples given of their preferred use in different clinical situations including those associated with children. Adherence to the usage advocated here is proposed as helpful in theory formulation and discussion as well as in clinical practice. When reference is made to individuals of various sexual-minority groups such as transsexual or intersexual persons, the distinctions offered are particularly advocated.

Key Words

Sexual identity, gender identity, sexual orientation, transsexuality, intersexuality, transvestite, transgender, ambiguous genitalia

Introduction

For the last several decades the term *gender* has come into common usage particularly as a synonym for *sex*. The term has proved useful in many ways although distinctions between the two words, *sex* and *gender*, when one might be more appropriate than the other, has not been firmly established. In most instances, particularly in casual conversation, the words gender and sex are used interchangeably and it seems to make little difference. If there is room for doubt the context generally makes the meaning clear. However, in scientific, medical, legal or

political and even religious discourse the discrepant use of the terms can lead to confusion and a lack of understanding.

Here is a quote from a recent report (Schmidt 2001): "the findings [of a second gene related to sex determination] offer new hope for parents whose babies are born with this [ambiguous genital] condition - as well as valuable information to help physicians more accurately and quickly diagnose the newborn's gender." Knowing the genetics of a child's sex in cases with ambiguous genitalia is not always helpful in knowing what a child's genitals would look like and certainly rarely helpful in predicting a child's gender. The term *sex* is related to anatomical structure, the term *gender* is related to an imposed or adopted social and psychological condition. Explaining the difference to anguished parents and confused physicians occupies a good part of my time. Both parents and many professionals assume that knowing sex infers gender but this is not always the case.

Maintenance of clear conceptual distinctions between the two words *sex* and *gender* and associated concepts is particularly helpful for the psychological understanding of identity. This paper attempts to show that, in certain contexts -- particularly those involving transsexuality and intersexuality but in other instances as well-- it is most useful to recognize and encourage the distinction.

The term *sex*, since classical times, has been used to designate matters related to biology and medicine when male, female or bisexual were in context. Thus animals, including humans, are categorized dependent upon whether they either produce gametes as, or similar to, spermatozoa (*males*) or ova (*females*), or have parts of the reproductive system appropriate to the development of and delivery or reception of such gametes. Among non-human animals bisexuality covers those cases where both male and female reproductive components are present.[1] Among animals the term bisexuality, unless specifically so-stated, usually refers to anatomy and not to sexual behavior. Classically, for humans, those individuals that had both male and female characteristics were called hermaphrodites. Presently the term intersex is preferred (Kessler 1998).[2]

The term *gender* has generally been used in social or cultural contexts, in distinction from biological ones. This was particularly associated with language. The first known use of the word gender was listed as 1387 CE when T. Usk wrote "No mo genders been there but masculine and femynyne, all the remnaunte been no genders but of grace, in faculte of grammar (Simpson and Weiner 1989)."[3] This context for gender has been expanded so that since the 1960s or 1970s the word is often used as a euphemism for the sex of a human being but the intended emphasis remains on the social and cultural, as opposed to the biological. United States Supreme Court Justice Anthony Scalia, in an attempt to clarify usage of the terms has written (J.E.B. 1994) "The word gender has acquired the new and useful connotation of cultural or attitudinal characteristics (as opposed to physical characteristics) distinctive to the sexes. That is to say, gender is to sex as feminine is to female and masculine is to male," According to U.S. Supreme Court Justice Ruth Bader Ginsburg, however, the words are interchangeable. She relates that she used them in composing her legal briefs about sex/gender related matters so the word

sex would not appear on every page. Supposedly her secretary encouraged this saying: "Don't you know those nine men [on the Supreme Court, when] they hear that word their first association is not the way you want them to be thinking (Case 1995)."

With these distinctions in mind, contemporary use of the terms often maintains these discriminations but frequently does not. Much seems to depend upon the proximity of the speaker/writer to a background or reference related to biology or medicine or to philosophical, social or anthropological studies. For most of those persons, who are biologically or medically attuned, sex appears fixed. The gonads determine sex or it is diagnosed by the gametes that the individual possesses or would be expected to possess on the basis of some other biological feature such as chromosomes.[4] Human males and females, as biological entities, are also categorized as male or female or intersexed (having biological features of both a typical male and female). As social entities, however, *men* and *women*, by virtue of the multitude of different roles they play in diversified societies, and by virtue of the many individual decisions they make in their own lives, are not so easily distinguished. Males can certainly live, work, or play, as girls or woman appropriate or not to their society, and females can equally live, work, or play, as boys or men. This mutable aspect of their lives is their *gender*.[5]

Roles and Identity

Most usually the roles that one enacts are sex-linked. The term *role* is used to indicate that the behavior patterns exhibited are learned or acted as if according to some sort of social script (Gagnon and Simon 1973). Men and men's roles are typically associated with strength and dangerous occupations while woman and women's roles are more often associated with child rearing and nurturing pursuits. But even so, these distinctions are increasingly being blurred. What was seen as a man's job at one time came to be seen as a woman's job and now anyone's job today (e.g., telephone operator). Since these aspects of life are seen to vary in different cultures and to be changing at different rates the society and learning-bound nature of culture is acknowledged.

Many of the cultural and social differences in behavior patterns associated with the two genders, man and woman, have came to be accepted and recognized as societal constructs -notions or abstractions which carry with them certain expectations and classifications. *Man* in a technological Western society means different things than does man in a non-technological African society. *Woman* in both types of societies also brings to mind different things. It is particularly this cultural flexibility that is central to the arguments of writers like Michel Foucault (Foucault 1980). To Foucault gender, unlike sex, should be recognized and accepted as a fluid variable that shifts and changes in different contexts and times.[6]

For transsexuals and intersexuals the distinction between sex and gender, as presented here, can become central to their being. The values each group or individual transsexual or intersexual person assigns to sex and gender, however, might be quite different. It is also suggested that to psychologists, philosophers and

others it is also of benefit to clarify the differences between the two concepts. To best understand these distinctions one other set of definitions should first be made clear. These terms are related to the concept of *identity*.

Identity is a term that has usage in psychology but is also a term used in everyday conversation. Commonly, people 'identify" themselves as homosexual or see their 'identity" as heterosexual. Individuals may identify, recognize themselves, as transsexual or intersexed without being specific as to what the term means. This usage of the terms is in an affiliative sense. It is as if one might identify as a Conservative, a Unitarian or a mechanic.

The following terms are defined as some others and I use them. While they might be considered somewhat idiosyncratic, I find them useful (e.g., Diamond 1976; 1979; 1994; 1995) and so have others.

Sexual identity[7] speaks to the way one views him or her self as a male or female. This inner conviction of identification usually mirrors one's outward physical appearance and the typically sex-linked role one develops and prefers or society attempts to impose. *Gender identity* is recognition of the perceived social gender attributed to a person. Typically a male is perceived as a boy or a man where boy and man are social terms with associated cultural expectations attached. Similarly, a female is perceived as a girl or woman. The distinctions made between boy and girl and man and woman are of age and usually again represent differences in societal expectations that go along with increases in maturity.

Gender and *gender role* refers to society's idea of how boys or girls or men and women are expected to behave and should be treated. A display of gender, as with a gender role, represents a public manifestation of gender identity. It can be said that one is a sex and one does gender; that sex typically, but not always, represents what is between one's legs while gender represents what is between one's ears. A sex role usually involves the acting out of one's biological predisposition. In young males this is associated typically with their greater aggressive, combative, and competitive nature than is usual with young females. In young females their sex roles are usually manifest by nurturing and compromising behavior, less frequently seen in boys. These might actually better be called sex-typical (*male-typical*; *female-typical*) behaviors. *Gender* roles are those behaviors imposed overtly or covertly by society. As described by Gagnon and Simon (Gagnon and Simon 1973) gender roles are behaviors that can be considered "scripted" by society. Examples of this is how girls learn to keep their knees together or adjust their dresses and apply cosmetics while boys actively memorize the rules of sports and games. Gender has everything to do with the society, in which one lives and may or may not have much to do with biology (Gagnon and Simon 1973).

This usage and terminology presented is somewhat different from that used by John Money and Anke Ehrhardt (1972). These investigators do not use the term *sexual identity* and have generally conflated the meanings above under the terms *gender identity/role* and offer, in addition, their own definitions: "Gender identity is the private experience of gender role; and gender role is the public manifestation of gender identity . . .'gender identity' can be read to mean 'gender identity/role.

(Page 146)." But here again the terminology has not been consistent with that used by others. Stoller (1968), for example, called this inner realization of self-identity as a male or female "core gender identity."[8]

Intersexual Child

Let us see how these terms and concepts might involve a developing child.9 A mother of an 8-year-old chromosomal XY male with ambiguous genitalia said to me:

"My child has questions on her gender. Oddly enough, we have raised her as a complete female child, to date...she does not know of her condition. We thought best to wait, as a young child would never understand. ...Increasingly over the years she has said things like ' I'm not a girl...I'm a boy'...clothing desired is neutral...teachers' complaints (they are unaware) is that she is very tomboyish.... all her friends are boys. At home it is her brothers she hangs out with. And her strength...wow!"

The mother, at the child's birth, had been advised by her physician to raise the child as a girl due to its lack of a penis. This was a standard recommendation until just several years ago (Diamond and Sigmundson 1997a; b; Diamond 1998; Kipnis and Diamond 1998; Diamond 1999). The child's sex is male but it had an imposed gender of girl. It had been raised since birth as a girl. Obviously here is a case where sex and gender are not in agreement.

The child knows it is being raised as a girl and encouraged by its parents and physicians to live as one. The child recognizes it is being seen and reacted to as a social girl. It is, thus, aware of its (social) *gender* identity. Yet, although raised as a girl, the child manifests gender roles more typical of a boy. Further, despite its rearing and ignorance of its biology, the child has developed the (inner) *sexual* identity of a boy; i.e. the child feels at his core that he is a boy or should be a boy. This realization comes about by comparing his feelings, interests, attitudes and preferences with those of male and female peers and judging that his living as a boy is a better "fit" with the reality he sees and comes to know (Diamond, 1999).

The child has male chromosomes (is an intersexed male pseudohermaphrodite) with the imposed gender of a girl. When the child matures and becomes more aware of his history I predict he will likely come to live as a man or in as close to a neuter gender as possible. He will come to recognize that he is intersexed and might or might not openly identify as such.

The mother asked if I thought it would be better to allow the child to switch to live as a boy or proceed with the prepubertal feminizing hormone administration advised by her physicians. My advice was to allow the child to live as a boy and foster typical male development. Despite the genital ambiguity such management would allow gender and sex to be better matched than is presently so. Genital reconstruction can occur later if desired.

Potential Transsexuality

penile reconstruction and the buccal mucosa to create the urethra. Only one of these patients experienced complications associated with urethral necrosis, requiring a perineal urethrostomy. All patients reported good results in terms of the appearance of the penis.

Of the eight patients with ovotesticular DSD, three were raised as boys and five as girls. From a total of 24 patients with mixed gonadal dysgenesis (MGD), eight were raised as boys and 16 as girls. Although the reported incidence of dysphoria was relatively low for these groups, the small sample size prevents a more detailed evaluation. Many clinicians and researchers argue that patients with both dysgenesis and ovotesticular DSD should be raised as girls, especially if testicular tissue is removed. On the other hand, patients with these conditions who display a high degree of virilization (a relatively rare presentation) might develop well when raised as boys.[36,38] According to one study, 46,XY children who are affected by cloacal exstrophy, penile agenesis, or PAIS and demonstrate a high degree of virilization should be raised as boys.[16] However, only the study by Woelfle *et al.*[20] reported the incidence of gender dysphoria in patients initially raised as boys. In this study of 16 patients with CAH and a high level of virilization, three patients developed gender dysphoria.

Surgical treatment

Until 40 years ago, 46,XY patients with DSDs and gender dysphoria were commonly treated with a partial or total clitoridectomy. In 1973, Spence and Allen[39] proposed removal of the shaft and crura in order to preserve the gland, which is then attached to the pubic periosteum. A year later, Kumar *et al.*[40] suggested excision of the corpus cavernosum with preservation of the dorsal neurovascular bundles. Another widely utilized technique is subtunical resection of the cavernous tissue of the hypertrophied clitoris, keeping the neurovascular bundle of the glans intact. Following excision of the erectile tissue, the glans is attached to the pubic bone and partially covered with skin.[41]

As the risk of vaginal stenosis is significant when surgical reconstruction is performed in early infancy, one commonly used approach is to perform clitoroplasty and vaginoplasty at the start of puberty. The type of surgery chosen depends, fundamentally, on the position of the urogenital sinus. When this is positioned on the perineum, a simple cutback vaginoplasty can be performed.[10] A lower vaginoplasty is more appropriate for situations in which the urogenital sinus is distal to the sphincter; this procedure is performed using a perineal skin flap. In patients with higher degrees of virilization, vaginal repair is often performed. Hendren[42] described reconstruction of the introitus using a technique that involves traction of the lower vagina combined with the use of perineal skin flaps. When it is necessary to construct a neovagina, sigmoid colon is the first choice of material in many clinics as the incidence of stenosis is quite low, practically eliminating the need for vaginal dilation after surgery.[43]

Today, with a greater body of knowledge regarding clitoral innervation at our disposal, there is growing concern regarding the preservation of sensitivity during clitoroplasty—a factor that can influence the future development of psychosexual disorders.[44,45] Baskin *et al.*[46] evaluated the relationship between the dorsal nerve of the clitoris, female cavernous nerve, and vaginal plexus, and concluded that surgical treatment for patients with severe clitoral virilization should preserve erectile function and innervation of the clitoris. Of the 18 studies highlighted in this Review, only one considered whether clitoroplasty was performed to preserve innervation of the dorsal clitoris.[21]

Age of patient at surgery

In total, eight studies reported the age at which genitoplasty was performed;[17–22,26,27,29] two reported surgeries performed in the first few months of life,[17,26] four reported surgeries performed at age 1–3 years,[18,21,22,29] one reported surgery in patients age 3–7 years[20] and one referenced procedures performed during adolescence.[27] Although the majority of patients were operated on before the age of 3 years, the age at which surgery was performed did not seem to influence the onset of psychosexual disorders.

Studies performed in the 1950s suggested that sex reassignment surgery can be performed until age 18 months without causing psychological problems to the patient.[47] However, concepts have evolved over time and, in the 1990s, Reiner and collaborators[48] began to advocate a new treatment paradigm—known as 'full consent policy'—whereby an operation is only performed immediately following a diagnosis of gender dysphoria in cases of extreme necessity. This approach enables patients to make informed decisions regarding their gender when they feel they are ready to do so.[48] When a procedure is performed prematurely, complications—such as difficulty with penetration during sexual intercourse, anorgasmia, and problems with self-image—can arise as the child matures. Gender dysphoria is a major cause of emotional and behavioural disorders. Observational evidence has even suggested a link between dysphoria and increased risk of suicide, although further research is needed to confirm this association.

Data from the few studies that have asked patients about the best time to perform surgery suggest that the majority of patients with CAH prefer to have genitoplasty at a young age.[49–51] In a study of 41 patients with CAH, only 7 opined that the best time for genitoplasty would be during adolescence or adulthood, the majority thought that surgery was more appropriate as a toddler ($n = 9$) or during infancy ($n = 15$).[49] In one study, patients with CAH and high virilization scores who were raised as girls did not seem to express concern regarding their enlarged clitoris. The study author attributed this finding to the fact that these girls were 'too young' to be aware of an average size for the clitoris.[52] However, contradictory data from a study of adolescent surgical patients with CAIS suggests that the majority of patients are satisfied with delaying surgery until adolescence.[27] When questioned about the best period for performing surgical procedures, only two patients said that they would

Table 1 | Principle characteristics of patients with genital ambiguity

Study	Patients (*n*)	DSD	Total incidence of dysphoria	Dysphoria incidence according to DSD	Gender assignment		Treatment	
					With dysphoria	Without dysphoria	Surgical	Clinical
Fagerholm *et al.*[21]	24	CAH (*n*=16); CAIS (*n*=3); PAIS (*n*=5)	12.5% (*n*=3)	CAH (*n*=1); CAIS (*n*=1); PAIS (*n*=1)	All girls (*n*=3)	All girls (*n*=21)	Clitoroplasty (*n*=19); other surgery (*n*=5)	NR
Woelfle *et al.*[20]	16	All CAH (*n*=16)	18.75% (*n*=3)	All CAH (*n*=3)	All boys (*n*=3)	All boys (*n*=13)	Clitoroplasty and vaginoplasty (*n*=9); gonadectomy and hysterectomy (*n*=6); gonadectomy and testicular prosthesis (*n*=1)	Testosterone treatment during adolescence (*n*=16)
Reiner *et al.*[16]	84	CAH (*n*=11); cloacal exstrophy (*n*=45); PAIS/MGD (*n*=28)	38% (*n*=32)	Cloacal exstrophy (*n*=18); craniofacial anomalies (*n*=2); ovotesticular DSD (*n*=1); MGD (*n*=6); PAIS (*n*=4); penile agenesis (*n*=1)	All girls (*n*=32)	All boys (*n*=13)	NR	Prenatal androgen therapy (*n*=84)
Schoeber *et al.*[28]	10	CAH (*n*=1); CAIS (*n*=1); PAIS (*n*=3); ovotesticular DSD (*n*=1); 46,XY DSD (*n*=1); 46,XX DSD (*n*=1); unknown DSD (*n*=2)	20% (*n*=2)	CAH (*n*=1); 46,XY DSD (*n*=1)	All girls (*n*=2)	Girls (*n*=6); boys (*n*=2)	NR	NR
Berembaum *et al.*[22]	43	All CAH (*n*=43)	11.6% (*n*=5)	All CAH (*n*=5)	All girls (*n*=5)	All girls (*n*=38)	NR	Prenatal androgen therapy (*n*=43)
Zucker *et al.*[18]	31	All CAH (*n*=31)	16.2% (*n*=5)	All CAH (*n*=5)	All girls (*n*=5)	All girls (*n*=26)	Clitoroplasty (*n*=26); none (*n*=3); NR (*n*=2)	NR
Hines *et al.*[25]	25	All CAH (*n*=25)	20% (*n*=5)	All CAH (*n*=5)	All girls (*n*=5)	Girls (*n*=11); boys (*n*=9)	NR	NR
Slijper *et al.*[17]	59	CAH (*n*=18); CAIS (*n*=12); cloacal exstrophy (*n*=4); gonadal dysgenesis (*n*=9); PAIS (*n*=8); ovotesticular DSD (*n*=2); other DSD (*n*=6)	11.9% (*n*=7)	CAH (*n*=2); cloacal exstrophy (*n*=1); PAIS (*n*=1); ovotesticular DSD (*n*=1); other DSD (*n*=2)	All girls (*n*=7)	Girls (*n*=47); boys (*n*=5)	NR	NR
Cohen-Kettenis[31]	127	5α-RD2 deficiency (*n*=99); 17β-HSD3 deficiency (*n*=28)	61.4% (*n*=78)	5α-RD2 deficiency (*n*=62); 17β-HSD3 deficiency (*n*=16)	All girls (*n*=80)	All girls (*n*=47)	NR	NR
Meyer-Bahlburg *et al.*[26]	4	All CAH (*n*=4)	100% (*n*=4)	All CAH (*n*=4)	All girls (*n*=4)	–	Clitoroplasty (*n*=3); none (*n*=1)	Glucocorticoid treatment in infancy (*n*=2); none (*n*=2)
Meyer-Bahlburg *et al.*[51]	15	All CAH (*n*=15)	None	–	–	All girls (*n*=15)	NR	Prenatal dexamethasone therapy (*n*=15)
Lee *et al.*[19]	12	All CAH (*n*=12)	None	–	–	All boys (*n*=12)	Oophorectomy and testicular prosthesis (*n*=12)	Testosterone therapy (*n*=12)
Hurtig *et al.*[23]	9	All CAH (*n*=9)	None	–	–	All girls (*n*=9)	NR	Glucocorticoid treatment in infancy (*n*=9)
Greenfield *et al.*[30]	14	CAH (*n*=3); gonadal dysgenesis (*n*=4); PAIS (*n*=1); ovotesticular DSD (*n*=4); other DSD (*n*=2)	None	–	–	Girls (*n*=8); boys (*n*=6)	NR	NR

Table 1 (Cont.) | Principle characteristics of patients with genital ambiguity

Study	Patients (*n*)	DSD	Total incidence of dysphoria	Dysphoria incidence according to DSD	Gender assignment		Treatment	
					With dysphoria	Without dysphoria	Surgical	Clinical
Money *et al.*[29]	7	All CAH (*n*=7)	None	–	–	Girls (*n*=4); boys (*n*=3)	NR	Glucocorticoid treatment in infancy (*n*=7)
Slijper *et al.*[24]	41	All CAH (*n*=41)	None	–	–	Girls (*n*=22); boys (*n*=19)	NR	NR
Ehrhardt *et al.*[15]	15	All CAH (*n*=15)	None	–	–	Girls (*n*=8); boys (*n*=7)	NR	NR
Wisniewski *et al.*[27]	14	All CAH (*n*=14)	None	–	–	All girls (*n*=14)	Vaginoplasty (*n*=6); gonadectomy (*n*=14)	Oestrogen replacement (*n*=14)

Abbreviations: 5α-RD2, 5α-reductase 2; 17β-HSD3, 17β-hydroxysteroid dehydrogenase 3; CAH, congenital adrenal hyperplasia; CAIS, complete androgen insensitivity syndrome; DSD, disorder of sex development; MGD, mixed gonadal dysgenesis; NR, not reported; PAIS, partial androgen insensitivity syndrome.

have preferred to be operated on during childhood. The rest indicated that adolescence or adulthood is the best time for surgery, when a greater degree of patient participation in the gender definition process is possible.[27] However, the small sample size and lack of controls limit the conclusions that can be drawn from this study. Further studies are needed to assess the psychological effects of operating on children with CAH during, or even after, adolescence.

Nonsurgical treatment

Hormonal replacement at the start of puberty is important for the development of secondary sexual characteristics. It can be delivered via intramuscular injections of testosterone esters every 4 weeks. Alternatively, it can be administered via oral, subcutaneous, or transdermal routes.[53] Patients with 5α-reductase deficiencies are given dihydrotestosterone. This is administered in gel form and applied directly to the penis, increasing circulating hormone levels and penis size.[54] Patients with 46,XY DSDs, PAIS, or CAIS who have undergone a gonadectomy require oestrogen and progesterone replacement. As well as promoting secondary sexual development, this therapy also protects patients against osteoporosis.[53] Once feminization therapy has been completed, ovulation and pregnancy can be stimulated with the use of gonadotropin-releasing hormones (GnRHs).[55]

In many clinics, treatment is initiated during the pre-puberty period; however, some studies have suggested that it should begin during the neonatal period. There is some evidence to support the potential benefits of hormone replacement in the neonatal period for patients with congenital hypogonadotropic hypogonadism. Conventional GnRH therapy—commenced during puberty—seems to only partially correct genital abnormalities and defects in spermatogenesis, particularly in patients with severe virilization associated with cryptorchidism and micropenis. Neonatal treatment with gonadotropin—either alone or combined with follicle-stimulating hormone—has been associated with enhanced development of secondary sex characteristics, as well as increased testicular volume and testosterone levels.[55] Two ongoing studies have aimed to evaluate the results of administering prenatal dexamethasone treatment to pregnant women whose first child was diagnosed with classic CAH.[55,56] Although the preliminary results from these studies suggest that this approach is highly effective for preventing the formation of ambiguous genitalia, reports of delays to child development and cognitive deficiency are concerning and further studies are needed before this treatment can be safely recommended.

Given that gender determination for individuals with DSDs is influenced, not only by sex chromosomes, but also by associated behavioural issues, some experts have adopted a more conservative approach to treating gender dysphoria. In certain cases, a joint decision is made between the physician and the patient's parents to avoid indicating a gender during childhood. For these children, gender determination might be affected by social factors and both parents and children should participate in the decision to delay gender assignment.[4] The Research Group on Bioethics in DSD (based in Germany) published a paper that evaluated the importance of patient and parent participation in the sex assignment process, highlighting ethical concerns from the perspective of patients and their families.[57] There are clinicians who advocate raising these children as a third gender (neither masculine nor feminine, but intersex), although this approach has not been accepted by the majority.[58]

Regardless of treatment regimen, multidisciplinary teams should provide care and support to the patient and their families. Each patient should be informed regarding the various treatments options available to them and reassured that appropriate treatment can enable individuals with DSDs to lead a normal life. Parents should also be educated regarding the disorder, as they will have an important role in treatment decisions. Patients are

encouraged to have contact with adults who have dealt with similar problems as DSDs can result in feelings of shame and social isolation.[8]

Conclusions

In general, the incidence of gender dysphoria seems to be relatively low in patients with DSDs; eight studies (from a total of 18) observed no such cases.[14,15,19,23,24,27,29,30] In the remaining ten studies, the rate of dysphoria generally varied from 8.5–20%.[16–18,20–22,25,26,28,31] Although one paper reported a 38% incidence of dysphoria, this study included a substantial proportion of patients with severe conditions, such as cloacal exstrophy or penile agenesis.[16] Despite advances in genetic investigation and multidisciplinary care, there is still no consensus on the best treatment approach for gender dysphoria, particularly in relation to timing. The difficulties associated with systematically reviewing data from methodologically diverse studies are well known, but this topic presents a particular challenge. Different concepts of gender dysphoria exist, as well as different methods for diagnosis. It has been estimated that molecular diagnosis is performed in only 20% of patients with DSD and only about half of all 46,XY patients with DSDs have been reliably diagnosed from a genetic viewpoint.[8] Numerous questionnaires have been used to assess gender identity, including Zucker's Modified Questionnaire,[22] Sexual Behavior Assessment Schedule,[29] Gender Dysphoria Identification Questionnaire,[18] Rosenberg Self-Esteem Scale and Masculine Gender Identity Score,[19] and Bem Sex-Role Inventory,[23] as well as several questionnaires created specifically for DSD-associated gender dysphoria.[16,25,28,29] Another resource used for the diagnosis of dysphoria is the Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association.[16] However, as Heino Meyer-Bahlburg aptly noted, intersexuality is an exclusion criterion for using the DSM to classify dysphoria.[26]

In the studies that used Prader's scale, a lower incidence of dysphoria was observed in children with a high degree of virilization (Prader IV or V) when they were raised as boys.[14,15,19,20] This suggests that patients with a significant degree of masculinization and male gender assignment rarely experience psychosexual disorders, regardless of patient karyotype. Similar classifications for virilization should be incorporated into the methodology of future studies. Alternatively, the external masculinization score—which considers size of the phallus, labioscrotal fusion, the site of the gonads, and the location of the urethral meatus—should be utilized. Although the score does not serve as a clinical diagnosis, it has proven useful for prompting further investigation for DSDs in boys with undermasculinized genitalia.[59] Another rating system is Quigley's classification, which has the advantage of describing the involved anatomical abnormalities in more detail.[60] For example, level 4 of this classification system refers to patients with an intermediate phallic structure (between penis and clitoris), level 1 refers to patients with normal external male genitalia, and level 7 refers to patients with normal female genitalia. One point that was apparent throughout this review of the literature was the need for consistency regarding nomenclature. In 2005, a group of specialists met in Chicago to discuss all commonly used terms and definitions; they produced a set of guidelines known as the Chicago Consensus.[8] In 2009, a survey showed that the majority of European research groups have adopted these guidelines.[61] Increased global use of these definitions and diagnostic criteria could increase the reliability of future studies.

Review criteria

An extensive search was conducted of the PubMed, Medline, LILACS and Scielo databases, as well as the Cochrane Library, for English-language articles published between January 1968 and August 2011. The following search terms were used: "gender dysphoria", "disorders of sex development", "gender identity", "congenital adrenal hyperplasia", "virilization", "sexual orientation", and "genital ambiguity". Two researchers evaluated the articles; a third researcher acted as an arbitrator during the first stage of evaluation. Retrospective and prospective studies were included (with or without control groups). Initially, 228 studies were identified regarding gender dysphoria. After evaluating each work, 199 articles that did not reference gender dysphoria in patients with genital ambiguity were excluded. Among the remaining 29 studies, 11 were excluded that did not reference gender dysphoria among their outcomes. The final review concentrated on 18 studies; 17 articles were full-text papers and one was an abstract.

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Author contributions

F. Moraes researched the data for the article. P. Furtado and U. Barroso Jr wrote, discussed, edited and reviewed the manuscript. M. Toralles, L. O. Barros and R. Lago made substantial contributions towards discussions of the article and reviewed the manuscript prior to submission.

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SPECIAL SECTION: DSM-5: CLASSIFYING SEX

Classifying Intersex in DSM-5: Critical Reflections on Gender Dysphoria

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Abstract The new diagnosis of Gender Dysphoria (GD) in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013) defines intersex, renamed "Disorders of Sex Development" (DSD), as a specifier of GD. With this formulation, the status of intersex departs from prior editions, especially from the DSM-IV texts that defined intersex as an exclusion criterion for Gender Identity Disorder. Conversely, GD—with or without a DSD—can apply in the same manner to DSD and non-DSD individuals; it subsumes the physical condition under the mental "disorder." This conceptualization, I suggest, is unprecedented in the history of the DSM. In my view, it is the most significant change in the revised diagnosis, and it raises the question of the suitability of psychiatric diagnosis for individuals with intersex/DSD. Unfortunately, this fundamental question was not raised during the revision process. This article examines, historically and conceptually, the different terms provided for intersex/DSD in the DSM in order to capture the significance of the DSD specifier, and the reasons why the risk of stigma and misdiagnosis, I argue, is increased in DSM-5 compared to DSM-IV. The DSM-5 formulation is paradoxically at variance with the clinical literature, with intersex/DSD and transgender being conceived as incommensurable terms in their diagnostic and treatment aspects. In this light, the removal of intersex/DSD from the DSM would seem a better way to achieve the purpose behind the revised diagnosis, which was to reduce stigma and the risk of misdiagnosis, and to provide the persons concerned with healthcare that caters to their specific needs.

Keywords DSM-5 · Gender identity disorder · Gender incongruence · Gender dysphoria · Disorders of sex development · Intersexuality

Introduction

The clinical category of "intersex" defined as "physical abnormalities of the sex organs" was introduced in DSM-III in the context of the first formulations of psychosexual "disorders" in gender identity (American Psychiatric Association [APA], 1980, pp. 263–265). In Table 1, I offer a synopsis of the different terms provided for intersex/DSD in the successive DSM texts. The initial classification for gender identity "problems" included two specific diagnoses: Transsexualism for adolescents and adults (Transsexualism), and Gender Identity Disorder of Childhood (GIDC); and a residual diagnosis named Atypical Gender Identity Disorder (Atypical GID). In the DSM classification, residual categories were designed for clinical presentations in patients who did not meet all the criteria of a specific diagnosis, here Transsexualism and GIDC. DSM-III-R (APA, 1987) retained the specific diagnoses of Transsexualism and GIDC, removed Atypical GID, and introduced two new categories: Gender Identity Disorder of Adolescence or Adulthood, Nontranssexual Type (GIDAANT) and Gender Identity Disorder Not Otherwise Specified (GIDNOS).

In DSM-IV (APA, 1994) and DSM-IV-TR (APA, 2000), Transsexualism and GIDC were substituted by the generic category of Gender Identity Disorder (GID) with distinct criteria sets for the two age groups. The DSM-5 diagnosis of

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Gender Dysphoria (GD) is an overarching category that includes two criteria sets: one for Children (302.6), and one for Adolescents and Adults (302.85). GD also includes a DSD specifier for both age groups. Accordingly, the diagnosis comes in two "versions": with or without a DSD.

The changed status of intersex/DSD in DSM-5 has received little attention so far. It is the least documented of all revisions, and the reasons for this particular change remain unexplained in the "Memo Outlining Evidence for Change in Gender Identity Disorder in the DSM-5" (Zucker et al., 2013). It is even unclear whether or not the inclusion of a DSD specifier is meant to constitute a change. It is omitted in the appendix entitled "Highlights of Changes from DSM-IV to DSM-5" that mentions, however, the addition of a "posttransition specifier" for those adolescents and adults who have successfully transitioned (APA, 2013, pp. 814–815). This omission may suggest that the former is considered a minor change or no change at all.

This article offers a conceptual history of the overlooked new status of intersex/DSD in GD from a critical perspective inspired by feminist theory and the social studies of science and medicine. My discussion is based for the most part on the DSM literature produced during the fourth and fifth revisions, and focuses on how gender identity "disorder" experts conceptualized intersex/DSD in these contexts and beyond. I first discuss the various ways in which intersex/DSD was classified in the successive editions, from DSM-III to DSM-5. I highlight in this manner the unique features of the specifier option compared to earlier formulations, in particular in the DSM-IV texts. I then identify the historical turning points and the conceptual moves that account for these features. I here consider the DSM-5 reports, the revision recommendations, and the specific ways in which the longstanding but key notions of gender incongruence and gender dysphoria have been redefined (or not) so as to "naturalize" the full inclusion of intersex/DSD in the revised diagnosis, incorrectly assuming in the process that such a move is self-evident. At that point, I ask whether GD is an intersex condition. The short answer is no, because the healthcare issues particular to individuals with intersex/DSD are not taken into account. After explaining why, I finally consider how the risk of stigma and misdiagnosis and other classification problems are amplified in DSM-5 compared to DSM-IV, which eventually undermines the applicability of the diagnosis of GD to individuals with intersex/DSD.

Intersex/DSD in the DSM

Over the years, five distinct statuses have been defined for intersex relative to the various diagnostic categories for gender identity "problems": (1) exclusion; (2) inclusion via Axis III; (3) inclusion allowed in the absence of an exclusion clause; (4) inclusion in the residual category of GIDNOS; (5) finally, full inclusion as a specifier in DSM-5.

Exclusion

With the notable exceptions of DSM-III-R and DSM-5, the presence of intersex ruled out the specific diagnostic categories for "disorders" in gender identity. Criterion D ("Absence of physical intersex or genetic abnormality") for the diagnosis of Transsexualism in DSM-III, and Criterion C ("The disturbance is not concurrent with a physical condition") for the GID diagnosis in DSM-IV and DSM-IV-TR defined such exclusion clauses (APA, 1980, p. 264, 1994, p. 551, 2000, p. 581). Both DSM-IV and DSM-IV-TR added a further precision emphasizing the "normality" of the sex organs as the somatic condition of possibility for making a GID diagnosis: "Individuals with Gender Identity Disorder have normal genitalia (in contrast to the ambiguous genitalia or hypogonadism [underfunctioning testes or ovaries] found in physical intersex conditions)" (APA, 1994, p. 548, 2000, p. 579).

Inclusion via Axis III

The possibility of diagnosing intersex individuals—children, adolescents, and adults—with a gender identity "disorder" existed since DSM-III. The relevant diagnoses were GIDC in DSM-III and DSM-III-R, as well as Transsexualism in DSM-III-R (APA, 1980, p. 265, 1987, pp. 73–74).[1] Strictly speaking, the specific (not residual) diagnoses of GIDC in DSM-III and DSM-III-R and of Transsexualism in DSM-III-R did not include individuals with intersex. But the "physical disorder" could be linked to a psychiatric diagnosis (coded on Axis I), provided that the clinician resorted to another "dimension" in the DSM classification system. To be more precise, and as indicated in the supporting texts, "the physical disorder should be noted on Axis III" (APA, 1980, p. 265, 1987, p. 73), which described medical/physical conditions relevant in diagnosing and treating a psychiatric disorder.[2]

Inclusion in the Absence of an Exclusion Clause and in the GIDNOS Category

DSM-III and DSM-III-R also comprised a few residual categories that made no mention of intersex, and thus did not formally exclude but rather permitted the presence of the "physical disorder." These categories were: Atypical GID in DSM-III; GIDAANT and GIDNOS in DSM-III-R. In the DSM-IV editions, the supporting texts would make explicit that the GIDNOS

[1] The reason why the initial formulation in DSM-III excluded the presence of intersex, while the same diagnostic label permitted it in the revised edition remains obscure (see Meyer-Bahlburg, 1994, p. 23).

[2] The (five) axes and all the Not Otherwise Specified (NOS) categories were eliminated from DSM-5.

Table 1 Intersex/DSD in the DSM

DSM	(Sub-)classes	Diagnostic categories	Terms provided for intersex/DSD
DSM-III (APA, 1980)	Gender identity disorders In: psychosexual disorders	Transsexualism [adolescents and adults]	Criterion D: "Absence of physical intersex or genetic abnormality." (p. 264)
		Gender identity disorder of childhood (GIDC)	"Physical abnormalities of the sex organs are rarely associated with [GID]; when they are present, the physical disorder should be noted on Axis III." (p. 265)
		Atypical gender identity disorder	"This is a residual category for coding disorders in gender identity that are not classifiable as a specific Gender Identity Disorder." (p. 266)
DSM-III-R (APA, 1987)	Disorders usually first evident in infancy, childhood, or adolescence	Transsexualism [adolescents and adults]	"In the rare cases in which physical intersexuality or a genetic abnormality is present, such a condition should be noted on Axis III." (p. 74)
		Gender identity disorder of childhood (GIDC)	"Physical abnormalities of the sex organs are rarely associated with [GIDC]; when they are present, the physical disorder should be noted on Axis III." (p. 73)
		Gender identity disorder of adolescence or adulthood, nontranssexual type (GIDAANT)	[No mention]
		Gender identity disorder not otherwise specified (GIDNOS)	[Intersex not listed in the examples]
DSM-IV (APA, 1994) and DSM-IV-TR (APA, 2000)	Gender identity disorders In: sexual and gender identity disorders	Gender Identity Disorder -GID in childhood -GID in adolescents and adults	Criterion C. "The disturbance is not concurrent with a physical condition." (APA, 1994, p. 551, 2000, p. 581)
		Gender identity disorder not otherwise specified (GIDNOS)	"Examples include: 1. Intersex conditions (e.g., androgen insensitivity syndrome or congenital adrenal hyperplasia) and accompanying gender dysphoria." (APA, 1994, p. 552)
			The DSM-IV-TR phrase is identical except for the addition of "partial" to "androgen insensitivity syndrome" (APA, 2000, p. 558)
DSM-5 (APA, 2013)	Gender dysphoria	Gender dysphoria in children Gender dysphoria in adolescents and adults	"Specify if: With a disorder of sex development [...]." (p. 452, p. 453)
		Other specified gender dysphoria	[No mention]
		Unspecified gender dysphoria	[No mention]

category could "be used for individuals who have a gender identity problem with a concurrent congenital intersex condition" (APA, 1994, p. 550, 2000, pp. 580–581). By definition, i.e., by virtue of the exclusion criterion C ("The disturbance is not concurrent with a physical condition"), individuals with intersex could not be diagnosed otherwise.

The DSM-5 categories of Other Specified Gender Dysphoria and Unspecified Gender Dysphoria resemble, in part, the former GIDNOS category. They can be considered residual categories (indeed, residual categories of the GIDNOS residual category, see Footnote 2), since they also apply when the clinical presentations "do not meet the full criteria for gender dysphoria" (APA, 2013, p. 459). But they are distinct from GIDNOS, as they are less a function of the phenomenology of the "disorder" itself in a patient than of the clinician's latitude to indicate (Other Specified GD) or not (Unspecified GD) to her peers or healthcare providers the reasons why a patient does not meet the full criteria.

Full Inclusion as a DSD Specifier

Compared to prior editions, the DSM-5 formulation is unprecedented with respect to intersex. The new diagnosis of Gender Dysphoria (GD)—with and without a DSD—involves two major changes. The first is the change in name from intersex to DSD in reference to the new medical terminology adopted in 2006 in the "Consensus Statement on Management of Intersex Disorders" (Hughes, Houk, Ahmed, & Lee, 2006; Lee, Houk, Ahmed, & Hughes, 2006). Prior to the Consensus Statement and to DSM-5, the expressions "intersex/intersex conditions" or "intersexuality," often described as "physical" or "somatic,"

were used in the DSM. But the lexical change in DSM-5 from the category of intersex to the DSD terminology adopted in the Consensus Statement is not just an update in nomenclature as we shall see in more detail below.

The second change concerns the new status of intersex as a DSD specifier (in other words, a subcategory or subtype) of the overarching diagnosis of GD. The specifier—with or without a DSD—is meant to convey additional clinical information about the presentation, course, possible special features, etc. of GD in patients who have a DSD and those who have not. But the DSD specifier does not simply provide the clinician with a more specific description of GD, other things being equal.

Prior to DSM-5, as we have seen, the inclusion of intersex in the various diagnostic categories for gender identity "problems" was restricted to certain categories and only possible under particular conditions. Residual diagnoses permitted the presence of intersex in the absence of any precision in this regard (e.g., Atypical GID in DSM-III; GIDNOS in DSM-III-R), although it was sometimes more explicit (e.g., intersex is among the examples cited for GIDNOS in the DSM-IV texts). In and by themselves, specific (as opposed to residual) gender diagnoses were never applicable to intersex. Some of them could apply but only with recourse to Axis III (e.g., GIDC in the DSM-III and DSM-III-R; Transsexualism in DSM-III-R). Most importantly, the first formulation of Transsexualism in DSM-III and of GID in the DSM-IV texts contained an exclusion criterion that ruled out the diagnosis in the presence of intersex.

In DSM-5, the former restrictions or particular conditions under which intersex compared to non-intersex individuals could be diagnosed with a "disorder" in gender identity no longer exist. Further, and I will return to this below, the rationale behind the formal exclusion of intersex from the predecessor of GD, the GID diagnosis, was that the gender identity "problems" of intersex (compared to non-intersex) individuals were not psychiatric conditions. Conversely, physical intersex has become an integral part of a mental "disorder" in DSM-5: with the DSD specifier, the new diagnosis of GD is an overarching category designed to apply directly and equally to individuals with and without a DSD. This formulation, I suggest, is unique and radically new—newer than the much-publicized notions of gender incongruence and gender dysphoria—because the inclusion of a DSD specifier amounts to subsume the physical condition under the mental "disorder." How come?

The Fifth Revision: Historic Points and Key Concepts

The revision process of the controversial GID diagnosis generated various reactions, criticisms, and alternative recommendations by health professionals, transgender associations, and the lesbian, gay, bisexual, and transgender [LGBT] community at large (De Cuypere, Knudson, & Bockting, 2010; Knudson, De Cuypere, & Bockting, 2010a, b; Vance et al., 2010). According to the GID Subworkgroup, the new diagnosis of GD can be considered a compromise guided by two major but contradictory concerns: the concern to lessen the stigma attached to a psychiatric label for transpeople, which, for some, meant removing the diagnosis from the DSM; and the concern to defend access to healthcare and insurance coverage for surgical and hormonal treatments, especially for those individuals with lesser economic means, which required retaining the diagnosis (Drescher, 2010, 2013; Drescher, Cohen-Kettenis, & Winter, 2012; Meyer-Bahlburg, 2010; see also Karasic & Drescher, 2005). Whether the new formulation is the best answer to this dilemma, and whether it will make a difference for transpeople, or whether it is "just semantics," are questions beyond the scope of this article.

In comparison, the lack of debate about issues of stigma and healthcare issues for people with intersex/DSD is striking: the question of whether intersex should be removed from the DSM or retained in the revised diagnosis or whether intersex conditions should be renamed and reconceptualized in this context as "variations" instead of "disorders" of sex development,[3] and, most importantly, whether the DSD specifier option would be beneficial or not to the persons concerned was addressed nowhere. With the relative exception of Meyer-Bahlburg (2010), the reports published by the GID Subworkgroup say very little about intersex/DSD in general or about the related diagnostic category and criteria issues in particular (Cohen-Kettenis & Pfäfflin, 2010; Drescher, 2010[4]; Zucker, 2010[5]).

[3] As suggested, for example, by Diamond and Beh (2006) in response to the adoption of the DSD label in the Consensus Statement. On this issue, see also Feder and Karkazis (2008), Hinkle (2006), and Reis (2007).

[4] Drescher (2010) mentioned in passing corrective surgeries on intersex infants as an instance of the medical enforcement of gender binaries in Western societies. However, the implications of such surgeries in terms of mental healthcare or the GID revision were not discussed.

[5] It should be noted that the "Proposed Revision to the DSM-IV Diagnostic Criteria for Gender Identity Disorder in Children" by Zucker (2010) is the only DSM-5 report that proposed retaining the exclusion criterion for intersex, but the reason for this specific recommendation is not discussed. However, Zucker's view on the DSD specifier option was that "debating the DSD was secondary to debating whether or not to delete GID from the DSM-5 in its entirety." He further explained: "I was not prepared to argue for or against a DSD specifier until the subworkgroup made a decision about the larger issue. Personally, I have never had a strong feeling against its inclusion in one form or the other because I have seen many DSD children (and some adolescents or adults) with gender dysphoria who, in many ways, are indistinguishable in phenomenology from non-DSD-children with GD. So, I disagree strongly with your [the author] assertion about misdiagnosis. DSM is largely agnostic regarding etiology: a rose is a rose, regardless of what causes a plant to be a rose." (K. J. Zucker, personal communication, August 30, 2014). On the DSM's so-called agnosticism or "atheoretical" stance towards etiology, see my discussion about a non-personal etiological factor for GD (APA, 2013, p. 451) and Posttraumatic Stress Disorder (PTSD).

In the rare cases where intersex/DSD issues were more (Meyer-Bahlburg, 2010) or less (Cohen-Kettenis & Pfäfflin, 2010) discussed, they were collapsed into considerations about "gender identity variants" (from typical masculinity or femininity) or GID *without* intersex/DSD. A telling example of this can be found in the report by Cohen-Kettenis and Pfäfflin (2010) on "The DSM Diagnostic Criteria for Gender Identity Disorder in Adolescents and Adults." The authors' single concern about intersex/DSD is "the potential risk [for transpeople] of unnecessary physically invasive examinations to 'rule out' intersex conditions if the [exclusion] C criterion remain[ed] part of the diagnosis" (p. 503). Such risk should definitely be prevented, but it could have also been prevented with the removal of intersex/DSD from DSM-5. This alternative to the DSD specifier was not discussed. The risk of further stigmatizing intersex/DSD individuals with a psychiatric diagnosis could have been addressed had exclusion criterion C been removed and replaced by the specifier option in the revised diagnosis. This was not discussed either.

The report by Meyer-Bahlburg (2010) offers another, more elaborate example of the same kind of problem. Meyer-Bahlburg is a psychologist and one of the leading experts in the area of intersex/DSD. He has been involved in the successive revisions of the DSM since DSM-III-R (see Meyer-Bahlburg, 1994, p. 23). As a member of the Subcommittee on GID during the DSM-IV revision process, he authored the report on "Intersexuality and the Diagnosis of Gender Identity Disorder," which argued for the exclusion of intersex from the GID diagnosis (Meyer-Bahlburg, 1994). I will discuss this report in more detail below. Since then, Meyer-Bahlburg has been defending this consistent position for more then 20 years (see Meyer-Bahlburg, 2008, 2009). The only exception, it seems, is his report on "gender identity variants" for the DSM-5 revision (Meyer-Bahlburg, 2010). For all these reasons, his reference publications and expert positions are of special interest for my overall discussion.

DSD as a Subtype of a Special Category for "Gender Identity Variants" Named Gender Incongruence

To return to the report by Meyer-Bahlburg (2010), it is noteworthy that DSD issues are not discussed at length (pp. 464–466) or per se, but as examples for a larger argument about the "dilemmas in conceptualizing gender identity variants as psychiatric conditions" (see the subtitle of his report). The dilemma arising from the DSD examples is this: is gender change initiated by individuals with a DSD better conceived of as a "mental disorder" (to be diagnosed with the GIDNOS category) or, rather, as a "correction" of the (wrong) gender assignment at birth (pp. 464–465)?[6] The DSD examples and the related classification problem did not raise the question of removing intersex from the DSM. They served to reconsider the stigmatizing GID definition of gender change in individuals *without* a DSD in light of the apparently less stigmatizing notions of "gender correction" and "gender identity variants." This argument depends on a transgender-centric conceptualization of "gender identity variants," in which DSD are defined as simple variations on this theme.

As a result, and among the various options Meyer-Bahlburg (2010) considered for the revised diagnosis, he recommended the creation of "a special category for gender identity variants" named Gender Incongruence, where "[i]ndividuals with Gender Incongruence associated with a somatic DSD could be classified as a subtype" (p. 471). The report gave no particular reason why the proposed revision should change the DSM-IV exclusion criterion for intersex to an inclusive one and, further, include intersex/DSD as a subtype in the revised diagnosis as if that were self-evident (pp. 464–466). It is not. Yet, the new diagnosis, renamed GD instead of Gender Incongruence, includes, all the same, the suggestion for a DSD subtype—a specifier in the final text. In contrast, sexual attraction as a long-standing specifier (formerly sexual orientation as a subtype) of gender identity "problems" was removed from DSM-5.

From Gender Incongruence to Gender Dysphoria

Although Gender Incongruence was not retained as a diagnostic name, it is a key notion of GD. The notion itself is not new and can be traced back to the initial classification of psychosexual "disorders" in gender identity. Since DSM-III, the core feature of gender identity "problems" has been defined as an "incongruence between anatomic sex ["assigned sex" since DSM-III-R; "assigned gender" in DSM-5[7]] and gender identity" (APA, 1980, p. 261, 1987, p. 71, 2013, p. 452). Two kinds of "deviations" from gender "norms" have always been required to diagnose an incongruence: cross-gender identification and cross-gender role/-play/behaviors. In DSM-5, these diagnostic criteria are subsumed under the same (A) set of criteria (see Table 2). Four of these—one in Children (A.1.) and three in Adolescents and Adults (A.4., A.5., and A.6.)—acknowledge that transgender identifications are not limited to the "other gender" but can include "some alternative gender [to either masculine or feminine] different from one's

[6] Gender change initiated by intersex individuals has been documented before DSM-III, i.e., before the first formulation of psychosexual "disorders" in gender identity. At the time, these changes were, therefore, not defined as mental "disorders," and medical treatment for intersex individuals desiring to change their sex did not depend on a psychiatric diagnosis. Money (1969) considered that such cases were partly due to the parents' ambivalence about the sex assigned to their child at birth, while Stoller (1964) postulated a "silent," "congenital, perhaps inherited, biological force" to account for these situations (pp. 224, 225).

[7] In fact, "assigned gender" in DSM-5 means "the sex recorded on the birth certificate." I will return to this below (see also Lawrence, 2014, p. 1264).

Table 2 Gender dysphoria

Diagnostic criteria
Gender dysphoria in children
A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion A1)
1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender)
2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing
3. A strong preference for cross-gender roles in make-believe play or fantasy play
4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender
5. A strong preference for playmates of the other gender
6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities
7. A strong dislike of one's sexual anatomy
8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender
B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning
Specify if:
With a disorder of sex development (e.g., a congenital adrenogenital disorder such as [...] congenital adrenal hyperplasia or [...] androgen insensitivity syndrome)
Coding note: Code the disorder of sex development as well as gender dysphoria
Gender dysphoria in adolescents and adults
A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:
1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
3. A strong desire for the primary and/or secondary sex characteristics of the other gender
4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender)
5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender)
6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender)
B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning
Specify if:
With a disorder of sex development (e.g., a congenital adrenogenital disorder such as [...] congenital adrenal hyperplasia or [...] androgen insensitivity syndrome)
Coding note: Code the disorder of sex development as well as gender dysphoria
Specify if:
Posttransition: The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen—namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female)

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assigned gender" (APA, 2013, p. 452). This is consistent with the non-dichotomous concept of "gender identity variants" promoted in the more recent clinical literature (e.g., Meyer-Bahlburg, 2010).

Initially, gender incongruence per se was considered a psychiatric condition. Formally, this has not been the case since DSM-IV, although it is DSM-5 which has been lauded for this progressive change. DSM-IV is well known for having tried to formalize a (sometimes controversial) definition of "mental disorders" as a function of their "clinical significance," so as to reduce false positive diagnoses. This new and obligatory criterion redefined gender incongruence as a clinical problem if, and only if, the manifestations were concurrent with "clinically significant distress or impairment in social, occupational, or other important areas of functioning" (Criterion D in DSM-IV and DSM-IV-TR, APA, 1994, p. 551, 2000, p. 581; Criterion B in DSM-5, APA, 2013, pp. 452–453). To use the DSM-5 terminology, gender

incongruence must be accompanied with gender dysphoria.

Gender Incongruence was the diagnostic name initially recommended for the GID revision,[8] with the good intention of depathologizing gender identity variance (see again, e.g., Meyer-Bahlburg, 2010). Unintentionally, however, it increased the risk of (over-) diagnosing individuals who experience gender incongruence, but live well with it and are thus not gender dysphoric. For this reason, the World Professional Association for Transgender Health (WPATH) in particular argued instead for a name change to Gender Dysphoria (De Cuypere et al., 2010, pp. 121–122; see also Drescher et al., 2012; Zucker et al., 2013). The very name of the DSM-5 diagnosis reflects the shift in focus from gender incongruence to the decisive criterion (B) for clinical significance, i.e., to gender dysphoria (APA, 2013, pp. 452–453).

Gender Dysphoria in the 1970s: A "Liberal" Concept

The key notion of gender dysphoria in DSM-5 and the diagnosis itself, I suggest, are conceptually very similar to the initial formulation elaborated by Fisk (1974; see also Fisk, 1973) at the beginning of the 1970s. The diagnostic term of gender dysphoria was designed as a new concept (rather than just an umbrella term) to minimize the relevance of defining a differential diagnosis between four conditions that "many authorities on gender aberrations" considered at the time to be mutually exclusive: transsexualism, transvestism (cross-dressing), homosexuality *and* "biologic intersex" (Fisk, 1974, p. 387). Clinical attention should be refocused instead, Fisk argued, on the "high level of dysphoria concerning [one's] gender of assignment or rearing" (p. 388). This distinctive symptom defined the valid criterion for approving sex change operations (pp. 386, 389).

The therapeutic agenda behind the newly forged concept was to "liberaliz[e] indications for total gender reorientation"; in other words, to "broaden" the "indications for surgical sex conversion therapy" (pp. 386–389). This agenda should not be romanticized in retrospect. At the time, it was stated explicitly by the "liberal" clinicians in response to the fact that the patients expressing the wish for hormonal and surgical treatments presented themselves as "virtual textbook cases of classical transsexualism" as defined by Benjamin (1966) in opposition to transvestism and homosexuality (Fisk, 1974, p. 388). The introduction of the concept of gender dysphoria was thus fueled with the concern (and the suspicion) that trans narratives were not "authentic" but "rehearsed."

The pro-sex-change-surgeries agenda was also a professional one. The "liberal" clinicians sought to promote a surgical and (neuro)endocrinological behaviorist treatment plan for gender identity "problems," in a context where physical treatments for transsexualism were made possible by available technologies of bodily transformation, and increasingly desired by gender dysphoric individuals. Yet, these treatments were still highly controversial in the U.S. compared to Europe, not to say opposed by the majority of their colleagues—mostly by psychoanalysts (p. 390; see also Green & Money, 1969; for historical discussion, see Hausmann, 1995; Meyerowitz, 2002). The therapeutic and professional agendas were mutually reinforcing. The promoted "liberalization" of indications for sex change operations was accompanied by the "liberal" clinicians' self-promotion as operation gatekeepers—a "mandatory period of trial cross-living" was requested for 12–18 months—and as medical chaperons for post-operative (mostly male-to-female) individuals in "gender rehabilitation" programs, including "grooming clinics" (Fisk, 1974, p. 389).

Gender Dysphoria Against Gender Identity Disorder

Since the 1970s, one diagnostic feature of gender dysphoria has become more strongly emphasized: the "wish for sex reassignment" expressed by gender dysphoric individuals. Such a wish was an integral part of the initial symptomatology, but it has gained an increased salience over the years. Some gender historians have even argued that it came to function as the decisive criterion for assessing the severity of gender dysphoria (e.g., Hausmann, 1995, pp. 126–127). The following quote drawn from a reference textbook documents this point:

> The diagnostic label *gender dysphoric* is much broader than *transsexual*. This term is the only one available to refer to the whole gamut of individuals, who at one time or another, experience sufficient discomfort with their biological sex to form the wish for sex reassignment. (Steiner, Blanchard, & Zucker, 1985, p. 5, emphasis in original).

In the DSM, however, it must be underscored that the various categories for gender identity "problems" have never formalized the expressed wish for sex reassignment as a diagnostic criterion per se for gender dysphoria, even less as a valid criterion for approving sex reassignment surgeries. Rather, the notion of gender dysphoria was used along with the DSM taxonomy, sometimes as shorthand for the B Criterion of the GID diagnosis, i.e., "Persistent discomfort with one's assigned sex or sense of inappropriateness in that gender role (often referred to as 'gender dysphoria')" (Meyer-Bahlburg, 1994, p. 25). During the DSM-IV revision, the Subcommittee on GID even expressed "the desire to *uncouple* the clinical diagnosis of gender dysphoria from criteria for approving patients for sex reassignment surgeries (SRS)" (Bradley et al., 1991, p. 338, emphasis added).

Gender dysphoria is certainly not a diagnostic term among others in and outside the DSM. I see two main reasons why it could be mobilized effectively against the GID diagnosis as

[8] It remains the proposed name in the draft for the forthcoming 11th revision of the *International Classification of Diseases* by the World Health Organization.

an alternative concept during the fifth revision. First, gender dysphoria has been the least disputed term in use among DSM experts on GID, transgender health professionals, and the various actors involved over the last decades.[9] Second, as a consensual term, gender dysphoria opened up the possibility of reversing the change effected in DSM-IV; in other words, of tentatively re-coupling what had been un-coupled in the context of the fourth revision, i.e., the clinical diagnosis and the approval for sex reassignment surgeries. As already mentioned, the two were coupled in the initial concept with the explicit purpose of broadening the indications for such surgeries (Fisk, 1974); further, gender dysphoria also defined the valid criterion for approving such sex change operations and predict their success (p. 387).

I leave it to the prospective clients to tell us whether the new diagnosis of GD is more or less "liberal" than the initial concept. But it should be underscored that the supporting text relates a person's suffering from gender dysphoria to a non-personal etiological factor despite the self-proclaimed atheoretical stance since DSM-III: "Although not all individuals will experience distress as a result of such incongruence, many are distressed if the desired physical interventions by means of hormones and/or surgery are not available" (APA, 2013, p. 451). This statement has no equivalent in prior editions. If we push the reasoning to its logical conclusion, this means that the conventional relation between diagnosis and treatment is overturned in DSM-5: the problem of the non-access to the available hormonal and surgical treatment is logically—not to say etiologically—prior to the gender dysphoria expressed by a client and diagnosed by the clinician (but not the gender incongruence, which is no longer a psychiatric condition per se). The practical implication of this is then to facilitate access to such treatments when they are desired.

Intersex/DSD as a Specifier of Gender Dysphoria

According to Hausmann (1995, note 69, p. 227), the diagnostic term of gender dysphoria as defined by Steiner et al. (1985, p. 5; quoted above) "does not include intersexual subjects." If this observation is correct, it would point to a conceptual change from the initial formulation, where intersex was relevant to thinking about gender dysphoria. From a clinical perspective centered on gender dysphoria (instead of differential diagnosis), as we have seen, intersex was not considered differently from transsexualism, transvestism, and homosexuality although Fisk (1974) admitted the need for the clinician to be aware of the physical condition:

> While I would agree that the elucidation of biologic intersex is an essential prerequisite to the treatment of gender disorders, I feel rather strongly (given the experience of the Stanford University gender dysphoria program) that the differential diagnosis aimed at clearly identifying a subgroup of patients termed transsexuals is in many instances a rather non-productive effort. (p. 387).

It seems to me that the idea that the categories of intersex and gender dysphoria have departed from each other over time needs to be qualified. It is rather contradicted by the fact that gender dysphoria has been explicitly used since DSM-IV as a diagnostic term (although not a category) to refer to gender identity "disorders" in the presence of intersex. Indeed, the item "Intersex conditions [...] and accompanying gender dysphoria" was listed among the examples for GIDNOS (APA, 1994, p. 552, 2000, p. 582). Obviously, individuals with intersex could already be diagnosed with gender dysphoria prior to the DSM-5 diagnosis of GD. However, and this is a crucial difference, the term applied precisely only because the physical condition was an exclusion criterion that ruled out the GID diagnosis. For this reason, one could argue that gender dysphoria and GID (rather than intersex as suggested by Hausmann, 1995) were mutually exclusive diagnostic terms relative to intersex in the DSM-IV texts.

The changed status of intersex/DSD from an exclusion criterion to a specifier in DSM-5 does not simply derive from the replacement of GID by a diagnosis named Gender Dysphoria. As previously discussed, GD with a DSD specifier follows the recommendation made by Meyer-Bahlburg (2010) to include DSD as a subtype of a category named Gender Incongruence. However, in addition, I suggest here that intersex was retained in the DSM and came to be conceptualized as a specifier of a mental "disorder" at a particular moment in the history of gender identity "problems": when the controversial GID diagnosis exits the DSM, disorders of sex development enter. This is just one of the many paradoxes that undermine the relevance of the revised diagnosis for individuals with intersex/DSD.

Is Gender Dysphoria an Intersex Condition?

In February 2010, Organization Intersex International (OII) Australia and OII Aotearoa (New Zealand) addressed a position statement to the APA and WPATH to oppose the proposed revisions for DSM-5 and the seventh revision of the Standards of Care (SOC) that define treatment recommendations for transpeople respectively.[10] According to OII, the

[9] See the Harry Benjamin International Gender Dysphoria Association founded in 1979, now known as the WPATH; the "Interim Report of the DSM-IV Subcommittee on Gender Identity Disorders" (Bradley et al., 1991; Money 1994); the reports by the DSM-5 GID subworkgroup (Cohen-Kettenis & Pfäfflin, 2010; Drescher, 2010; Meyer-Bahlburg, 2010; Zucker, 2010); the "Response of the [WPATH] to the Proposed DSM-5 Criteria for Gender Incongruence" (De Cuypere et al., 2010), etc.

[10] For the initial February 2010 position statement, see https://oii.org.au/6576/organisation-intersex-international-position-statement-dsmv-draft-february-2010/. The submission was updated in June 2012 (Morgan, Wilson, & O'Brien, 2012).

revisions do not apply to intersex people; they are misconceived and even detrimental to them:

> OII Australia and OII Aotearoa have significant concerns about the pathologisation and diagnosis as mentally disordered of intersex people. [...] intersex people are often in a situation where their gender presentation at time of diagnosis with a mental disorder in accordance with the DSM is iatrogenic—it arises from medical treatment. It is [...] essential that the iatrogenic nature of gender-related distress in intersex people is acknowledged. In cases of iatrogenic gender presentation, it is insulting and damaging for people who have been made to more closely conform to an arbitrary binary gender to be told they have a psychiatric disorder or condition if they reject that assignment. (Morgan et al., 2012, pp. 5, 11)[11]

The objection made by OII in the above quote about the iatrogenic nature of gender dysphoria in intersex people points to a crucial difference between individuals with and without intersex/DSD relative to cosmetic genital surgeries and hormone therapy. Medical treatments are imposed—i.e., carried out without the child's consent[12]—upon the first group to "normalize" the appearance of the "ambiguous" genitalia at birth or during early infancy according to the treatment plan defined in the 1950s by Money and colleagues (Money, Hampson, & Hampson, 1955b; for critical discussions, see, e.g., Fausto-Sterling, 2000; Dreger 1999; Karkazis, 2008; Kessler, 1990, 1998; Kraus, Perrin, Rey, Gosselin, & Guillot, 2008; Swiss National Advisory Commission on Biomedical Ethics, 2012). No such treatments are imposed upon individuals in the second group, although they can sometimes express a wish for such treatments when they grow up, but the timing (non-consensual versus consensual) and purpose ("fixing sex" or transitioning) of the treatments are very different, not to say opposite. Whether some individuals with intersex/DSD want to access the same treatments to change (back or "correct" as some would argue) their gender at an older age, and whether some transpeople just want therapy but no physical treatment, does not disprove this fundamental difference in the clinical management of the two conditions.

This contrasting situation is reflected in their respective activist agendas. Trans activists demand (more open) access to hormone substitution therapy and sex change operations when they are desired by the persons concerned. On the contrary, the central focus of intersex activism has always been to put an end to non-consensual medical treatments, in particular early genital surgeries.[13] In this regard, the "Consensus Statement on the Management of Intersex Disorders" (Hughes et al., 2006; Lee et al., 2006) is a major disappointment: the "existing consensus recommendations are uncomfortably nonspecific" (Byne et al., 2012, p. 789[14]) and, in fact, not always very different from Money's treatment plan, especially concerning the opportunity and timing of genital surgery.[15] This practice is continued and remains one of the most contentious issues from the perspective of the persons concerned and biomedical ethics (see, e.g., Karkazis, 2006; Swiss National Advisory Commission on Biomedical Ethics, 2012).

The Irreducible Difference Between Consensual and Non-consensual Treatments

The possibility that gender dysphoria in intersex people has something to do with the medical treatments that continue to be routinely imposed on them as newborns or children to "fix" the anatomical problem is conveniently bracketed in DSM-5. This is all the more paradoxical, one could argue, since the new diagnosis clearly indicates a non-personal etiological factor for gender dysphoria in *non*-intersex/DSD individuals: as we have seen, gender dysphoria is said to result in many cases from the non-access to the desired medical treatments (APA, 2013, p. 451). The clinical reasoning is thus asymmetrical here: there is no logical reason why the same medical treatments could not generate clinically significant distress and impairment, sometimes because these treatments are wanted and not available (gender dysphoria), sometimes because they were initially not wanted but imposed at birth or during early infancy ("iatrogenic" gender dysphoria). The exception would be if one erases the irreducible difference between consensual and non-consensual medical treatments. The DSM-5 text is rather convoluted on this issue:

> Most individuals with a disorder of sex development who develop gender dysphoria have already come to medical attention at an early age. For many, starting at birth, issues of gender assignment were raised by physicians and parents. Moreover, as infertility is quite common for this group, physicians are more willing to perform cross sex-hormone treatments and genital surgery before adulthood. Disorders of sex development in general are frequently associated with gender-atypical behavior starting in early childhood. However, in the majority of cases, this

[11] For an earlier activist statement about the reasons why GID was not an intersex condition either, see Koyama (n.d.).

[12] Technically, "assent" for minors. Ford (2001) discusses "The Fiction of Legal Parental Consent to Genital-Normalizing Surgery on Intersexed Infants."

[13] See the agenda of the most influential intersex association over the last 2 decades (1993–2008), the Intersex Society of North America (ISNA; http://isna.org); see also, e.g., Intersex Initiative (http://www.intersexinitiative.org), the Androgen Insensitivity Syndrome Support Group (http://www.aissg.org/), OII International Network (http://oiiinternational.com), Zwischengeschlecht (http://zwischengeschlecht.org), etc.

[14] This quote is derived from the section entitled "G[ender] V[ariance] in Persons with Somatic Disorders of Sex Development (Intersexuality)" in the "Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder" (Byne et al., 2012, pp. 786–790).

[15] This shows more clearly in Houk and Lee (2008) than in Hughes et al. (2006) or Lee et al. (2006).

> does not lead to gender dysphoria. As individuals with a disorder of sex development become aware of their medical history and condition, many experience uncertainty about their gender, as opposed to developing a firm conviction that they are another gender. However, most do not progress to gender transition. Gender dysphoria and gender transition may vary considerably as a function of a disorder of sex development, its severity, and assigned gender. (p. 456)

This quote (which is essentially the only reference to DSD in the GD chapter) euphemizes the problematic timing and nature of the "medical attention," i.e., early, non-consensual and appearance-normalizing treatments of atypical genitalia. It also obscures the fact that the whole rationale behind these treatments has always been to maintain and fortify the child in the assigned sex: the child was either "boyed" or "girled" depending on the size of the phallus at birth and the hormono-surgical possibilities of reconstructing "normal" male or female-looking genitalia (Money et al., 1955b; see also Hughes et al., 2006; Lee et al., 2006). In contrast, the aim of trans therapy is not consolidation of the assigned sex, but sex change.

Gender Dysphoria: A Second-Order Diagnosis

The problem is, in fact, even more acute. In individuals with intersex/DSD, the diagnosis of intersex/DSD and the medical assignment of the child as boy or girl precede—both chronologically and logically, as we have seen—any identifiable gender "problem":

> Very rarely are DSD individuals identified as having a gender identity problem before a medical DSD diagnosis has been made. Thus, most DSD individuals who develop GIV [gender identity variance] have already acquired medical "caseness" as DSD beforehand, and for many the gender assignment has been problematized in the eyes of their medical service providers as well as their parents from birth on. By contrast, GIV individuals without DSD usually look normal at birth, undergo routine gender assignment, and come to professional attention because of gender-atypical behavior/identity, not because of gender-atypical primary or secondary somatic sex characteristics. (Meyer-Bahlburg, 2009, p. 228)

In other words, gender dysphoria is a "second-order" diagnosis that depends, conceptually and in practice, on the "first-order" diagnosis—and the previous medical treatment—of intersex/DSD. Again, this is clearly not the case for non-intersex/DSD individuals.

If one does not minimize the difference between consensual and non-consensual treatment, one understands that the relevant question for intersex/DSD people is not whether the diagnosis of GD is a more or less acceptable compromise between the concern about stigma and the concern to secure the reimbursement and access to medical treatments. The debate about the GID revision was framed in these terms. But, individuals with intersex/DSD did not consent to medical treatments, since they were minors at the time of such treatments. It is for this reason that OII asks why should they endure the added stigma of having a mental "disorder" in the event that they reject, at an older age, their sex assignment.

This question is relevant from the critical perspective of OII Australia and Aotearoa and other intersex associations for two main reasons. First, intersex activists "oppose non-consensual genital 'normalizing' surgeries on intersex children primarily because they are harmful physically, emotionally and sexually, and not necessarily because they might get the gender of the child 'wrong'" (Koyama, n.d.[16]). They are less concerned about their gender identity than about the right to bodily integrity. Second, gender itself is, in fact, not the real issue: as claimed by ISNA, "intersexuality is primarily a problem of stigma and trauma, not gender."[17] In this respect, and assuming that intersex individuals in need of mental healthcare should be given a psychiatric diagnosis, the DSM provides us, one could argue, with just the right category: PTSD, which has existed since DSM-III. One advantage of this category for intersex/DSD individuals is of course that PTSD is about trauma, and not necessarily gender. The other significant advantage would be that PTSD is the only diagnostic category in the DSM that does *not* diagnose a mental "disorder," but a "normal reaction to an abnormal situation" (see Fassin & Rechtman, 2009)—the abnormal situation here being the violence inherent to non-consensual treatments.

Mental Health Care for Intersex as Disorders of Sex Development

One important reason why the question of stigma and the specific healthcare issues of individuals with intersex/DSD were not addressed during the revision process is the lack of critical discussion about the "Consensus Statement on Management of Intersex Disorders" (Hughes et al., 2006; Lee et al., 2006). First of all, and following the same de-stigmatizing arguments that favored GD over GID as a diagnostic label, it would have made sense to keep the term "intersex" in DSM-5. All the more so, one could argue, since this term—rather than the co-existing medical categories of hermaphroditism prior to the Consensus

[16] As Koyama (n.d.) makes it precise, "most intersex people identify and live as ordinary men and women, and are gay, lesbian, bisexual, or straight." See http://www.intersexinitiative.org/articles/intersex-faq.html.

[17] See the ISNA website: http://isna.org. See also Zwischengeschlecht (http://zwischengeschlecht.org).

Statement—was consistently used in the DSM prior to the fifth revision.

More importantly, the DSD clinical framework promoted in the Consensus Statement makes recommendations for the management of gender identity "problems" in individuals with DSD that are highly compatible with the new formulation of GD with a DSD. The "compatibility" is not limited to the fact that gender dysphoria is the diagnostic term used to qualify the discomfort expressed by some individuals with a DSD in the Consensus Statement. It was also the case of the GIDNOS category in the DSM-IV texts. In the section entitled "Psychosocial management," the Consensus Statement makes explicit that individuals with a DSD who "report significant gender dysphoria" and a persistent "desire to change gender" should be referred to "a specialist skilled in the management of gender change" (Lee et al., 2006, pp. e492–e493).

In practice, this means that the reference framework for intersex/DSD individuals with gender dysphoria is the clinical management of gender identity "disorders" and gender change in non-intersex/DSD individuals. To put it plainly, the consensus recommendations involve "transsexualizing" the gender "problems" in individuals with intersex/DSD, regardless of their distinctive medical histories. Just like the diagnosis of GD, the DSD framework obscures the fact that gender dysphoria can only be a second-order diagnosis in the presence of intersex/DSD and, additionally, that individuals who are diagnosed with intersex/DSD have non-consensual treatment imposed upon them before they can want, and consent, to another medical treatment to change their gender. The clinical framework proposed in the Consensus Statement does not, however, account for all the problems inherent to the inclusion of DSD in GD.

Classification Effects of Professional Dynamics

Following the Consensus Statement, the relevant literature continued to emphasize the differences between DSD and GID in terms of diagnosis and treatment:

> [T]he differences between these two categories of gender-variant individuals [with DSD and with GID] in phenomenon, context of presentation, etiology, and treatment options are so large that identical diagnoses and treatment approaches are not justified and may actually be detrimental to the individuals in need of care. (Meyer-Bahlburg, 2008, p. 345; see also 2009, p. 231; see also Mazur, Colsman, & Sandberg, 2007)

Since 2008, there has been no dramatic new evidence in the DSD literature to justify a radical change of opinion about the diagnostic status of intersex in the DSM (see Meyer-Bahlburg, 2010). In this light, there is no particular reason why the similarities between gender "problems" in DSD and non-DSD individuals should have been emphasized for the fifth revision (p. 465), while emphasis was put on the marked differences during the fourth revision (Meyer-Bahlburg, 1994) as we shall see in more detail below.

One reason for such inconsistencies may be related to the organization of labor in the area of mental healthcare for gender "problems":

> [I]n terms of the provision of clinical psychosocial and medical services to both categories of patients, there is increasing overlap in professional care personnel, psychosocial assessments methods, selected aspects of medical and psychosocial management, and also in regard to support groups and gender activism. (Meyer-Bahlburg, 2008, p. 345, see also 2009, p. 231)

This point is particularly relevant, as it draws attention to the professional, institutional, and gender activist dynamics that accompanied the revision of the diagnostic categories and criteria for GD in favor of the inclusion of DSD as a specifier of a mental "disorder."

Historically, psychosexual "disorders" in gender identity in the DSM itself were classified in reference to the well-known studies by Money and his colleagues on "human hermaphroditism" (Money et al., 1955a, b; see also Green & Money, 1969; Money, 1994), and to the related theory by Stoller (1964, 1968) about the establishment of a "core gender identity" in early infancy (for historical discussions, see Hausmann, 1995; Meyerowitz, 2002). However, and as earlier said, the timing and purpose of the hormono-surgical treatments for hermaphroditism/intersex/DSD versus gender identity "disorders" are quite different. For this reason, there is an existing and persisting tension, not to say antagonism—rather than an overlap as assumed by Meyer-Bahlburg (2008) in the above quote—between "support groups and [within] gender activism" that focus on the need to facilitate access to medical treatments or, to the contrary, to put an end to non-consensual treatments.[18]

The increasing professional "overlap" between the clinical management of gender "problems" in individuals with and without intersex/DSD may not fill all the gaps in the apparently self-evident inclusion of DSD in GD. But awareness of this overlap may explain why the report by Meyer-Bahlburg (2009) on "Variants of Gender Differentiation in Somatic Disorders of Sex Development"—solicited this time by the WPATH for the 7th revision of the SOC—is so careful to emphasize crucial differences between the gender identity "problems" in DSD and non-DSD individuals. It is noteworthy that in this context, i.e., in a report addressed to transgender health professionals and focusing on treatment (not diagnostic categories) these differences

[18] A typical example is ISNA. It was founded in political alliance with feminist, queer, and LGBT struggles for the rights to self-determination, but on the distinctive claim that "intersexuality [was] primarily a problem of stigma and trauma, not gender.".

were sometimes asserted even more strongly and clearly than in the intersex/DSD literature itself.[19]

Interestingly, and in parallel to the APA GID subworkgroup, the WPATH formed a separate workgroup on DSD (Knudson et al., 2010a, p. 56). But just like the DSM-5 report by Cohen-Kettenis and Pfäfflin (2010) mentioned earlier, the WPATH report on DSD focused on the pros of removing intersex as an exclusion criterion for the revised diagnosis (Richter-Appelt & Sandberg, 2010). The "Response of the World Professional Association for Transgender Health to the Proposed DSM-5 Criteria for Gender Incongruence" is highly revealing (De Cuypere et al., 2010). Contrary to the position statement that OII Australia and OII Aotearoa (Morgan et al., 2012[20]) submitted to the APA and the WPATH, the latter concludes that the DSD specifier is an improvement for individuals with intersex/DSD:

> Adding a specifier of "with or without a Disorder of Sex Development" is an improvement over the need to use the "Not Otherwise Specified" diagnosis because individuals with intersex conditions may have a similar experience regarding their gender identity and may desire corresponding treatment interventions. (De Cuypere et al., 2010, p. 120)

Symptomatically, but not surprisingly, the WPATH—again, contrary to OII—emphasizes the similarities between intersex and transgender experiences and, among these, the purported shared desire to access sex reassignment treatments on the same accounts, i.e., as if gender dysphoria was a first-order diagnosis for intersex/DSD individuals, while it is not. This logical error, I suggest, constitutes the condition of possibility for the diagnostic category and criteria of GD to apply equally to individuals with and without a DSD.

The Risk of Stigma, Misdiagnosis, and Other Classification Problems (DSM-IV to DSM-5)

Let me now turn to the contrasting expert opinions expressed some 20 years ago in support of the exclusion of physical intersex from the GID diagnosis. This recommendation for exclusion was grounded in clinical reasoning that took seriously the risk of stigma, misdiagnosis, and other classification problems if gender identity "problems" in intersex individuals were diagnosed as psychiatric conditions. These important arguments need to be recalled, since they are discussed nowhere in the DSM-5 revision literature.

[19] See especially pp. 228–229, 232–234 in Meyer-Bahlburg (2009).

[20] Let's recall here that OII's initial statement was issued in February 2010.

Of Apples and Oranges

During the fourth revision of the DSM, one report was entirely dedicated to "Intersexuality and the Diagnosis of Gender Identity Disorder" with the purpose to outline specific recommendations in this regard (Meyer-Bahlburg, 1994). Contrary to the DSM-5 reports on GID, but consistent with the intersex literature at the time (and until today, as we have seen), the 1994 report underscored the "marked differences between intersex patients with gender identity problems and non-intersex patients with GID" in terms of "prevalence, age of onset or presentation, sex ratio, and associated or predictive factors" (p. 21; see also Meyer-Bahlburg, 2008, 2009). These "marked differences" explained the "difficulties encountered in applying the DSM category and criteria of [GID] to [intersex] patients" (Meyer-Bahlburg, 1994, p. 21). One of these, as seen earlier, is to conceive their desire for gender change as a mental "disorder" rather than a "correction" of the (wrong) gender assigned at birth.

In the context of the DSM-IV revision, this classification problem was not just considered a "dilemma," as Meyer-Bahlburg (2010) would put it in his DSM-5 report. Rather, it constituted a strong obstacle to the inclusion of physical intersex in GID. Consequently, the 1994 report concluded that "[p]atients with intersexuality or similar medical conditions should be excluded from the GID diagnosis" (Meyer-Bahlburg, 1994, p. 21). This recommendation was favored among four options outlined in the report (pp. 33–36): "1. [C]ontinue the practice of DSM-III-R"; 2. "Use the GIDNOS category for all intersex patients with gender problems"; 3. "Exempt all intersex patients from the GID diagnosis"; 4. "Create a new diagnostic category, Gender Identity Problem [GIP] of Intersexuality." As we are well aware, option 2 was endorsed in DSM-IV and continued in the Text Revision.[21]

Among the respective advantages and disadvantages listed for each option, the following are of particular interest for my discussion. First of all, and compared to the other options, the distinctive advantage of excluding intersex from the specific GID diagnosis (Option 3) was to "avoi[d] the risk of stigmatization of intersex patients with a mental disorder

[21] Initially, I wrote that options 2 and 3 were included in DSM-IV, since the final text both included intersex patients in the GIDNOS category (Option 2 in Meyer-Bahlburg, 1994) and excluded them from the GID diagnosis (Option 3). I thought these two options were not necessarily mutually exclusive in the DSM-IV report itself. However, Meyer-Bahlburg explained that "the recommended Option 3 made it into the DSM-IV Option book, but was overridden subsequently by the Task Force [...] in favor of Option 2" (H. F. L. Meyer-Bahlburg, personal communication, September 10, 2014). It is unclear why the Task Force favored Option 2. Meyer-Bahlburg was not part of the "full Task Force" and did not participate in the final decision. However, if Option 3 was not included in DSM-IV, this means that the recommended option involved removing intersex from DSM-IV. This provides more convincing support for the point I make here and my overall argument.

label" (p. 35). It is noteworthy that the risk of stigma was not only acknowledged as a problem, but also as a risk that had to be prevented. The 1994 report further defined a decisive criterion to discriminate between the four options. The new category of GIP of Intersexuality (Option 4) was rejected at the time precisely on that account: it would effectively stigmatize "all intersex patients with gender problems," since "the gender problem itself w[ould] be labeled a mental disorder, although it m[ight] not be one" (p. 36). At stake in the concern about stigma was the related concern to avoid misdiagnosis by mistaking apples for oranges.

The Increased Risk of Stigma and Misdiagnosis in DSM-5

Compared to DSM-IV, I argue that the risk of stigma and misdiagnosis is increased in the new diagnosis of GD. This is also true for the proposed special category of "Gender Incongruence with a DSD subtype" (Meyer-Bahlburg, 2010) which inspired the final formulation, except that the accompanying recommendations "not [to] classify [Gender Incongruence] as a psychiatric disorder per se" and to place it under "Other Conditions that May be a Focus of Clinical Attention" (p. 471) were not followed in DSM-5. The main problem lies elsewhere however.

Unlike the hypothetical category of GIP of Intersexuality (rejected in the 1994 report), GD with a DSD is not a diagnostic category per se, but a subcategory of the overarching diagnosis of GD. This does not mean that the latter is any less problematic than the former. Both define a psychiatric condition and are, according to the DSM-IV reasoning, equally stigmatizing in this regard. But the status of DSD as a specifier accrues the risk of misdiagnosis for intersex/DSD individuals, because the diagnostic criteria for GD are defined for the overarching category and not specifically for individuals with intersex/DSD. These criteria do not take into account the clinical significance of the first-order diagnosis for intersex/DSD and the previous medical treatment of the physical condition.

The hypothetical category of GIP of Intersexuality certainly had the disadvantage of stigma. However, compared to GD, it also presented at least one advantage: again hypothetically, it would have involved defining specific diagnostic criteria according to the distinctive features and manifestations of gender identity "problems" in intersex/DSD (versus non-intersex/DSD) individuals, which are emphasized in the literature as we have seen—the notable exception of the DSM-5 reports notwithstanding.

A Persisting But Irreducible Classification Problem

This classification problem emerges in a very concrete manner with GD, where the notion of "gender incongruence" defines the core feature of the diagnosis (APA, 2013, p. 453). In the many various cases of intersex/DSD, the question is of course: how shall we define such "incongruence between one's experienced/expressed gender and assigned gender" (p. 452), and in reference to what?[22] This question was raised in the 1994 report in the following terms: "In many cases with ambiguous genitalia or with ambiguous secondary sex characteristics or with complicated medical histories, there may be problems to define or justify the sex of reference for GID" (Meyer-Bahlburg, 1994, p. 34; see also p. 35).[23] Awareness of such problems may explain why DSM-III-R effected a change in wording pertaining to the notion of sex itself. In DSM-III, the essential feature of GID was defined as an "incongruence between anatomic sex and gender identity" (APA, 1980, p. 261). In DSM-III-R, "anatomic sex" was changed to "assigned sex (i.e., the sex that is recorded on the birth certificate)" (APA, 1987, p. 71; see also p. 72). The expression "assigned sex" was continued in the DSM-IV texts.

The shift from anatomy to the question of assignment as the reference term for sex in DSM-III-R is more consistent with the possibility of diagnosing intersex individuals with gender identity "disorders." As seen earlier, this possibility existed for GIDC in DSM-III, and was extended to the diagnosis of Transsexualism in DSM-III-R. Indeed, if the sex of reference is anatomical, identifying an incongruence in intersex individuals is far more problematic than if such incongruence is defined in reference to the "sex recorded on the birth certificate." But the latter conventional definition of sex contains its own problem, since it raises the question of how to assign a sex, and which sex, to intersex individuals. At stake for my present argument is the question of whether intersex individuals can experience any incongruence—not per se, but as defined in the DSM—between their assigned sex and gender identity in the first place. The answer is "yes" if we assume that the assigned sex is correct (for whatever reason), regardless of whether the individual identifies with it when growing up. The answer is "no" if we admit that intersex individuals sometimes seek to "correct" rather than change their assigned sex.

The problem with the sex of reference remains unresolved in DSM-5. One could even argue that the shift in clinical focus from cross-gender identification and behavior to the key notions of gender incongruence and gender dysphoria amplifies the problem. The declared change in wording from sex

[22] From a different perspective, Lawrence (2014, p. 1264) raises a similar question, but discusses it essentially for GD without a DSD.

[23] Such problems with the sex of reference were considered inherent to two options considered in the report: to continue the practice of DSM-III-R, or to use GIDNOS for all intersex individuals (options 1 and 2 respectively in Meyer-Bahlburg, 1994, pp. 33–35). Again, these options were discarded in favor of the recommendation to exclude individuals with physical intersex from GID.

to gender makes no difference in the matter, although it is offered as a solution to the problem:

> In the wording of the criteria, "the other sex" is replaced by "the other gender" (or "some alternative gender"). *Gender* instead of *sex* is used systematically because the concept of "sex" is inadequate when referring to individuals with a disorder of sex development. (APA, 2013, p. 814, emphasis in original)

The novelty of this change is clearly overstated, given that Money (1955) coined the term "gender"—"gender role" to be more precise (p. 254)—60 years ago (see also Money et al., 1955a, p. 285, b, p. 302). Furthermore, the announced change from sex to gender in DSM-5 is systematically undermined in the supporting text: in the chapter presentation of GD, several notions are clarified, among which the *distinction* between sex and gender rather than the *replacement* of sex with gender (APA, 2013, p. 451). The expression "assigned *sex*" in fact continues to be used in the text (p. 458, emphasis added), a symptomatic error which suggests that gender is perhaps used simply as a synonym of sex (see also Lawrence, 2014, p. 1264). More fundamentally, sex is defined in terms of maleness and femaleness and in reference to reproductive biology, which implies "nonambiguous internal and external genitalia" (APA, 2013, p. 451; see also p. 829). Because of this binary and procreation-centered definition of sex, the concept of sex itself appears unsuited for intersex individuals: they have no sex, but a "disorder of sex development."

This problematic definition of sex brings into critical focus the ways in which the revised diagnosis of GD contains—in the double sense of "hold" and "withhold"—fundamental classification problems that undermine the validity of the diagnosis in its own terms. It is precisely when the classification problem becomes the most serious that we are confronted with an instructive aporia: technically—i.e., not per se, but by virtue of the DSM-5 definition of sex—individuals with a DSD cannot experience "anatomic (in fact, genital) dysphoria." This notion, overlooked in the revision reports, is defined as an "incongruence between experienced gender and somatic *sex*" (p. 455, emphasis added). This is almost exactly the same definition provided by DSM-III for the essential feature of GID as a subclass (not a diagnostic category as in DSM-IV) of Psychosexual Disorders: "The essential feature of the disorders included in this subclass is an incongruence between anatomic sex and gender identity" (APA, 1980, p. 26). This equivalent formulation is highly instructive: it tells us that *gender* dysphoria (a term in professional usage since the beginning of the 1970s) is, and has always been from a clinical perspective about *anatomic* dysphoria (see again Fisk, 1974), and further that anatomic dysphoria is "*about sex*, not gender" (see Money, 1994, p. 167, emphasis added).

At this point, we need the full definition of "sex" (and "sexual") provided in the chapter for GD: "sex and sexual refer to the biological indicators of male and female (understood in the context of reproductive capacity), such as in sex chromosomes, gonads, sex hormones, and nonambiguous internal and external genitalia" (APA, 2013, p. 451). Given this definition of sex, anatomic dysphoria must be logically restricted to individuals who experience gender dysphoria *without* a DSD. The logical exclusion of DSD from anatomic dysphoria is the one thing that makes sense in GD, but this exclusion undermines the applicability of all the criteria pertaining to anatomic dysphoria, namely: Criteria A.7. and A.8. for GD in Children; and Criteria A.1., A.2., and A.3. for GD in Adolescents and Adults (see Table 2). One could argue that this leaves us with just the right number of A criteria to diagnose a "marked gender incongruence" in Children (indeed 6 out a total of 8, plus A.1. which is required for this age group), and in Adolescents and Adults (2 out of 6, none of which is obligatory). While this possibility exists, it is internally contradictory, in particular because the (obligatory) B criterion for clinical significance refers to the *non*-access to "cross-sex [sic] hormone treatment or gender reassignment surgery" (p. 453). It does not refer to the nonconsensual "access" to such medical treatments from the 1950s until now, when an individual has been diagnosed with intersex/DSD.

Whichever way we look at it, whether we call sex "gender," whether the etiology for gender identity "problems" is said to be psychological (emphasized since DSM-III despite the self-proclaimed atheoretical stance), biological (considered in DSM-5), or biopsychosocial (as promoted in DSM-5), or even whether the diagnostic name and categories are more or less stigmatizing, the problem with the *referent* for the assigned sex or gender (and not just "the sex of reference," i.e., which sex for intersex?) is irreducible. There is not one, but *two* referents for assigned sex (gender in DSM-5). Indeed, the sex recorded on the birth certificate is produced differently depending on whether the newborn (or even the fetus or sometimes the adult individual) is diagnosed or not with intersex/DSD. The reason for this is, again, that intersex defines no sex but a "disorder of sex development," in the medical conception and in DSM-5, a "disorder" that must "fixed."

In the presence of atypical genitalia, the referent for the sex recorded on the birth certificate is medically assigned, often surgically and hormonally, but never without a complete physical exam and numerous tests. In the absence of intersex/DSD, sex is not assigned in this specific manner—including in a medical setting (the delivery room)—although the practice of "boying" and "girling" a newborn with more-typical genitalia is performative, i.e., a sort of action that "does things with words" (Austin, 1975; Butler, 1990).

Because of past and current practices in the clinical management of intersex/DSD, this difference is irreducible to this day. In the area of mental healthcare, it calls into question the relevance of a psychiatric diagnosis for intersex individuals. In the specific case of the DSM-5 diagnosis, it undermines the

applicability of the diagnostic criteria for gender incongruence in general (A set of criteria) and for anatomic dysphoria in particular (see above) as well as the decisive B criterion for clinical significance. This testifies to the self-contradictory nature of the terms under which a gender diagnosis can (not) apply to individuals with intersex/DSD.

A Logical Conclusion: Remove Intersex/DSD from the DSM

In this article, I have analyzed from a historical and conceptual standpoint the problematic ways in which the inclusion of a DSD specifier in the new diagnosis of Gender Dysphoria paradoxically excludes the specific healthcare issues of individuals with intersex/DSD, and the important question of the stigma attached to a psychiatric diagnosis. These issues were said to be central to the DSM-5 revision of the GID diagnosis. In the first step of my line of argument, I have discussed the reasons why they had not been addressed in relation to intersex/DSD. These reasons include, but may not be limited to: the expert silences in the DSM-5 reports; the transgender-centric conceptualization of "gender identity variants"; the uncontroversial and very attractive nature of the concept of gender dysphoria over the years; the overlooked distinction between consensual and non-consensual medical treatments; the unexamined assumption that GD with a DSD is a first-order instead of a second-order diagnosis; the problematic Consensus Statement recommendations in the area of mental healthcare that involve "transsexualizing" intersex/DSD; and, more broadly, the increasing professional "overlap" between the clinical management of gender identity "problems" with and without intersex/DSD that exacerbates the existing tensions between transgender and intersex activism regarding the timing and opportunity of hormono-surgical treatments. Thus, I draw the obvious conclusion that the DSD specifier was not an improvement for intersex/DSD individuals compared to DSM-IV.

In the second step of my line of argument, I highlighted a striking contrast in clinical reasoning at a 20-year interval. During the DSM-IV revision process, professionals expressed their concern with the risk of stigma, and consequently rationalized the exclusion of physical intersex from the GID diagnosis. They also engaged critically with the problem of classifying "gender dysphoria" in intersex individuals as a psychiatric condition. One of these was the problem with the sex of reference (which sex for intersex individuals?), which is amplified in DSM-5. I have contended that the risk of stigma and misdiagnosis was, in fact, increased in DSM-5 compared to DSM-IV. I have consequently argued that the diagnostic criteria for GD do not apply to intersex/DSD individuals, because they fail to take into account the irreducible difference between GD with and without intersex/DSD, i.e., between medically and non-medically assigned sex, and between non-consensual and consensual medical treatments, respectively. Furthermore, the criteria are also flawed on their own terms: these terms are inconsistent, even self-contradictory. The logical conclusion from my analysis is therefore to call for the removal of intersex/DSD from the DSM.

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Consensus Statement

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Global Disorders of Sex Development Update since 2006: Perceptions, Approach and Care

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Key Words
Disorders of sex development · Intersex · Ambiguous genitalia

Abstract
The goal of this update regarding the diagnosis and care of persons with disorders of sex development (DSDs) is to address changes in the clinical approach since the 2005 Consensus Conference, since knowledge and viewpoints change. An effort was made to include representatives from a broad perspective including support and advocacy groups. The goal of patient care is focused upon the best possible quality of life (QoL). The field of DSD is continuously developing. An update on the clinical evaluation of infants and older individuals with ambiguous genitalia including perceptions regarding male or female assignment is discussed. Topics include biochemical and genetic assessment, the risk of germ

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cell tumor development, approaches to psychosocial and psychosexual well-being and an update on support groups. Open and on-going communication with patients and parents must involve full disclosure, with the recognition that, while DSD conditions are life-long, enhancement of the best possible outcome improves QoL. The evolution of diagnosis and care continues, while it is still impossible to predict gender development in an individual case with certainty. Such decisions and decisions regarding surgery during infancy that alters external genital anatomy or removes germ cells continue to carry risk.

Disorders of sex development (DSDs) were defined as congenital conditions within which the development of chromosomal, gonadal and anatomic sex is atypical at the Chicago Consensus Meeting in 2005 [1]. This is an update since the Consensus Statement published in 2006. Perceptions and the approach to the diagnosis and care of individuals with DSDs continuously change. Data remain inadequate to address major concerns including the assignment of male or female sex, predictors of gender identity development, surgical issues regarding timing and consent and the best possible fertility preservation measures. It is clear than gains in perceptions, approach and care since 2006 need to be reviewed and considered. A large number of individuals with differing opinions participated in the endeavor. The following update has been endorsed by the European Society for Pediatric Endocrinology (ESPE), the Pediatric Endocrine Society (PES-NA), the Australian Pediatric Endocrine Group (APEG), the Asian Pacific Pediatric Endocrine Society (APPES), the Japanese Society of Pediatric Endocrinology (JSPE), the Sociedad Latino-Americana de Endocrinologia Pediatrica (SLEP) and the Chinese Society of Pediatric Endocrinology and Metabolism (CSPEM).

DSD Nomenclature

The broad term DSD, adopted at the Consensus Conference, has been generally accepted by many medical professionals but not universally by some patient and support groups [1, 2]. Positive aspects about having a term include providing for scientific accuracy within a biological and medical context, bona fide genetic disorders facilitate access to healthcare and insurance, an umbrella classification helps in generating comprehensive and integrated models of care, at the same time it avoids confusion by not overlapping with conditions such as transgender, gender dysphoria and homosexuality, and it provides a framework for knowledge accumulation and research funding.

Negative connotations of DSD perceived by some advocacy organizations [3] include the stigma of 'disorder' and perceived implications that 'sex' involves sexual behavior. The term DSD is not felt to be applicable to all individuals included, such as males with congenital adrenal hyperplasia (CAH), resulting in participant refusal regarding research under this heading [2]. Some people consider 'intersex' to be a better term than DSD, especially for infants requiring male or female assignment, some substitute the word 'disorders' by 'differences', whilst still others call for an alternative nomenclature.

Incidence

The terminology has led to confusion regarding the incidence of conditions included [4]. There are no clear estimates of the incidence rate of subjects presenting with ambiguous genitalia at birth, and only a proportion of them present a major challenge regarding male or female assignment. However, it has been estimated to be approximately 1 in 4,500–5,500 [5]. Data are not available to determine the exact frequency of specific DSDs, while only a small fraction of those with DSDs require extensive multidisciplinary assessment to reach a recommendation for gender assignment.

The incidence rate among subjects with 46,XY to have a DSD has been estimated to be 1 in 20,000 births. Ovotesticular DSDs have been estimated to occur in 1 of 100,000 live births [6]. The frequency of testicular or mixed gonadal dysgenesis is estimated at 1:10,000 [7]. The worldwide incidence of 46,XX DSD, consisting primarily of CAH – mostly 21-hydroxylase deficiency –, has been estimated to be 1 in 14,000–15,000 live births [8], but it varies by regions because of ethnic differences in gene mutation frequency. CAH and mixed gonadal dysgenesis constitute about half of all DSD patients presenting with genital ambiguity [9].

When all congenital genital anomalies are considered, including cryptorchidism and hypospadias, the rate may be as high as 1:200 to 1:300 [10]. Among patients with hypospadias and cryptorchidism, currently the diagnosis of specific DSD conditions is generally limited to those with proximal hypospadias with cryptorchidism. The overall incidence estimations also include those with

Klinefelter syndrome (estimated in 1:500 to 1:1000 live births) and Turner syndrome (about 1:2,500 live births). These known estimates hopefully provide a useful perspective.

Support Groups

The 2006 Consensus Statement [1] was a landmark for providers caring for individuals with DSDs and the larger community. Increasingly collaborative relationships are occurring in care settings and at national peer support group (PSG) meetings, reflecting growing prioritization of patient perspectives focusing on health and well-being outcomes. Community priorities for improvement have been identified, while disagreements regarding mutual goals for patient-centered research and care persist.

Peer support (PS) is a key component of the 2013–2020 WHO Mental Health Action Plan [11]. This relieves patients from isolation and provides a unique source of identity support, anticipatory guidance and medical information accessible to individuals of all levels, in keeping with the Consensus Statement's call for improved evidence and diagnosis-specific recommendations. Rather than the monolithic approach to treatment, community members now call for evidence-based interventions, the consistent inclusion of evidence and of controversies in informed consent processes and the creative identification of alternative strategies, including psychosocial support and PS as primary interventions.

Many PSGs are eager to collaborate in research focused on patient-centered outcomes, promoting high-quality nonduplicative research through input into the research design and goals while limiting participant 'research fatigue' to improve recruitment. For example, the Androgen Insensitivity Syndrome (AIS)-DSD support group (SG) created a research policy that facilitates participation in projects if a SG medical advisor serves as project consultant [12]. Furthermore, clinicians could utilize PSGs as reservoirs of qualitative lived experience of patients and families to define an affirmative care model similar to the World Professional Association for Transgender Health (WPATH) standards of care for transgender individuals, emphasizing liberal referral to PS and psychosocial support [13].

Given the numerous current barriers/controversies including language, best practices and human rights organizations' positions on children's rights to self-determination (UN Intersex Fact Sheet: United Nations Office of Human Rights High Commissioner) [14], a patient-clinician forum like that organized in the early 2000s by the AISSG UK and University College London Hospitals (UCLH) [15] could provide a framework for an effective collaboration among PSGs, clinicians and other stakeholders.

The collaboration with existing PSGs is crucial for developing more support for specific conditions, for integrating PS into the model of healthcare and for encouraging patient-centered research. A 2014 study showed that several established PSGs already enjoy the involvement of clinicians, and that the overwhelming majority are receptive to closer relationships [16]. Cultivating relationships with these groups allows clinicians to access existing programs or to collaborate on new resources. Many PSGs provide an umbrella of support for multiple diagnoses, including condition-specific sessions at their meetings. PSGs may also be able to direct clinicians to unpublicized local resources and private social media groups. An updated comprehensive list of international PS and advocacy resources is included in table 1.

Local individuals who volunteer themselves in clinics or through PSGs can enhance the teams' psychosocial services, especially with standardized training. Besides integrating PS into clinical practice, the inclusion of an affected person as a resource on the care team ensures routine consideration of patient perspectives. The Children's Hospital in Denver, Colo., USA, is successfully piloting this model. Other helpful strategies are making volunteers available during clinic hours and including them in clinical conferences. In London, UK, PSGs participate in Clinic Open Days, which are sometimes condition specific, e.g. XY-female or Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, at UCLH. Patients have the unique opportunity to receive medical information from clinicians and to learn about PSGs from group representatives.

Routine incorporation of PS into clinical care at the earliest possible time can ease what can be a bewildering experience for parents. The discovery of reproductive variation or the delivery of a baby with genital difference can leave families feeling isolated, overwhelmed and immobilized. One of the most comforting things parents can hear is that differences of sex development are more common than most people realize, and that there are many families successfully raising children like theirs. Messages like 'We know this is challenging, but lots of families like yours are raising happy healthy children. May we share your contact information so one of them can get in touch?' can reduce distress and isolation. Relieving parents of the responsibility to initiate contact by having an experienced

Table 1. PS and advocacy resources for DSD and intersex

Organizations based in Africa		
MRKH (Mayer-Rokitansky-Küster-Hauser syndrome) Africa Foundation	https://www.facebook.com/MRKH-Africa-Foundation-752051251535281/?fref=ts	
East Africa		
Androgen Insensitivity Syndrome Support Group (AISSG) East Africa		aissgeastafrica@gmail.com
South Africa		
Organization Intersex International (OII) South Africa – Intersex South Africa	http://www.intersex.org.za	info@intersex.org.za
South African Androgen Insensitivity Syndrome Support Group (SAAIS)		saais@iafrica.com
Uganda		
Support Initiative for People with Atypical Sex Development (SIPD) – Uganda	https://www.facebook.com/SIPD-Uganda	
Organizations based in Asia		
Androgen Insensitivity Syndrome Support Group (AISSG Asia, UK, eastern Europe)	http://www.aissg.org	uk@aissg.org
Bangladesh		
MRKH (Mayer-Rokitansky-Küster-Hauser syndrome) Bangladesh	https://mrkhbangladesh.wordpress.com	
China		
Organization Intersex International (OII) China	http://www.oii.tw/	hiker@oii.tw
Japan		
Androgen Insensitivity Syndrome – Differences of Sex Development (AIS-DSD0 SG) Japan	http://aissgjp.org/	support@aissgjp.org
Intersex Initiative	http://intersexinitiative.org/	info@intersexinitiative.org
Peer Support for MRKH Japan	http://ps4mrkh.wix.com/peer-support-4-mrkh	
Myanmar		
AISSG-Myanmar		aissgmy@gmail.com
Philippines		
OII Philippines – InterSex Philippines	https://www.facebook.com/IntersexPhilippines	Jonalyn V. Bulado: mobile number +63 92 77 754 317
Organizations based in Australia/New Zealand		
Australia		
Androgen Insensitivity Syndrome Support Group (AISSG) Australia	http://www.aissga.org.au/	aissgaustralia@gmail.com
Organization Intersex International (OII) Australia	https://oii.org.au/	https://oii.org.au/information/contact/
Sisters for Love MRKH Foundation – Mayer-Rokitansky-Küster-Hauser syndrome	http://www.sistersforlove.org	http://www.sistersforlove.org/contact.html
New Zealand		
IANZ Intersex Awareness New Zealand	http://www.ianz.org.nz/	http://www.ianz.org.nz/contact/
Organizations based in Europe		
Organization Intersex International (OII) Europe	http://oiieurope.org/	http://oiieurope.org/ http://oiieurope.org/about/contact//contact/
Austria		
OII Austria -VIMÖ | Verein Intersexueller Menschen Österreich – Intersex People Austria	http://vimoe.at/	info@vimoe.at
Belgium		
OII Belgium – Genres Pluriels Asbl	http://www.genrespluriels.be/	contact@genrespluriel.be
Eastern Europe		
Androgen Insensitivity Syndrome Support Group (AISSG)	http://www.aissg.org	uk@aissg.org

Table 1 (continued)

France		
Association syndrome de Rokitansky – Mayer-Rokitansky-Küster-Hauser syndrome (MRKH)	http://www.asso-mrkh.org	info@asso-mrkh.org
Germany		
OII Germany	http://www.intersexualite.de/	http://www.intersexualite.de/index.php/kontakt-und-impressum/
Intersexuelle Menschen e.V. – Intersex People German	http://www.intersexuelle-menschen.net/	vorstand@intersexuelle-menschen.net
Intersexuelle Menschen Self Help Group for Intersex Adults	http://www.intersexuelle-menschen.net/switch-shg.php	info@shg.intersexuelle-menschen.net
Intersexuelle Menschen Self Help Group for Intersex Parents	http://www.intersexuelle-menschen.net/switch-shg.php	info.eltern@shg.intersexuelle-menschen.net
Intersexuelle Menschen Self Help Group for XY Women	http://www.intersexuelle-menschen.net/switch-shg.php	info@xy-frauen.de
Intersexuelle Menschen Self Help Group for XY Parents	http://www.intersexuelle-menschen.net/switch-xy.php	info.eltern@xy-frauen
MRKH Syndrom	http://www.mrkh-syndrom.net/	InesR@gmx.at
Iceland		
OII Iceland – Intersex Ísland	http://intersex.samtokin78.is/	
Italy		
Associazione Italiana Sindrome da Insensibilità agli Androgeni	http://www.aisia.org	info@aisia.org
OII Italy – Intersexioni (AISIA)	http://www.intersexioni.it/	info@intersexinitiative.org
The Netherlands		
DSDNederland	http://www.dsdnederland.nl	http://www.dsdnederland.nl/contact/algemeen-contact
Nederlands Netwerk Intersekse/DSD – OII Netherlands	http://nnid.nl/	http://nnid.nl/contact/
Stichting MRKH	http://www.stichtingmrk.nl/	
Norway		
MRKH Norge	http://mrkhnorge.no	mrkh@mrkhnorge.no
Russia		
Association of Russian-Speaking Intersex People (ARSI)	https://www.facebook.com/ groups/intersex2013/	
Russian/Ukraine Мы райт Россия CPMK	http://rokitansky-syndrome.jimdo.com	
Serbia		
Gayten-LGBT, Center for Promotion of LGBTIQ Human Rights – Serbia	http://www.transserbia.org/	gayten@gmail.com
Spain		
AMAR – Asociación de Apoyo a Mujeres para la Aceptación del Síndrome de Rokitansky: MRKH	http://www.amar-mrkh.org/ http://www.amar-mrkh.org/p/sobre-amar.html	info@amar-mrkh.org
GrApSIA – Asociación y grupo de Apoyo a favor de las personas afectadas por el Síndrome de Insensibilidad a los Andrógenos y condiciones relacionadas – AIS and related conditions	http://grapsia.org/	grapsia@gmail.com
Sweden		
Intersexuella i Sverige – Intersex People of Sweden	http://www.inis-org.se/	kontakta@inis-org.se
Switzerland		
AISSG-Switzerland	http://intersex.ch	kontakt@intersex.ch
United Kingdom		
Androgen Insensitivity Syndrome Support Group – AISSG	http://www.aissg.org	uk@aissg.org
Children Living with Inherited Metabolic Diseases (CLIMB) CAH Support Group	http://www.livingwithcah.com/	http://www.livingwithcah.com/contact.html
*dsd*families.org	http://www.*dsd*families.org	info@*dsd*families.org
Intersex in the UK – OII UK	http://oiiuk.org/	http://oiiuk.org/contact/
Intersexuk	https://www.facebook.com/ intersexuk	
Kallmanns.org – Kallman Syndrome and hypohypogonadotrophic hypogonadism	https://www.facebook.com/KallmannSyndrosme/http://www.kallmanns.org/	http://kallmanns.org/contact

Table 1 (continued)

Klinefelter Syndrome Association UK	http://www.ksa-uk.net	chair@ksa-uk.net
Living MRKH	http://livingmrkh.org.uk/	
MRKH Connect	http://www.mrkhconnect.org	info@mrkhconnect.org
Turner Syndrome Support Society	http://tss.org.uk/	turner.syndrome@tss.org.uk
Organizations based in North America		
Canada		
West Coast AIS-DSD Support Group		aisparent@gmail.com nyphilla@gmail.com
Mexico		
Brújula Intersexual – Intersex Compass	https://www.facebook.com/ Brujulaintersex	
Sindrome de Rokitansky	http://sindromederokitansky.blogspot.no	
USA		
Accord Alliance	http://www.accordalliance.org	http://www.accordalliance.org/contact/email-us/
Advocates for Informed Choice	http://aiclegal.org	info@aiclegal.org
Androgen Insensitivity Syndrome-Differences of Sex Development (AIS-DSD) Support Group	http://www.aisdsd.org	aisdsd@hotmail.com
Association for the Bladder Exstrophy Community	http://www.bladderexstrophy.com/	http://www.bladderexstrophy.com/about/
AXYS Association for X and Y Chromosome Variations	http://www.genetic.org	info@genetic.org
Beautiful You MRKH (Mayer-Rokitansky-Küster-Hauser syndrome) Foundation	https://www.bymrkh	bymrkh@gmail.com
Congenital Adrenal Hyperplasia Support Education and Research (CARES) Foundation	http://www.caresfoundation.org/	contact@caresfoundation.org
Hypospadias Epispadias Association (HEA)	http://heainfo.org	lakebylake@aol.com
Inter/Act	http://interactyouth.org/	inter.act@aiclegal.org
Intersex Initiative	http://intersexinitiative.org/	info@intersexinitiative.org
Intersex Support for Parents	https://www.facebook.com/groups/IntersexPS/	
IntersexKidsChina	https://groups.yahoo.com/neo/groups/IntersexKidsChina/info	
Kallmanns.org – Kallman Syndrome and Hypohypogonadotrophic Hypogonadism	http://www.kallmanns.org/ https://www.facebook.com/KallmannSyndrome/	http://kallmanns.org/contact
MAGIC Foundation	http://www.magicfoundation.org	ContactUs@magicfoundation.org
Mid-Atlantic MRKH Foundation	http://www.mid-atlanticmrkh.org/	
MRKH Organization	http://www.mrkh.org	info@mrkh.org
Organization Intersex International	http://oiiinternational.com/	http://oiiinternational.com/contact/
Turner Syndrome Society of the United States	http://turnersyndrome.org	http://www.turnersyndrome.org/ – !contact-us/cuy5
Turner Syndrome Foundation	http://www.turnersyndromefoundation.org/	info@tsfusa.org
XXY Brain Trust	https://www.facebook.com/xxybraintrust	
Organizations based in South America		
Argentina and Colombia		
GrApSIA – Asociación y grupo de Apoyo a favor de las personas afectadas por el Síndrome de Insensibilidad a los Andrógenos y condiciones relacionadas – AIS and related conditions	Based in Spain with contacts in South America	Argentina: grapsiaargentina@gmail.com Colombia: grupoapoyoorg@gmail.com
Chile		
Ninfas de Rokitansky	http://ninfasderokitansky.blogspot.no/	

family reach out removes the stress of having another unknown to deal with. While they await contact, families can be directed immediately to PSGs and other resources with reassuring information, such as *dsd*families.org and the *Handbook for Parents* (www.accordalliance.org/dsdguidelines/htdocs/parents/).

Researchers often contact PSGs for help recruiting participants in studies that are already IRB (institutional review board) approved; on the other hand, PSGs have found that they can be extremely effective in supporting the development of research that meets the needs of affected communities when involved from the inception of research in the design of methods and goals, when able to

give input into sensitive language and when engaged to ensure that the specific concerns of the community regarding human research ethics are addressed. A suggested collaborative model that has proved successful in improving models of care in conditions such as breast cancer is community-based participatory research (CBPR), in which patient advocates, clinicians and researchers collaborate in the design of research [17]. One goal of a stakeholder forum might be the development of a community-based participatory research project to create surveys of patient priorities for care and research. Stakeholders' openness to use a mix of methods might resolve historical differences on issues as basic as the value of quantitative versus qualitative evidence. For example, a narrative analysis may reveal themes such as emotional openness or resilience that could lead to studies of effective psychosocial interventions [18].

Clinical Evaluation

The clinical evaluation of a child with atypical or ambiguous genital development begins with a thorough history and physical examination [19]. The management of a patient with a DSD involves a team approach to arrive at a definitive diagnosis based on available data [20].

Many individuals with a DSD are recognized in the newborn period, when ambiguous genital development is noted on the infant's first physical examination. In some instances, discordance between the prenatal karyotype, the prenatal ultrasound report and the newborn's genital appearance prompts an evaluation. Later presentations can occur in children, adolescents and adults. Examples of clinical findings associated with later presentation include progressive clitoromegaly, inguinal/labial mass(es) in a phenotypic girl, delayed or incomplete pubertal development, progressive pubertal virilization in a phenotypic girl and cyclical hematuria in a phenotypic boy.

For all patients, especially infants, a thorough prenatal history should be obtained. The medical history for older children includes questions pertaining to presence and timing of genital and pubertal development. Was the mother exposed to any known teratogens, potential environmental disrupting agents or medications? Are there other family members with atypical genital development in the family? Did any unexplained deaths occur in the family? Probing for consanguinity may be helpful especially when an autosomal recessive disorder is being considered in the differential diagnosis. A detailed family history regarding fertility of the grandparents, aunts and uncles may be helpful particularly in families with complete AIS.

The prenatal diagnosis of DSD has become more frequent with increased fetal monitoring during pregnancy. Improved ultrasound technology has made it possible to visualize the genitalia. Prenatal karyotyping has enabled the detection of sex chromosome mosaicism and discrepancies between chromosomal sex and phenotypic sex, either with prenatal ultrasound or at the birth of the child. A retrospective review suggests that prenatal genetic testing is not practical for rare DSD conditions without a family history and that prenatal karyotyping with fluorescent in situ hybridization (FISH) is the most useful when ambiguous genitalia are suspected [21].

Evaluation of an Infant with Ambiguous Genital Development

The initial physical examination should be meticulous, organized and unhurried. Anthropometric features should be assessed as well as vital signs. The facies, limbs and digits should be carefully examined for dysmorphic features. Skeletal features associated with Antley-Bixler syndrome suggest POR deficiency, whereas campomelic dysplasia suggests *SOX9* mutations [22]. Midline facial/neural defects and/or optic nerve hypoplasia suggest the possibility of one or more pituitary hormone deficiencies [23].

The examination of the external genitalia starts with observation to ascertain whether the external genital structures are symmetric or asymmetric. The degree, if any, of labioscrotal hyperpigmention should be gauged. Careful palpation is necessary to establish whether gonads are present in the labioscrotal folds, inguinal area or nonpalpable. Bilateral nonpalpable gonads raise suspicion that the infant is a virilized female with CAH. Asymmetry of the external genitalia, i.e. a unilateral palpable gonad, may indicate gonadal dysgenesis associated with a 45,X/46,XY karyotype. Transverse testicular ectopia indicates persistent Müllerian duct syndrome.

Insufficient testosterone concentrations in a 46,XY fetus during the critical window of male sex differentiation are typically associated with a spectrum of external genital development ranging from apparent female to ambiguous [23]. The length and diameter of the phallus need to be assessed. The position of the urethral meatus must be located. The urethral meatus may be present in its usual location on the glans penis, along the shaft of the penis or on the perineum. It is important to determine whether there is a single perineal opening representing a urogeni-

tal sinus. Although it has been suggested that the anogenital distance may provide information regarding prenatal androgen exposure, delineation, precision of measurements and lack of normative values hinder the use of this measure [24]. Rather, an external masculinization score can be calculated on the basis of scrotal fusion, phallic length, position of the urethral meatus and location of the gonads [19].

Some infants present with a global developmental field defect such as cloacal anomalies, anorectal malformations or bladder exstrophy-epispadias complex anomalies [25]. The absence of the anal opening indicates an underlying anorectal malformation that may be associated with additional anomalies such as the VATER or VACTERL associations [26]. Penoscrotal transposition with hypospadias and aphallia/penile agenesis represent primary developmental anomalies of the external genitalia. These infants show an abnormal external genital anatomy that cannot be easily categorized according to the Prader scoring system [26]. These disorders are typically associated with normal gonadal development and function.

Evaluation of an Adolescent

During adolescence, patients with DSD can present with primary amenorrhea or progressive virilization in a phenotypic girl. Has there been progressive clitoromegaly? The adolescent may present with delayed or incomplete pubertal development. Sensitivity to privacy needs, emotions and cognitive function is essential when evaluating and treating an adolescent. The diagnosis of a DSD may devastate an adolescent's personal identity and self-esteem and alarm the family.

A comprehensive physical examination including anthropometric features, blood pressure measurements and the evaluation for dysmorphic features is appropriate. Individuals with a 45,X/46,XY karyotype may have clinical features typically associated with Turner syndrome [27]. Wilms' tumor may be the presenting feature for Denys-Drash syndrome associated with *WT1* mutations. Secondary sexual characteristics including the presence/absence of breast development, the extent of sexual hair, symmetry of external genital structures and the size/development of the clitoris/penis need to be ascertained. The palpation of the labioscrotal folds and inguinal areas is important to ascertain for gonads. Small firm testes accompanied by learning difficulties and tall stature are clinical features suggestive of Klinefelter syndrome [28]. Females with MRKH syndrome generally present with normal breast development and primary amenorrhea; they may have associated renal and vertebral anomalies.

Biochemical Evaluation

Hormone measurements need to be interpreted in relation to the specific assay characteristics and to normal values for gestational and chronological age. In some cases serial measurements or stimulation tests may be needed.

Which Newborn/Infant Should Be Investigated and How Extensively?

An extensive investigation is required when the external genitalia are sufficiently ambiguous to hamper sex assignment or inconsistent with the results of prenatal tests.

The first-line testing in newborns includes measuring 17-hydroxyprogesterone (17-OHP) and serum electrolyte, androgen, anti-Müllerian hormone (AMH) and gonadotropin levels, together with investigations to define the sex chromosomes. Serum 17-OHP is usually unreliable before the age of 36 h, and in the salt-losing form of CAH, serum electrolyte levels usually do not become abnormal before day 4 of life.

Steroid hormone determination should be performed after an extraction or chromatography to avoid concerns of analytical specificity [29, 30]. Serum levels of testosterone are low in the normal male newborn during the first 7–14 days of life [30], and increase progressively thereafter until the age of 2–3 months [30, 31], thus results should be interpreted in that context. Gas chromatography or liquid chromatography linked with tandem mass spectrometry (GC/MS or LC-MS/MS) allows multiple analyte analysis from a single sample while maintaining specificity [32, 33].

The existence of testicular tissue can be assessed by serum AMH determination [34]. Although AMH is expressed by both testicular Sertoli cells and ovarian granulosa cells, AMH is detectable at birth at much higher circulating concentrations in boys than in girls [30]. With these tools, an initial diagnosis can be reached. In 46,XX newborns, elevated 17-OHP and androgen levels are distinctive of CAH, with hyponatremia and hyperkalemia in salt-wasting variants. With the availability of genotyping, a salt-losing crisis is no longer required for the diagnosis of this variant. When androgen and AMH values are above the female range, ovotesticular DSD is likely, whereas when androgen values are elevated but AMH is in the normal female range, aromatase deficiency should

be suspected. If androgen levels decrease progressively, together with the degree of virilization, maternal virilizing tumors could be the source [35]. In Y chromosome-bearing newborns, low AMH and androgen levels are indicative of dysgenetic gonads, low androgen values and normal/high AMH suggest steroid production defects, and normal/high AMH and androgen values are characteristic of androgen insensitivity or nonendocrine malformative DSDs [35, 36]. Gonadotropin levels may also be helpful, since they are usually very high in dysgenetic DSDs and normal or only slightly elevated in steroid synthesis defects and partial androgen insensitivity. They can even be low in patients with complete AIS [37].

Further biochemical tests are needed to clarify the etiological diagnosis in newborns or infants with isolated perineal hypospadias, isolated micropenis, isolated clitoromegaly, any form of familial hypospadias and those who have a combination of genital anomalies with an external masculinization score <11 [19]. In addition to repeated measurements of basal AMH and androgen levels, decision-making algorithms include hCG and ACTH stimulation tests to assess testicular and adrenal steroid biosynthesis and urinary steroid analysis by LC-MS/MS, together with imaging studies and a biopsy of gonadal tissue.

Basal AMH and androgen levels are indicative of the mass of functional Sertoli and Leydig cells. Their levels may range from very low in XY patients with severely dysgenetic gonads or XX patients with ovotesticular DSDs with predominant ovarian tissue to normal male values in mildly dysgenetic DSDs or ovotesticular DSDs with abundant testicular tissue. Since AMH and androgens levels are normally low in the male newborn and increase progressively after the third week of life [30, 38], repeated measurements may be needed.

Prolonged hCG stimulation may be necessary in some cases to assess defects of steroidogenic proteins [39, 40], although this should only be done after careful consideration as there may be negative effects upon the testes. An ACTH test may help when a steroidogenic defect affecting both the gonads and the adrenals is suspected.

Which Adolescent Should Be Investigated and How Extensively?

Adolescents may typically present with a suspected DSD as girls with primary amenorrhea (with or without breast development) or with signs of virilization. In 46,XY girls with breast development and primary amenorrhea, elevated androgen and AMH levels and an absent uterus, complete androgen insensitivity is most likely [35]. If there is no breast development, severe Leydig cell-specific steroid synthesis defects may be the cause. Extremely low levels of all gonadal steroids are indicative of LH receptor mutations, whereas low testosterone levels with elevated androstenedione values suggest 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3) deficiency. The appearance of clitoromegaly and hirsutism at puberty in the presence of primary amenorrhea may be due to 17β-HSD3 or 5α-reductase type 2 deficiency and less typically to partial AIS; some degree of ambiguous genitalia may have been noticed at birth in these cases. In 46,XX ovotesticular DSDs, the signs of virilization, which may have been overlooked at birth, are suggestive of the existence of testicular tissue. The differential diagnosis would include CAH and androgen-secreting tumors of the ovary or adrenal gland. AMH and testosterone levels are above the female range. A 24-hour urine collection for a urinary steroid profile will confirm CAH or adrenocortical tumor [33, 41].

Genetics

The development of rapid diagnostic tools are enabling better diagnoses/classifications and provide for a better understanding of DSD conditions, better genetic counseling, assessment of reproductive options and more precise outcome studies.

New genetic and genomic technologies are expanding our knowledge of the underlying mechanisms of DSDs and open novel clinical diagnostic strategies. At patient presentation, the current approach is to (a) search for additional phenotypic information, including urgent metabolic and endocrine testing and imaging studies; (b) rapidly identify the sex chromosome complement by karyotype analysis or FISH with X and Y probes and chromosome microarray, and (c) test for copy number variants in regions associated with known DSD genes. Gene sequencing, either of single candidate genes or a gene panel, based on information gleaned from previous phenotypic investigations, is often the last step of the diagnostic process.

Only limited numbers of the many identified genes involved in sex development are currently available for clinical testing. The current standard for genetic diagnosis is sequencing a small number of known DSD-causative genes chosen as likely candidates based on disease phenotype. Large numbers of patients do not receive a clinical molecular diagnosis using this narrow scope, and it is assumed that many DSD-causative genes remain to be identified.

An alternative diagnostic approach could use next-generation sequencing (whole exome or whole genome sequencing) as a first-line clinical test and lead to a rapid and definitive diagnosis in the majority of cases. However, this approach is faced with hurdles including long turn-around times, high costs, a lack of insurance approval or national healthcare system coverage and difficulties in the interpretation of the results, such as questions about reporting of nonrelated incidental findings or sequence variations which are significant but not recognized as such. These obstacles are likely to be overcome in the future, and next-generation sequencing is likely to become one of the first methods used for the diagnosis of DSD.

Currently, in instances in which a genetic diagnosis and the risk of recurrence are known, there is the possibility of prenatal diagnosis in subsequent pregnancies.

A review of human sex determination genetics has recently been published [42]. The complexity of genetic regulation, even with advanced technology to identify mutations and copy number variations, is insufficient to explain the observed phenotypes. Genetics alone remains unable to explain the biological and psychological issues related to individuals with DSDs.

Advancing and Evidencing Psychosocial and Psychosexual Well-Being

The psychological aspects of DSDs have either been narrowly conceptualized as brain gender research [43] or as a 'catch-all concept' incorporating any broad social or psychological concepts [44]. An emergent conceptualization is evident in the 2006 Consensus Statement: 'Psychosocial care provided by mental health staff with expertise in DSD should be an integral part of management to promote positive adaptation. This expertise can facilitate team decisions about male or female assignment/reassignment, timing of surgery, and sex-hormone replacement.' [1]. Psychological interests have broadened, but require conceptual clarity [45]. Reported research has weaknesses [46]. Methods are suggested below to facilitate future applied psychosocial research. Currently, well-being is defined as scores on popular quality of life (QoL) scales. Any causal link between a diagnosis and a single psychometric measure is flawed [47], since the effects of a diagnosis on well-being depend on a wide range of intrinsic and extrinsic factors across time including physical health, age, social values and access to resources including work, education, supportive relationships and health-care experiences. Well-being may be affected in highly specific ways at certain times, such as at the initial diagnosis, during the developmental stage, at symptom control, during fertility treatment or at the beginning and end of an important relationship.

Psychologically informed research with adults using a wider range of methods has captured specific difficulties, often despite medical interventions, such as dissatisfaction with binary gender [48], dissatisfaction with the DSD terminology [49], fear of devaluation [50], negative body image [51], social isolation [52], non-entitlement to relationships [53], preoccupation with heterosexual intercourse [54], functional sexual difficulties [55], barriers to communication with significant others and experiencing normalizing surgery as dilemmatic [56]. These studies have highlighted salient experiences and numerous potential mitigating factors which impact long-term outcome.

It has been hypothesized that body differences associated with DSDs may harm well-being although inconsistently. The high prevalence of normalizing surgery makes it impossible to separate the psychosocial impact of body differences and surgical management. In some cohorts, adults' dissatisfaction with their early surgery is high [57], while others report more positive long-term outcomes [58, 59]. Parental awareness of management options and consequences of decision making due to inadequate information are important topics [60].

Affected people make daily decisions about managing differences in the social sphere. It is unclear how self-disclosure relates to well-being, a concern of most care users. Minority stress (chronically high stress levels faced by members of stigmatized minority groups) research and studies of the impact of advocacy groups to mitigate distress have not been applied in DSD studies [16]. Advocates and clinicians recommend team and communication skills training for health professionals to advance well-being [61].

Group psychological interventions can improve well-being for women with MRKH syndrome [62], and group cognitive behavioral therapy can reduce specific stresses [63]. Group work drawing on cognitive and narrative approaches appears to improve self-evaluation of women with Turner syndrome [64].

A broader methodological approach is required [65], using a combination of existing methods that are highly relevant [66]. The open-endedness of qualitative approaches offers a greater scope for participants to define their own challenges and articulate emotions. With the emergence of well-designed and properly conducted nation-wide studies, methodology may become less constrained by the scarcity of research participants and hope-

fully benefit from more thorough epistemic considerations.

It is recommended to build on the small body of work using mixed methods, drawing on communication, organizational development, social studies and applied healthcare psychology research.

Evolving Perceptions: Male or Female Assignment, Reassignment and Outcome

The following is caretaker focused, while delaying decision options and involvement of the patient are discussed in the Ethical, Legal and Cultural Issues section.

There are ongoing debates after the incorporation of some individuals with DSDs under the psychiatric diagnostic category of gender dysphoria [67] including those dissatisfied with their male or female assignment. The construct of gender identity itself and related theories of gender identity development recognize a higher degree of complexity hopefully better representing biopsychosocial reality than previously [68].

The concept of 'gender identity' is a psychological one and poses a number of challenges for the clinician. In recent years, several tools have been developed for the systematic assessment of gender identity that aim at both the characterization of individuals in terms of gender categories within the primary binary gender system with its additional niches or categories and also in terms of a dimensional gradation of gender identity, usually on a bimodal continuum [69]. In the presence of significant intrafamilial and/or societal stigmas associated with gender-identity atypicalities, some individuals may keep private their gender dysphoria or the incongruence of their self-perceived gender identity with their assigned gender [e.g., 70]. A biomarker of gender identity is not (yet) available. Although a number of studies have published differences in central nervous system (CNS) structures between transgender and cisgender adults [71], these studies use a variety of brain-imaging (or cadaver-sectioning) techniques; the findings are heterogeneous and lack replication; and where there are structural differences, they usually overlap to a considerable degree between transgender and cisgender samples, so that they are not yet useful for individual gender categorization. Moreover, our current knowledge of the structures and functions of the CNS underlying gender identity is insufficient to read MRIs for the presence of a specific gender identity. Even if at some point in the future such an interpretation of MRI findings should become possible for individuals at later stages of cognitive development, it is questionable that the brain of a newborn is developed enough for the prediction of gender identity years later, given the gradual development of critical sex-dimorphic aspects of the CNS [72].

Considering newborn male or female assignment, there is increasing evidence, especially for 46,XX individuals with DSDs and when gender identity is assessed dimensionally rather than in terms of binary categories, that prenatal androgen levels have effects on human gender-related behaviors including sexual orientation and gender identity [73–75]. Those without fetal exposure (complete AIS or 46,XY complete gonadal dysgenesis), born with female-appearing external genitalia assigned female maintain that gender on long-term follow-up with rare exceptions [76]. Genital status at birth is moderately correlated with summary scales of later gender-related behavior, but not at all in syndromes involving nonhormonal malformations such as cloacal exstrophy or penile agenesis. Moreover, postnatal androgens, both in early infancy [77] and at later stages, may also contribute to long-term gender outcome. This is presumably mediated through organizational effects on the developing brain as well as the psychosocial effects of somatic virilization. Virilization may impact self-image and lead to negative social reactions, as seen in poorly controlled 46,XX CAH patients, untreated 46,XY 5α-reductase deficiency patients and 17β-HSD3 deficiency patients [78].

For most patients presenting with genital ambiguity so severe that a multidisciplinary group is needed to consider male or female assignment, the Consensus Conference summary [1] made the following recommendations. Female assignment is suggested for those with (1) 46,XX and CAH, since 95% develop female gender identity; (2) complete AIS, and (3) 46,XY LH receptor deficiency. Male assignment is recommended for those with 5α-reductase deficiency, since 60% later identify themselves as male, and for 17β-HSD3 deficiency, since >50% later switch to male. The suggested assignment for ovotesticular DSDs was as discussed below, with similar approach for mixed gonadal dysgenesis.

Overall factors to be considered for male or female assignment included probable adult gender identity (considered most important, but only tentatively predictable), anticipated quality of sexual function, surgical options/indications/risks, fertility potential, evidence of fetal CNS exposure to androgens, gonadal malignancy risk and psychosocial factors (familial, social and cultural). While most difficult to predict, the anticipated quality of sexual function is a key factor. Evidence suggests that this may not be influenced so much by genital anatomy as other

less tangible factors, related to interpersonal relationships. Among women with CAH [79], the ability to achieve an orgasm is not correlated with sensitivity, and neither this nor satisfaction with sexual life are different from control women. Hence, neither the anatomy nor a consult with sexual medicine can predict the quality of sexual function, since it depends upon interpersonal dynamics and the individual's abilities to participate and respond during sexual situations.

Sexual function scores were higher in patients satisfied with their sexual lives and with their surgical result [79]. Discrepancies were noted between CAH women's perception of the impact of their condition on their lives and what health professionals assumed based on clinical examination. The more severely affected (having the null genotype) scored lower on both sex function and sexual life satisfaction. In another report from the same study cohort, the psychological general well-being did not differ from that of the control group [80]. However, more CAH women, particularly those in the null genotype group, had male-dominant occupations, a greater interest in rough sports and motor vehicles. Nonheterosexual orientation occurred more frequently in the more severe genotype groups. The higher incidence of problems, particularly in those with severe CAH (like the null genotype group), may help to inform gender decision making in the severely virilized CAH infant. While sexual orientation should not be considered as a marker of favorable outcome, the higher incidence of nonheterosexual orientations in these patient subtypes suggests an important trend of the influence of fetal androgen on outcomes.

Patient care should be individualized even within clear etiologic diagnostic categories. For example, among 46,XX patients with CAH with Prader 4 and 5 genitalia at birth, available outcome data from patients raised male with follow-up well beyond midlife suggest for those essentially fully masculinized in utero that a male assignment be considered when social and cultural environment are supportive. 46,XX newborns with marked genital masculinization are more likely to show marked masculinization of behavior. This in combination with the risks of feminizing genital surgery to cosmesis and sexual functioning have led to a call for consideration of male rearing of these newborns [81].

The previously widespread routine assignment of 46,XY newborns with markedly hypomasculinized genitalia as females has given way to more detailed considerations of biological factors involved in combination with gradually increasing evidence for syndrome-specific long-term outcomes. Physicians are now more likely to suggest male assignment of 46,XY newborns who presumably had normal-male prenatal androgen levels with nonhormonal genital malformations, such as cloacal exstrophy of the bladder or penile agenesis [82, 83]. Evidence-based recommendations taking into account genital variables need to consider both gender-identity and QoL outcomes for male or female sex of rearing.

While there has been a trend to assign most 46,XY patients with DSDs as male [83], individualized caution must be taken with male assignment based on evidence of androgen responsiveness and CNS androgen exposure during fetal life. Although 60% of all 46,XY patients with 5α-reductase deficiency develop a male gender identity, there are reports of those assigned female with satisfactory sexual activity [84]. Hence, individual male or female assignment should be based of physical development, hormonal secretion, the presence/absence of genetic mutation and the response to hormonal therapy, particularly DHT. Among those with partial AIS, male assignment should be based upon a demonstrable response with phallic growth to testosterone therapy and genetic assessment if a causative variant of the gene is found, while female assignment must be considered for those without evidence of androgen effects. For those with 46,XY with 17β-HSD3 deficiency, care must be taken to assess all aspects, since there is evidence of satisfactory sexual function both among those raised male and those raised female. Among those raised male, there is considerable penis length dissatisfaction, and among those raised female, there is clinical distress. For those with 46,XY and a micropenis, male assignment is preferable for most regardless of penis size except for those with partial AIS. Among men with 46,XY and noncategorized hypospadias, the overall body image and psychosexual functioning do not differ from controls, while those with surgically repaired hypospadias reported less satisfaction than controls with penile cosmetic appearance with differences related to hypospadias severity (more proximal). A subset of patients with hypospadias and those with a micropenis have an insufficient penile length to achieve penetrative intercourse, hence, the issue of adequate penis size persists. It is clear that the same care plan cannot be applied to all individuals with a given diagnosis/syndrome and severity; each must be carefully individualized with specific assessment of each aspect. Since genital appearance and function dissatisfaction may jeopardize sexual QoL, psychological support is strongly recommended.

Bias in gender decisions and the urgent need for evidence-based consensus are illustrated by assignments of infants with ovotesticular syndrome, about half of whom

are assigned male or female regardless of karyotype [85]. The location of the urethral meatus and associated surgical challenges, dysgenetic testicular tissue and the presence of a uterus and normal ovarian tissue influenced the assignment in the past [86]. Case studies report gender dysphoria and/or patient-initiated gender change in either direction in patients [87, 88]. For this condition and others, only systematic large long-term gender outcome and QoL data will constitute a solid empirical basis for determining crucial factors involved in assignment decisions. This will likely include the realization that all with the same etiological diagnosis and karyotype will not necessarily have the same male or female assignment.

Information and Decision Making Regarding Male or Female Assignment

Historically, health professionals – primarily physicians – did not openly and fully communicate with patients and families about their DSDs, in part because of the belief that there would be difficulties accepting a full disclosure. Without complete information, parents and eventually the affected person had an inadequate understanding about DSDs and their specific diagnosis. Now, it is clear that open and complete communications are mandatory when there is uncertainty in decision making. Education and psychological support regarding the impact are needed for each individual to make sense of the condition, relate to their community and establish relationships.

The lack of outcome data and different preferences make it difficult to determine whether and when to pursue gonadal or genital surgery. Shared decision making is necessary and can be viewed as the 'crux of patient-centered care' [89], combining expert health-care knowledge and the right of a patient or surrogate to make fully informed decisions. This entails a process of education, sharing of risks/benefits, articulating the uncertainties in DSD care and outcomes and providing time for the patient and family to articulate back the risks and benefits of each option. The goal of all involved should be to individualize and prioritize each patient.

There are efforts to improve clinical communication, including E-learning and prepared scripts that help physicians practice sharing information with patients and their families about a diagnosis [90]. Some clinics incorporate former patients and patient advocates to support families and patients. PSGs are dedicated to serving individuals. Educational materials have been created and can be found at www.dsdfamilies.org, www.interactyouth.org, www.dsdgenetics.org and www.accordalliance.org as well as other advocacy and SGs (table 1). An ongoing project of clinics and patient advocates within the US-based DSD-Translational Research Network is to develop a customizable list of educational material to provide to children, youth, families and adults in their clinics and make the sharing of resources more systematic in DSD teams.

Decision aids and support tools (DASTs) can enhance decision quality by increasing knowledge and understanding, promoting confidence in decisions and reducing decisional regret. A web-based DAST for parents of newborns or young children with DSD is currently being developed [91].

Continued efforts in effective communication also include viewing DSDs as similar in some aspects to other complex care situations, thereby allowing the incorporation of lessons learned from research and the continued efforts to improve collaborative work between researchers, clinicians and advocacy groups.

DSD health-care teams, developed largely since 2005, can be multidisciplinary, interdisciplinary or transdisciplinary, implying different degrees of collaboration and professional autonomy [92]. Multidisciplinary involves simultaneous, but independent, contributions of team members from two or more disciplines (fig. 1a). Team members in the interdisciplinary model work jointly, each from a discipline-specific perspective, but with acceptance that elements of knowledge and skills are shared to address a common problem (fig. 1b), thereby reducing turf battles. Finally, a transdisciplinary approach synthesizes discipline-specific concepts, creating new models to address a common problem. A cardinal feature of the transdisciplinary approach is that providers from all disciplines are jointly responsible for every clinical goal (fig. 1c).

As with other chronic conditions diagnosed during pediatric years, the transition of individuals with DSDs to adult care is not ideal. With limited exceptions, persons with DSDs may not, in the short-term, experience negative consequences from poor treatment adherence or avoidance of providers. However, such avoidance places the person at risk for long-term complications such as osteoporosis, gonadal malignancy, and poor psychosocial and psychosexual adaptation. The practice of withholding medical history details, along with the possibility of negative medical experiences, likely contributes to patients with DSDs frequently being 'lost to follow-up.'

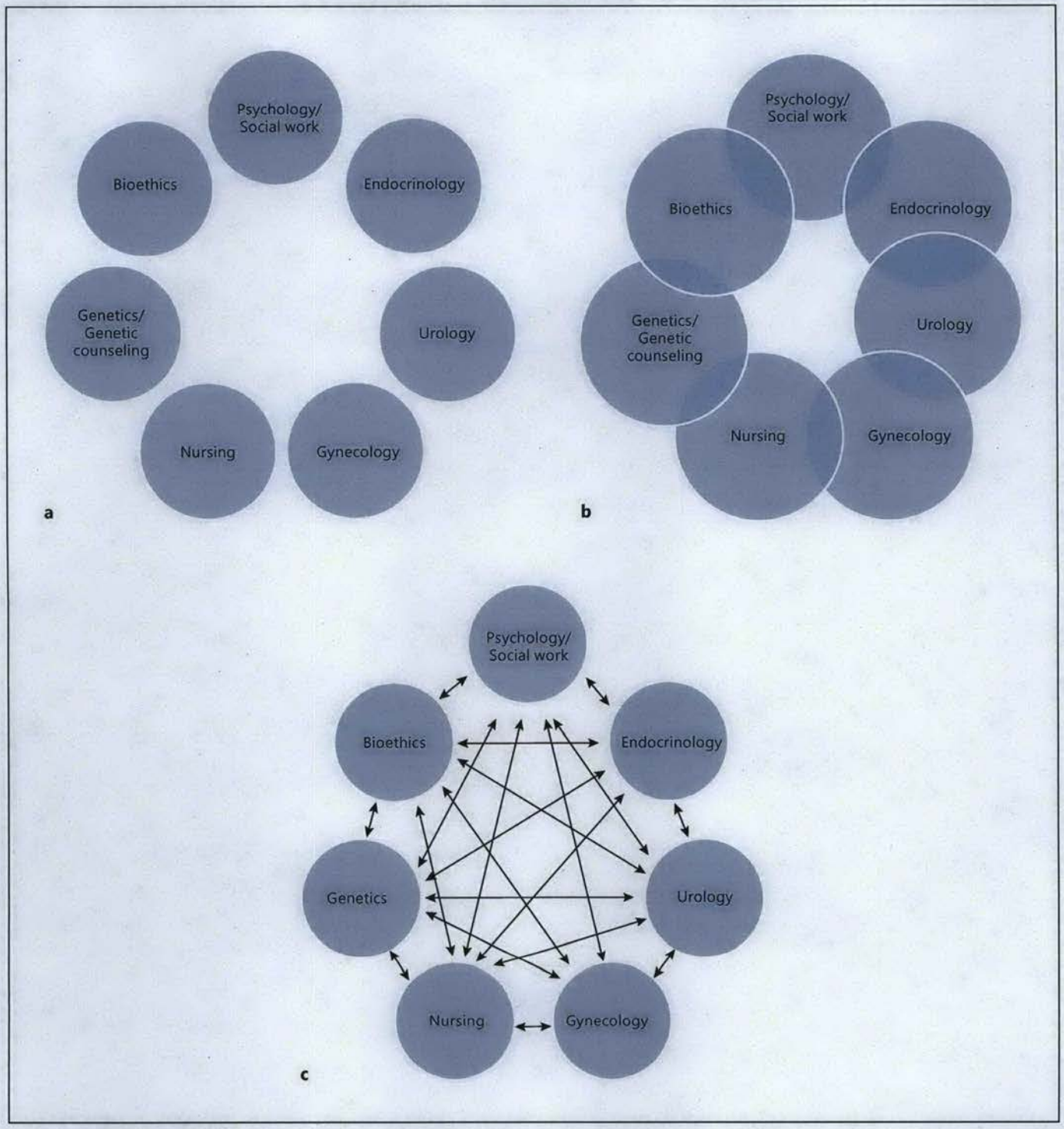

Fig. 1. Models of DSD team care: **a** simultaneous independent contributions of team members from two or more disciplines; **b** team members work jointly, each from a discipline-specific perspective, with acceptance that elements of knowledge and skills are shared to address a common problem; **c** a transdisciplinary approach synthesizes discipline-specific concepts, creating new models to address a common problem with all disciplines being jointly responsible for every clinical goal. Based on Institute of Medicine Report [77].

Other challenges for adolescents and young adults with DSDs include anticipatory anxiety related to romantic and sexual relations because of an atypical genital anatomy, function or infertility, and fears of stigmatization. Patient education in a developmentally sensitive manner is essential to facilitate an optimal medical and psychological follow-up [93]. Although adolescents may be reticent regarding their contact with patient support organizations, the potential benefits of speaking with others who have shared experiences should be reintroduced if initially rejected [16]. Guidance on preparing adolescents and young adults with chronic conditions for transition to adult care, in general [94] and specifically in DSDs [95], is available.

Hormonal Treatment of Patients with DSDs

With the exception of therapy for CAH, hormonal treatment primarily involves pubertal induction for hypogonadism, hormone replacement therapy (HRT) at various ages and, in some instances, pubertal suppression. Patients with DSDs lacking functional gonads require HRT during adolescence to re-enforce gender identity, promote congruent secondary sexual characteristics, growth, bone health and psychosexual and social well-being. Pubertal induction is usually at age 10–12 in girls and 11–13 in boys, depending on the maturity, desires and informed consent of the patient and parents. Options for hormonal treatment for patients with DSDs are limited by practical considerations, such as pharmacokinetic properties and effectiveness of steroid hormone preparations, and availability.

Cultural factors also influence parents' and patients' expectations and desires for these treatments. A definitive diagnosis based on biochemical and genetic data enables providers to counsel the family about the natural history of the condition and may help inform decisions about therapy. Best practices to ensure that the chosen treatments lead to high patient satisfaction are needed. Such should include recommendations concerning monitoring of therapy with hormone and bone density measurements.

For pubertal induction in individuals with a female gender identity and a uterus, the standard approach remains a low dose of estrogen, gradually increasing the dose over 2–3 years mimicking the normal tempo of puberty. A slow titration of estrogen is especially important in patients in whom stature is of concern, i.e. Turner syndrome. All preparations are not available in all countries. A recent trend is to use estradiol, which can be measured in serum to adjust dosing, rather than equine or synthetic estrogens. The disadvantage is that the bioavailability of oral estradiol (0.5–2.0 mg/day) is highly variable. Compared to equine estrogens and ethinyl estradiol, the use of transdermal estradiol patches appears to be more physiological and consistent, by avoiding a first pass through the liver and allowing estradiol levels to be titrated to the mid-normal range for Tanner stage. Transdermal estradiol doses start at 6 μg/day and are increased gradually over 3 years to 25–100 μg/day, based on estradiol levels and clinical response. After 1–3 years of estrogen or the occurrence of break-through bleeding, medroxyprogesterone 5–10 mg/day or micronized progesterone 200 mg/day for 10–14 day/month facilitate menses in patients with a uterus. Pubertal induction in those with a female identity who do not have a uterus typically follows a pattern of escalating estrogen doses similar to that of girls with a uterus. However, in the absence of a uterus, no progestin is required. Some women are trying testosterone in addition to estrogen, although no clinical trial results are currently available.

For induction of male puberty, a variety of regimens are available. Testosterone ester injections have been used successfully for decades, given in frequencies of every 1–4 weeks. One regimen involves starting with 50 mg monthly, advancing the dose every 6–12 months, and eventually reaching 100 mg/week or 200 mg twice monthly for the full adult dose. Testosterone undecanoate can be injected every 10–12 weeks. Transdermal patches and gels are now available and may provide more physiological daily exposure without peak-and-trough cycles. There is no evidence for their superiority over injections, and the gels may fail to produce testosterone values in the normal male range. Many have found that patches and gels are not popular because of the frequency of application, time required and reactions such as itching with the patches. Topical dihydrotestosterone, where available, is being tried for patients with 5α-reductase deficiency, although its efficacy has not been well documented. Long-acting depot formulations, primarily testosterone undecanoate, might offer the unique advantage of stable serum testosterone levels with injections every 10–12 weeks, but data are limited in adolescents. There is also some experience with testosterone pellets.

Gonadotropin-releasing hormone antagonists are being tried in contrasexual puberty to delay changes in patients with functional gonads whose gender identity is either uncertain or incongruent with the gonadal hormones. Under these circumstances, HRT and surgery

should commence only after a full psychological evaluation at the appropriate age for each fully informed patient.

Once patients become mature, the choice of hormones, doses and schedules should fit the patient's needs and optimize long-term outcomes, including bone density, mental health, metabolic state, QoL and sexual satisfaction as well as interest in fertility and potential for assisted reproduction techniques.

Optimal replacement therapies for patients with gonadal failure beyond age 50 are not known. Estrogen replacement in symptomatic menopausal women is conventionally continued for approximately 5 years and then tapered, suggesting that the same should apply to agonadal women. Men typically continue to take testosterone throughout life, but the risk of prostate disease should be discussed. Women given estrogens require screening mammography, and men taking testosterone require hematocrit, prostate exam and prostate-specific antigen testing according to national guidelines.

Risks of Tumor Development

Patients with DSDs have an increased risk of developing cancers of the germ cell lineage, malignant germ cell tumors or germ cell cancer (GCC) compared to the general population. Although precursor lesions are formed during embryonal or early post-partum development, the progression to invasive growth only occurs during or after puberty, often cited as a reason to delay surgery. A defined number of parameters are relevant in determining if and to what extent an individual patient is at risk. These include (1) genomic constitution, i.e., the presence of the *Gonadoblastoma on the Y chromosome* [GBY] region, and of the current best candidate gene *TSPY*; (2) the expression of the embryonic germ cell markers OCT3/4 (POU5F1) and/or KITL (stem cell factor) beyond the age of 1 year, and (3) the anatomical localization of the gonad(s). The histology of the precursor lesion depends on the level of gonadal testicularization, being carcinoma in situ (CIS)/intratubular germ cell neoplasia unclassified (IGCNU) of the (dysgenetic) testis (i.e., a higher risk level) and gonadoblastoma (GB) of the dysgenetic gonad(s) (i.e., a lower level). The earliest identifiable stage giving rise to GB is known as undifferentiated gonadal tissue. In general, the supportive cells of CIS/IGCNU are Sertoli cells (positive for SOX9), while those of GB are granulosa cells (positive for FOXL2), although costaining can be identified even within a single gonad. The diagnosis must be made by an experienced pathologist, supported by immunohistochemical staining data, and with full knowledge of the parameters and clinical data. Particularly, the possibility of delayed maturation must be considered in young children or the nonscrotal localization of a testis. Histological information is obtained from either a gonadal biopsy or gonadectomy. A well-designed stratified approach can be followed to identify individuals who can undergo spontaneous puberty, possibly even life-long retention of no-risk or low-risk gonads.

It is well recognized that the highest risk prevalence (30–50%) is seen in conditions characterized by disturbed gonadal development such as incomplete testis development combined with a full block of embryonic germ cell maturation in patients with 46,XY gonadal dysgenesis and in some patients with 45,X/46,XY DSDs. The degree of testicularization is reflected to some extent in the patient's phenotype with a low external masculinization score indicating a poorly differentiated gonad. Combined with knowledge on the underlying condition, GCC risk can be predicted. Conversely, individuals with testosterone biosynthesis disorders and androgen action disorders show a much lower risk (<1–15%) for CIS development during childhood and a limited tendency towards invasive progression of the lesions, possibly inversely correlated to the degree of testosterone exposure/action. The clinical value of putative interesting diagnostic approaches, such as a more precise molecular diagnosis (next-generation sequencing) and noninvasive screening methods based on identified risk SNPs and novel serum (microRNA) markers, must be evaluated by skilled multidisciplinary DSD teams.

A recent publication proposes a model to assess the combined effect of epigenetic and environmental factors on the pathogenesis of GCC development [96]. Table 2 includes guidelines concerning the clinical management of GCC risk.

Surgical Issues

Since the Consensus Meeting in Chicago [1], DSD surgery continues to raise unresolved questions and dilemmas regarding indications, timing and procedures in the various categories of DSDs [97].

DSD surgery includes 4 main components [98]: (1) surgery of the genital tubercle which can be reduced in size (clitoroplasty) or reconstructed (hypospadias repair or phalloplasty; fig. 2–4); (2) the management of the Mül-

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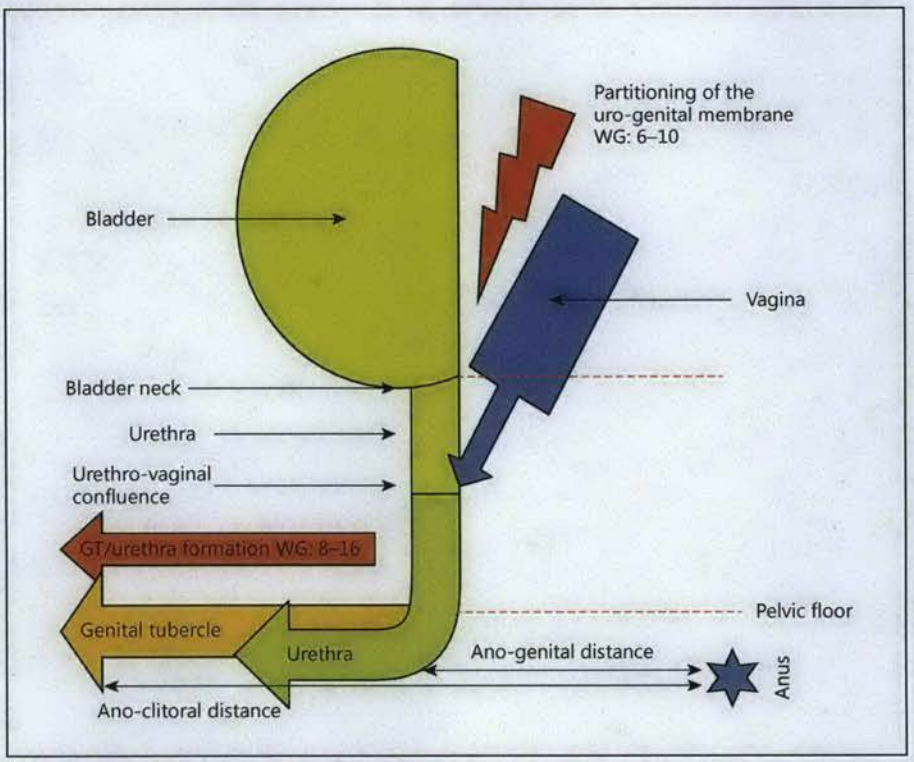

Fig. 2. Anatomy of CAH genitalia showing the 3 main criteria to evaluate the degree of virilization: (1) the distance between the urethro-vaginal confluence and the perineal surface; (2) the length of the genital tubercle and the availability of urethral tissue to refashion the vaginal introitus, and (3) the fusion of the genital folds measured by the ratio ano-genital distance to ano-clitoral distance. WG = Week of gestation; GT = genital tubercle.

Table 2. GCC risk: clinical management

	Male	Female	Unclear gender
Gonadal dysgenesis (45,X/46,XY and 46,XY)	Undescended testes – Orchiopexy with biopsy – Self-examination – Annual ultrasound (post-puberty) Post-pubertal biopsy – Based on ultrasound and results of first biopsy – If CIS becomes GB → gonadectomy Low threshold for gonadectomy if ambiguous genitalia	Bilateral gonadectomy at diagnosis	Low threshold for gonadectomy if ambiguous genitalia If intact, gonadectomy depends on gender identity
Undervirilization (46,XY: partial AIS, complete AIS, testosterone synthesis disorders	Undescended testes – Orchiopexy with biopsy – Self-examination – Annual ultrasound (post-puberty) Post-pubertal biopsy – Bilateral, CIS → gonadectomy/irradiation Repeat biopsy at 10 years of age – Consider gonadectomy to avoid gynecomastia or if on testosterone supplementation	Partial AIS and testosterone synthesis disorders – Prepubertal gonadectomy Complete AIS – Postpubertal gonadectomy or follow-up – GCC risk low, allow spontaneous puberty	Partial AIS and testosterone synthesis disorders – Bilateral biopsy – Low threshold for gonadectomy Intensive psychological counseling and follow-up

No data are available on the value of cryopreservation or safety if a precursor lesion for GCC is present.

lerian structures (vagina, uterus) which includes the connection of a vaginal cavity to the pelvic floor, vaginal substitution, dilatation of a vaginal cupule or removal of Müllerian remnants; (3) surgery of the gonads involves descent (orchiopexy), removal (tumor risk/late virilization) or biopsy for pathology or the preservation for reproduction, and (4) refashioning of the perineum (perineoplasty). Considerations for each of these procedures involve indications, timing, technical aspects, possible complications and long-term outcome. Such issues must

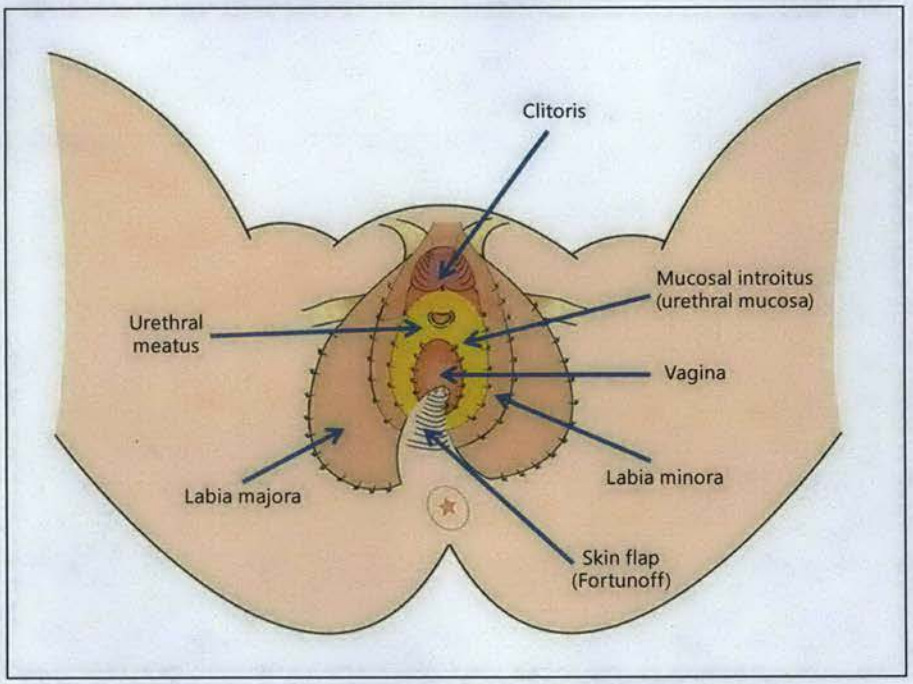

Fig. 3. Anatomy of CAH genitalia after surgical repair showing the connection of the vagina to the perineum, the mucosal introitus, the reduced genital tubercle and the refashioned labia.

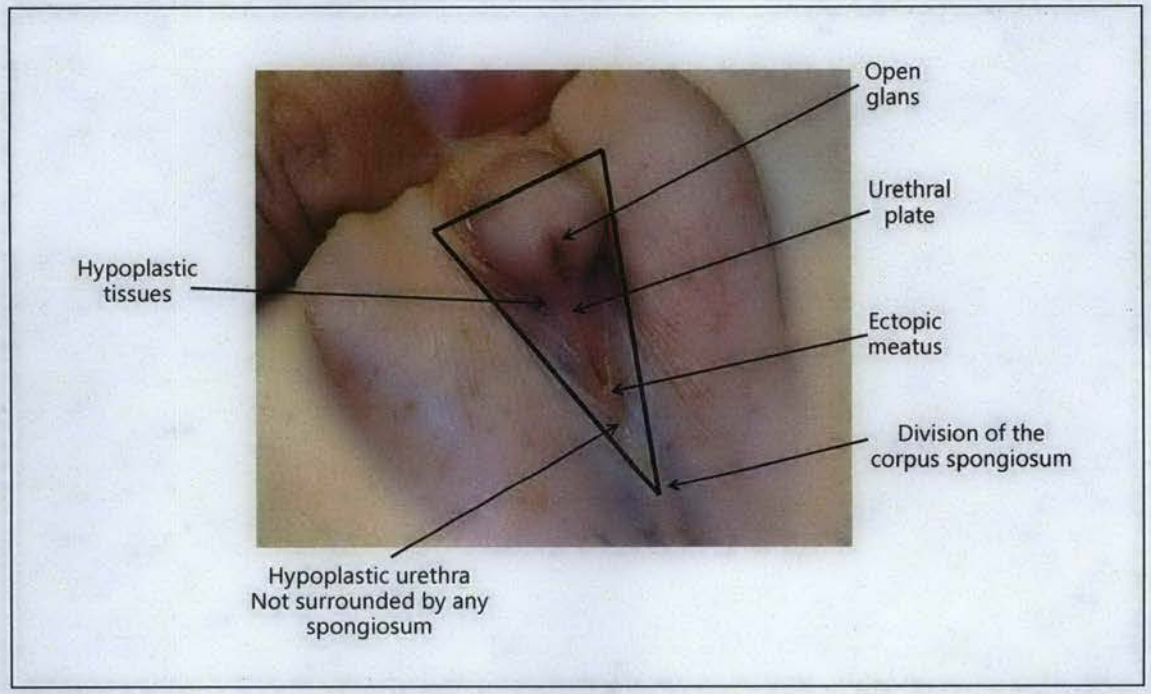

Fig. 4. Ventral aspect of a hypospadiac genital tubercle showing the ventral triangular defect formed by the proximal division of the corpus spongiosum. The tissues located in this triangle are hypoplastic and explain the ventral curvature of the genital tubercle.

be individually discussed with each patient/family for each DSD category.

A questionnaire considering the most sensitive situations in surgery has been circulated among a group of 32 experts (see consortium list in the Appendix), primarily surgeons, in order to establish some consensual guidelines for each specific situation. There is still no consensual attitude regarding indications, timing, procedure and evaluation of outcome of DSD surgery. The levels of evidence of responses given by the experts are low (B and C), while most are supported by team expertise. Literature reports are primarily short clinical series that cannot be compared because of heterogeneous pathologies and management. However, most experts agree with (1) the need for identifying centers of expertise with a multidisciplinary approach [19]; (2) a conservative management of the gonads in complete AIS patients [99, 100]; (3) avoidance of vaginal dilatation during childhood; (4) keeping asymptomatic Müllerian remnants during childhood which can be removed later if necessary [101]; (5) removal of biopsy-confirmed streak gonads [96], and (6) keeping 46,XY cloacal exstrophy patients in the male gender [82, 102].

Timing, choice of the individual and irreversibility of surgical procedures are sources of concerns. There is no evidence regarding the impact of surgically treated or non-treated DSDs during childhood for the individual, the parents, society or the risk of stigmatization. The low level of evidence for management should lead multidisciplinary expert teams to design collaborative prospective studies involving all parties and using protocols of evaluation.

Fertility

The advancement of assisted fertility techniques has continued so that the potential for fertility is more likely albeit expensive. Fertility may be possible utilizing sperm retrieval and ICSI in patients who have functional gonads and do not require testosterone at puberty such as XO/XY mosaicism, 5α-reductase deficiency and partial AIS patients. Further, if germ cells are present in the gonads such techniques may be possible among those requiring HRT. Among females, stimulation of ovulation and embryo transfer using fertilized donated ova have been used, including in females with CAH and Turner syndrome.

Ethical, Legal and Cultural Issues

No area of pediatric endocrinology engenders more controversy than the management of DSD conditions affecting reproductive development. With some variations, guidance from clinicians and ethicists has focused on principles and processes aimed at fostering the overall well-being of the child and future adult by: (1) minimizing physical and psychosocial risk; (2) preserving potential for fertility; (3) upholding the individual's rights to participate in decisions that will affect their now or later; (4) leaving options open for the future by avoiding irreversible treatments that are not medically necessary until the individual has the capacity to consent; (5) providing psychosocial support and PS; (6) supporting the individual's healthy sexual and gender identity development; (7) using a shared decision-making approach that respects the individual's and parents' wishes and beliefs; (8) respecting the family and parent-child relationships, and (9) providing patients with full medical information appropriate for age, developmental stage and cognitive abilities [103–105]. While each of these principles is important, striking the appropriate balance among them becomes challenging in the clinical setting. For example, respecting parents' wishes for early genital surgery may impinge on the child's right to participate in decision making and may reduce the child's options for the future.

In addition to guidance from within the medical community, there has been a recent marked increase in initiatives by governments and related agencies to develop ethical and legal frameworks for care [106–112]. Surgical intervention, in particular, has come under intense scrutiny, with a number of agencies condemning or calling for a complete moratorium on elective genital surgery or gonadectomy without the individual's informed consent [108, 111, 112]. Although parents are responsible for consenting to interventions believed on the basis of available evidence to be in the best interests of their child, their right to consent to non-medically necessary irreversible procedures that may adversely affect the child's future sexual function and/or reproductive capacity has been questioned, particularly when such parental decisions preclude the child's ability to be involved in decision making. In addition, many guidelines deem children's participation and input indispensable to decisions, especially those that will have a life-long deeply personal impact on their lives, with heightened awareness that young children, in particular, may not be able to vocalize adverse reactions to many interventions [106, 110, 111].

As a consequence of the efforts of some patient advocacy groups in partnership with allies within and beyond the medical community, legal challenges have been brought against practices that were considered standard of care in the management of children with atypical genital or reproductive anatomy in the 1970s to 1990s. This has resulted in litigation or ruling against the practice of genital surgery or gonadectomy without patient consent as a breach of fundamental reproductive rights and bodily autonomy in some circumstances [e.g., Columbia, Australia, Kenya, South Carolina (USA)]. In addition, provision has been made in some jurisdictions (e.g., Australia, Germany, Malta) for the registration of the sex of a child to be postponed or lodged as 'other' in situations in which it is unclear.

Although fundamental human rights are generally considered universal, irrespective of race, gender, nationality, religion or other factors, the interpretation of those rights is shaped by the cultural and socioeconomic context, contributing to even greater complexity in ethical and legal frameworks regarding care. An evaluation of the application of ethical principles developed in Western settings would be useful in other cultural settings.

The disciplines of ethics and law are dynamic, and a continuing evolution is to be expected as individuals within and across fields address a genuine struggle regarding appropriate care for children and families living with these conditions. Physicians working with these families should be aware that the trend in recent years has been for legal and human rights bodies to increasingly emphasize preserving patient autonomy.

Appendix

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Errata

The Australasian Pediatric Endocrine Group (APEG) contributed substantially to the composition of the recent publication 'Global disorders of sex development update since 2006: perceptions, approach and care' by Lee et al. [Horm Res Paediatr 2016;85:158–180, DOI: 10.1159/000442975], but did not endorse this document. Dr. Peter Koopman provided considerable input and should have been listed among the members of the Global DSD Update Consortium.

In the appendix of the recent publication by Lee et al. entitled 'Global disorders of sex development update since 2006: perceptions, approach and care' [Horm Res Paediatr 2016;85:158–180, DOI: 10.1159/000442975], Massimo Di Grazia, Psychologist, is incorrectly mentioned to be from Cosenga, Italy. The correct city is Trieste, Italy.

CHAPTER 13

Intersex

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The term *intersex* is most often used to describe infants who have ambiguous genitalia at birth. The genital appearance does not indicate whether the chromosomes are male, female, or mosaicism or whether a mutation in one of the critical sex differentiation genes has altered the genital appearance. Nor are there any clues as to the internal sex structures such as the uterus, fallopian tubes, and wolffian duct derivatives. Furthermore, the genital appearance in infancy does not predict the future gender identity or sexual orientation in adulthood.[1-5]

The genital abnormalities are the result of defects in hormone production or hormone action. The most common cause of intersex in 46,XX is congenital adrenal hyperplasia (CAH). Other etiologies include abnormalities in gonadal differentiation and function; androgen underproduction in genetic males or defects in androgen action.

Intersex may not be diagnosed until later in childhood or adulthood if the genitalia are female appearing at birth. Examples include a 46,XY adolescent girl who fails to menstruate or have sexual hair growth or is found to have a testis in an inguinal hernia (eg, complete androgen insensitivity syndrome [CAIS], or 17α-reductase deficiency).

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Nonhormonal morphologic abnormalities of the pelvis and perineum may resemble intersex disorders, but their etiology is different (eg, cloacal anomalies, epispadias, bladder exstrophy, or penile agenesis). The genitalia may be variably ambiguous, or there may be no ambiguity as in penile agenesis[6] or unambiguous isolated micropenis. Isolated micropenis is defined as stretched penile length in the newborn ≥1.9 cm or 2.5 standard deviations below the mean for age.

MOLECULAR BIOLOGY OF SEXUAL DIFFERENTIATION

Sexual differentiation is controlled by genes located on both the sex chromosomes and autosomes (Fig 1). Their interplay and function have been reviewed recently.[1]

The mesoderm is the embryonic tissue from which the genital ridge (WT-1) and the primitive kidney (SF-1) are formed. A mutation in the WT-1 gene causes Frasier syndrome, which is characterized by failure of the kidney and the primitive gonad to differentiate in 46,XY males. Usually males die of renal insufficiency in infancy and have female-appearing external genitalia and malformed testes. Genital ridge differentiation into the bipotential gonad depends on SOX9, WNT-4, and DMRT 1,2. The X- and Y-bearing germ cells determine whether the bipotential gonad becomes a testis or an ovary.

Testicular differentiation depends on the SRY gene on the short arm of the Y chromosome.[1,7,8] A mutation in the HMG region of the SRY gene causes testicular failure, female phenotype (sex reversal), or genital ambiguity. SRY is transiently expressed in the brain and the testis; this gene induces the differentiation of the Sertoli cells, seminiferous tubules, and Leydig cells. SRY may function by activating genes needed for male development, or it may serve to inhibit male-suppressing genes. Mutations in SRY are not present in all 46,XY sex-reversed persons, and only 25% of 46,XY females have a mutated SRY gene. An SRY gene is not usually found in 46,XX males with testes and genital ambiguity. Autosomal genes also play an important role in sex differentiation. SOX9, located on 17q24-25, is essential for Sertoli cell differentiation. The SOX genes have similarities to the SRY HMG box region, hence the abbreviation for S_RY homeob OX-like genes. SOX9 haploinsufficiency in a 46,XY male causes skeletal dysplasia, female phenotype, and streak ovary–like gonads (campomelic dwarfism).[8] SRY is presumed to suppress the DAX 1 gene on the X chromosome and activate the SOX9 gene on 17q24-25. This illustrates that a critical interplay exists between sex chromosomal and autosomal genes.

Ovarian development appears to depend on suppression of SOX9. Other testis-suppressing genes include DAX 1, SOX 3, and

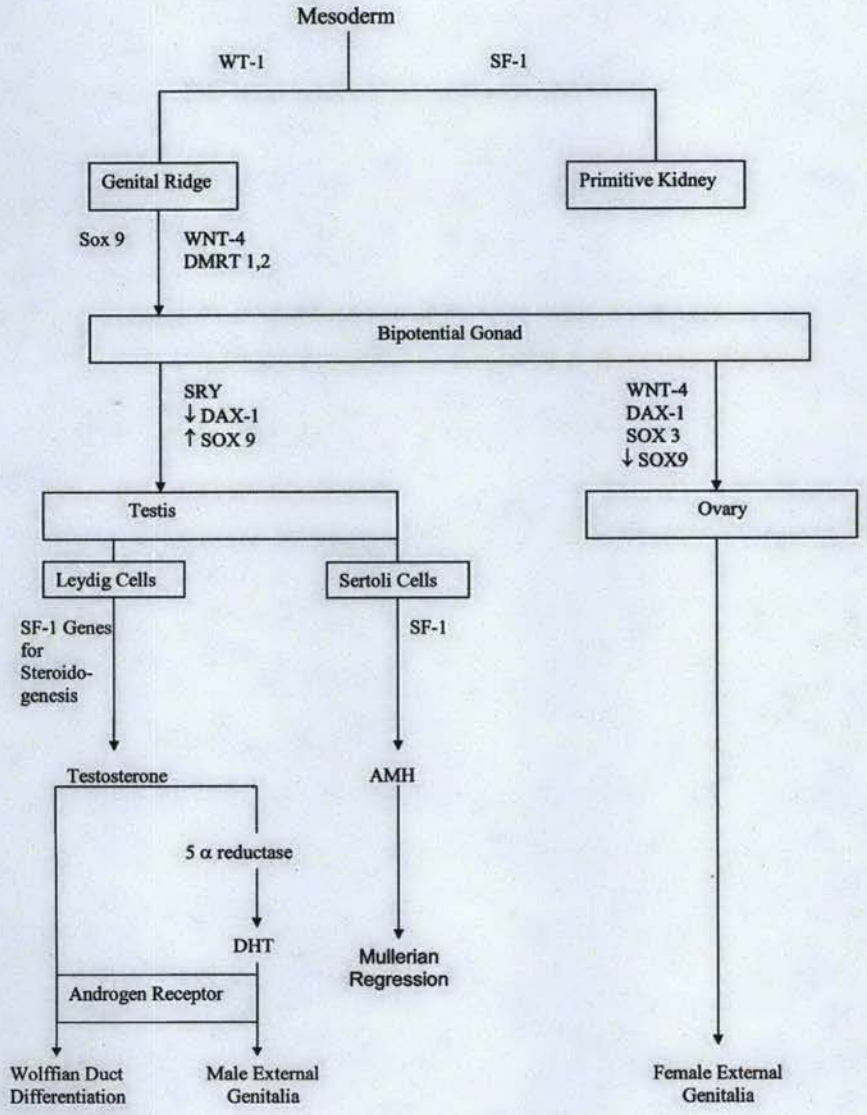

FIGURE 1.

Genes involved in the pathway of sexual differentiation. *Abbreviations: DHT,* Dihydrotestosterone; *AMH,* antimüllerian hormone.

WNT 4. Under this scheme, DAX 1 in the ovary inactivates SOX9, thereby blocking testis differentiation in the bipotential gonad. In the differentiating ovary, WNT 4 appears to block androgen production by Leydig cell precursors and also induces müllerian development.[9] Deletion of WNT 4 causes masculinization of 46,XX females and 46,XX mice as well as degeneration of müllerian duct derivatives. Duplication of SOX9 is an autosomal cause of 46,XX sex reversal.[10] Ovarian differentiation is likely to be an active process, and the critical genes on the X chromosome probably have dosage-sensitive functions—this is based on the loss of germ cells in girls with Turner syndrome. In the ovary, DAX 1 on the X chromosome is an antitestis gene.

Males inherit the DAX 1 gene from their mothers, and SRY suppresses DAX 1, thereby allowing expression of SOX9, which plays an important role in male development. Males who inherit a duplication of DAX 1 have sex reversal and gonadal dysgenesis because SOX9 is unable to suppress the double dose of DAX 1. The DAX 1 duplication may be located on the X chromosome, or there may be a translocation of the second DAX 1 gene to the fetal Y chromosome.[10,11] 46,XY sex reversal may also result from WNT 4, which acts upstream and in concert with DAX 1. In 46,XY sex-reversed persons, duplication of WNT 4 causes upregulation of DAX 1 in the embryonic testis and suppression of SOX9, which leads to a female phenotype.[12,13]

Tables 1 and 2 list the defects in SF 1 and other sex-determining genes that cause 46,XY gonadal dysgenesis and a female phenotype.

In the 46,XY fetal male, DAX 1 is essential for adrenal development as well as gonadotropin production by the fetal pituitary gland. Absence of DAX 1 in these males leads to adrenal hypoplasia congenita (congenital Addison disease) as well as hypoplastic testes and micropenis caused by hypogonadotropic hypogonadism.[14]

The genes controlling development of the müllerian and wolffian duct derivatives are shown on Figure 1. Wolffian duct differentiation into epididymis, vas deferens, seminal vesicles, and ejaculatory duct is dependent on the local (paracrine) production of testosterone by the Leydig cells, whereas müllerian duct differentiation is suppressed by the antimüllerian hormone (AMH) made during early fetal life in the Sertoli cells. AMH production continues to the age of 8 to 10 years in boys.

In girls, the müllerian ducts differentiate into the fallopian tubes, uterus, and upper third of the vagina in the absence of AMH. The WNT 4 gene is also involved in this process in addition to its

TABLE 1.
Genes Controlling Sexual Differentiation

Gene/Chromosome	Family/Function	Clinical Phenotype
SRY, Yp 11	HMG protein, transcription factor	XY gonadal dysgenesis
WT 1, II p13	Zinc finger protein transcription factor	Denys-Drash syndrome Frasier syndrome
SF 1, 9q33	Orphan nuclear receptor transcription factor	XY gonadal dysgenesis Adrenal insufficiency
DAX 1, Xp21.3	Orphan nuclear receptor transcription factor	Duplication causes: – XY sex reversal Mutation causes: – XY adrenal hypoplasia congenita (AHC) and gonadotropin deficiency
SOX9, 12q24	HMG protein transcription factor	Mutation causes: – XY sex reversal – Campomelic dysplasia
WNT 4, 1p32.36	Growth factor	Duplication causes: – 46,XY sex reversal Deletion causes – Masculinization of 46,XX female

role in the ovary, where it prevents androgen production by precursors of Leydig cells in the interstitium and facilitates oocyte survival.

The primordial external genital structures are identical in males and females up to the age of 8 weeks. Male differentiation depends on the adequacy of testosterone production and its conversion to

TABLE 2.
Causes of 46,XY Testicular Dysgenesis

1. XY gonadal dysgenesis
2. Denys-Drash syndrome, WT 1 mutation
3. Frasier syndrome, WT 1 mutation, also nephropathy, gonadoblastoma
4. XO-XY mosaicism—Mixed gonadal dysgenesis
5. Campomelic dysplasia—SOX9 mutation
6. DAX 1 duplication (dosage-sensitive sex reversal in 46,XY males [DSS] syndrome)
7. WNT 4 duplication
8. SF 1 mutation
9. Deletions: 9p-, 10q-
10. Duplication: X p +

5α-dihydrotestosterone, as well as normally functioning androgen receptors.[15-17] The genital tubercle is the precursor of the glans penis. The urethral folds develop into the penile shaft and urethra, and the genital swellings become the scrotum. In the female, these primordial structures become the clitoris, the labia minora, and the labia majora, respectively. Thus, differentiation of the external genitalia is bipotential, and differentiation depends on the presence of androgens in males and the absence of androgens in females. Androgen production in the female fetus (CAH, aromatase deficiency) or exposure to androgens made or ingested by the mother causes virilization of the external genitalia in female infants.[18-20] In contrast, male infants will have undervirilized external genitalia if the production or action of androgens is deficient.

HISTORICAL BACKGROUND ON THE EARLY MANAGEMENT OF INTERSEX INFANTS

Approximately 50 years ago, Lawson Wilkins, John Money, and collaborators[21] at The Johns Hopkins Hospital formulated the "optimal gender" approach to the management of infants born with ambiguous genitalia. They assumed that gender identity (subjective conviction of an individual as male, female, or ambiguous) was not fully established at birth and that sex of rearing and the early environment (nurture) had a major role in the development of gender identity. This approach required that parents be unequivocal in their support of the assigned gender, which was usually done prior to the age of 18 months to 2 years.[22]

In the early decades, there was a sense of urgency to make the gender assignment decision during the first days of life, followed by genital reconstruction in the early months of infancy. The complexity of adult female sexual responses, the importance of the clitoris to sexual satisfaction, and the essential roles of nerve innervation and blood supply to the clitoris were underestimated. Nor was it anticipated that vaginal construction might be problematic and give poor outcomes because of the pain during intercourse resulting from postoperative scarring and inadequate vaginal size for penile entry.[23-30] Surgical techniques have markedly improved. Clitoral amputation is no longer performed, and clitoral recession or reduction is reportedly being done without sacrificing sensation and vascularity.[30] Present-day critics of early surgery still argue that clitoral atrophy and loss of sensation may occur during the childhood years, and recommend delaying surgery. Whether vaginoplasty should be done early or delayed is a debated subject that has involved medical experts as well as adult patients.[20,26,29] More information on the out-

comes in patients having the newer surgeries will provide us with much needed information.

Money and colleagues acknowledged that there were no ideal outcomes for the most severe cases, and based their sex assignment decisions on the extent of the masculinization or feminization of the external genitalia, the future potential for sexual functioning, the potential for fertility, and the future need for sex hormone therapy during adolescence and adulthood. In retrospect, the emphasis on penis size and penile-vaginal intercourse may have influenced the tendency to sex reassign genetic males with ambiguous genitalia to a female sex of rearing. Also, they believed that genetic males should be reassigned to a female sex of rearing because they would not be sexually competent adult males.

During the early years, some physicians withheld information from parents and later from children because they were concerned that the data on gonadal histology or chromosomal tests might have a negative impact on the psychological well-being of parents and children. In the context of today, it is evident that many former patients are angry about their inability to obtain their medical records and their lack of access to accurate information about their past medical care.

CURRENT APPROACHES TO THE MANAGEMENT OF INTERSEX PATIENTS

As intersex children reached adulthood, former patients began to express criticisms about their past medical care and the misinformation they were provided. Also, they were dissatisfied with the poor surgical results and the decisions that were made without their consent. Other complaints included the discomfort they had with penile-vaginal intercourse, with sex assignment decisions and lack of sexual satisfaction resulting from arousal issues. Some patients sex reassigned themselves in adulthood, and many needed psychological treatment. Not infrequently, adult patients expressed they felt ashamed, isolated, depressed, and freakish because they were examined repeatedly in childhood by strange medical students and residents in training. Some patients were angry with their parents and their doctors because of the secrecy and lack of information.

Patient advocacy groups, including members of the Intersex Society of North America, the Androgen Insensitivity Society, and those with CAH, have established Web sites to educate the medical community and the general public about the dissatisfaction of many adult intersex patients (isna.org, cah.org.uk, and medhelp.org/www

/ais). The Intersex Society of North America recommended a moratorium be placed on genital surgery unless there was a medical necessity. It believed that sex assignment should be made in infancy, but advocated delaying surgical reconstruction of the external genitalia in order to obtain an appearance that matched the assigned sex of the patient. Also, they strongly recommended complete and honest information be given at the outset to the parents and later to the children in an age-appropriate manner.[31,32]

Many factors have prompted reassessment of the care given to infants with intersex:

- Questions about the exact role of prenatal androgens in the establishment of gender identity
- Confirmation of the influence of prenatal androgens on gender role/behavior (tomboyish behavior, selection of toys, games, and activities that are considered masculine, etc)
- Current pivotal research on sex differences in brain development and how this may affect gender development
- The importance of cultural and religious beliefs of the families
- The need to give complete and honest information to parents and later to patients relative to gonadal histology, internal sex organs, and karyotype
- Outcome studies
- The possible/ probable need for lifelong hormone replacement therapy
- Criticisms from former dissatisfied patients
- Potential problems with sexual satisfaction in adulthood
- Fertility issues
- Possible or probable need for additional surgery later in life
- Discomfort or lack of sexual responsivity if there is loss of nerve innervation to the clitoris and genital area
- The potential for patient-initiated gender reassignment in adulthood

Most physicians now believe that information about Web-based sites such as the Intersex Society of North America should be provided to families.[18-20]

There is general agreement that genetic females with CAH should be raised female regardless of the degree of genital virilization, although a minority of physicians believe that the girls with a penile urethra (Prader 5) can be raised as males after gonadectomy and male hormone therapy. At present, opinions differ as to the timing of vaginoplasty, with some doing surgery before 6 months of life and others preferring to wait till later in adolescence. An argument

has been made to postpone vaginoplasty until late adolescence if menstrual blood can be passed through a functional connection between the upper vagina and the urogenital sinus. Also, many surgeons are reluctant to perform clitoral recession if there is a mildly to moderately enlarged clitoris (Prader 1 or 2). The newer surgical clitoral recession techniques are presumed to be less injurious to the innervation of the genitalia and may result in better sexual satisfaction, but more outcome studies are needed. This recommendation for delaying surgery is based on the assumption that an educated patient is better able to do the postoperative care of the vaginoplasty, which requires dilatation to preserve optimal size for future sexual function. Clitoral recession on occasion has required additional revisions in girls who are noncompliant with glucocorticoid replacement. The dose of hydrocortisone (8 mg/m^2) is lower than those used previously, and almost all patients receive oral fludrocortisone daily rather than subcutaneous deoxycorticosterone acetate pellets every 4 to 6 months. Low-dose dexamethasone once daily has also been used with success. Serum levels of 17α-hydroxyprogesterone, renin, and androgens (androstenedione and testosterone) are used to adjust the doses of hormone replacement.[18-20,33-40]

Genetic males with 46,XY karyotype and CAIS are always raised female. The timing of gonadectomy is variable depending on the age at diagnosis. If the testes are removed in infancy, the patient must be informed that she will need estrogen in the adolescent years and that she will not menstruate or grow sexual hair. When information about the 46,XY karyotype is given at a later age, the patient's level of maturity, stability, and interest must be taken into consideration. If the diagnosis of CAIS is made in adulthood, the patient will need to be informed about the potential for gonadal neoplasm and the need for gonadectomy and lifelong estrogen replacement to protect skeletal strength and breast size. Also, the patient must be told she has no uterus and will need to adopt her children. Providing information about the 46,XY karyotype is recommended, but this should be done in a private and sensitive manner. Psychological support is extremely important.[41,42]

Genetic males with ambiguous genitalia are a major challenge. There is a growing tendency to raise these infants in a male sex of rearing and to augment penis size in early infancy with depot testosterone injections (25 mg per month given intramuscularly for 3 months) or topical testosterone applied directly to the penis. The response of the penis to testosterone treatment is better if the infant has primary or secondary/tertiary hypogonadism. Subsequent surgical repair of the hypospadias is facilitated by the previous testos-

terone treatment. Genetic males with partial androgen insensitivity (PAIS) are a particular challenge because they are more likely to respond suboptimally to testosterone treatment.[41-43] Nevertheless outcome studies, although limited in size, have reported that adult males with a small penis experience satisfaction with their quality of life and sexual functioning, even though they expressed concern about their penis size.[44] If these experiences are confirmed by larger numbers of adult male patients, the recommendation to raise genetic males with ambiguous genitalia in a male gender would have greater scientific validity.

MECHANISMS CONTROLLING GENDER IDENTITY AND GENDER ROLE BEHAVIOR

Our understanding of the factors that control why persons identify themselves as male, female, or ambiguous is far from complete. We accept that prenatal androgen exposure has a significant effect on gender role behavior because females with CAH exhibit behavior and interests that are considered more masculine compared with control females.[36-39] These girls also have a female gender identity even though there is a higher frequency of homosexuality in this population—this observation suggests that prenatal androgen exposure may influence sexual orientation in some of this population.

There has been much debate about the rationale for the sex reassigning of genetic males to a female gender identity. Some adult intersex patients reared female have sex reassigned themselves to a male gender, while others are satisfied with their assigned sex of rearing.[40-43,45,46]

Are prenatal hormones the only factor that controls gender identity and gender role behavior? Other mechanisms need to be considered because transsexual individuals have normal levels of sex hormones, a normal karyotype, normal genitalia, and a normal body phenotype. Yet these individuals are convinced they belong to the opposite sex and seek medical intervention to sex reassign themselves in adulthood. The sex change may involve changing from a genetic male to female gender or genetic female to male gender. These observations suggest that there must be other variables that control gender identity and possibly gender role.

New information has indicated that the brain is the most important sex organ, and that the brain begins to develop differently in males and females before the differentiation of the gonads and before hormones are produced.[47-49] The earlier beliefs about the critical influence of hormones came from the observation that early castration in male rabbit fetuses resulted in them developing as females,

and from newborn female guinea pigs acting as males after exposure to testosterone. More recently, the influence of hormones in the development of gender identity came from observations in the zebra finch, which is genetically male on the right side with plumage and testis and genetically female on the left with dowdy feathers and an ovary. Clearly, the circulating hormones did not control gender outcomes because the brain was exposed to the same mix of male and female hormones. It was also determined that the neural circuits that control male song were much larger on the right side of the brain. More evidence came from transplanting female forebrains into Japanese male quail embryos and finding that the testes failed to develop normally, indicating that a male brain was essential for male gonad development in these animals.[49] The most compelling evidence was obtained when the brains of male and female mouse embryos were studied with DNA microarrays to evaluate gene activity during the earliest stage of development. Vilain and colleagues[48] found that 51 of 12,000 genes showed different levels of expression in the brains of male and female mouse embryos before the formation of the gonads. This observation suggests that the mammalian brain has different paths from the outset before hormones have been produced. Vilain[48] and other investigators[47] are focusing on genes located on the Y chromosome by creating knockout mice to identify which genes influence brain development and sexual behavior. The SRY gene is of particular interest. To study its role, the SRY gene was knocked out in the brain while leaving it intact in the testes of mice. Studies of nonhormonal influences on sexual differentiation of the mammalian brain are of particular interest to our understanding of transsexualism, which may be the result of genetic factors since the condition sometimes runs in families. Vilain hypothesizes that some of the genes expressed in the brains of normal males and females may be altered in persons who are transsexuals. These studies have the potential for proving that transsexualism has a genetic or biologic etiology and is not the result of a lifetime choice.

Could identification of the DNA sequences that predict the future gender identity of an infant with intersex have practical importance? Such an outcome might lessen the controversy surrounding the sex of assignment in genetic males with intersex and might result in greater patient satisfaction.

Although Vilain[48] and others recommend delaying surgery until the child can give informed consent or exhibit gender-specific behavior, many clinicians and parents are hesitant to accept this advice. Follow-up studies have suggested that most patients are satisfied with their assigned gender, whereas approximately 8% have a

poor outcome.[41-43,50,51] This does not mean that all patients are completely satisfied with their genital appearance and level of sexual functioning. Gary Warner, as reported in Dennis, has surveyed untreated intersex individuals in Vietnam and India and reports that many wish they had had surgical reconstruction in infancy.[49] More research is needed to increase our understanding of the factors influencing favorable and unfavorable outcomes for intersex individuals.

LEGAL ISSUES PERTAINING TO SEX ASSIGNMENT AND TIMING OF SURGERY

Under current guidelines, parents have the primary right and responsibility for making decisions for all aspects of the care of their children. In the past, many parents and later some patients complained they had not been included in the decision-making process leading to sex assignment. Today, most physicians involve parents from the outset in discussions pertaining to sex assignment decisions and timing of surgery.

The Constitutional Court of Columbia issued a landmark decision protecting the rights of intersex individuals and the authority of parents and physicians concerning genital surgery. The Court ruled that children are individuals with dignity and rights, but they are unable to give consent, and that parents can give surrogate consent after considering the necessity, urgency, risk, and invasiveness of treatment and the age and autonomy of the child. For the parents to make a fully informed decision, they must understand the recommendations provided by a team of specialists including pediatric endocrinologists, surgeons, psychologists, geneticists, social workers, and radiologists. Also, the information provided must be complete, honest, and accurate and also should include information about the Web sites set up by advocacy groups who articulate dissatisfaction with their previous medical care. Cultural and religious beliefs of the family must be respected, and parents must be able to comprehend the information given to them.[3,43,46,50,51]

ETHICAL ISSUES PERTAINING TO MEDICAL CARE GIVEN TO INTERSEX PATIENTS

Information from retrospective studies is urgently needed, even though medical care has undergone many changes in the past decade. Retrospective studies are challenging because many adult intersex patients are not fully informed about their condition or their past medical care, and some will not want that information revealed to them. The dilemmas of conducting retrospective studies are re-

viewed by Sytsma,[52] who concludes that full disclosure of the condition and details about past medical care are not necessary to meet the requirements of informed consent providing that information is not withheld or altered to deceive the patient. Also, it is not necessary to give the patient all the details about the goals of the study. Sytsma reasons that the major risk of doing retrospective studies is psychological, not physical. To minimize harm, the inviting contact letter should give participants information about the questions to be asked and should invite questions from prospective participants. Those who are confused about gender and sexual issues are unlikely to participate. She recommends that skilled interviewers who do not have access to the medical history or the patient's condition would protect the patient's confidentiality. Inclusion of dissatisfied intersex adults would strengthen the scope of the data from retrospective studies, but such patients may not be willing to participate.

As a rule, ethicists and bioethicists are not usually members of the team of specialists caring for infants with intersex. Some ethicists have formulated opinions about the care given to intersex patients based on their academic rather than their practical qualifications. Many have not kept up with the new developments in the field of molecular biology as it relates to sexual differentiation and hormone action. Others have hypothesized that genital defects are variants of normal, even though there is a lack of scientific support for this opinion. Some have hypothesized that there are as many as 5 sexes rather than the traditional male, female, and male/female.[53-57]

A dialogue between ethicists and medical specialists is urgently needed because many changes have occurred in the medical care of intersex patients during the past decade. Now, greater attention is given to the role of parents in the decision-making process. Also, there is full disclosure to the families about the diagnostic tests, chromosomes, internal and external anatomy, medical and psychological outcomes in adulthood, and the criticisms from former patients and the Web sites they have established. Some of these evolving care initiatives may not be known to ethicists unless they are part of the medical/psychological team. Also, ethicists may not be aware of the recent developments in the molecular endocrinology of sexual differentiation or the possible role played by nonhormonal factors in the embryonic central nervous system that control gender identity, or the new, improved techniques for genital surgery, including avoidance of total clitoridectomy and avoiding surgery to correct mild to moderate genital virilization in the genetic female with CAH. The timing of vaginoplasty is under debate, with some experts recommending postponement to the adolescent years and

others continuing to advise vaginoplasty in infancy. There is fairly general agreement about the need to begin to inform children between 6 and 8 years of age about their past medical care and to do so with age-appropriate language given privately and gradually. Information pertaining to karyotype is individualized and is patient dependent. The importance of cultural and religious beliefs to decisions involving the sex of assignment cannot be underestimated by the medical or ethical specialists, even though there may be discordance between genetic sex and the sex of rearing. Intersex patients are entitled to their medical records and to all information about past laboratory tests, gonadal histology, surgeries, and diagnoses if known. Fertility potential and the possible need to adopt children must be shared in a private setting. Repetitive genital examinations in the presence of unfamiliar medical personnel should be minimized or avoided to prevent intersex patients feeling they are teaching objects or freaks.[3,17,43,46,50,51,58]

A recent questionnaire given to parents of girls with CAH revealed that most thought they were well informed and involved with the medical care given their daughters.[42,43] A majority of the parents chose to have genital surgery in infancy, even though they understood there was a risk of later reduction in genital sensitivity. It is clear that medical specialists are now involving and educating parents to a greater degree in the care given to their intersex child. Such was not the practice in the early years when physicians attempted to protect families from information they considered potentially harmful to the psychological well-being of both parents and affected children.

OUTCOME STUDIES

At present, the opinions of dissatisfied intersex adult patients are listened to but not always followed; these groups advocate avoidance of genital surgery in infancy except when medically necessary. They have educated the medical specialists about the importance of genital comfort and arousability during sexual experiences, the variability in the outcome, and the technical challenges involved in performing successful vaginal surgery. Some of the details about the opinions of these patients have been discussed above. It is not clear whether the dissatisfactions felt by intersex advocacy groups are a widespread problem, or how many silent former intersex patients have similar opinions. The efforts of the advocacy groups have been a motivating force that has prompted the collection of outcome data and a reassessment of clinical management practices. Collaboration between clinicians and activists has the potential for educating both

groups and for improving the quality of medical care given to intersex children during childhood and in adulthood. We need more information about the outcome of retrospective as well as prospective studies, since the field is in flux.

A recent review of published studies of 46,XX CAH patients by Dessens and colleagues[40] reported that approximately 95% of 250 children raised female had female gender identity and no gender dysphoria, regardless of the severity of genital masculinization. Previous studies have indicated that some females with CAH feel less typically female compared with controls. Five percent or 13 patients had gender identity or gender dysphoria problems, which is higher than the prevalence in 46,XX transsexual patients who change from a female to a male gender identity. Among these 13 CAH patients, 7 had dysphoria, 5 wished they were in the opposite sex during the past 12 months, and 1 was confused about her female identity. The Dessens review included 33 CAH 46,XX females who were raised in a male gender identity. One identified as female, and 3 were gender dysphoric. More gender problems seemed to be present in the 46,XX patients raised male, but the incidence of problems in those raised male or female was not statistically significant. These authors agreed with Berenbaum[38,39] that it was not necessary to substantially change the medical or psychosocial management of CAH, but cautioned that gender-related problems need more attention. At present, it is not possible to predict which patients will develop gender identity problems. Thus, access to good psychological care is of extreme importance. Dissatisfied as well as satisfied patients should be included in outcome studies in order to avoid underestimating the prevalence of problematic outcomes. Prenatal androgens appear to play a role in gender behavior but do not seem to control core gender identity even in extremely virilized females.[36,37] The review stressed the importance of early sex assignment and cautioned against gender reassignment in late childhood.[40]

Mazur[58A] reviewed the outcome of 156 published cases of 46,XY patients with CAIS; all were raised female, and none initiated a gender reassignment to male. There was no evidence of gender dysphoria or atypical gender role in these patients.

Mazur also reviewed the outcome of published 46,XY cases of PAIS, which numbered 99 patients, of whom 9 patients initiated a change in gender in later life. Three of the 9 changed from female to male, and 6 changed from male to female. A minority of these patients experienced gender dysphoria, defined as feeling imperfect or like a man/woman. The author concluded that self-initiated gender reassignment in adulthood was rare.[58A]

In Mazur's review of 46,XY patients with micropenis, 10 of the 89 patients were sex assigned and reared female. Those reared male reported they were more masculine, and those reared female felt more feminine. In general, the patients were satisfied with their gender identity, but 80% of the women had questioned their gender or their sex of rearing.[58A]

In conclusion, Mazur's review of the literature indicated that all CAIS patients have a female gender identity, that the majority with PAIS maintained their initially assigned gender identity, and that all the patients with 46,XY micropenis continued to live in their initially assigned gender whether male or female. The best predictor of adult gender identity was the initial gender assignment.

Among the 72 intersex patients with 46,XY karyotype (from a total of 96) cared for by Migeon and colleagues[42] at The Johns Hopkins Hospital, 32 were reared male and 40 were reared female. Their ages ranged from 18 to 60 years, and 9 were black. The diagnoses were CAIS, PAIS, and unambiguous micropenis. None of the CAIS group questioned their sex assignment except for 1 patient. Fifty-six percent of intersex patients reared female in the CAIS or micropenis groups expressed some uncertainty about gender. In contrast, 21% of those with a male gender identity reported some uncertainty about their gender identity. Patients who were dissatisfied in the PAIS and micropenis groups were more inclined to endorse a third gender. Sixty-eight percent of 31 intersex patients reared males rated their penis as too small, and 39% of those reared female were dissatisfied with the appearance of their genitalia. Satisfaction with sexual functioning was highest in the CAIS group. The incidence of dissatisfaction (45%) was higher in the women belonging to the PAIS or micropenis groups, compared with the incidence of dissatisfaction (18%) in the men in these groups. Most intersex patients (78%) in the PAIS and micropenis groups recommended that genital surgery be done before adulthood, and 45% stated it should be done in infancy. All patients in the CAIS group opted for surgery in adulthood. Satisfactory sexual functioning correlated with satisfaction with gender and genital appearance.

Cohen-Kettenis[59] reviewed the current literature on the outcome of 99 patients with autosomal recessive 5α-reductase-2 deficiency raised female and reports that 63% of these patients underwent a gender role change in adolescence or adulthood. In an additional 110 patients raised female, there was less clear information about gender outcome. In this group, 56% changed to a male role in adolescence or adulthood. 5α-Reductase-2 is an enzyme that converts testosterone to dihydrotestosterone, which is responsible

for virilizing the external genitalia and for prostate size in 46,XY infants. The degree of genital masculinization at birth in the study population was not found to be a determinant of gender change later in life. The findings raised doubts about the belief that children are psychosexually neutral at birth. The role of prenatal exposure to androgens was not clearly evident because a significant number of these patients remained as females. It is possible that many who changed to a male gender role did so because of the advantages of being male within their culture. Other potential factors include parental influences and the presence of a masculine appearance in combination with masculine behavior during childhood in some patients. Also, the sexual attraction of those reared female for other women may have influenced some patients to change to a male role. In this population, those reared males from the onset almost never changed to a female role. These data suggest that prenatal androgens and the degree of genital virilization are not the only factors determining gender identity.

Among patients with autosomal recessive 17β-hydroxysteroid dehydrogenase-3 deficiency (17B-HSD-3), there is insufficient testosterone production in fetal life and genital ambiguity. In later life, male secondary sexual characteristics develop in puberty because of the presence in peripheral tissues of 17β-hydroxysteroid dehydrogenase isoenzymes, which convert androstenedione to testosterone. These bodily changes are only seen in unoperated children who were raised female in infancy. Cohen-Kettenis[59] reported that when explicit psychosexual information was provided, 63% of 28 patients raised female changed to a male role. When less psychosexual information was available, 39% of 49 patients raised female changed to a male role. Thus, many but not all of these patients reared female changed to a male role in later life, even when there was a prenatal deficiency of testosterone production. This observation strengthens the hypothesis that factors other than prenatal androgens or sex of rearing are influencing gender role decisions.

What were the outcomes of infants with nonhormonal genital malformations and normal prenatal androgen levels? In a review of 46,XY males with penile agenesis, testes descended or cryptorchid, fused scrotum, and urethral-rectal communication, Meyer-Bahlberg[60] observed that 14 of 16 patients with 46,XY penile agenesis assigned a female gender were living as females (2 of the 16 females had gender dysphoria), and 2 were living as males. Only 4 of the 16 were older than 18 years. Of the 17 patients with penile agenesis raised male, all were living as males, but only 6 of them were

adults. Statistically, there was a significant difference in the outcomes of male-raised patients compared with female-raised patients.

Cloacal exstrophy of the bladder is a severe form of the bladder exstrophy–epispadias–cloacal exstrophy complex that is characterized by omphalocele, abdominal wall defect, bladder exstrophy, short gut syndrome, separated pubic bones, and sometimes spina bifida and clubfoot. The penis is either absent or bifid. Morbidity and mortality are less severe with newer surgical techniques, which have permitted survival to adolescence and adulthood. Of the 51 patients with cloacal exstrophy who were assigned to a female gender, Meyer-Bahlberg[60] found that 33 were living as females, 7 as females with gender dysphoria, and 11 as males. However, only 8 were adults. Among the 15 patients with cloacal exstrophy who were raised male, all were living as males. The gender outcome was highly significant statistically between the male-raised and the female-raised patients.

All the 294 patients with classic bladder exstrophy who had been assigned to a male gender were living as males, but 1 patient had possible dysphoria. Most of these patients were adults. Only 2 patients with classic bladder exstrophy were assigned a female gender in infancy, and 1 of them changed to a male role after puberty.[60]

Meyer-Bahlberg reported on the outcome of 7 patients with traumatic loss of the penis in infancy or early childhood. All were sex assigned to a female gender, and gonadectomy was done between 6 months to 5.5 years. Four of them lived as females, 1 as a female with gender dysphoria, and 2 as males. Of the latter 2 patients, only 1 was an adult. The most famous case of penile ablatio was a male, one of twin brothers, who lost his penis after circumcision at 8 months of age. His sex reassignment surgery was done at 22 months of age, and the patient self-reassigned himself to a male gender in adolescence and married a woman in adulthood. This is a unique patient in that penis loss was at a relatively late age in infancy, he had a twin brother, and sex reassignment and surgery were also done when he was almost 2 years of age.[61] This patient was not born with intersex; nevertheless, his history and outcome are extremely informative.

None of 46,XY patients with nonhormonal genital malformations who were sex assigned a male gender in infancy have initiated a change to a female gender, although there is one possible case of gender dysphoria. Psychological adjustment problems and quality-of-life issues are common in this population. Also, more information is needed of those raised female to determine whether their

quality of life or incidence of psychopathology is different from that seen in those raised male.

In summary, most 46,XY intersex patients express overall satisfaction with their assigned gender, genital status, and sexual functioning. A majority do not support a third gender option. Most do not recommend delaying surgery until adulthood. More 46,XY intersex patients reared female expressed experiencing past gender uncertainty than those reared male. Small penis size was a concern in those reared male. It is possible that these clinic patients present too positive a picture and that activists present too negative an outcome. The overall data suggest that the optimal gender policy may be a valid one, but care must be given to the small sample size and the finding of a higher incidence of dissatisfaction and past gender uncertainty in intersex patients reared female. A larger sample size and more detailed assessment protocols are needed to answer many of the questions pertaining to improving the care given to intersex individuals.[62]

SURVEYS OF CLINICAL DECISIONS BY PEDIATRIC ENDOCRINOLOGISTS AND PEDIATRIC UROLOGISTS

A Web-based survey invited members of the Lawson Wilkins Pediatric Endocrine Society and the Society for Pediatric Urology to give their opinions about the medical care given to 5 case examples of intersex patients.[63] The response rates were 55% and 54% for endocrinologists and urologists, respectively. Nonparticipation was due to retirement, a focus limited to research only, or to not seeing intersex patients. Males accounted for 62% of endocrinologists and 95% of urologists. A majority (77% and 66%, respectively) were in medical schools/hospitals and in large cities (62% and 72%, respectively). Both groups recommended telling the patient details of the earlier genital surgery, with some doing so between 6 and 10 years and others doing so after 11 years of age. Also, giving karyotype information between 11 and 17 years of age or later was endorsed by 90% of the endocrinologists and 83% of the urologists.

The main difference between the groups was the frequency of male sex assignment for PAIS male infants. Forty-seven percent of endocrinologists assigned these infants to a male gender, whereas 83% of urologists favored a male gender assignment.

Both groups favor early surgery to normalize genital appearance, which concurs with the preference of parents and differs from the recommendation of the advocacy society. However, the specialists agreed that parents should be informed that they could refuse the surgery. Approximately a third of each group favored female sex

assignment for genetic males with complete absence of penis or cloacal exstrophy. There was a strong preference for having the genital surgery done in centers of excellence. About one half of each group supported parents contacting advocacy groups before doing surgery. Endocrinologists were twice as likely to believe they should not give advice as to whether the surgery should or should not be done (51% vs 25%, respectively).

Both groups believed that prenatal androgens are a major determinant of gender identity, and that the presence of tomboyish behavior does not indicate that an error was made in the gender assignment decision. Also, favorable outcomes were more likely if the family was functioning at a high level, and if there was respect for the religious, ethnic, and educational factors of each family. Furthermore, both groups agreed that it was likely additional genital surgery would be necessary in the future, and both agreed that intersex patients might later reject the sex assignment made in infancy.

A majority wanted to have a mental health worker to help with the care of the child, but only 15% to 25% of groups had such an expert on their team. About a half of the groups wanted the mental health worker to see the intersex children on an ongoing basis, whereas the remainder wanted to use them as consultants.

It is likely that current opinions about the medical care of intersex patients will change as we obtain more data from much needed outcome studies

WHERE ARE WE TODAY?

Males born with micropenis and reared male are reported to be having satisfactory heterosexual adult experiences, even though they wish their phallic size was larger. The growth potential of an infant's penis is greater than was previously believed. There is now a greater tendency to raise males with micropenis as males than in previous times.

The difficulties of vaginal construction and function are a major challenge, and the timing of vaginal surgery is being debated. The importance of the clitoris and the preservation of innervation and vascularity are central to sexual arousability and sexual function. Clitoral recession is the procedure of choice if the clitoral size is very large, but we need more information about the outcomes when the slightly to moderately enlarged clitoris is left untouched. Whether a moratorium should be declared on genital surgery is a topic that has advocates and opponents, but parents and former patients as well as unoperated intersex patients lean towards early corrective surgery provided the outcome ensures good sexual function in

adulthood. Prenatal diagnosis and dexamethasone treatment of the mother during pregnancy has greatly lessened the degree of virilization of female offspring with CAH and led to better preservation of an intact vaginal canal

More information is needed on sexual avoidance in patients with nonhormonal genital malformations who are more likely to have multiple physical abnormalities such as urethrostomy or colostomy. There is an increased risk of later gender change to male when 46,XY infants with nonhormonal genital malformations are assigned a female gender in infancy.

Informing intersex patients about their past tests, operations, and karyotype is becoming an accepted practice, as medical specialists appreciate that misinformation and withholding data are more harmful and that it isolates, angers, and confuses the patients as they go through adolescence and adulthood. How to tell and when to begin to tell are major challenges, with most specialists starting to give anatomic and surgical history around 6 to 8 years of age and giving the information in a private setting and gradually over time. Others recommend disclosure in early to mid adulthood when the patient is more mature. Repetitive physical examinations and discontinuity of medical care have had an adverse effect on the patients' well-being and their relationship to their care providers and their parents. These practices must cease.[64-66]

The availability of mental health specialists is highly desirable throughout the childhood and adult years because of the complex emotional stresses experienced by intersex patients.[66]

Current research indicates that prenatal exposure to androgens, androgen action, and gonadal function influence to some degree gender identity and that androgens have a profound effect on gender role behavior, but prenatal androgens do not fully control core gender identity. New research indicates that the central nervous system bifurcates along a male or female pathway before the development of gonads or hormones. If this finding is further strengthened by molecular endocrine research, it is likely that we will better understand why transsexuals who are endocrinologically normal males and females are convinced they must change to a gender different from the one they were born into. How this information will affect the evolving management of intersex infants is unknown at present.

Is society sexually dimorphic, that is, comprised of males and females? It would appear that there are male, female, and bisexual individuals. The hypothesis that there are multiple sexes which are variants of normal is not supported by scientific evidence. All abnormalities of the genitalia in intersex patients are the consequence of a

gene mutation in the sexual differentiation pathway. The scientific evidence for multiple genotypic sexes and biologic phenotypic variability requires that normal molecular processes result in a diversity of phenotypic outcomes. This is not the case; the phenotypic variability in intersex patients is always the consequence of abnormal gene function. The present challenge is to provide our intersex patients with support and expert medical care so that they are informed and accepting of the experiences they have shared with parents, their medical specialists, and mental health care providers.

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Principles of Transgender Medicine and Surgery

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Chapter 12

Intersex: Definition, Examples, Gender Stability, and the Case Against Merging with Transsexualism

Tom Mazur
Melissa Colsman
David E. Sandberg

INTRODUCTION

Important distinctions between individuals with transsexual and intersex conditions are, at times, blurred in both popular and scientific literature. While individuals with an intersex syndrome may share some features (e.g., gender dysphoria and identity concerns) with those diagnosed with transsexualism, persons with intersex conditions diverge from transsexuals in terms of associated features including prevalence, age of onset, and sex ratio when presenting with a gender identity disorder (GID) (Meyer-Bahlburg 1994).

Historically, in an effort to obtain professional help, some transsexuals claimed to be intersex or hermaphrodites. More recently, the term "intersex" has been subsumed by some writers under the broader term "transgender," which also includes individuals who "transgress usual gender roles" such as "cross-dressers, drag artists, gender queer, [and] androgynes," among others (Monro 2005; Raymond 1994). Additionally, some neuroanatomical studies contribute to a merging of the entities into a single category. For example, one postmortem study of the brains of transsexuals showed that the central subdivision of the bed nucleus of the stria terminalis (BSTc) in seven male-to-female (MTF) and one female-to-male (FTM) transsexuals differed from that of a comparison group without GID. Furthermore, the size of this nucleus in the MTF and FTM transsexuals was comparable to female and male comparison groups, respectively (Kruijver

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et al. 2000). Another recent study in rats demonstrated that gene expression prior to the time of prenatal hormone activation may differ in male and female brains (Arnold 2004; Dewing et al. 2003; Vawter et al. 2004). These findings have led to speculation that neuroanatomic substrates in the central nervous system of transsexuals contribute to the development of a form of intersexuality (Meyer-Bahlburg 2005a). Noted scholars in gender research have suggested that transsexualism can be considered to be a neurodevelopmental condition of the brain (Gender Identity Research and Education Society 2002).

Failure to differentiate between individuals with and without a clearly identifiable intersex condition may hamper studies of etiology and optimal clinical management. Given that our understanding of etiologic factors in GID in physically typical individuals (i.e., transsexuals) and in those with intersex conditions is incomplete, it would be prudent to consider them as separate entities when initiating an evaluation of GID in these two groups.

The purpose of this chapter is to propose that intersexuality and transsexuality are different—even though persons classified as either may present with gender dysphoria and/or a desire to change their gender. This chapter will define intersexuality, review the typical sexual differentiation process, provide examples of the most frequently occurring intersex syndromes and related conditions, summarize recent data on gender identity stability and dysphoria in adults whose gender assignment at birth was in question as the result of an intersex condition, compare and contrast the clinical presentation of GID in intersex and nonintersex persons, and discuss evaluation and treatment strategies.

INTERSEXUALITY DEFINED

The term "intersex" refers to discordance between any level of genotypic and phenotypic expression of sexually dimorphic features. As such, intersex conditions may or may not include atypical genital appearance. Intersex has been used synonymously with "hermaphroditism," which refers to congenital ambiguity of the sexual anatomy that, in appearance, is neither fully female nor fully male (Money 2002). Other terms adopted by researchers and clinicians include: disorders of sex development, physical intersex conditions, sex errors of the body, ambiguous genitalia, birth defects of the sex organs, and male and female pseudohermaphroditism. Intersex occurs in genetic males (46XY), genetic females (46XX), individuals with sex chromosome mosaicism (e.g., 45X/46XY), or aneuploidy (i.e., one or more extra or missing chromosomes; for example, Klinefelter syndrome [47XXY] or Turner syndrome [45X]). When ambiguity of the external genitalia is

present, it is typically the result of defects in prenatal sex hormone production or action (MacGillivray and Mazur 2005).

TYPICAL SEXUAL DIFFERENTIATION PROCESS

Development of the sexual reproductive system involves the internal (Figure 12.1) and external (Figure 12.2) sex organs. These organs develop through a series of steps. At the outset, sex determination occurs when either a Y- or an X-bearing sperm fertilizes the ovum. If the resulting genetic sex is XY, then the undifferentiated and bipotential gonad develops as a testis. A single gene located on the short arm of the Y chromosome, referred to as the sex-determining region of the Y chromosome, or SRY, is responsible for this event. Testes develop approximately in the sixth to seventh week of pregnancy in an XY embryo. The bipotential gonad develops into an ovary in the absence of SRY (i.e., XX sex chromosomes) (Grumbach, Hughes, and Conte 2003).

The process of sexual differentiation begins once the Leydig cells of the testes secrete two hormones, testosterone and anti-Müllerian hormone (AMH), at weeks eight to nine of pregnancy. Testosterone causes the Wolffian (male) duct to differentiate into the epididymus, vas deferens, seminal vesicles, and ejaculatory ducts. AMH suppresses Müllerian (female) duct development: fallopian tubes, uterus, cervix, and upper third of the vagina. Müllerian duct differentiation unfolds in the absence of hormonal stimulation, (i.e., the ovary is quiescent during this stage of development). In the absence of testosterone exposure, the Wolffian duct regresses.

After completion of the internal sexual reproductive structures, differentiation of the external genitalia begins (week 10). The external genitalia, male and female, are created from a single set of structures, in contrast to the internal genitalia, which differentiate from a double system, Wolffian and Müllerian. Thus, the external genitalia, like the gonads, are bipotential, differentiating and developing into either male or female external sex organs.

Dihydrotestosterone (DHT), the 5-alpha reduced metabolite of testosterone, is responsible for differentiation of the genital tubercle into a penis in an XY fetus (Conte and Grumbach 2004). The labioscrotal swellings fuse to form the scrotum. Urethral-labia folds form the shaft and foreskin of the penis. Male external genital differentiation is complete by weeks twelve to fourteen of pregnancy. Penile enlargement continues during the second and third trimesters of pregnancy.

In an XX fetus, the ovary secretes no masculinizing hormones. The genital tubercle becomes a clitoris. The labioscrotal swellings become the labia

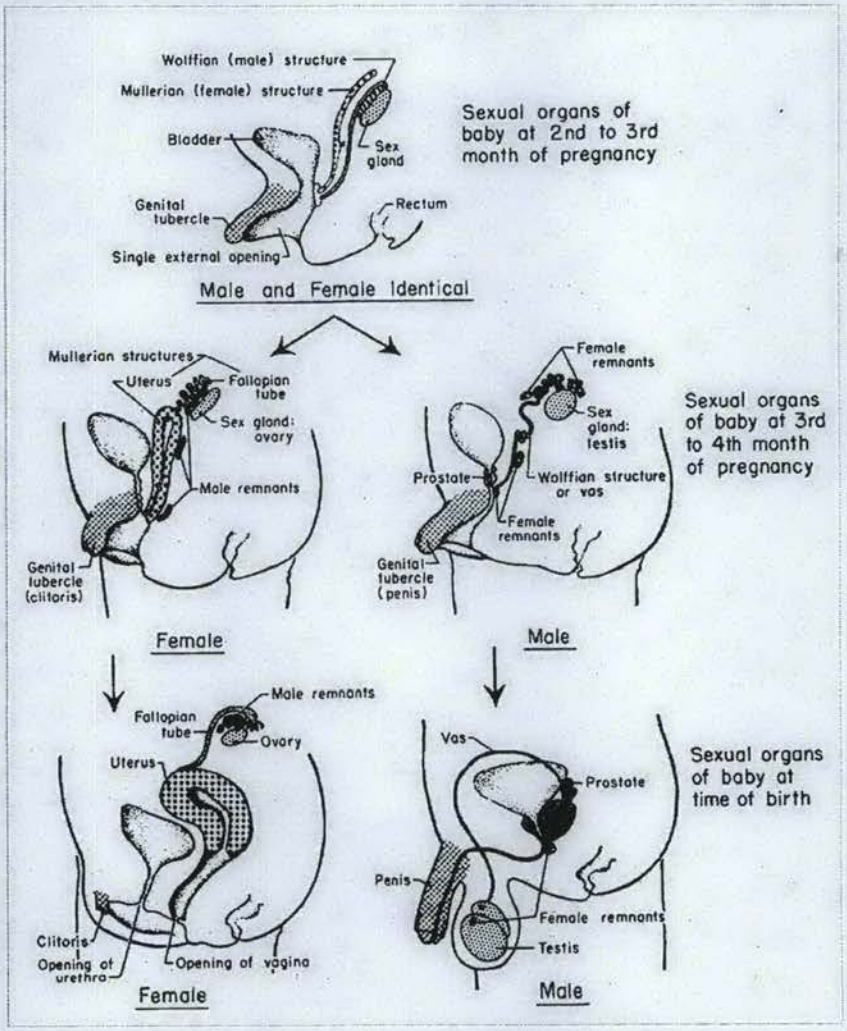

FIGURE 12.1. Differentiation of the internal genital ducts. (*Source:* J. Money [1994]. Sex errors of the body and related syndromes: A guide to counseling children [Second ed., p. 32], Baltimore, MD: Paul H. Brookes Publishing Co. Reprinted with permission. Reprinted also with permission of the estate of John Money.)

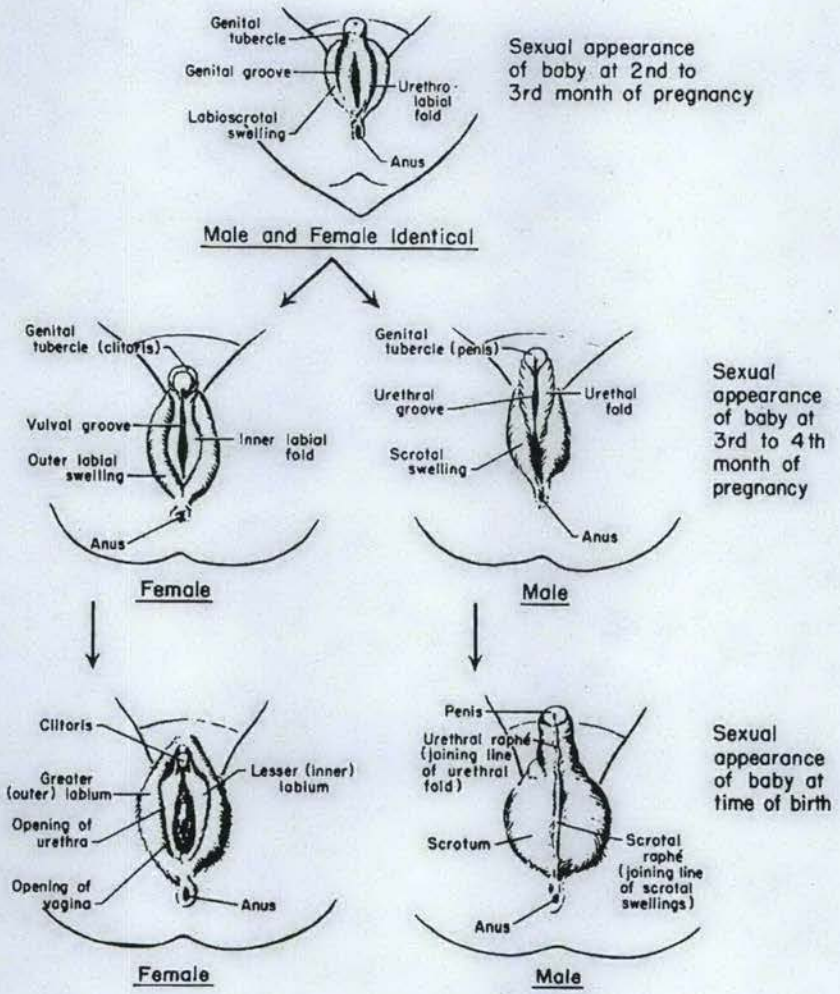

FIGURE 12.2. Differentiation of external genitalia. (*Source:* J. Money [1994]. Sex errors of the body and related syndromes: A guide to counseling children [Second ed., p. 36], Baltimore, MD: Paul H. Brookes Publishing Co. Reprinted with permission. Reprinted also with permission of the estate of John Money.)

majora. The urethral-labia folds become the labia minora and the clitoral hood. Intersexuality occurs as a consequence of disorders of androgen biosynthesis or action, partial or complete, in genetic males, or excess androgen exposure in genetic females.

INTERSEX SYNDROMES AND RELATED CONDITIONS

Atypical sexual development occurs in multiple syndromes and related conditions; the most commonly encountered are summarized in the following text, which uses the endocrine classification system of atypical sexual development found in Conte and Grumbach (2004). The reader is also referred to this review for a more thorough endocrine review; for brief descriptions of the behavioral characteristics of persons diagnosed with these conditions, see Cohen-Kettenis and Pfafflin (2003).

Disorders of Gonadal Differentiation

Klinefelter Syndrome (KS)

KS is a nonheritable genetic condition in which an extra X chromosome is present (Zurenda and Sandberg 2003a). The most commonly found chromosomal pattern is a single extra X (47XXY), but other variations (e.g., 48XXYY) and mosaicism (e.g., 46XY/47XXY) have been documented. Incidence is estimated at 1:600 live male births (Nielsen and Wohlert 1991).

KS is typically diagnosed during puberty when small, firm testicles are palpated on physical exam. Additional features, which assist in making the diagnosis, include tall stature and disproportionately long legs (Ratcliffe, Butler, and Jones 1990). Infertility is almost certain because the testes do not produce a normal volume of sperm. However, assisted reproductive technologies (ART), such as intracytoplasmic sperm injection (ICSI), are helping men with KS to father children with a normal karyotype (Denschlag et al. 2004). Additional features of KS may include unilateral or bilateral breast development (gynecomastia), incomplete masculine body build, and social and/or cognitive-educational problems (Grumbach and Conte 1998). Puberty may also be delayed (Nielsen and Wohlert 1991), and individuals will need testosterone replacement in adolescence and adulthood to prevent osteoporosis and maintain physical energy, sexual function, and a general sense of well being (Zurenda and Sandberg 2003a).

Neurocognitively, individuals with KS characteristically achieve a Full Scale IQ that falls in the average range, but Verbal IQ is typically significantly lower than Performance IQ. This profile is associated with language

and reading problems, speech and language delays in childhood, and poor school performance. Many individuals with KS are described as having a passive personality and a tendency to internalize problems, and exhibit chronic difficulties with peer relationships (Sandberg and Barrick 1995).

Psychosexually, men with KS, on average, exhibit decreased interest in women, less dating, and limited sexual experience (Mazur and Dobson 1995). A twenty-year-long follow-up study showed that 59 percent of KS individuals were married or involved in a long-standing heterosexual relationship (Nielsen and Pelsen 1987). While most persons with KS establish a male gender identity, there are reports of GID in individuals who transition to live fully as female (Seifert and Windgassen 1995; Cossey 1991).

Turner Syndrome (TS)

TS is the consequence of a chromosomal genetic abnormality in females characterized by a missing or partially deleted X chromosome (Fennell 2003). Incidence is estimated at 1:2,500 live female births (Fennell 2003; Hook and Warbuton 1983).

Several dysmorphic features characterize the physical appearance of those with TS, including low-set ears and hairline, high-arched palate, webbed (thick) neck, broad chest, and short stature (Fennell 2003; Sybert and McCauley 2004). The number and degree of physically dysphoric features is variable in individuals with TS. Additionally, hearing problems, malformed kidneys, and cardiovascular abnormalities may be present. The Wolffian ducts regress and the Müllerian ducts differentiate normally in TS; individuals with TS typically have streak (nonfunctioning) gonads resulting in infertility. For most women, the external genitalia are normal in appearance. For the majority, endocrinological intervention includes hormone replacement therapy to initiate puberty and to maintain secondary sexual characteristics. Growth hormone is used to treat marked short stature. Various assisted reproductive techniques are now available for achieving pregnancy. For those women who do not have functional ovaries, oocyte or embryo donation can be used to achieve pregnancy (Saenger et al. 2001).

Neurocognitively, individuals with TS characteristically achieve a Full Scale IQ that falls in the average range, but Performance IQ is typically significantly lower than Verbal IQ. TS is associated with a variety of learning problems such as poor math skills, which may be related to poor visual-perceptual abilities (Mazur and Dobson 1995; Sandberg and Barrick 1995; Sybert and McCauley 2004). Hyperactivity and inattentiveness in childhood are noted in the literature (Sandberg and Barrick 1995). Women with TS exhibit difficulties in establishing satisfying long-term social relation-

ships and are at risk for having low self-esteem (Sandberg and Barrick 1995; Sybert and McCauley 2004).

Psychosexually, gender identity in TS is unambiguously female. To our knowledge, there are no reports of a woman with TS transitioning to live in the male gender.

True Hermaphroditism (TH)

TH is associated with a number of chromosomal patterns: 46XX (most common), combined 46XX/46XY chimerism, or 46XY (rare). Stated to be "uncommon," but "reported in more than 400 individuals," the incidence of TH is unknown (Grumbach, Hughes, and Conte 2003, p. 908).

TH is defined by the presence of both testicular and ovarian tissue in the same individual (Grumbach, Hughes, and Conte 2003). The internal reproductive ducts differentiate in accordance with the gonad on that side of the body, i.e., female internal reproductive structures if an ovary is present. The external genitalia in these individuals may range from typical male to typical female. Breast development is common and menses may occur in more than half of individuals with TH. Clinical management depends on the age at diagnosis and functional capacity of the reproductive structures.

Individuals diagnosed with TH have been assigned to either the male or the female gender. Comprehensive reviews of long-term psychosocial or psychosexual outcomes in TH have not been performed (Meyer-Bahlburg 2005a).

Female Pseudohermaphroditism

Congenital adrenal hyperplasia (CAH). CAH is the result of an enzyme deficiency (most commonly 21-hydroxlase) that occurs in both males and females. CAH is inherited as an autosomal recessive disorder and has an estimated incidence of 1:15,000 live births (Speiser and White 2003), with considerable variation between ethnic/racial populations.

Genetic males with CAH show no ambiguity of their external sex organs at birth. In contrast, the prenatal androgen excess in genetic females results in varying degrees of masculinization of the external genitalia. In the most extreme form (Prader stage 5), the genitalia of the 46XX infant look typically male, with the urethral meatus terminating at the tip of an enlarged phallic structure and fused labia which resemble a scrotum. There are no gonads in the scrotum, as the internal genital ducts are typically female, with ovaries and uterus in the typical position. CAH is associated with excess of adrenal androgen production in utero and, sometimes, an accompa-

nying deficiency in the salt-retaining hormone, aldosterone. Depending upon the degree of aldosterone deficiency, an electrolyte imbalance due to salt loss can occur, which can be life threatening. Endocrine intervention is lifelong: cortisol replacement controls excess androgen production and, if needed, mineralocorticoid treatment controls salt loss.

Neurocognitively, individuals with CAH characteristically achieve a Full Scale IQ that falls in the average range; however, some affected individuals may demonstrate decreased global IQ or specific cognitive deficits resulting from salt-wasting crises during infancy (Zurenda and Sandberg 2003b). Females with CAH represent the most systematically studied of all intersex syndromes, with emphasis on behaviors that show significant gender-related variation. Some 46XX CAH infants have been gender-assigned male, but the Standard of Care calls for a female assignment. Gender identity is characteristically female, gender role behavior is often masculine or "tomboyish," and there is a higher likelihood of CAH females experiencing bisexual or homosexual erotic/romantic dreams, fantasies, and sexual attraction, when compared to unaffected women (Zurenda and Sandberg 2003b). Dessens, Slijper, and Drop (2005) reviewed the extensive literature on CAH and found that the majority (94.8 percent) of 46XX CAH-reared females established a female gender identity with no dysphoria. However, thirty of 250 (5.2 percent) individuals had "serious problems" of gender identity. This percentage is higher than the prevalence of FTM transsexuals in the general population of 46XX females. They also reported that four of thirty-three 46XX CAH individuals (12.1 percent) assigned male at birth and reared as male had serious gender problems; one identified as female and the other three experienced gender dysphoria.

Male Pseudohermaphroditism

Androgen insensitivity syndrome (AIS). AIS is an X-linked disorder which occurs as a result of a mutation of the androgen receptor (AR) gene, making the tissue completely or partially unresponsive to the influence of androgens, although testes form and synthesize androgens normally.

In complete androgen insensitivity syndrome (CAIS), the external genitalia have a typical female appearance because of the lack of tissue responsiveness to androgens. Likewise, the Wolffian ducts fail to develop but the Müllerian ducts regress, due to the action of AMH. Breasts develop under the influence of androgens that are metabolized into estrogen. The diagnosis is usually made at puberty when lack of menstruation becomes a concern. Gender assignment is always female, gender identity is unambiguously female, gender role is feminine, and their sexual orientation in both

overt behavior and fantasy is typically heterosexual (Cohen-Kettenis and Pfafflin 2003). Estimated incidence of CAIS (unfortunately still diagnostically coded as "Male pseudohermaphroditism with testicular feminization," International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9-CM, 257.8) is 1:20,400 (Bangsboll et al. 1992).

Partial androgen insensitivity syndrome (PAIS) results in an individual born with ambiguous external genitalia. The genital tubercle is enlarged but is not typically of normal male size, a partially fused labia/scrotum may be present, and severe hypospadias is often present. Infants with PAIS have been gender assigned as males and as females (Conte and Grumbach 2004). The incidence of PAIS is unknown.

A recent literature review of gender identity stability in individuals diagnosed with CAIS and PAIS showed self-initiated gender change and was observed only among those with PAIS, and the change occurred in both directions (Mazur 2005a). AR gene mutations were documented in PAIS individuals who changed gender and in those who did not. A specific AR-gene mutation was not associated with gender identity outcomes. This finding is similar to Wilson's (2001) finding that gender change is not related to the severity of the AR-mutation.

5-alpha-reductase deficiency (5-ARD). 5-ARD is an enzyme deficiency secondary to a gene deletion or mutation in 46 XY individuals. It is an autosomal recessive disorder, which results in an inability of testosterone to be converted to DHT by peripheral tissue in utero. DHT is required for the development of external male genitals and prostate. Consequently, infants with 5-ARD are born with ambiguous external genitalia. The underdeveloped penis resembles a clitoris and the scrotum appears as labia majora; as such, infants may have been assigned either a female or a male gender at birth. The natural course of this condition is a virilizing puberty with voice deepening, phallic enlargement, increased muscle mass, and the development of male-pattern facial and body hair growth. This masculinization is probably due to increase in an enzyme that converts pubertal testosterone into DHT (Wilson 2001).

A second autosomal recessive disorder similar to 5-ARD is 17β-hydroxysteroid dehydrogenase-3 deficiency (17β-HSD-3). External genitals appear ambiguous or not completely masculinized and either male or female gender may be assigned. The prevalence in the general population for both of these autosomal recessive disorders is unknown (Cohen-Kettenis 2005; Conte and Grumbac, 2004).

There has been considerable controversy over the stability of gender identity and gender role behavior of these individuals, especially as they transition through puberty. Recently, Cohen-Kettenis (2005) reviewed the

world literature on this topic. Fifty-six percent (62 of 110) of those individuals diagnosed with 5-ARD changed gender from female to male and 39 percent (19 of 49) of those diagnosed with 17β-HSD-3 changed from female to male. Cohen-Kettenis (2005) also identified twenty-eight individuals diagnosed with either 5-ARD or 17β-HSD-3 who were assigned and reared as male. None of them changed to the female gender or appeared to have any wish to do so. Gender change, in those initially assigned as female who did gender reassign, could not be explained by prenatal exposure to androgens or to the degree of external masculinization.

Unclassified Forms of Abnormal Development

Hypospadias. Hypospadias refers to the positioning of the urinary *meatus* (opening) at some point on the undersurface of the penis, rather than at its tip. Hypospadias is a feature of many malformation syndromes, but it can also occur alone (i.e., isolated hypospadias). A multifactoral etiological model has been proposed for hypospadias. The exact cause of isolated hypospadias, which occurs in 1:300 newborn males (Conte and Grumbach 2004), remains unknown in most cases.

Classified according to the position of the urinary meatus, the mildest and most common form (85 percent) is glandular or coronal hypospadias (Grumbach, Hughes, and Conte 2003). Research indicates that hypoandrogenization associated with hypospadias does not interfere with developing gender-typical (masculine) behavior in boys during middle childhood (Sandberg et al. 1995). Individuals with hypospadias report relatively normal sexual behavior and function and, as a group, they do not report any more behavioral/emotional problems than comparison groups (Mureau 1995).

Micropenis. Micropenis refers to a completely formed penis, with the urethral meatus at the tip of the glands, that measures at or below 2.5SD in length for age and stage of puberty when stretched from the pubis ramus to the tip of the glands (i.e., a penis <1.9cm in a newborn or <9.3cm in an adult qualifies as a micropenis) (Lee et al. 1980). Micropenis can result from a heterogeneous group of disorders; the most common of which is fetal testosterone deficiency (Conte and Grumbach 2004). A micropenis does not necessarily occur as part of a syndrome; rather, it can occur in isolated form or be associated with a number of other conditions. For this reason, the incidence is not known.

Using the *Adjustment Self-Report Questionnaire*, Lee and Houk (2004) reported no significant differences between a small group of adult males with isolated micropenis and controls regarding psychosocial and psycho-

sexual functioning. They also failed to identify any differences in psychiatric symptoms between these two groups using the *Hopkins Symptoms Checklist*. Money and Norman (1988) found an association between micropenis and central nervous system (CNS) impairments in four cases, all with CHARGE syndrome (coloboma, heart disease, atresia cloanae, retarded growth/development or CNS anomalies, genital hypoplasia, and ear anomalies).

Newborns with a micropenis have been assigned at birth to either the female or the male gender. In a review of extant literature with respect to gender stability in individuals with a micropenis reared as male or female, there was not a single documented case of gender change among the eighty-nine individuals studied, ten of whom were assigned to the female gender (Mazur 2005a).

Mayer-Rokitansky-Kuster-Hauser (MRKH). MRKH, marked by the absence of the vagina with abnormal or absent Müllerian structures, is a congenital syndrome that occurs in genetic females. The incidence is estimated at between 1:4000 (Rock and Breech 2003) and 1:5000 (Evans, Poland, and Boving 1981; Grumbach, Hughes, and Conte 2003) female births. Associated features include amenorrhea with normal ovarian function. Renal and skeletal abnormalities may be present. Hearing loss occurs in approximately 25 percent of women with MRKH (Grumbach, Hughes, and Conte 2003).

Follow-up studies describing the psychological health of women with MRKH are limited. With psychological support and proper medical intervention to create a vagina, a normal sexual life can be expected (Bean 2003). Gender identity is firmly established as female with no known published reports of gender change.

Penile agenesis. Penile agenesis (or aphallia) refers to complete absence of the penis as part of a developmental pelvic field defect (Cendron 2001). The incidence of penile agenesis in not known. There may be associated anomalies such as failure of one or both testes to descend, renal abnormalities, and pulmonary problems. In the most pure form, there is absolutely no penile tissue in the normal position, two testes in a fully formed scrotum and the urethral opening on or in the anus (Cendron 2001). To our knowledge, there are no psychosexual and neurocognitive studies of a group of these individuals due to the rarity of the condition.

Penile agenesis is different from penile ablation: penile ablation is not the result of an anomaly of genital development but refers to traumatic loss of the penis resulting from, for example, an accident during circumcision.

Cloacal exstrophy of the bladder (CE). CE, affecting both genetic males and genetic females, is a severe variant of a defect to multiple organ systems

involving, among others, the bladder complex, abdominal wall, and pubic bones (Gearhart 2001). It appears that the bladder and abdominal wall are turned inside out, thus exposing the bladder. In males, the penis is often aplastic and split into halves. Classical bladder exstrophy is less severe than CE, but severe malformations can occur in this condition as well. Exstrophy of the bladder is a rare, congenital anomaly occurring in live births in a 1:25,000 to 1:40,000 ratios. There is a male predominance over female in a ratio of about 2:1 (Dominguez 2003).

Adult Gender Identity Outcomes

Table 12.1 summarizes the results on gender stability and change in those intersex conditions recently reviewed in the world literature and referred to in the previous section. Several conclusions can be drawn from inspection of this table: (1) self-initiated gender change occurs in intersex syndromes and related conditions; (2) the prevalence of individuals who change gender varies by syndrome; (3) self-initiated gender change is not universal for any one syndrome or condition; (4) gender change is more frequent in XY persons than in those with an XX chromosomal pattern; (5) self-initiated gender change occurs in both directions, that is, male-to-female and female-to-male, although it more frequently occurs in the direction of female-to-male as exemplified in Meyer-Bahlburg's (2005b) review of penile agenesis, classical and cloacal exstrophy, and penile ablation; and (6) there are no published reports of gender change in micropenis regardless of whether the person was assigned and reared as male or female.

GID in Intersex and Nonintersex Conditions

Clinical investigators have been unable to determine whether the etiology of GID is biological, psychological/environmental, or both. However, there are several factors associated with GID in intersex and nonintersex individuals (Cohen-Kettenis and Pfafflin 2003; Zucker 2004). While there are some overlapping features in the putative etiology of GID in persons with intersex and nonintersex conditions, the presence of factors unique to those with intersex suggests the possibility that the pathway to GID differs between groups (Tables 12.2 and 12.3).

Meyer-Bahlburg (1994) reported that GID in individuals without intersex conditions appears quite early in life, that is, before the age of six years; in contrast, most marked gender problems appear for individuals with intersex during adolescence. With regard to the sex ratio, in persons without intersex conditions, boys far outnumber girls; in those with intersex

TABLE 12.1. Gender Stability in Intersex and Related Conditions

Study	Diagnosis	N	Initial Assignment	Gender Reassignment		
				n	%[a]	Direction
Cohen-Kettenis (2005)	5-ARD	110	F	62	56	F → M
	17β-HSD-3	49	F	19	39	F → M
Dessens et al. (2005)	CAH (46,XX)	250	F	4	2	F → M
	CAH (46,XX)	33	M	0[b]	0	N/A
Mazur (2005a)	CAIS	156	F	0	0	N/A
	PAIS	99		9	9	F → M (3) M → F (6)
	Micropenis	79	M	0	0	N/A
	Micropenis	10	F	0	0	N/A
Meyer-Bahlburg (2005b)	Penile agenesis	16	F	2	12	F → M
	Penile agenesis	17	M	0	0	N/A
	Penile ablation	7	F	2	29	F → M
	Cloacal exstrophy	51	F	11	22	F → M
	Cloacal exstrophy	15	M	0	0	N/A
	Classical exstrophy	3	F	2	67	F → M
	Classical exstrophy	279	M	0	0	N/A

[a] percentages rounded to the nearest whole number

[b] four of 33 (12.1 percent) were reported to have "serious gender problems; one individual lived as a male, but was convinced he was a woman starting at age 26 when he began to menstruate"

TABLE 12.2. Putative Etiologic and Associated Physical Factors in GID: Intersex and Nonintersex

Feature	Intersex	Nonintersex
Biologic	1. Prenatal hormones 2. Puberty discordant for asigned sex	1. Prenatal hormones 2. Handedness 3. Sibling sex ratio/birth order 4. Birth weight
Psychosocial	1. Late correction or uncorrected genitalia 2. Stigmatization regarding genitalia 3. Parental tolerance/encouragement of cross-gender behavior secondary to doubt about assigned gender 4. Parental psychopathology	1. Social reinforcement 2. Prenatal sex preference 3. Parental relationship and attachment

Adapted from: Zucker, K. J. (2004). Gender identity development and issues. *Child and Adolescent Psychiatric Clinics of North America*,13: 551-568.

conditions, there are more reports of individuals initially assigned female who change to male than the reverse (Table 12.1). As such, Meyer-Bahlburg concluded that it is unlikely that GID is the same entity for persons with intersexuality as those without such a condition.

The *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (American Psychiatric Association, 2000), classifies individuals expressing marked discomfort with their apparent or assigned gender, and who demonstrate persistent identification with the opposite sex, under the category of Gender Identity Disorder (GID; 302.6 Gender Identity Disorder in Children or 302.85 Gender Identity Disorder in Adolescents or Adults). Symptoms qualifying for the diagnosis of GID are observed among individuals born physically typical as well as in those born with a disorder of somatic sex development (i.e., intersexuality). Because the DSM-IV-TR is largely an nontheoretical diagnostic scheme based on descriptions of symptom clusters rather than on a unified psychopathological concept (Rutter and Tuma 1988), it would be incorrect to assume that the etiology of GID in individuals born with an intersex condition is the

TABLE 12.3. Comparison of Intersex and Nonintersex Features

Feature	Intersex	Nonintersex
1. Reproductive anatomy	Atypical/discordant	Typical/concordant
2. Gender assignment at birth	Delayed or reassigned	Unambiguous and immediate
3. Medical care associated with intersex condition		
a. Contact with health care professionals (e.g., endocrinologist, urologist)	Routine contact throughout lifetime	No routine contact
b. Surgical decisions and procedures	During infancy and childhood	None
c. Medication	May begin during infancy and continue throughout lifetime	None
d. Puberty	May be induced by exogenous hormones	Induced by endogenous hormones
4. Gender dysphoria		
a. Age of onset	Adolescence or later	Early childhood
b. Sex ratio	More common in those assigned female at birth	More common in males
5. Self-initiated gender change	May occur	May occur

same as for those without such a condition. In fact, the DSM-IV-TR implicitly acknowledges this possibility by restricting the diagnosis of GID to individuals in whom "the disturbance is not concurrent with a physical intersex condition." Individuals born with intersex conditions that experience the cardinal features of GID are classified as having GID, not otherwise specified (NOS).

Evaluation and Treatment Strategies

While the final explanation of GID in both groups awaits further research, it must be emphasized that persons with an intersex condition experiencing GID have different histories from those born without a somatic intersex condition (Tables 12.2 and 12.3). The intersex condition, from the very moment of birth, triggers a series of events that are not experienced by

either nonintersex individuals or their parents. These events relegate the affected individual and parents, at least through infancy, childhood, and adolescence, to monitoring by health care professionals, much like a person with a chronic illness. For the individual born with ambiguous genitalia, the question that immediately faces medical personnel and parents is to which gender to assign the infant. The history may even include a change of the initial gender of announcement, with parents having to reannounce the gender of their child to siblings, grandparents, and friends. There may also be an immediate necessity for lifesaving medication as in the case of infants with salt-wasting CAH. Eventually, there are issues surrounding surgical reconstruction of the genitals, hormone treatment to induce puberty, and general state of good health (i.e., continued hormone replacement to maintain physical health).

As a consequence, the context within which a child with an intersex condition grows and develops is much different from that for a child without a somatic intersex condition. Therefore, the clinician needs to obtain a thorough history including chromosomal pattern, diagnosis, etiology (if known), surgeries, hormone treatment, pubertal development, and history of medications taken (up to and including current prescriptions). When obtaining a medical history, particular attention should be paid to factors believed to be associated with gender change in persons with intersex. Questions to ask might include the following: Did the person have late (after age of three years) or no genital surgery? If the person is an adolescent or adult, is their puberty (secondary sexual characteristics) discordant with their assigned gender? Is the person sexually attracted to individuals of the same gender, meaning the gender to which the person with intersex was initially assigned?

Cohen-Kettenis (2005) hypothesized three factors as a possible explanation of self-generated gender change from female to male in 5-ARD or 17β-HSD-3 individuals. A masculine appearance in childhood coupled with masculine (tomboyish) behavior due, "perhaps," to prenatal androgen exposure, influences a gender change with the onset of physical changes brought about by puberty. The third factor, pubertal development, intensifies an "already existing gender discomfort" (dysphoria). This combination of a masculinized appearance, atypical gender-role behavior, and pubertal hormones precipitates a self-initiated gender change in a subgroup of these individuals.

It has also been suggested that uncorrected or late-corrected genital appearance may lead to parental confusion (or rejection) over the gender of rearing, as well as to the child's own confusion (Meyer-Bahlburg et al. 1996; Money, Devore, and Norman 1986). A discordant puberty may then

exacerbate this confusion and, in some, contribute to the development of GID (Cohen-Kettenis 2005). There is thus a developmental sequence of events that results in a "crystallized" gender dysphoria with the wish to self-reassign gender. Part of obtaining a detailed history of the condition is to ascertain what the person has been told (or not told) by parents and physicians about the person's medical history. More important than *what* they have been told is how they *understand* their intersex condition. For example, a patient who states, "I was told that I really was born a boy but reared as a girl," demonstrates a lack of specific knowledge about the diagnosis and sequelae of the condition.

Adults born with an intersex or related condition are at risk for misunderstanding their medical history, if accurate information about their birth circumstances and the rationale for the medical treatment in childhood is either not provided or withheld. Consequently, gender confusion, even GID, may result. Also, consider that due to the complexity of the information involved, a person may misinterpret accurate information. Therefore, a main difference between assessing a person with a possible GID, who also has an intersex condition, and assessing one who does not is in discerning to what degree the presenting gender problem is associated with, possible confusion, or lack of information about the intersex condition. Such an assessment requires that the clinician understand what is known etiologically about intersex conditions, know how and why the somatic discordance occurs, and, most importantly, be able to provide this information to the client, who is likely to have gaps in knowledge or misinformation.

An important distinction between the clinical management of individuals with intersex and the management of those with nonintersex is *psychoeducation* about their medical history and the known associated behavior. Such information may help resolve a person's gender concerns and/or clarify the history. Several helpful resources are available for clinician and patient use (Appendix A).

In the event the patient wants to proceed with reassignment, a comprehensive understanding of the medical condition and treatment history is essential, not only to increase self-knowledge but, in certain cases, to ensure prolonged good health (i.e., the rationale for endocrine life-sustaining intervention in salt-wasting CAH, pubertal induction, or maintaining bone strength). Therefore, the *first step* in managing GID diagnosed in a person with an intersex condition, regardless of age, is *not* to implement therapeutic support for a change of gender, but rather to obtain the medical history and make sure that the person has a thorough and accurate understanding of the condition. In children and adolescents, this includes parental understanding as well.

Discussion

The purpose of this chapter was to provide an overview of "intersex" as traditionally defined. A sketch of differentiation and development of the internal and external sexual/reproductive system was given to provide a background upon which to appreciate the various intersex syndromes in genetic males and females as well as related conditions. Selected examples of these syndromes and conditions were presented. Data on the stability of adult gender identity in the most commonly studied intersex syndromes indicate that gender dysphoria and self-initiated gender change do occur in individuals with intersex conditions, although the frequency varies by syndrome. Furthermore, there is no syndrome or condition where self-initiated gender change is universal.

While a chapter on intersex in a book on transsexualism might be surprising to some, its inclusion is important for several reasons. As mentioned, current reviews of various intersex and related conditions document that self-initiated gender change does occur and that gender dysphoria without gender change probably occurs as well. A recent survey (Mazur et al. 2005b) of the membership of the Harry Benjamin International Gender Dysphoria Association (HBIGDA), the professional organization dedicated to the treatment of individuals with gender identity problems and dysphoria, indicated that ninety-three members (40 percent of respondents) had provided service, in the past two years, to individuals with an intersex condition or who were born with a sex-atypical variant of genital differentiation. While the majority of HBIGDA members had seen just a few such individuals, ten members had seen more than ten affected persons and fifteen were members of a "gender team" involved in gender assignment decisions for newborns with an intersex condition. Seventy-three percent indicated that they wanted continuing education on the topic of intersexuality.

Another reason for the relevance of this chapter for those who work in the area of gender identity and dysphoria pertains to the multiple use of the term "intersex." Originally, intersex was used interchangeably with the term "hermaphroditism." Over time, other terms or phrases were created to describe intersex or hermaphroditic conditions. All terms referred to an anomaly of the sexual/reproductive system where, in most cases, the sex of the infant could not be immediately determined. All of these terms focused on an identifiable problem of physical development/differentiation of the sexual/reproductive system, regardless of whether a diagnosis or etiology could be determined. Recently, the term "intersex" has been used to refer to individuals with no discernable physical problem. One way of understanding this broadening of "intersex" is to recall Szasz's words (1970) over

thirty years ago as he addressed the use of language in psychiatry. He suggested that language has three main functions: to transmit information, to induce mood, and to promote action. Lumping individuals with intersex with those who are nonintersex but experiencing problems of gender, or who challenge conventional gender boundaries, enlarges the base of minorities, which, hopefully, increases their political influence and the opportunity to gain "rights" previously denied to them. Such blurring of distinctions and inconsistent language use for political (or other) uses can be advantageous; however, merging categories can complicate the work of both scientists and clinicians who are charged with the tasks of elucidating conditions' etiologies and developing effective treatment strategies.

APPENDIX A

Androgen Insensitivity Syndrome Support Group (AISSG)
www.medhelp.org/www/ais

AISSG is a consortium of worldwide support groups that originated in the United Kingdom in 1988. AISSG provides information and support to young people, adults, and families affected by complete and partial Androgen Insensitivity Syndromes, Swyer's Syndrome (XY Gonadal Dysgenesis), 5-alpha Reductase Deficiency, Leydig Cell Hypoplasia, Mayer-Rokitansky-Kuster-Hauser (MRKH) Syndrome, Mullerian Dysgenesis, Mullerian Duct Aplasia, Vaginal Atresia, and other related conditions.

Congenital Adrenal hyperplasia Research Education and Support (CARES)
www.caresfoundation.org

CARES Foundation provides information to individuals and families about how to manage Congenital Adrenal Hyperplasia (CAH). CARES has also strongly advocated for the expansion of newborn screening for congenital and life-threatening disorders to include CAH.

The Center for Young Women's Health
www.youngwomenshealth.org/search.html

The Boston Children's Hospital center provides information on a variety of medical conditions relevant for young girls and women. A second Web

We thank Ms. Elaine Mosher, MLS, Emily Foster Health Sciences Library of The Women and Children's Hospital of Buffalo for her library assistance.

site, www.childrenshospital.org/az/Site2067/mainpageS2067P0.html provides general information on ambiguous genitalia.

Hospital for Sick Children
www.sickkids.ca/childphysiology/default.asp

This animated, interactive Web site at The Hospital for Sick Children in Toronto, Canada teaches about the workings of the human body. It shows how various systems and organs develop and perform. The section on genital development depicts typical development and differentiation of the internal and external sex organs in an animated, interactive manner. The site also explains via animation how CAH and AIS develop. Other conditions will be displayed as the site expands.

Intersex Society of North America (ISNA)
www.isna.org

Started by a group of intersex patient advocates, ISNA is devoted to systemic change to end shame, secrecy, and unwanted genital surgeries for people born with an anatomy that someone decided is not standard for male or female.

The Johns Hopkins Hospital

The Johns Hopkins Hospital has two Web sites. One focuses on CAH: www.hopkinschildrens.org/specialties/categorypages/cah/index.html. The second provides general information on many types of atypical sexual differentiation: www.hopkinschildrens.org/specialties/categorypages/intersex/index.html.

Klinefelter Syndrome and Associates (KS and Associates)
www.genetic.org/ks

KS and Associates focuses on individuals who have an extra X chromosome (47XXY) and variations. This Web site provides information about when 47XXY was first discovered, common characteristics of Klinefelter syndrome, ongoing research and treatment, and support and educational services.

Magic Foundation
www.magicfoundation.org

MAGIC stands for Major Aspects of Growth in Children. Click on Genital and Reproductive Anomalies in Children (GRAC) link for information on a variety of intersex syndromes and related conditions.

Middlesex Centre
www.uclh.nhs.uk/gps+healthcare+professionals/clinical+services/womens+health+(ega)/gynaecology+-+middlesex+clinic

The Middlesex Centre is located at the Elizabeth Garrett Anderson Hospital, in London, England. It has multidisciplinary teams which provide clinical care, diagnosis, information, and highly specialized treatment to individuals with various intersex syndromes in the United Kingdom.

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

Sex Determination and Differentiation

David T. MacLaughlin, Ph.D., and Patricia K. Donahoe, M.D.

SEX DETERMINATION, WHICH DEPENDS ON THE SEX-CHROMOSOME COMplement of the embryo, is established by multiple molecular events that direct the development of germ cells, their migration to the urogenital ridge, and the formation of either a testis, in the presence of the Y chromosome (46,XY), or an ovary in the absence of the Y chromosome and the presence of a second X chromosome (46,XX). Sex determination sets the stage for sex differentiation, the sex-specific response of tissues to hormones produced by the gonads after they have differentiated in a male or female pattern. A number of genes have been discovered that contribute both early and late to the process of sex determination and differentiation. In many cases our knowledge has derived from studies of either spontaneous or engineered mouse mutations that cause phenotypes similar to those in humans. We will examine how mutations in these genes cause important clinical syndromes (Table 1 and Fig. 1) and discuss clinical entities that continue to elude classification at the molecular level. Knowledge of the molecular basis of disorders of sex determination and differentiation pathways will continue to have a strong influence on the diagnosis and management of these conditions. Terminology, when possible, adheres to that used in the Online Mammalian Inheritance in Man data base developed by the National Center for Biotechnology Information of the National Library of Medicine (http://www.ncbi.nlm.nih.gov).

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GERM CELLS

Primordial germ cells, which eventually localize in the gonad, first appear in the proximal epiblast, the outer ectodermal layer of the embryo, whence they migrate through the primitive streak and then to the base of the allantois, where they can be identified by alkaline phosphatase staining. The germ cells then migrate along the wall of the hindgut to the urogenital ridge, the site of the future gonad (Fig. 2). Interesting factors that specify the fate of these primordial germ cells have recently been elucidated in mice.[2] Two genes that are unique to the differentiating germ cells are *Fragilis* and *Stella*. *Fragilis* is first detected in the proximal epiblast, where its expression is influenced by the bone morphogenetic protein 4 (BMP4), then in the base of the allantois, where the expression of *Stella* commences. On migration of the germ cell to the genital ridge, the expression of *Fragilis* diminishes while that of *Stella* persists. Inactivation of BMP4 is associated with inhibition of the expression of *Stella* and *Fragilis* and results in the absence of germ cells, which attests to the necessity of these genes in germ-cell formation and development.[2] However, it is not clear how either *Fragilis* or *Stella* specifies the fate of germ cells. *Fragilis* belongs to an interferon-inducible family of transmembrane proteins involved in transducing antiproliferative signals and in adhesion, both of which may be important in the coalescence of germ cells at the base of the allantois. *Stella* transcribes a novel protein, the structure of which suggests that it may have a role in RNA processing and chromatin modification. This protein is thought to maintain the pluripotent state of the migrating primordial germ cells by silencing transcription of genes specific to somatic cells.[3] Only

Table 1. Mutations in Genes Involved in Sex Determination and Development and Associated with Intersex Anomalies.

Gene (Locus)	Protein and Proposed Function	Mutant Phenotype
WT1 (11p13)	Transcription factor	Frasier syndrome, Denys–Drash syndrome with Wilms' tumor
SF-1 (9q33)	Transcription factor, nuclear receptor	Gonadal and adrenal dysgenesis
SOX9 (17q24)	High-mobility-group transcription factor	Campomelic dysplasia, male gonadal dysgenesis or XY sex reversal
DAX1 (Xp21.3)	Transcriptional regulator, nuclear-receptor protein	Gonadal dysgenesis, congenital adrenal hypoplasia
SRY (Yp11)	High-mobility-group transcription factor	Gonadal dysgenesis
MIS, or *AMH*, type II receptor (12q12–13)	Serine threonine kinase receptor	Persistent müllerian duct syndrome
MIS, or *AMH* (19p13)	Secreted protein, causes regression of fetal müllerian duct; Leydig-cell inhibitor	Persistent müllerian duct syndrome
AR (Xq11–12)	Androgen receptor, a ligand transcription factor	Male pseudohermaphroditism, complete or partial androgen insensitivity syndrome
HSD17B3 (9q22)	17β-Hydroxysteroid dehydrogenase, 17-ketosteroid reductase 3	Male pseudohermaphroditism
SRD5A2 (5p15)	5α-Reductase type 2	Male pseudohermaphroditism*
CYP17 (10q24–25)	17-Hydroxylase: 20–22 lyase	Male pseudohermaphroditism
CYP21 (6q21.3)	21-Hydroxylase	Congenital adrenal hyperplasia, female pseudohermaphroditism
HSD3B2 (1p13.1)	3β-Hydroxysteroid dehydrogenase type II	Congenital adrenal hyperplasia
CYP11B1 (8q24)	11β-Hydroxylase	Congenital adrenal hyperplasia
StAR (8p11.2)	Steroidogenic acute regulatory protein	Congenital lipoid adrenal hyperplasia

* Virilization may occur at puberty.

the germ cells that reach the presumptive gonadal region differentiate and survive; germ cells outside this region undergo apoptosis, although some escape and can later become germ-cell tumors.[4]

MALE GERM CELLS

The proliferation patterns of male and female germ cells differ. XY germ cells undergo mitosis during migration but soon after reaching the gonads, their growth becomes arrested and they remain within the testis in the quiescent (G_0) phase of the cell cycle until after birth under the influence of an unknown inhibitory factor (referred to as meiosis inhibitory factor) secreted by either Sertoli or myoid cells[5] (Fig. 2). After birth, the male germ cells resume the cell cycle and undergo meiotic division, which halves the number of chromosomes to produce haploid spermatogonia. The Sertoli cells nurture the germ cells, which complete spermatogenesis at puberty under the influence of the gonadotropins follicle-stimulating hormone and luteinizing hormone from the pituitary. Important to this process are proteins secreted by Sertoli cells, including cytokines, müllerian inhibiting substance, inhibin, activin, and insulin-like growth factor I.[6]

FEMALE GERM CELLS

XX germ cells undergo mitosis as they migrate to the female genital ridge and enter the ovary; the cells then progress through the initial stages of the first meiotic division, becoming arrested at prophase 1 by birth (Fig. 2). At this stage the surviving germ cells become surrounded by a single layer of somatic granulosa cells, and in mice, a stimulatory adenylcyclase maintains the oocyte in this primordial follicular state.[7] Communication between oocytes and the surrounding granulosa cells occurs when the resting primordial follicles are stimulated to grow at the time of puberty as primary, secondary, and preovulatory follicles under the influence of follicle-stimulating hormone.[8] Also, oocyte-derived growth and differentiation factor 9 and BMP15, along with zona pellucida proteins 1, 2, and 3,[9] act synergistically with granulosa-cell products, surprisingly similar to those secreted by Sertoli cells, to maintain the oocyte and to control ovulation.

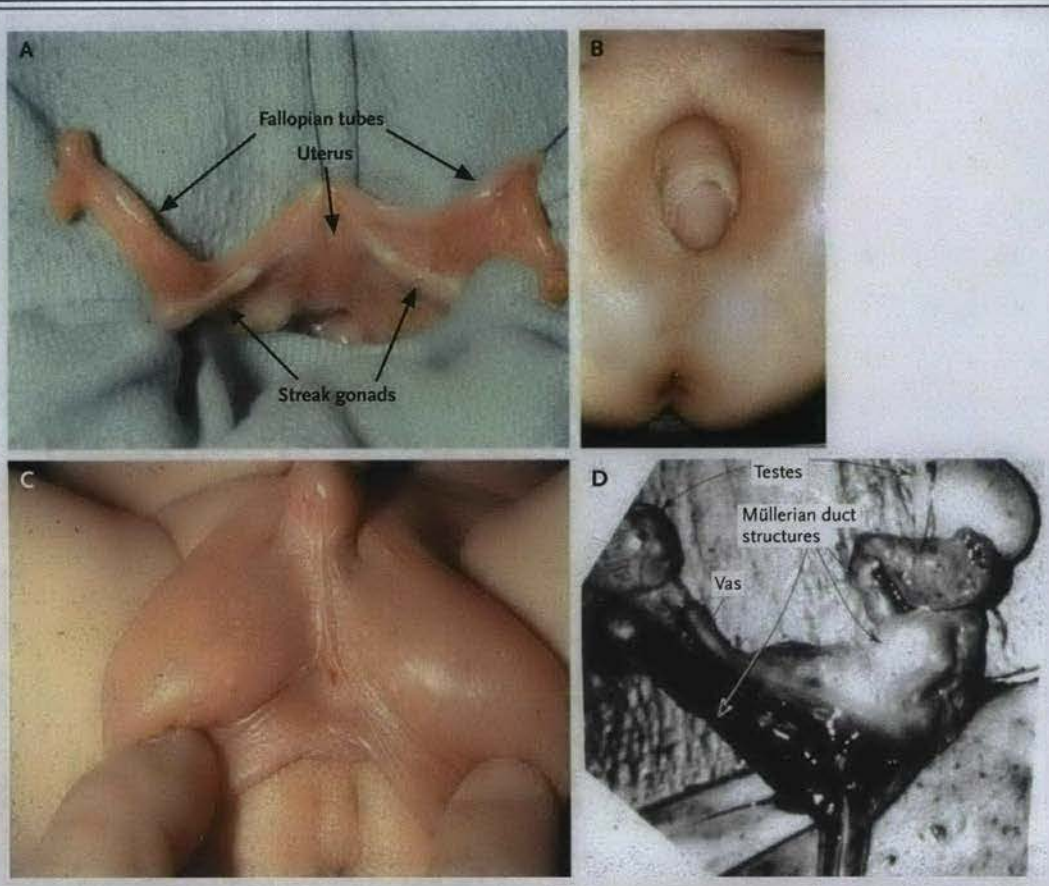

Figure 1. Clinical Examples of Intersex Abnormalities.

Panel A shows the internal structures of a 46,XY patient with pure gonadal dysgenesis. There are bilateral streak gonads with retained müllerian structures, fallopian tubes, and a midline uterus. Panel B shows severe clitoral hypertrophy caused by masculinization of the external genitalia of a 46,XX patient with female pseudohermaphroditism caused by congenital adrenal hyperplasia. Panel C shows incomplete masculinization of the external genitalia of a 46,XY patient with male pseudohermaphroditism. There is a microphallus with perineoscrotal hypospadias and bifid and prepenile scrota. Panel D shows internal genitalia of a 46,XY patient with persistent müllerian duct syndrome. There are müllerian structures (i.e., fallopian tubes and uterus) as well as wolffian structures (i.e., the vas deferens and epididymis). Panel B is reprinted from Donahoe and Crawford[1] with the permission of the publisher.

SYNDROMES OF ABSENT GERM CELLS AND RELATION OF GERM CELLS TO STEM CELLS

Germ cells are absent in the mutant strain of piebald mice[10] and in "Sertoli-only"[11] testes of infertile men who have deletions in the long arm of the Y chromosome in the azoospermia factor (AZF) regions that control spermatogenesis.[12] The recent elucidation of the sequence of the human Y chromosome[13] will provide a template to further our understanding of the structure and function of this chromosome, particularly of the elusive long arm (q). Stem-cell factor,[14] a ligand also known as mast-cell growth factor that is encoded by the steel locus on chromosome 12q, acts through its receptor, c-kit, and is important for the migration and survival of germ cells. Stem-cell factor, basic fibroblast growth factor,[15] and the glycoprotein 130 (gp 130) ligands lymphocyte inhibiting factor and interleukin-6 are all essential in immortalizing germ cells in vitro.[15] These specialized germ cells, in turn, can form embryoid bodies, which when injected into blastocysts can colonize all cell lineages.[16]

The isolation of embryonic germ cells led to the development of immortalized germ cells and eventually to the immortalization of human and primate embryonic pluripotent stem cells derived either

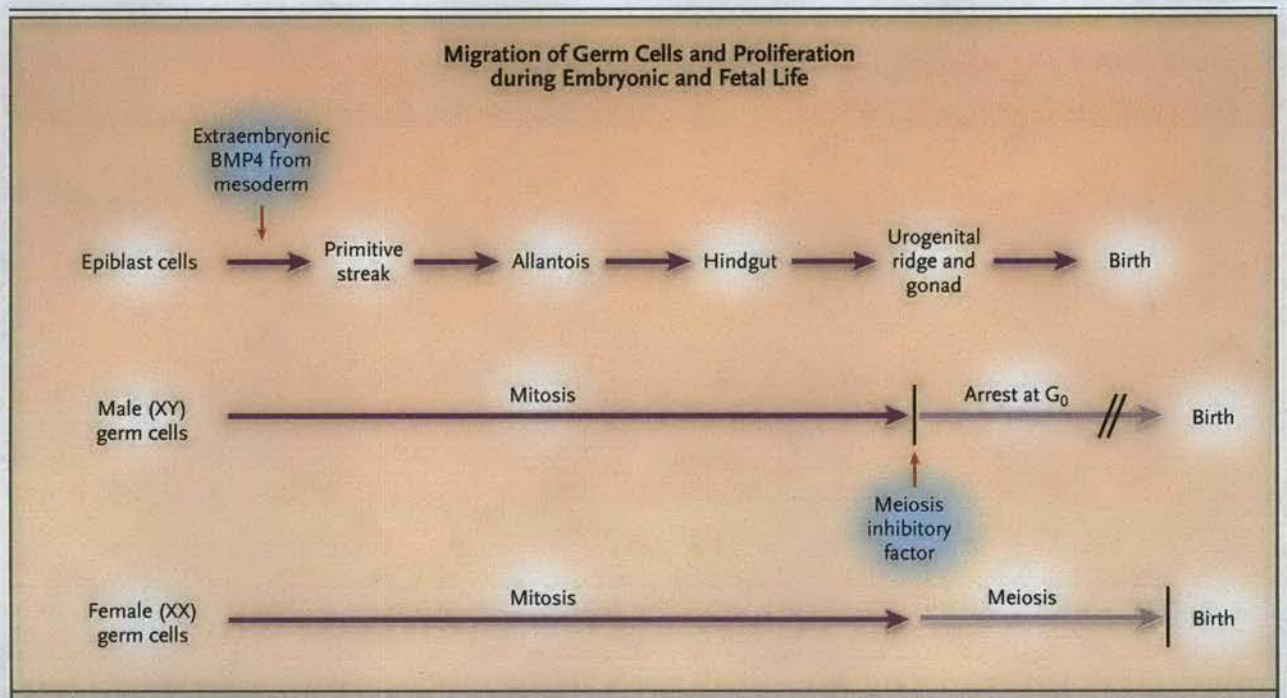

Figure 2. Migration and Proliferation of Germ Cells during Embryonic and Fetal Life.

Germ cells are first detected in the epiblast, where they are activated by bone morphogenetic protein 4 (BMP4) from the extraembryonic ectoderm. Migration occurs through the primitive streak to the base of the allantois, where alkaline phosphatase–positive cells can be detected. Subsequently, the cells migrate to the urogenital ridge, where the gonads form. The 46,XY and 46,XX germ cells undergo different patterns of mitosis and meiosis.

from fetal specimens[17] or from excess blastocysts generated by in vitro fertilization protocols.[18] These developments have increased our understanding of factors affecting pluripotency and have fueled hopes that therapeutic cloning can be used to create differentiated cell types for replacement therapy. Thus, germ-cell biology has contributed to the development of stem-cell biology. In turn, discoveries regarding pluripotency have also led to myriad ethical controversies[19] and initiated steps to ensure that cells will not be used unlawfully for reproductive cloning of humans.

SYNDROMES OF GONADAL DYSGENESIS

Investigations of the molecular events that occur during sex determination, coupled with an analysis of the phenotypes of mice in which candidate genes have been inactivated by homologous recombination (knockout mice), have increased our understanding of the pathophysiology of some of the clinical defects that are characterized by gonadal dysgenesis. As germ cells are migrating, the urogenital ridge forms from the intermediate mesoderm under the influence of a number of factors, including the transcription factors empty-spericles homeobox gene 2 (Emx2), GATA-4, Lim1, and Lim homeobox 9 (Lhx9) (Fig. 3). Mutations in the genes for these factors produce abnormal gonads in mice, but similar mutations have not yet been implicated in gonadal-dysgenesis syndromes in humans. However, three genes encode interacting proteins that are critical for the formation of the urogenital ridge in humans. The products of the Wilms' tumor-suppressor gene (*WT1*) are essential for both gonadal and renal formation. The steroidogenic factor 1 (SF-1) and the duplicated in adrenal hypoplasia congenita on the X chromosome (DAX 1) proteins are essential for gonadal and adrenal differentiation (Fig. 3). Our discussion of the clinical gonadal-dysgenesis syndromes will illustrate the important roles that these molecules play in the pathogenesis of the disorders.

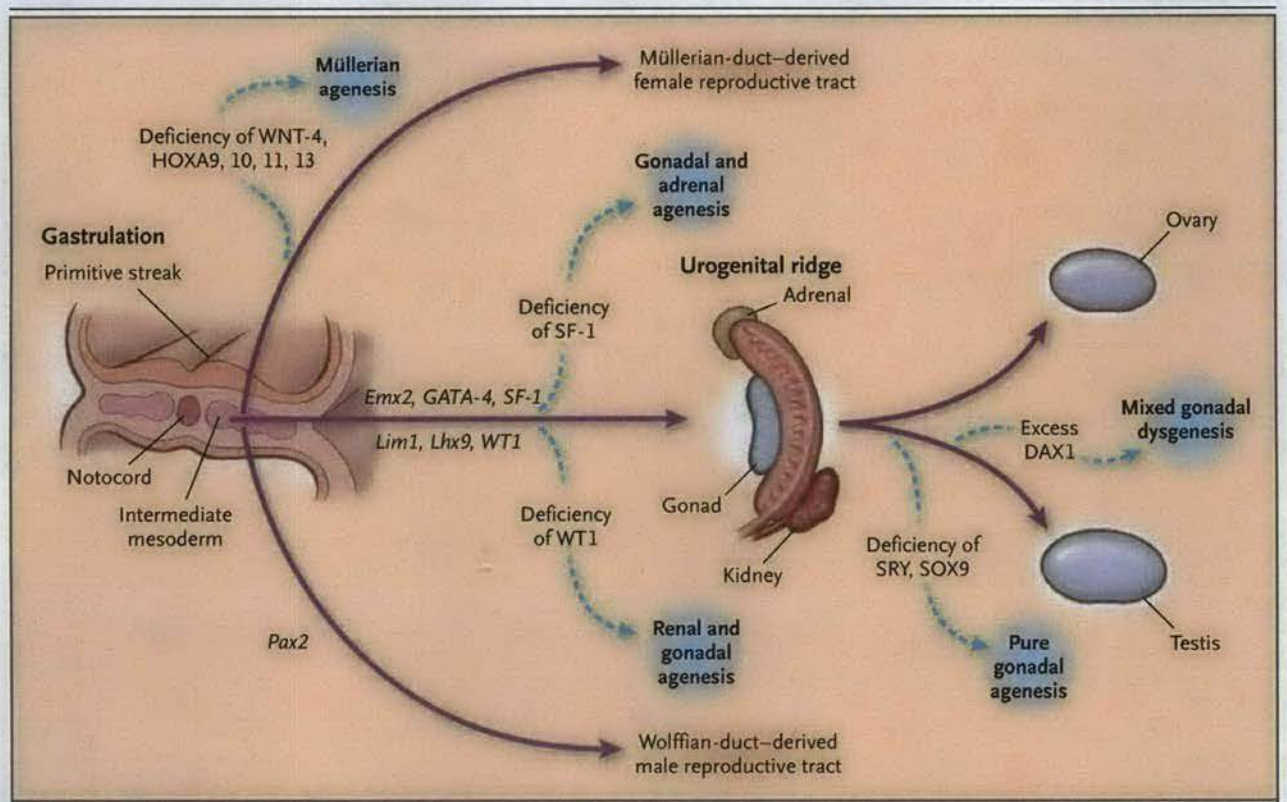

Figure 3. Syndromes of Dysgenesis during the Development of the Urogenital Ridge.

Mutations in various genes can lead to a variety of syndromes of dysgenesis involving the müllerian or wolffian ducts, gonads, kidneys, and adrenal glands as a result of a deficiency or excess of the proteins shown. *DAX1* denotes the gene for duplicated in adrenal hypoplasia congenita on the X chromosome 1; *Emx2* the empty spericles homeobox gene 2; *GATA-4* the gene encoding a protein that binds to a GATA DNA sequence; HOXA homeobox protein; *Lim1* a homeobox gene important for limb development; *Lhx9* a lim homeobox family member; *PAX2* paired box homeotic gene; *SF-1* the gene for steroidogenic factor 1; SRY sex-determining region of the Y chromosome; SOX9 SRY homeobox 9; Wnt-4 a protein that induces the development of the müllerian mesenchyme; and *WT1* Wilms' tumor-suppressor gene 1.

GONADAL AND RENAL ABNORMALITIES

The Frasier Syndrome and WT1

The Frasier syndrome is characterized by both gonadal dysgenesis and renal abnormalities that result in streak gonads coupled with the nephrotic syndrome (Fig. 3). If it occurs in the XY genotype then there is sex reversal. Study of the phenotype of *Wt1*-knockout mice revealed that the gene is involved in the early steps of the differentiation of both gonads and kidneys, helping to explain the association of gonad and kidney malfunction in the Frasier syndrome.

Alternative splicing of the *Wt1* gene in mice can result in up to 24 protein isoforms. Mutations of two of these isoforms lead to striking clinical manifestations, thereby demonstrating their importance in human sex determination. They are the –KTS and the +KTS variants, in which there is deletion (–) or maintenance (+), respectively, of three amino acids, lysine (K), threonine (T), and serine (S) between the third and fourth zinc fingers of the DNA-binding domain of this transcription factor. Hammes et al.[20] found that altering the expression of KTS in mice influences both kidney and testicular function. In the Frasier syndrome, the splice site of *WT1* that normally preserves the KTS triplet is mutated; therefore, patients with the syndrome produce only WT1 protein without KTS. Gonads lacking KTS have decreased production of the sex-determining region of the Y chromosome (SRY), a urogenital ridge protein that is critical for testicular differentiation. In these –KTS gonads there is also a decrease in müllerian inhibiting substance, a glycoprotein hormone derived from Sertoli cells that causes regression of the male müllerian ducts and whose presence is an early marker of testicular differentiation.[21] The findings

in the Frasier syndrome indicate that the +KTS WT1 isoform must be produced either at the same time or before the urogenital ridge produces the SRY that will induce gonadal differentiation. Persons with a 46,XY karyotype will have a female phenotype with retained müllerian ducts as well as nephropathy. The severity of the nephropathy varies, however, with the position of the mutation that disrupts the KTS region; some genotypes lead to renal failure in infancy, whereas others cause milder forms of nephrotic syndrome compatible with increased longevity. Patients with the Frasier syndrome who have a mutation that inactivates KTS, however, are not susceptible to Wilms' tumor.

The Denys–Drash Syndrome and WT1

Mutations outside the KTS region result in a WT1 protein that affects gonads later in development, leading to the Denys–Drash syndrome, in which gonads differentiate more completely than the gonads of patients with the Frasier syndrome. Thus, affected patients have a less severe functional deficiency. For example, male gonads are sufficiently developed to produce müllerian inhibiting substance, which ensures that regression of the müllerian ducts is normal, but the synthesis of testosterone is impaired. Although persons with a 46,XY karyotype have a predominantly male phenotype, low testosterone levels can cause male pseudohermaphroditism with various degrees of hypospadias and undescended testes.[22] Patients with the Denys–Drash syndrome also have a high incidence of Wilms' tumors and a nephropathy characterized by focal glomerular and mesangial sclerosis, which often results in end-stage renal disease and ultimately renal transplantation in the second or third decade of life.

These multiple molecular *WT1* variants resulting from alternative splicing of the KTS amino acid triplet have different clinical implications. Study of patients with the –KTS mutation has alerted clinicians to the fact that phenotypic girls with focal glomerular sclerosis or the nephrotic syndrome should be screened for XY sex reversal. Also, phenotypic girls with XY sex reversal who retain müllerian structures because the gonadal dysgenesis occurs before the production of müllerian inhibiting substance should be screened for the nephrotic syndrome. In addition, boys with mild undervirilization characterized by hypospadias and undescended testes who also have proteinuria may have the Denys–Drash (+KTS) variant and should be monitored carefully for focal glomerular nephropathy and Wilms' tumor.

Wilms' tumor can be associated with aniridia, genitourinary anomalies, and mental retardation — the WAGR syndrome.[23] These complex phenotypic associations are thought to occur because of the proximity of *WT1* on chromosome 11p13 to the paired box homeotic (*PAX6*) gene and two other genes in that region that are expressed in the embryonic brain. Patients with the Beckwith–Weidemann syndrome of hemihypertrophy,[24] caused by mutations of a gene on chromosome 11p15, are also prone to Wilms' tumor.

GONADAL AND ADRENAL ABNORMALITIES

Steroidogenic Factor

Another important gene in early gonadal development is SF-1,[25] which encodes a transcription factor homologous to steroid hormone receptors, but whose ligand is unknown, placing the receptor in a class of orphan nuclear hormone receptors. SF-1 binds DNA and regulates the expression of a number of genes that participate in sexual development. These include müllerian inhibiting substance[21,26-28] and all the cytochrome P-450 steroid hydroxylase enzymes[29] and 3β-hydroxysteroid dehydrogenase,[30] which are required for the synthesis of sex steroid hormones. *Sf-1*–knockout mice fail to develop adrenal glands and gonads and die at birth.[31] A human with adrenal insufficiency and 46,XY sex reversal was found to have a mutation in SF-1.[32,33] *Wt1* and *Sf-1* have been shown to interact in mice, with *Wt1* enhancing the effect of Sf-1 on downstream genes.[34]

DAX1

The *DAX1* gene codes for a member of the nuclear-receptor family of proteins. Since this protein lacks a DNA-binding domain but does have a ligand-binding domain, it presumably regulates gene expression through protein–protein interaction.[35] *DAX1* mutations are associated with adrenal hypoplasia congenita,[36] a syndrome of adrenal insufficiency due to impaired development of the adrenal cortex, and hypogonadotropic hypogonadism as a result of impaired development of the pituitary and the gonads (Fig. 3). Dax1 antagonizes the synergy between Sf-1 and Wt1[34] in mice, thereby inhibiting the transcription of *Sf-1* downstream genes, most likely by recruiting corepressors[37] or by blocking binding of Sf-1 to DNA.[38]

A Potential Role for DAX1 *in Mixed Gonadal Dysgenesis*

An intersex disorder resulting in dysgenetic and often asymmetric gonads is the enigmatic syndrome of mixed gonadal dysgenesis, which is most often associated with a mosaic 45,X/46,XY karyotype,[39] although a 46,XY karyotype is found in 40 percent of patients.[40] The mosaicism is characterized by the presence of at least two gonadal germ-cell lines with different chromosomal complements.[41] The percentage of cells with an intact XY genotype dictates the degree of testicular differentiation. In the classic form, there is a streak gonad on one side and a dysgenetic fibrotic testis with disordered tubular architecture on the other, retained müllerian ducts caused by a deficiency of müllerian inhibiting substance, and incomplete genital masculinization as a result of a deficiency of testosterone. It is not clear why gonadal asymmetry is such a prominent feature of mixed gonadal dysgenesis, but it is probably related to sex-chromosome mosaicism. The streak gonad, resembling those seen in patients with Turner's syndrome, is thought to result from a loss of the Y chromosome owing to embryonic nondysjunction, the failure of paired chromosomes to migrate to opposite poles during mitosis or meiosis. The phenotype of patients with mixed gonadal dysgenesis can vary, with gonads that are more normal at birth than those in patients with pure gonadal dysgenesis (see below) but that undergo early degeneration,[39] which may progress to dysgenesis and subsequent neoplastic transformation. Because of the possibility of neoplastic transformation, early removal of the gonads is recommended.[39,40] Less severe phenotypes can occur if the same 46,X/46,XY karyotype is found in a relatively small percentage of chimeric cells. In fact, 45,X/46,XY karyotypes are now being found incidentally in phenotypically normal males owing to the increased frequency of prenatal genetic testing.[41]

An X-linked molecule like DAX1 may have a role in mixed gonadal dysgenesis (Fig. 3 and 4), since DAX1 suppresses testicular differentiation.[35] The presence of two X chromosomes, albeit in different cells, one from 45,XO and the other from 46,XY, may be sufficient to prevent sustained testicular growth and differentiation by providing excessive DAX1 (or another inhibiting molecule), which suppresses testicular development. This concept is supported by the observation that the presence of a second X chromosome in XXY humans with Klinefelter's syndrome and in XXY mice leads to abnormalities of germ-cell development with early entry into meiosis.[42]

SRY AND *SRY* HOMEOBOX GENES IN PURE GONADAL DYSGENESIS

Patients with pure gonadal dysgenesis have bilateral streak gonads that fail to differentiate. Analysis of these patients and animal models led to the discovery of the *SRY* gene located on the distal short arm of the Y chromosome and to the detection on autosomes of SRY homologues, such as the SRY homeobox gene *SOX9*. The molecular basis for testicular differentiation became more clear when phenotypic males were produced after an *Sry* transgene was introduced into XX mice, confirming the role of *Sry* as a genetic switch that induces testicular differentiation.[43] Mutations in the DNA-binding region of the *SRY* gene, which is a member of a large high-mobility-group family, were found in a subgroup of 46,XY sex-reversed females with pure gonadal dysgenesis. These patients have characteristic bilateral streak gonads, which are small and fibrotic, without the typical germ-cell or supporting-cell morphology of testes or ovaries.[44] Campomelic dysplasia, a severe disorder characterized by 46,XY sex reversal, streak gonads, and severe skeletal malformation, occurs in patients with a translocation in the distal arm of chromosome 9p near the SRY-related *SOX9* gene[45] and other genes associated with sex reversal in lower organisms.[46] *SOX9* and *SRY* are coexpressed in the male but not the female urogenital ridge, implicating the two genes in testis determination (Fig. 3). The fact that *SOX9* activates the transcription of müllerian inhibiting substance[28,47] further supports the idea that it has a crucial role in male gonadal development.

TRUE HERMAPHRODITISM

An unusual cause of ambiguous genitalia is true hermaphroditism; in this syndrome, both ovarian and testicular tissue is present either in the same or in a contralateral gonad. This disorder is rare in North and South America but quite common in Africa and the Middle East. Asymmetry of gonads and subsequently of reproductive ducts and external genitalia is common, with testes, ovaries, and ovotestes present in various combinations in patients with a predominantly 46,XX karyotype.[48] The sex of rearing is dictated by the phenotype, which is directed by the predominant gonad. In true hermaphroditism,

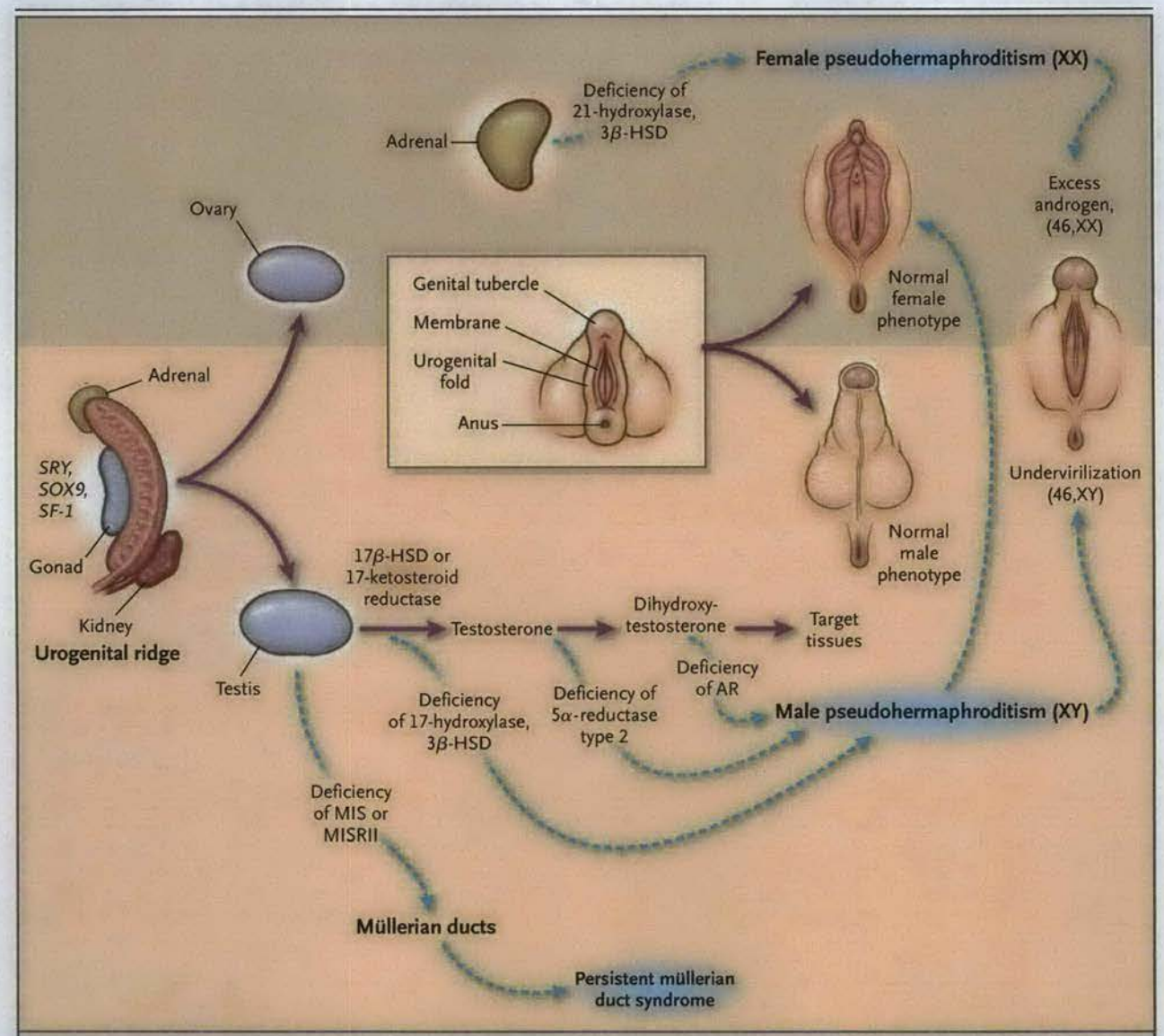

Figure 4. Functional Abnormalities of the Synthesis and Action of Hormones.

After the gonads have formed, reduced hormonal activity or signaling of specific receptors can lead to functional abnormalities of the reproductive tract, including persistent müllerian duct syndrome; male pseudohermaphroditism, causing undervirilization; and müllerian agenesis. After adrenal development, reduced enzymatic activity can result in female pseudohermaphroditism with excessive virilization. HSD denotes hydroxysteroid dehydrogenase, MIS müllerian inhibiting substance, MISRII müllerian inhibiting substance type II receptor, *SF-1* the gene for steroidogenic factor 1, *SRY* the gene for the sex-determining region of the Y chromosome, *SOX9* the gene for SRY homeobox 9, and AR androgen receptors.

the gonads have less severe dysgenesis[49] than do the gonads of patients with mixed gonadal dysgenesis. The molecular events leading to this unique disorder have not been elucidated, but a few cases have been attributed to translocation of a fragment containing the SRY gene to a cryptic site on the X chromosome.[50]

MÜLLERIAN AGENESIS

The undifferentiated gonad coexists with both male and female reproductive ducts. The paramesonephric, or müllerian, duct forms the uterus, fallopian tubes, and the upper vagina, and under the influence of testosterone, the mesonephric, or wolffian, duct forms the vas deferens, seminal vesicles,

and epididymides. A transcription factor gene common to the development of both müllerian and wolffian systems is PAX2. This gene is required for normal intermediate development of the mesoderm in both sexes; mutations in mice lead to müllerian-duct, wolffian-duct, and renal agenesis.[51] A mutation in the PAX2 gene has been reported in a family with the renal-coloboma syndrome,[52] which partially reproduces the results seen in mice. Failure of müllerian development occurs in 46,XX female patients with Mayer–Rokitansky–Küster–Hauser syndrome, which is characterized by vaginal or complete müllerian agenesis and kidney abnormalities, including a pelvic kidney or the more severe agenesis of the kidney.[53] Inactivation of *Wnt-4*, the gene encoding a member of the Wingless family of proteins, may be implicated in this disorder. Wnt is an acronym for a drosophila homologue of the Wingless family of proteins that is found in the mouse genome at a site where the mouse mammary tumor virus growth factor often integrates. The Wnt-4 protein is secreted by the müllerian-duct epithelium and induces the development of the müllerian mesenchyme. Early inactivation of *Wnt-4* causes failure of the formation of müllerian-duct derivatives in both sexes; however, a functional effect is manifested only in females, since in normal males, the müllerian duct regresses under the influence of müllerian inhibiting substance. Coincident kidney defects are lethal at birth in mice,[54,55] but humans with less severe phenotypes can survive.

Homeobox (Hox) transcription factors 9, 10, 11, and 13 are necessary for normal uterine and vaginal development; abnormalities in the expression of the genes for these factors account for some uterine and vaginal atresias.[56] Mutations in a *Hoxa13* allele are the cause of the hand–foot–genital syndrome, in which there are deformities of the hands and feet, vaginal abnormalities in females or hypospadias in males, spinal abnormalities, and extrophy of the bladder and cloaca.[57] Transfection of constructs with this mutation into the chicken-hindgut region reproduced these abnormalities.[58] Diethylstilbestrol has been known since 1971[59] to alter müllerian development. The fact that diethylstilbestrol suppresses another *Wnt* gene — *Wnt-7a* — and alters *Hox* gene expression in müllerian ducts in mice[60] provides a plausible molecular mechanism for the uterine abnormalities, vaginal adenosis, and rarely, carcinoma observed in patients who were exposed to diethylstilbestrol in utero.[59]

FUNCTIONAL ABNORMALITIES IN SEXUAL DEVELOPMENT

After normal morphologic development of the gonads, loss-of-function mutations of testicular proteins such as müllerian inhibiting substance or the müllerian inhibiting substance receptor can lead to the development of disorders characterized by retained müllerian ducts. Failure to produce testosterone or mutations in the testosterone receptor can produce 46,XY phenotypic females or phenotypic males with various degrees of diminished masculinization. Conversely, patients with congenital adrenal hyperplasia produce an excess of adrenal androgens, which can cause female pseudohermaphroditism in 46,XX patients.

PERSISTENT MÜLLERIAN DUCT SYNDROME

Persistent müllerian duct syndrome occurs in 46,XY males as a rare form of male pseudohermaphroditism that is caused by a defect in either the gene for the müllerian inhibiting substance,[21,61-63] located on chromosome 19p13,[64] or its type II receptor, located on chromosome 12q13[65] (Fig. 4). Patients with this syndrome[61] have retained müllerian ducts and unilateral or bilateral undescended testes, and they may also have crossed testicular ectopia caused by herniated uterine structures, which drag the contralateral gonad into one scrotum[66] with its ipsilateral gonad.

MALE PSEUDOHERMAPHRODITISM

Another important cause of male pseudohermaphroditism with sexual ambiguity is failure of androgen production or an inadequate response to androgen, both of which can cause incomplete masculinization of persons with the 46,XY karyotype. The clinical spectrum varies from mild failure of masculinization, with hypospadias and undescended testes, to complete sex reversal (Fig. 4) with a female phenotype. Androgen-receptor mutations[67,68] result in the androgen insensitivity syndrome in which testes can be intraabdominal or in the inguinal canals, but wolffian structures and external genitalia fail to respond to high levels of testosterone and its target-tissue metabolite dihydrotestosterone. Adequate müllerian inhibiting substance produced by the otherwise normal testes, however, results in complete regression of müllerian ducts.

Another cause of undervirilization arises from

defects in the synthesis of testosterone in patients with mutations in the steroidogenic enzymes responsible for the conversion of cholesterol to dihydrotestosterone — namely, steroidogenic acute regulatory protein,[69] cytochrome P-450 17-hydroxylase,[70] 3β-hydroxysteroid dehydrogenase,[71] and 17-ketosteroid reductase.[72] These defects cause low levels of androgen. Mutations in the 5α-reductase type 2 gene[73] result in low levels of dihydrotestosterone, which cause penoscrotal hypospadias, prepenile scrota, and an enlarged prostatic utricle,[73,74] often requiring surgical reconstruction.[75] As in the androgen insensitivity syndrome, regression of the müllerian duct occurs because the normal Sertoli cells produce normal or even elevated[76-78] levels of müllerian inhibiting substance. Many genetic males with a deficiency of 5α-reductase type 2 are born with female external genitalia and are raised as females. The curious virilization that occurs in these patients at puberty often leads to a change in sexual identity.[79] This paradox is explained by a normal increase at puberty in the activity of the 5α-reductase type 1 isoform, which results in sufficient dihydrotestosterone to complete the virilization of these genetic males.

CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia is caused by the inability of the adrenal to synthesize[80] sufficient cortisol, leading to excess testosterone and resulting in severe masculinization in 46,XX females. More severe forms involve decreased aldosterone production and salt wasting.[80] The most common mutation occurs in the cytochrome P-450 21-hydroxylase enzyme[81-83]; a less common form (5 percent of cases) results from a loss-of-function mutation in 3β-hydroxysteroid dehydrogenase.[71] Rarer still is 11β-hydroxylase deficiency, which can also result in prenatal or postnatal virilization.[84,85] Insufficient production of cortisol and the resultant failure of negative feedback in the hypothalamic–pituitary–adrenal axis causes excess corticotropin production, leading to adrenocortical hyperplasia. In addition, cortisol precursors are shuttled to other steroid pathways, causing high levels of adrenal androgenic steroids, which masculinize the female external genitalia to form a glans penis, rather than a clitoris, and scrota, rather than labia majora (Fig. 4). Under the influence of the excess androgens, the vagina fails to complete its descent to the perineum, causing a common urogenital canal or sinus with incomplete separation of the vagina and urethra. Ovaries and müllerian structures are otherwise normal, because their development is independent of sex steroids at this stage. The diagnosis can be made in utero, and early maternal dexamethasone therapy can ameliorate the masculinized phenotypes.[80,83,86] Surgical reconstruction can be performed in infancy to restore the female phenotype.[87]

SUMMARY

The study of patients with syndromes characterized by ambiguous genitalia and associated anomalies, together with analyses of spontaneous and engineered mutations causing similar abnormalities in animals, has elucidated many of the molecular defects causing sex reversal and disorders of reproductive function in humans. Our knowledge is expanding regarding the molecular events necessary to initiate the development of the urogenital ridge and to select and sustain further sex differentiation and development of gonads, reproductive ducts, and external genitalia. This deeper understanding has, in some cases, contributed to improved patient care both by increasing the likelihood of a positive outcome and by averting unfavorable events. This knowledge must be incorporated into treatment strategies in order to increase and sustain the function, happiness, and emotional fulfillment of patients with abnormalities of sex differentiation.

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GENDER ASSIGNMENT AND REASSIGNMENT IN INTERSEXUALITY: CONTROVERSIES, DATA, AND GUIDELINES FOR RESEARCH

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INTRODUCTION

In recent years, gender has become a hotly debated issue in regard to two clinical syndrome categories: Intersexuality, i.e., individuals with ambiguities of the genitalia, and Gender Identity Disorder (GID), i.e., individuals who have normal genitalia but desire gender change. The intersex controversy focuses on the assignment of gender and related issues of psychosocial and medical management. The GID debate centers on the question whether GID should be considered a mental disorder or be removed from the Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association (APA, DSM-IV, 1994) and declared a normal variant in analogy to the 1973 decision of the APA on homosexuality (Bayer, 1987)). The GID debate extends to intersexuality, because if intersex patients have significant gender identity problems, DSM-IV classifies them as GID Not Otherwise Specified (GIDNOS) which implies a mental-disorder status. In the current paper, however, we will leave the GID part of the debate aside and concentrate on the question of gender assignment and related issues in intersexuality.

Intersexuality is usually defined endocrinologically and includes prenatal hypo-androgenization in 46,XY males or prenatal hyper-androgenization in 46,XX females. However, there are a number of conditions where anomalies of the genitalia are not caused by endocrine disorders. This applies particularly to 46,XY individuals with penile agenesis, cloacal exstrophy of the bladder, and traumatic loss of the penis (ablatio penis) in infancy. When such cases are assigned to the female gender, gonadectomized, and later treated with estrogens, the management considerations are very similar to those in classical intersexuality. In the context of this chapter, I will therefore expand the term 'intersex' to cover both endocrine and non-endocrine categories of genital ambiguity.

Past and Present Policies of Gender Assignment

In regard to gender assignment and re-assignment of intersex patients, we distinguish two major policies (Meyer-Bahlburg, 1998). The traditional one has been to determine the true sex (since the 19th century usually understood as the true biological sex), to assign gender accordingly, and to expect that everything else will fall in line, more or less, with societal expectations—everything else meaning gender identity, gender role

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behavior, sexual orientation, courtship and love, sexual functioning, and psychological health in general. The true-sex policy underlies the ubiquitous question at birth: "Is it a boy or a girl?", implying that the infant is already a gendered person. Yet, what is the definitive criterion of the "true sex"? Traditionally, it had been the external genitalia, in the later 19th and beginning 20th century the gonadal histology (Dreger, 1998), and later the sex chromosomes. Each of those criteria can be ambiguous, and all three may be discrepant from one another.

The true-sex policy led some physicians to assign to the male gender patients with complete androgen insensitivity (CAIS), because the gonads had a male histology, although the defect in the androgen receptor permanently prevented the development of any physical masculinization. It was the policy that drove some intersex patients to suicide after their marriage plans were legally blocked because they had the wrong gonads. (It also was the policy that led some clinicians to declare Turners' syndrome girls 'neuters' because they had XO sex chromosomes and were therefore not deemed eligible for marriage.)

The second policy is to determine the optimal gender (Meyer-Bahlburg, 1998;1993) in terms of future functioning, i.e., to assign the gender that for a given child carries the best prognosis: for reproductive function (if attainable at all), sexual function, minimal medical procedures, an overall gender-appropriate appearance, a stable gender identity, and a reasonably happy life. The question the optimal-gender policy asks at birth is not: "Is this a boy or a girl?", but rather: "Will this child have a better chance for a reasonable life as a male or a female?" Thus, the basis for the gender-assignment decision is what one can predict in infancy, given the child's particular syndrome and its severity, and given all that is known about the natural history of the condition and its treatment options. Under this policy, early surgery of the external genitalia is recommended to avoid discrepancies between the child's assigned gender and genital appearance and, thereby, to facilitate consistent sex-typing by the parents and others. With other words, the rationale for early genital surgery includes gender-confirmation. Additional genital surgery may be necessary later to facilitate intercourse. After infancy, when gendered role behavior and identity become apparent, no gender re-assignment decisions are made without careful evaluation of the child's behavioral development and self-concept.

This is the policy proposed by John Money and the Johns Hopkins school of pediatric endocrinology in the mid-1950s (e.g., Money et al, 1955; Money, 1968;1994). It was formulated after literature reviews and direct evaluation of intersex patients had led to the conclusion that gender of assignment predicts long-term gender outcome better than the traditional biological criteria of true sex. Until recently, this policy was widely accepted in the U.S. and other countries, although there certainly was never a universal consensus. But even when there is a local consensus to follow the optimal-gender policy, decision making in the individual case can be difficult, because the prognostic criteria are not necessarily more definitive than the sex-diagnostic ones.

Critical Perspectives on Current Policies

The Critics

It is this optimal-gender policy, or rather certain aspects of it, that has increasingly come under attack in the past 5 years. Much of the current critique represents three perspectives. The biological determinists point to selected cases with 46,XY intersexuality who were raised as girls but changed gender to male in adolescence or adulthood. The latter include, for instance, the observations by Imperato-McGinley et al. (Imperato-McGinley et al, 1979; Imperato-McGinley, 1999) on 5-alpha-reductase deficiency (5-alpha-RD), the reports by Diamond (e.g., Diamond, 1997; Diamond et al, 1997) on scattered cases of other XY-intersex conditions such as the John /Joan case with a history of traumatic loss of the penis, and Reiner's work on 46,XY patients with cloacal exstrophy of the bladder or with penile agenesis (Reiner et al, 1995; Reiner, 1999). Given the extensive animal literature on the role of the sex hormones in the sexual differentiation of brain and behavior, it is entirely plausible that such biological explanations are also invoked for gender change in humans (Hines et al, 1993).Thus, it is assumed that the prenatal endocrine milieu does not only determine the sexual differentiation of the genitalia but also of the brain, and the status of the genitalia at birth is interpreted as an indicator of the degree of prenatal masculinization of either organ (except for the syndrome of 5 -RD where a metabolite of testosterone, dihydrotestosterone, is needed specifically for the masculinization of the external genitalia, and except for the conditions of non-hormonal genital abnormalities).

One has to keep in mind, of course, that the 1955 concept of the gender-undifferentiated neonate has long been discarded by John Money himself, after he began in 1964, together with Anke Ehrhardt and others, to investigate the prenatal hormone theory in humans. Already their first publications in 1967-1968 (Ehrhardt et al, 1967;1968(2); Money et al, 1972) showed masculinization of gender-role behavior in girls and women with a history of prenatal androgen excess, and these findings were confirmed in many subsequent studies (Ehrhardt et al, 1981; Dittmann et al, 1990; Zucker et al, 1996; Berenbaum, 1999). Thus, to some extent, the attacks of the biological determinists are historically outdated.

In contrast to the biological determinists, the social constructionists usually come with a perspective that is decidedly anti-essentialist, i.e., anti-biological. Thus, we have a curious constellation here: John Money, the non-essentialist of 1955 who saw the newborn as gender-undifferentiated and emphasized the importance of social factors in gender development, and then spearheaded the research that demonstrated the influence of prenatal hormones on human psychosexual differentiation, is now attacked jointly by biological determinists who vouch for the predominance of biological factors in gender development, and by social constructionists such as Kessler (Kessler, 1998) who object to the practice of making the status of the external genitalia the basis for sex assignment decisions in intersex newborns. However, the basic thrust of the social constructionists' argument is not the question of the etiology of gender in the specific psychobiological sense, but a critical examination – often from specific feminist, queer-theory, and/or

transgender perspectives—of the gender-assignment decisions and its underlying assumptions and of the related question of decision power (e.g., Dreger, 1998).

In regard to these questions, the social constructionists have common ground with the intersex activists, i.e., individuals who are living with an intersex condition and have personally experienced medical management and its consequences. Best known in the U.S. are the activists from the Intersex Society of North America (ISNA) (Chase, 1998). ISNA is a peer support group which provides an urgently needed meeting ground for intersex persons who are often desperately isolated. Moreover, it constitutes a forum particularly for those who feel wronged by medical management. Beyond these functions, ISNA has become, under the determined leadership of its founder, Cheryl Chase, a major public voice and promoter of policy change. The most outspoken members of ISNA belong to a generation of intersex patients who, when assigned and raised female, underwent excision of the clitoris ("clitorectomy"), a procedure which tends to markedly diminish erotic sensitivity and orgasmic capacity. As a consequence, ISNA's primary focus is genital surgery and its risks to sexual function, and ISNA's 1995 Recommendations (ISNA, 1995) advocate a delay of all elective genital surgery until the patient herself/himself can give informed consent. In addition, many from the now middle-aged generation of intersex patients have experienced marked difficulties in finding out about their medical condition and gaining access to their medical records.

The Major Questions

As the intersex debate is conducted in many diverse media such as pamphlets, newsletters, websites, internet lists, videos, newspaper reports, meeting presentations, and scientific publications, it focuses on three major clusters of issues: gender assignment, genital surgery, and information management. In regard to gender assignment, the key questions are:

1. How strong are the hormone effects on brain development; do they really determine the outcome in terms of gender identity?
2. For which condition and to what extent can penile size at birth be interpreted as an indicator of prenatal androgenization of the brain?
3. Dependent on the answer to the first two questions: Which XY individuals should be assigned female, and which XX should be assigned male?
4. Is it appropriate to insist on a two-gender classification, and should our society not make room for a third gender or for an even more flexible arrangement of genders?

The primary questions concerning genital surgery are:

A. Which outcome criteria should be the critical ones in making surgical decisions?
B. Should we in all cases of elective genital surgery hold off until the patient reaches the age of legal consent?
C. If genital surgery is planned, which techniques of clitoral, vaginal and penile surgery yield the outcome that is seen as most important?

A third major area of controversy has to do with the management of medical information such as the patient's history of sex assignment and re-assignment, including the history of genital surgery, the histology of the gonads, or his/her sex-chromosome complement, with the following main questions:

1. About what, when, and how does one inform the parent, and about what, when, and how does one educate the intersex child?
2. Are there any grounds to withhold any information from any adult intersex patient, for instance those with a major psychiatric disorder?
3. And what role can patient and parent support groups assume in information management?

Essentially, all of these questions are based on adverse outcomes that have been observed in individual cases. The answers should be formulated for the goal of minimizing adverse outcomes and be based on systematically researched empirical evidence. But here we face a major dilemma, namely, a very limited database because of the relative rarity of patients with an intersex condition. Only long-term follow-up can definitively demonstrate whether decisions on gender assignment and genital surgery were successful, or what the range of consequences of variations in information management are. Ideally, we would have prospective studies following sizable numbers of intersex individuals from infancy to late adulthood. But given the low incidence of such children and the diversity of syndromes and conditions, the logistical difficulties in conducting prospective follow-up studies are daunting. Also, the small number of investigators working on psychosocial intersex issues has slowed the progress in the methodology of assessment and other aspects of research design. It is therefore not surprising that the overall status of long-term outcome research in this area leaves much to be desired. We do not have the space here to deal in detail with all the questions listed above, but will focus the discussion on psychosocial aspects that are particularly relevant to the urologist.

Long-term Outcomes: Goals/Criteria

General Considerations

Psychosocial goals of clinical intersex management that most patients and professionals can agree on are a good overall quality of life, including a stable and unconflicted gender identity, attainment of a level of education commensurate with intellectual potential, appropriate functioning in work, the capacity for long-term partnering (with child-rearing if desired), satisfying sexual functioning, a reasonable social life, and freedom from significant psychopathology. These goals can be operationalized for the assessment of long-term outcomes. Ideally, the clinical management would serve to diminish the putative differences in long-term outcome between intersex patients and non-intersex control groups. The underlying assumption is that without medical and psychosocial intervention, intersex patients will show increased

rates of impairment in the various outcome domains listed. To date, impairment of intersex patients who did not undergo a professional intervention is mostly inferred from clinicians' experiences with individual cases some of which were published over the past 150 years, but we still lack epidemiologically sound studies that could serve as a scientific framework for the evaluation of clinical management. (Incidentally, strictly speaking, there is hardly any intersex patient who does not experience some form of an intervention, because in most cases the social environment responds to the condition at birth or whenever it is recognized or diagnosed later, and these responses themselves may foster and/or hinder the development of psychological health.) When the long-term outcome of a patient is less than desirable, the reasons may lie in biological factors associated with the condition itself, in secondary biological/medical side effects of the condition over time, in the spontaneous reactions of the social environment, in the side effects of the professional interventions, or in an interaction of such factors. Only careful investigations of patient samples of sufficient size can give us reasonably definitive answers. One needs to withstand the temptation of attributing the cause of impaired outcomes to a particular medical intervention or some of the other potential factors on the basis of mere suspicion.

Outcome Criteria for Genital Surgery

For the urological surgeon, the psychosocial goals of genital surgery are of particular interest. As mentioned earlier, the major focus of ISNA's 1995 Recommendations (ISNA, 1995) is the avoidance of genital surgery unless required for reasons of medical health. Presumably, no one would argue against genital surgery if it were always successful, but quite a few intersex patients feel that genital surgery did them more harm than good, mostly because of impairment or loss of sexual function, in some cases also because of the loss of the distinctive 'intersex' characteristic (e.g., ISNA, 1998). Thus, one has to consider a variety of potential goals of genital surgery and their corresponding outcome criteria, and these have to be operationalized and reported in detail. The current surgical literature is replete with surgical outcome assessments where investigators label surgical results "satisfactory" or "excellent" without specifying the outcome criteria, the rating procedure, or the raters (Kessler, 1998). Such reports do little to advance our knowledge. Editors of medical journals are in a particularly powerful position to effect rapid improvements of standards in this area.

Potential goals and outcomes of genital surgery include the following.

1. There are purely medical criteria, e.g., the absence of acute surgical complications or of marked scarring, or later complications such as the development of vaginal stenosis, penile fistulas, and clitoral loss, or the attainment of appropriate urinary function (form, direction, and quality of the urinary stream), etc., but they will not be further considered here because they are dealt with in greater detail elsewhere in this volume.

2. The most frequently quoted criterion in the surgical literature is cosmetic: The external genitalia look normal in size, shape, and location and do not raise any question of abnormality.
3. Looking normal also means looking typical for the assigned gender which constitutes the gender-confirming goal of the surgery of the external genitalia. If the genitalia look markedly gender-atypical, consistency of rearing in the assigned gender may be threatened.
4. Also normal urinary function may serve to confirm the assigned gender: the children can assume the gender-typical position for urination. Otherwise, intersex children may have to employ gender-atypical urination procedures. For example, in the John/Joan case (Diamond et al, 1997), Joan's urinary opening after the feminizing surgery was still located so high that she had to direct her urinary stream downward with her fingers. Or such children may experience teasing by peers and, thereby, become highly sensitized, or may need special bathroom privileges in school which constitutes another opportunity for stigmatization, etc.
5. From a long-term perspective, one hopes that, during puberty, the external genitalia can develop in size and shape as is typical of the adolescent's gender. If the genital appearance in older adolescents and adults is gender-atypical, the patient may develop anticipatory anxiety about exposing his/her nude body and what a potential sex partner's reaction might be, and the anxiety, in turn, may become a barrier to courtship and sexual involvement.
6. A major outcome, of course, is sexual functioning. It is often interpreted as the anatomic fit of a penis and vagina, which is what the simplistic 'pole' and 'hole' statements of the past referred to. There are certainly many examples of patients for whom a minuscule or non-erectile penis or a stenotic vagina presented a major impediment in their sexual lives. But the traditional pole/hole consideration represented a rather crude and incomplete understanding of sexual functioning. It also disregarded the fact that there is a substantial minority of intersex patients to whom the heterosexual paradigm does not apply.
7. At least as important as the aspect of anatomical fit, and for many patients more important, are erotic sensitivity and orgasmic capacity, be it during sex with a partner or by self-stimulation. Both aspects of sexual function have major implications for overall sexual satisfaction. (In reviewing the literature, one gets the impression, that, in the context of the post-industrial Western society, medicine tends to underrate the importance of erotic pleasure and overrate the importance of reproduction.) Both male and female genitalia are complex systems relying on an intricate interplay of muscular, vascular, neural, and biochemical elements. The recognition of the role of the neurovascular bundle in clitoral functioning has led to significant progress in clitoral surgery (Schober, 1998), but as a recent report (O'Connell et al, 1998) has shown, even the anatomic features of the clitoris are not yet fully understood. There is now a consensus that clitorectomy is likely to variably reduce or even eliminate erotic sensitivity and orgasmic capacity (Meyer-Bahlburg, 1999). But the data available on erotic function after clitoral resection and clitoral recession are quite unsatisfactory, and recent reports (e.g., Alizai et al, 1999) raise doubts as to how universal the frequently claimed successes of these procedures really are, particularly from a long-term perspective.

8. In question is not only the patient's own erotic sensitivity. The appearance and function of the patient's genitals may also have implications for the erotic functioning of the sexual partner, and the couple's sexual and emotional relationship overall. For instance, when working clinically with heterosexual couples including intersex patients and their partners, one hears that quite a few women find the intra-vaginal sensation of a full-sized erect penis and of its pre-ejaculatory volume increase arousing, and some may need the experience of deep thrusting for obtaining orgasm. Many men consider peno-vaginal intercourse the only 'real sex' which can become problematic when the woman partner has vaginal stenosis. It is likely that sexual problems of intersex patients can be somewhat ameliorated by sex counseling/therapy, but to what extent is not known.
9. Last, but not least, there is the outcome criterion of reproductive potential. For instance, considerations of reproductive potential play a major role in the gender assignment of infants with true hermaphroditism as practiced in France (Fekete, 1999), while the presence of functional internal female reproductive structures and their preservation along with the preservation of fertility has always been a major argument for the assignment of 46,XX patients with CAH to the female gender, even in the presence of male-like external genitalia.

Overall, we need substantial studies on the quality of life – also to include the quality of sexual life – for a full evaluation of all aspects of outcome of genital surgery. We need to learn from the intersex patients themselves what they see as their priority goals for genital surgery. We also may need to take into account that patients vary considerably in the importance they themselves attribute to various outcomes.

Who Makes Management Decisions?

If we reconsider and diversify the goals of genital surgery, we also have to revisit the question of who makes the decision on genital surgery. If the outcomes of genital surgery essentially belong to the domain "quality of life," the patient ought to be the one to weigh the beneficial outcomes against the risks. But in the intersex situation, the patient is usually a child. ISNA (ISNA, 1995) recommends, therefore, to wait with all elective surgery until the child is old enough to give informed consent. But can one wait that long? Those aspects of genital surgery that serve to confirm the assigned gender start having their impact, if any, much earlier already. Also, a child may experience significant teasing by the peer group because of urination problems, or an adolescent may develop marked anxieties and related romantic and sexual inhibitions because of genital inadequacies. And how is a sexually inexperienced young adult going to weigh the benefits of sexual pleasure? In this context, it is important to note that in a recent written survey of ours on adult 46,XY patients (Meyer-Bahlburg et al, 1999) the majority of respondents did not agree that genital surgery should be postponed to adulthood, when the individual can legally provide fully informed consent. More survey data of this kind—including data from parents—will be needed for a comprehensive reconsideration of such policy issues.

ISNA (ISNA, 1995) demands that, instead of elective genital surgery, counseling by professionals experienced in psychosocial intersex issues be provided to all patients to facilitate gender-consistent rearing. On the basis of my clinical experience, I certainly consider counseling a very important part of psychosocial management, although a systematic documentation of its effectiveness in the intersex area has not been attempted, not only because of logistical problems but also because of the ethical problems the establishment of a non-counseled control group would pose. I doubt, however, and we certainly do not have the data to demonstrate, that preventive counseling can sufficiently take care of all genital-status-related problems and make elective genital surgery in childhood totally obsolete. Also, it is quite unlikely that the needed counseling services will be available in the foreseeable future, given the current HMO climate in the provision of medical services.

Thus, I expect that for the foreseeable future considerable decision-making on genital surgery will remain with the parents, in consultation with their child's physicians, during the intersex child's early years. If the parents are to give truly informed consent, however, the full range of outcomes needs to be discussed with them, and the information on outcomes should be based on data, or at least the parents ought to know what is data based, and what represents opinion. Here again, we run up against the difficulty that the database is so limited.

Long-term Outcomes: Data on Gender and Sexual Functioning

What is known about long-term outcomes of intersex patients? What we have for most syndromes, is data from individual case reports or from small series of cases that vary tremendously in what is investigated and how it is assessed. Only for classical CAH do we have several studies from independent investigators who evaluated modest-sized clinical samples of adult patients. My own team is currently conducting follow-up studies in collaboration with several clinics, covering both female and male pseudohermaphroditism. From everything that is available in the literature and in our own data, we can summarize some preliminary conclusions concerning gender development and sexual functioning of patients in these two categories. (For reasons of space, the literature on true hermaphroditism is not reviewed here.)

46,XX Pseudohermaphroditism

Patients with 46,XX pseudohermaphroditism are mostly represented by classical CAH with 21-hyrodxylase deficiency (21-OHD). One can visualize best the variability in genital appearance at birth in terms of the Prader (Prader, 1954) stages of genital differentiation which range from mild clitoral enlargement (Prader 1) to extreme male-like masculinization with a penile urethra (Prader 5). (If normal females and males were added to the Prader scale, they would be classified as 0 and 6, respectively.) The CAH condition can be associated with any of these stages. Of the two major subtypes of classical 21-OHD, Simple Virilizers (SV) and Salt Wasters (SW), the SW subtype, on average, shows more severe masculinization of the genitalia (Therrell et al, 1998), but

both subtypes range across all Prader stages. (Note that classical Prader staging may not be appropriate for CAH patients who have undergone prenatal dexamethasone treatment, because the latter may differentially affect the development of the external and internal genitalia, depending on the timing of the treatment.) Major psychological findings on CAH females are as follows.

In comparison to control groups, CAH females are behaviorally masculinized, but with much interindividual variability (Ehrhardt et al, 1968(2);1981; Money et al, 1972; Dittmann et al, 1990; Zucker et al, 1996; Berenbaum 1999). The psychological masculinization is much more pronounced in SW than in SV women (e.g., Dittmann et al, 1990; Meyer-Bahlburg et al, 1999). There is great variability of gender-role behavior within each CAH subtype. Some of this variability is probably accounted for by variations in prenatal masculinization as represented by the Prader stages. Thus there is some degree of a dose-response relationship between prenatal androgen excess and gender-role behavior (Meyer-Bahlburg et al, 1999).

In spite of this variability in childhood gender-role behavior, almost all CAH females maintain a female gender identity. This illustrates that a core gender identity can accommodate much variation in gender role behavior. Only very rarely do women with CAH change to a male gender in adulthood (Meyer-Bahlburg et al, 1996). If gender change occurs, it seems to happen among those who had prolonged genital ambiguity in the early years and/or lack of consistent androgen suppression by glucocorticoid treatment during childhood. On the other hand, some 46,XX CAH infants with high genital Prader stages are mistaken for cryptorchid 46,XY and assigned to the male gender. When their condition is finally diagnosed in adolescence, most elect to stay male and apparently do reasonably well in all spheres of life except fertility (for references, see Meyer-Bahlburg et al, 1996), but good systematic follow-up data on even a moderate-sized adult sample are lacking.

Diamond and Sigmundson (Diamond et al, 1997) have suggested to assign all Prader-stage 5 females with CAH as males. This recommendation is presumably based on the belief that the penile masculinization indicates the same degree of (male-typical) brain masculinization in the 46,XX infant as in the 46,XY infant, but at this time we do not have the comparative data to support this assumption. In addition, such an assignment would involve ovarectomy and hysterectomy and, thereby, iatrogenic infertility. However, we currently do not have the data to show that the psychological and sexual functioning and the subjective quality of life are better one way or the other. Most physicians would be reluctant to deliberately deprive a person of his or her reproductive capacity, unless there is a demonstrable gain in the function and quality of life in the selected gender. We need systematic comparative follow-up data to support a policy change with empirical evidence.

Studies of sexuality show in CAH women as a group delayed and reduced sexual activity and libido (Meyer-Bahlburg, 1999; Meyer-Bahlburg et al, [in press]). They also show less heterosexual activity and imagery, and (in a minority) increased bi- and homosexuality.

Again, the differences from control groups are more pronounced in SW than SV women, and there is much within-group variability.

One factor in the relatively reduced sexual activity of women with CAH is the genital status in later adolescence and adulthood. Quite a few CAH women – especially those

with the SW subtype—find intercourse painful or even impossible or stay away from heterosexual involvement altogether because of their awareness of having an inadequate vagina (Meyer-Bahlburg, 1999; Meyer-Bahlburg et al, [in press]; Mulaikal et al, 1987). When clitorectomy is used, diminution or loss of erotic sensitivity and orgasmic capacity, and with it, of sexual satisfaction, are probably quite frequent, although some women appear to retain both to varying degrees. To what extent the more recent techniques of clitoral resection and recession improve the picture remains to be studied. Published functional outcomes of these techniques appear promising (for refs. see Meyer-Bahlburg, 1999), but a recent report (Alizai et al, 1999; see also Passerini-Glazel, 1999) raises troubling questions. Only detailed studies on sexual functioning in adult patients will provide the answers we need.

46,XY Male Pseudohermaphroditism and Related Conditions

For many syndromes of 46,XY male pseudohermaphroditism, genital staging can be assessed by means of the Quigley (Quigley et al, 1995) scale, ranging from 1 (normal male) to 7 (normal female). Originally, the scale was defined only for the spectrum of androgen insensitivity (AIS) patients. Straightforward Quigley staging is not appropriate for 5-alpha-RD, where the androgenization deficit is limited to the dihydrotestosterone-dependent external genitalia, and to androgen-independent penis anomalies such as penile agenesis, cloacal exstrophy of the bladder, and ablatio penis. Where Quigley staging can be used, it is again assumed that the genital stage reflects the degree of prenatal androgenization.

The extreme degree of undermasculinization, that is, Quigley stage 6, in combination with estrogen exposure is represented by the syndrome of Complete AIS (CAIS) in which both the genitalia and the brain appear to be underandrogenized. The other end of the masculinization spectrum is represented by children who were born with normal male internal and external genitalia (Quigley stage 1) but lost the penis later, and were then re-assigned to the female gender. In such cases, we have to assume that both genitalia and brain were fully prenatally androgenized. When the patients are gender re-assigned and their external genitalia surgically feminized, their brains are not medically altered and stay masculinized. In addition to children with penile ablatio, children born with normal testes but with agenesis of the penis or cloacal exstrophy of the bladder also fall in this category of masculinization. It is possible that also the syndrome of 5-alpha-RD belongs here as far as brain masculinization is concerned, depending on whether testosterone or its metabolite dihydrotestosterone play the major role in the prenatal sexual differentiation of the brain (which is currently not known). All other types of male pseudohermaphrodites fall in between the two poles of the Quigley scales.

The data available on long-term gender outcome in male pseudohermaphrodites are very limited (Meyer-Bahlburg, 1999). By and large, the findings are in line with expectations . Gender-role behavior is least masculinized when there was no effective prenatal androgen effect in peripheral tissues as illustrated by patients with CAIS. By contrast, there are strong indications of behavioral masculinization in patients with a male-typical prenatal sex-hormone milieu, as is the case in the non-endocrine conditions of genital ambiguity in 46,XY patients.

In the least masculinized syndrome, CAIS, no female to male gender change has been reported. By contrast, patient-initiated female to male gender change in the most masculinized syndromes (cloacal exstrophy, aphallia, penile agenesis) may perhaps approach 50% ([Reiner), but these data are as yet unpublished and based on very small samples. In the other syndromes, some gender change from female to male occurs, particularly when there is prolonged visible genital ambiguity (Money, 1986), but it is relatively uncommon.

In our ongoing collaborative follow-up study of adult 46,XY pseudohermaphrodite patients at Johns Hopkins Hospital, now at a sample size of 58, the vast majority of male pseudohermaphrodites are satisfied with their gender, regardless of having been raised as males or females, although about one third had experienced times in their life when they were uncertain (Meyer-Bahlburg et al, 1999). Thus, these data appear to confirm the studies by Ellis (Ellis, 1945) and Money et al. (Money et al, 1955) which led to the conclusion that most intersex patients identify with the gender to which they have been assigned.

Diamond and Sigmundson (Diamond et al, 1997) have recommended that 46,XY individuals with penile agenesis, cloacal exstrophy, traumatic loss of the penis, or 5-alpha-RD, all of whom presumably have normal testes, be routinely assigned to the male gender, and that the same decision be made for 46,XY individuals with other intersex syndromes who have genitals of Quigley stages 2-3, as well as for patients with micropenis. Again, only good comparative studies of patients in sufficient numbers who have been raised in one gender or the other can provide definitive answers to the question in which gender psychological and sexual functioning and the subjective quality of life are really better for a given condition. There are individual case reports or small-sample studies showing good and poor outcomes on both sides (for references, see Meyer-Bahlburg, 1999), but no data that permit an estimate of the differences in rates of positive or negative outcomes.

Concerning sexuality, much less is known about 46,XY pseudohermaphrodites than about 46,XX classical 21-OHD. The spotty data available suggest increased rates of homosexuality (gynecophilia) in female-raised 46,XY patients other than CAIS (Money et al, 1986) and especially in those syndromes where gender change to male is common in adolescence and adulthood (Imperato-McGinley et al, 1979; Imperato-McGinley, [ ]; Rosler et al, 1983). Case reports suggest the dependence of sexual activity level and libido on appropriate androgen replacement where indicated, but the evidence is insufficient for more specific conclusions. The majority of the 46,XY pseudohermaphrodites in our own ongoing collaborative project with the Johns Hopkins Hospital clinic are 'mainly' or 'somewhat satisfied' with their sexual functioning, independently of their gender (Meyer-Bahlburg et al, 1999). A few reports have specifically addressed the sexual functioning of men with a micropenis or microphallus with a female partner and presented encouraging results (Money et al, 1985; Reilly et al, 1989), but we need more detailed assessments in unbiased samples of reasonable size to have solid empirical evidence.

Summary

In summary, we have learned a great deal about syndrome-specific patterns of behavioral development. For both female and male pseudohermaphrodites, the data seem to be compatible with a prenatal-androgen model of human psychosexual differentiation. Wherever we compare two conditions whose relative degrees of peripheral prenatal androgenization are known to us, we find that the condition with the higher degree shows more masculinization (Meyer-Bahlburg, 1999), although there is again much unexplained within-group variability. The lack of studies that share identical assessment procedures does not permit us a simultaneous comparison of multiple groups from the existing publications and therefore no finer quantitative analysis. The data are also insufficient to solve the question of penile size as an indicator of brain androgenization (apart from the fact that in some conditions – such as 5-alpha reductase deficiency or penile agenesis – a penis does not develop, although male-typical prenatal testosterone levels are present). Thus, the evidence is insufficient for the answers to the most pressing questions that were listed earlier.

Methodological Problems and Guidelines for Future Research

Conceptualization

In an earlier section, we identified the three major issues of the current debate: gender assignment, genital surgery, and information management. For all three issues empirical data are needed as a basis for decisions on management policy. From the psychosocial perspective, long-term outcome studies have the highest priorities, because only they can give us the necessary feedback on the long-term effects of specific management decisions and techniques.

The age group of patients to be studied depends on the focus of investigation. For instance, in regard to the outcome of gender assignment, we need data on adult patients until at least midlife in order to get an appropriate overview of the frequency of patient-initiated gender change. But if we want to understand the factors that contribute to gender change – especially the psychosocial ones – we also need to study our patients in childhood and adolescence, preferably prospectively, because retrospective assessment of child-rearing behavior is so difficult to do. In regard to genital surgery, we need to study its gender-confirming aspects particularly in childhood, but investigation of the impact of surgery and resulting genital status on courtship and sexual functioning obviously has to wait until the individual is old enough for dating and sexual activity. Regarding the outcomes of specific surgical techniques, we have to take into consideration the difference between efficacy—the outcome of a newly developed specific technique as performed in systematic trials by an expert, usually the inventor—and the efficiency—the outcome when a technique is routinely adopted by a wider range of surgeons. In the area of information management, acute and short-term follow-up studies of medical education and counseling concerning issues of information transmission and affective response of

both patients and parents would be desirable. At present, however, we are also in need of long-term follow-up surveys in regard to the patient's severe emotional reactions (including suicidality) to the disclosure of medical information – also via the media --, the impact of frequent genital examinations by diverse medical staff, patients' experiences with access to medical charts, the benefits and disadvantages of patient contacts with patient-support groups – both face to face and over the internet, and so on.

As to the question, which syndromes should have priority for long-term follow-up investigation, one has to say that none have been studied sufficiently to provide a fully satisfactory basis for the policy management decisions we are facing. Because of their relative frequency and homogeneity, we know relatively more about 46,XX patients with classical CAH than any of the male pseudohermaphrodite syndromes, but even here major questions are poorly researched, for instance, the comparison of long-term outcome of 46,XX CAH born with a penile urethra in male-assigned versus female-assigned patients, or sexual functioning in dependence on the technique of genital surgery. The diversity of syndromes and the low prevalence of each has hampered follow-up research on male pseudohermaphrodites even more, and all of the various 46,XY syndromes and conditions are understudied in all psychosocial respects.

Sampling

To provide the data base needed for improving the psychosocial prognosis and thereby the empirically based rationale for decisions on gender assignment and genital surgery, we need to analyze outcome data by patient groups that are defined on the basis of both definitive endocrine and molecular-genetic criteria where applicable and by the degree of genital ambiguity at birth in terms of Prader (Prader, 1954) and Quigley (Quigley et al, 1995) stages, rather than by current genital status alone. We also need to systematically compare patients with the same condition who have been reared female to those who have been reared male. Similarly, we should try to assess the natural history of a condition, i.e., compare the outcome of surgically and hormonally untreated patients, where available, to the outcome of treated patients.

The question of control data and control groups needs to be carefully considered. For instance, gender change also occurs in non-intersex persons with a certain prevalence (Meyer-Bahlburg, 1999). Problems in sexual functioning among intersex patients should not be compared to an assumed standard of 100% perfection, but to community samples where sexual dysfunctions such as anorgasmia in women are not uncommon. For instance, Laumann et al. (Laumann et al, 1999) found for a nationally representative sample that about a quarter of sexually active women had periods of several months or more in the 12 months prior to study when they were unable to achieve orgasm.

Ideally, we would conduct prospective follow-up studies of regional or national cohorts formed by the systematic screening of newborns, both those with an intersex diagnosis and non-intersex controls. In recent years, this has become possible for the syndrome of CAH for which systematic newborn screening has been introduced in a number of states. However, given the urgent need for outcome studies, we cannot wait until such cohorts reach mid-adulthood, but must also conduct follow-up studies on patients who are now in their early and middle adult years.

The existing literature relies mostly on small clinical samples or individual case reports. Even if reports concern groups of patients, the sample sizes are usually too small for reasonably definitive conclusions, given the variability in diagnosis, genital status at birth, surgical history, and sex-hormone treatment history. In order to obtain clinical follow-up samples of sufficient size, we urgently need multisite collaborative studies with uniform protocols across clinics. A centralized regional or national registry of intersex patients could also be extremely valuable in this regard.

Case reports in particular are suspect of selection bias, since it is often not the average patient, but the one with special characteristics who is considered worthy of publication. Some single cases have been totally overvalued in their importance; the widely publicized John / Joan case (46,XY with penile ablatio; Money, 1975;1999, Diamond et al, 1997) is a prime example. Originally, the case was overused as an illustration for the power of social rearing. Currently, the case is overused as an example for the power of biological factors in gender development (Meyer-Bahlburg, 1999), notwithstanding the publication of another case with the same condition, but a different outcome (Bradley et al, 1998).

Selection bias is not limited to case reports. It may also seriously affect follow-up samples collected by clinics. For instance, clinic populations of patients with a specific genotype or endocrine phenotype are often not representative of people with the same genotype or phenotype in the general population, and marked referral biases in terms of severity of the medical condition, socioeconomic status of the family, and local demographic factors such as race/ethnicity are quite typical. As a consequence, clinics may differ in the demographic or other characteristics of patients seen.

In addition, there is the bias of differential attrition. Long-term follow-up studies typically suffer from very substantial loss of patients over time. Who stays with a clinic over many years and who participates in follow-up research ist determined by many psychological factors. These include satisfaction with the doctor-patient relationship and the medical management. Dissatisfied patients are likely to leave a clinic and to not cooperate with research studies initiated by that clinic; the limitation of the study to the remaining patients may create a bias towards positive outcomes.

Selection bias is not limited to clinic samples. For instance, when researchers like Diamond specifically search for XY patients raised female who later change to male, they deliberately introduce a patient-selection bias in the research process—which may be heuristically useful, but does not provide an epidemiologically satisfactory sample. Another example is ISNA: the outspoken people among its members appear to include increased numbers of patients with dissatisfaction about their gender or genital status. Perhaps, intersex organizations such as ISNA that are highly critical of medicine and appear to have many members who are dissatisfied with their medical management may be in a position to complement clinic studies by studying their membership, provided such studies are conducted with appropriate methodology and protection against assessment bias. Alternatively, patient support groups could be asked to collaborate with clinics so that patient participation and representativeness are increased.

Sample selection biases often affect psychosocial outcome variables more strongly than biological measures. Thus, careful planning of sampling procedures and the detailed characterization of non-participants in order to gauge the generalizability of findings are very important. How many of the original population have died, and does this number

indicate just medical risks or also suicide risks? How many prospective participants could not be traced, and does this imply a socioeconomic bias or a selection for personality characteristics? Who are the refusers, and have their refusal reasons to do with unsatisfactory management and inadequate outcome? The participation in such studies of social or psychiatric epidemiologists would be highly desirable.

Assessment

The outcome assessments employed in the available literature are often not systematic and sometimes highly impressionistic. In view of the small sample sizes typical of most studies in this area, there is an urgent need for the employment of standardized outcome measures across studies so that results can be combined for greater statistical power. The problem is the paucity of standard measures available for behavioral intersex research. There is a need for the development of additional systematic assessment tools in this area.

As I have argued elsewhere (Meyer-Bahlburg, 1999), research on health-related quality of life (HRQL) constitutes a useful guideline for long-term outcome assessments of intersex patients. Formal HRQL assessment needs to take place on three levels: (a) generic broad-band assessments; (b) intersex-specific assessments of gender role/identity and sexuality that vary with gender and developmental stage; and (c) syndrome-specific assessments, e.g., of specific cognitive deficits or specific techniques of genital surgery used (for available methods see refs. Meyer-Bahlburg, 1999; McDowell et al, 1996). A good example of an HRQL approach to intersex research is the study by Kuhnle and co-workers (Kuhnle et al, 1995).

Quantitative assessments, e.g., systematic ratings or multi-item scales, should be sufficiently fine-graded so that we can achieve a good differentiation of syndromes and individual cases along psychological continua. For instance, the employment of finely differentiating gender scales shows that subtypes of patients with classical CAH differ markedly in gender-role behavior (Meyer-Bahlburg et al, 1999), which has implications for both etiological research and clinical management.

Particularly on the syndrome-specific level, systematic qualitative interviews will be an important additional tool, either in preparation for the development of new quantitative or structured assessment methods or as a complement to the latter. 'Qualitative' in this context does not mean 'impressionistic' or 'unsystematic'. Rather, qualitative techniques as used in anthropology and other social sciences constitute a rigorous approach to the inductive development of pertinent constructs and their operationalizations from the narratives that interviewees provide to open-ended question (Krueger, 1988; Berg, 1998). An important source of qualitative material can be autobiographic accounts of intersex patients (Dreger, 1999). Money's Biographies of Gender (Money, 1991) is an outstanding illustration of the qualitative approach at the case-report level. Qualitative assessment is also a good starting point for the studies of parents' attitudes to specific aspects of intersex genitalia such as clitoral size or hypospadias, of parents' – and, later, patients' – primary concerns and worries regarding an intersex condition, of patients' reasons for satisfaction and dissatisfaction with post-surgical genital appearance and functioning, and of patients' reasons for refusing genital

surgery, dilatation procedures, and wearing intravaginal forms, or for avoiding going to physicians altogether.

As this chapter is not suited for a detailed and comprehensive review of the assessment methods available, we will list below the instruments we have used and/or are using in our own work in this area.

Gender

Gender identity, i.e., the sense of being male or female (or some form of transgender), can be assessed by asking a person directly although there is no standard formulation in use. Often, the presence of a gender identity as male or female is derived from the absence of frank gender change or of gender doubts and other signs of gender dysphoria.For the latter, Zucker and co-workers (Zucker, 1993) have developed a Gender Identity Interview for Children which seems applicable from preschool to the end of childhood. It was developed for the the assessment of GID in non-intersex children, but we are using it clinically and in an ongoing research project for intersex children and find it very useful (unpublished data). Two analogous scales for adults, which, however, also include items on gender-role behavior and sexual orientation, are the Gender Identity Scale for Males (Freund et al, 1977) and the equivalent for females (Blanchard et al, 1983). Both were originally developed for non-intersex adults with GID, but are used by my team also for intersex patients (e.g., Meyer-Bahlburg et al, 1996).

Gender-role identity, i.e., the degree to which a person experiences him/herself as masculine and as feminine, can be assessed in adolescents and adults by a simple numerical 5- or 7-point rating scale with the extremes labeled "not at all masculine" and "very masculine" (or feminine), respectively.

For gender-role behavior in childhood, our unit uses several measures. Two of these are parent-administered questionnaires, the Child Game Participation Questionnaire (CGPQ; Meyer-Bahlburg et al, 1994) and the Child Behavior and Attitude Questionnaire (CBAQ; Meyer-Bahlburg et al, 1994) which are modified, re-scaled and re-normed versions of earlier forms originally developed by Bates and Bentler. Their most comprehensive subscales, 'Gender' of the CGPQ and 'FEM' of the CBAQ were found to yield very large effect sizes for gender of 3.9 and 5.7, respectively, in the norm population of 6-10 year olds. The Gender-Role Assessment Schedule – Child (GRAS-C; Meyer-Bahlburg et al, 1988; Cosentina et al, 1993) is a comprehensive semi-structured interview for children; a very similar version, the M-GRAS-C (Meyer-Bahlburg et al, 1988), can be administered to the mothers to report on their children. Both interviews take 1-2 hours to administer, and statistical analysis is done by individual item or on the basis of item groupings to be determined for each study. For adolescents and adults we use analogous interviews, the GRAS-A and M-GRAS-A (Ehrhardt et al, 1984(2)); they combine recalled and concurrent information. More recently, Zucker's team has developed a brief self-administered questionnaire, the Recalled Childhood Gender Identity Scale (Mitchell et al, 1991; Zucker et al, 1996) which combines retrospective items of gender-role behavior and gender-role identity.

A recall questionnaire for adults that focuses on play behavior is the Child Play Activities Questionnaire from Bentler's team (Grellert et al, 1982). The closest to a

comprehensive adulthood questionnaire concerning concurrent gender-role behavior is the Sex-Role Behavior Scale-2 by Orlofsky et al. (Orlofsky et al, 1982), but it is only now being applied by us in a study of intersex patients.

Recently, Berenbaum has developed specific measures for selected subdomains of gender-role behavior, for instance, a scale for assessing interest in infants in childhood (Leveroni et al, 1998) and a new self-report scale for assessing sex-typed activities and interests, including vocational interests, in adolescence (Berenbaum, 1999). To what extent individual component variables of human sex-dimorphic behavior are differentially affected by the dosage and timing of prenatal hormone exposure – as we know it for specific variables of sex-dimorphic behavior in lower mammals – is an unsolved issue, and the development of such more specific measures for humans may allow us to address that question.

There are many other psychological scales for the measurement of gender-role behavior and gender attitudes for the general population (Beere, 1990), but most of these are not specific enough for the needs of intersex research, and their effect sizes for gender are usually rather modest. The psychological literature on gender often discusses the question whether a bipolar (male- female) continuum is an appropriate construct for the operationalization of sex-dimorphic behavior, or whether two independent (masculine versus feminine behavior) or more dimensions are more appropriate. As I have demonstrated elsewhere (Meyer-Bahlburg et al, 1994), the answer to this question depends to a large extent on one's investigative goal and on the procedure chosen for the development of such measures. For research designed to prepare a policy on gender-assignment decisions in a two-gender culture, a bipolar composite scale seems to be an adequate instrument to start with.

Sexuality

Many instruments are available for the assessment of sexual behavior in the general population (the best sourcebook is Davis, 1998), but they lack specificity for the intersex population. Both clinically and in our own research we use a comprehensive sexual-history interview for adolescents and adults, the Sexual Behavior Assessment Schedule (SEBAS-A) (Meyer-Bahlburg et al, 1983), which captures psychosexual milestones, sexual orientation, and current sexual activity, but requires trained interviewers.

The SEBAS-A also includes a detailed section on sexual dysfunctions. Two good general screening questionnaires for sexual dysfunctions in the general population are the Brief Sexual Function Questionnaire for men by Reynolds et al. (Reynolds et al, 1988) and the Brief Index of Sexual Functioning for Women by Rosen et al. (Rosen et al, 1998). However, given the particular genital status and surgical history of many intersex patients, such standard instruments must be complemented by more specific inquiry, at this stage of our knowledge preferably by qualitative interviews. In addition, specifically tailored rating scales such as the ones used by Mureau (Mureau et al, 1995;1996;1997) can be used for patients' ratings of satisfaction with cosmetic and functional results of genital surgery. Ideally, studies of sexual functioning would utilize both physiological and psychological assessments. For instance, if it can be shown that pudendal nerve conductance is preserved at the end of genital surgery (Gearhart et al, 1995), we know

that a basic component of the genital system is functional at that time, but we still need confirmation that erotic sensitivity and orgasmic capacity are retained in adulthood (Chase, 1996).

General Assessment Procedures

The utilization of multiple informants – independently assessed – can strengthen interview- and self-report-based findings considerably. This is obvious if one deals with sexual functioning where former and current spouses and lovers can validate crucial aspects of sexual activity and function. It also applies to gender role behavior and gender identity change where observations and impressions of family members and peers can be a valuable adjunct to the patient's own account.

As in rigorous treatment studies generally, assessments of outcome for systematic research purposes should not be conducted personally by those who provided the patient care, be it by way of genital surgery, hormone treatment, or intersex counseling. The risk of inadvertent biases in favor of the intervention is too high. In behavioral studies, the use of written self-report questionnaires or audio-computer-assisted interviews (Turner, et al, 1998) administered by research assistants may help in this regard. Analogous considerations apply to the evaluation of somatic outcomes of medical treatment.

Behavioral outcome studies should be done under blind conditions whenever possible. This may require that the initial sections of a follow-up interview protocol are conducted by interviewers who are unaware of the medical diagnosis and genital condition of the research participant, while the latter is instructed not to disclose his/her medical condition to the interviewer. Other sections are conducted later in the protocol after the interviewer has been informed about the medical situation.

Assessment topics such as gender identity, sexual functioning, genital status, and reaction to medical management are of central importance to outcome research on intersex patients, but often highly emotionally charged because of societal taboos or personal experiences. The results may be self-presentation bias including underreporting and distortions. A number of techniques have been developed to facilitate disclosure and diminish distortions by the interviewee (Money, 1991, ch. 1; Catania et al, 1995; Money, 1994, chs. 6 and 7).

Research interviewing is a social process (Catania, 1997) in which considerable demands for social skills and research discipline are put on the interviewer. Great care must be taken that research interviewers in this sensitive area of inquiry are well selected and well trained in research interviewing , both in regard to general research interviewing technique and coding and in regard to rapport building and the facilitation of self-disclosure and accurate reporting on part of the study participants. In my experience, clinical training and experience in either medicine or mental health does not automatically qualify someone to conduct good research interviews. The opposite is often the case: Medical professionals tend to lack patience for psychological complexities; mental-health clinicians tend to get over-involved in them; and neither may be free of judgmentalism in matters of gender and sexuality. Some systematic manuals are available for other areas of sex research interviewing (e.g., Gruen et al, 1991; Dugan et al, 1997) that can serve as models for interviewer selection and training in the intersex area.

Conclusions

In the mid-1950s, the optimal gender policy constituted a significant step forward in planning intersex management. In its general approach, this policy appears still valid. It is no accident that most of the practical clinical guidelines of Diamond and Sigmundson (Diamond et al, 1997) are essentially the same as those that can be found in Money's many summaries on the subject (e.g., Money, 1968;1994). Moneys guidelines are based on his own immense clinical experience in the psychosocial management of such patients while most of his critics are either not clinicians or at least not specialized in this area.

On the other hand, not only has society changed, but our scientific knowledge of intersexuality has greatly increased since 1955. Thereby, the accuracy of our prognosis of the psychosocial outcome has improved for at least some patients with specific syndromes, and this continuing development will gradually increase our ability to make more syndrome- and severity-specific decisions regarding gender assignment and surgery. Planned policy changes should be informed by empirical data and followed by assessments of the long-term outcome of the new management approaches. This demand is in line with the recent increase in requirements for changing diagnostic criteria in the preparation of DSM-IV (APA, 1994) and the grounding of psychological therapies in systematic studies of outcome (e.g., Heiman, 1997). As illustrated by these two examples, such guidelines should not be left to individuals, but should be arrived at by multidisciplinary committees of appropriate specialists with opportunities for input from others working in this area and the patients themselves. The work of such Committees is not going to be easy. It is highly unlikely that follow-up studies will result in simple clear-cut findings. Even if we should find ways of integrating outcomes over different syndromes and conditions, we will probably end up with mixed patterns of more or less probable advantages and disadvantages of gender assignments, surgical procedures, etc., and it will require a gradual process of consensus development to arrive at management guidelines that can be endorsed by at least a clear majority of committee members.

The history of science teaches us that most scientists - and others - see only a limited piece of the legendary elephant. Many grasp a kernel of truth, but the entire elephant is much more than the parts we have our hands on. Thus, skepsis is advisable regarding any individual viewpoint. This also applies to intersex research, particularly when it comes to psychosocial matters. A constructive approach to this dilemma is to begin with the assumption that everyone has something to contribute and to refrain from oversimplifying the positions of others with whose views we disagree. Respect for different perspectives is in order, along with an attempt to understand in which context various individuals try to provide answers to which questions. Then, wherever applicable, let sound empirical research evidence be the arbiter. Sound psychosocial research also needs to take into account the historical changes societies undergo, and how these changes affect outcome evaluation. In Western post-industrial societies, for example, societies' definition of gender roles are changing, transgender individuals encounter more tolerance, and patients have achieved greater autonomy in medical decision making. Such societal changes influence the life experiences of the afflicted patients and, thereby, the evaluation of long-term outcome, and need to be considered in any revision of the psychosocial and medical management of intersexuality.

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SEXUAL BEHAVIORS, SEXUAL ORIENTATION AND GENDER IDENTITY IN ADULT INTERSEXUALS: A PILOT STUDY

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ABSTRACT

Purpose: Sexual preference and adjustment of intersexuals have rarely been investigated. Interview techniques were used to explore these issues.

Materials and Methods: Ten adult intersexuals (average age 34.2 years) were randomly selected from Intersex Society of North America members. Of the 10 subjects 8 had initially been gender assigned as female and 2 as male. A structured telephone interview was used to assess sexual orientation, sexual activity and satisfaction with gender assignment.

Results: Sexual debut occurred at age 18.1 years (range 15 to 22). At debut, 4 females and 2 males engaged in heterosexual intercourse, and 4 females engaged in gynephilic (female) sexual contact. Despite female gender assignment of 8 and initial heterosexual activity by 4 subjects, the final choice of a sexual partner was female in all 8. Both males had initial heterosexual contact but only 1 continued to prefer female partners. Current number of sexual partners averaged 0.9 (range 0 to 2) and total number of sexual partners ranged from 1 to 300. Currently, 9 subjects are in a committed sexual relationship and 8 are able to achieve orgasm. Of the subjects 8 preferred being identified as intersexual, 1 male as male and 1 female as female. Two intersexuals with initial female gender assignment were undergoing male reassignment.

Conclusions: Most intersexuals preferred being identified as intersexual and had female partners. Most reported being satisfied with overall physical appearance but satisfaction with genitalia was highly variable. Based on these results, further study of a larger population is warranted.

KEY WORDS: hermaphroditism, orientation, gender identity

For intersexual adults gender identity and psychosexual development are shaped by constitutional and social forces. During the last 40 years medical and surgical interventions have encouraged feminizing solutions for intersexual conditions. Some studies have shown that intersexuals are satisfied with assignment[1,2] but increasing documentation suggests that patients with altered genitalia, sometimes incongruent with chromosomal sex, do not identify as assigned.[3] Recent studies by Reiner et al indicated that many female assigned intersexuals are expressing male gender identity.[4] Prenatal and perinatal androgenization of the brain has been studied in animals, primates and humans, and is responsible for masculinizing sexual behavior and sexual orientation.

Sexual orientation and adjustment of intersexuals have rarely been studied in detail because of lack of specifically designed instruments.[5–8] We have become increasingly aware that intersexuals may not always establish a firm conviction for gender identify or sexual orientation in adolescence or even in early adulthood. In this pilot study a new instrument with questions specifically designed for intersexual possibilities was used to assess adult gender identity, sexual orientation, sexual activity and satisfaction with gender assignment in an effort to understand and appreciate better the intersexual condition.

MATERIALS AND METHODS

Intersexual adults representing individuals across the United States were randomly selected from a list of approximately 300 Intersex Society of North America members. Intersex Society of North America is an organization comprised of intersexuals, parents, physicians and counselors dedicated to advocacy, peer support and education regarding the intersexual condition. The group comprised 10 adults. Mean subject age was 34.2 years (range 22 to 47), and 8 had been gender assigned as female and 2 as male (table 1). All subjects who were contacted agreed when asked to participate in a 2-hour telephone interview following a prepared questionnaire.

To improve this pilot survey, the participants were requested to comment on importance, appropriateness, clarity and intrusiveness of each question. Satisfaction with physical appearance was assessed on a Likert scale of 1 to 5, with 1 indicating complete satisfaction and 5, complete dissatisfaction. Likert scores were averaged. Questions considered historical development of sex patterns for each individual, beginning with sexual debut (sexual activity and partner choice) and final or present relationship (sexual activity and partner choice). Sexual adjustment and gender identity were also explored as were sexual satisfaction, type and frequency of sexual activity, genital sensitivity and orgasm. Descriptive statistics were used to analyze the data.

RESULTS

Overall satisfaction with physical appearance was reported as satisfactory or completely satisfactory in 90% of cases (average Likert score 2.1, table 2). Satisfaction with specific physical markers for sex averaged 2.35 for breast, waist, hips and legs, and genital average score was 3.3. When considering responses for satisfaction with genitalia, more reticence was encountered. The subjects were in some instances unwilling to score satisfaction because the reconstructed genitalia did not resemble typical sex specific genitals and because in some individuals portions of external genitals had been removed. Also, in some cases testes had been removed despite male assignment.

TABLE 1. *Adult intersexuals*

Pt. No.	Diagnosis	Age Testicular Tissue Removed	Initial Gender Assignment	Present Gender Assignment	Gender Identity	Sexual Orientation		No. Total Sexual Partners	Partner Orientation
						Initial	Current		
1	True hemaphrodite	18 Mos.	Female (male until age 3 yrs.)	Female	Intersexual	Female	Female	40	Female to female
2	Salt wasting, CAH		Female	Male	Intersexual	Female	Female	12	Female to female
3	Female pseudohemaphrodite		Female	Female	Female	Male	Female	3	Female to female
4	Kallman's syndrome	3 Yrs.	Male (physicians advised female)	Male	Male	Female	Female	1	Female to male
5	Partial androgen insensitivity syndrome	Infancy, 12 yrs.	Female	Female	Intersexual	Female	Female	13	Female to female
6	Male pseudohemaphrodite	Before 2 yrs.	Female	Male	Intersexual	Male	Female	4	Female to female
7	Mosaic karyotype	1 Mo.	Female	Female	Intersexual	Male	Female	50	Female to female
8	Large clitoris, no diagnosis		Female	Female	Intersexual	Male	Female	6	Female to female
9	Partial androgen insensitivity syndrome	Not removed	Male	Male	Intersexual	Female	Male	300	Male to male
10	Partial androgen insensitivity syndrome	1 Yr.	Female	Female	Intersexual	Female	Female	15	Female to female

TABLE 2. *Satisfaction with physical appearance*

Lickert Score	1 Completely Satisfied	2 Satisfied	3 Neutral	4 Dissatisfied	5 Completely Dissatisfied	Total Score	Av. Score
Overall physical appearance	1	8		1		10	2.1
Face	2	8				10	1.8
Breast/chest	4	3		2	1	10	2.3
Waist	2	4	1	3		10	2.5
Hips	2	5	1	2		10	2.3
Legs	2	5	1	2		10	2.3
Clitoris/penis	2			1	2	5*	3.2
Vagina		2	1			3	2.3
Inner labia		1			3	4	4.3
Outer labia		2	1			3	2.6
Testes					1	1	5

* Decrease in numbers reflects unwillingness to discuss issues related to genitalia.

Patient opinion of gender identity revealed that 8 preferred being identified as intersexual, 1 male as male and 1 female as female. Two intersexuals with initial female gender assignment were undergoing male reassignment.

Of the 10 subjects 8 (80%) demonstrated more masculine behaviors and preferences and 2 had more feminine patterns of behavior. Initial diagnoses of the latter 2 cases were male pseudohemaphrodite and the partial androgen insensitivity syndrome, respectively. For final sexual orientation in adulthood 8 subjects chose a female sexual partner despite female gender assignment and 1 male with the partial androgen insensitivity syndrome (the most masculine in appearance) chose a male partner.

Sexual debut occurred at age 18.1 years (range 15 to 22). Of the subjects 4 gender assigned females and 2 gender assigned males initially engaged in heterosexual activity with heterosexual partners. Four females initially engaged in gynephilic (female) sexual contact. Despite female gender assignment in 8 and initial heterosexual activity by 4, the final choice of sexual partner was female by all 8 (exclusively gynephilic partners). Both males had initial heterosexual contact but only 1 continued to prefer a female partner who was exclusively heterosexual and 1 now chooses male partners (all homosexual males except the most recent who is also an intersexual that prefers male partners). Current number of sexual partners ranges from 0 to 2 (average 0.9) and total number of sexual partners ranged from 1 to 300 (table 1). Presently, 9 subjects are involved in a committed sexual relationship.

Considering sexual function and genital sensitivity, 8 intersexuals are able to achieve orgasm by masturbation in 5, stimulation of the clitoral or penile area in 8, stimulation of the vaginal area in 2 and stimulation of the breast in 1. Frequency of sexual activity was reported as regular sexual activity by 7 intersexuals, occasional by 2 and none by 1. Of the intersexuals interviewed 2 were completely satisfied with sexual relationships, 6 were satisfied and 2 gender assigned females were dissatisfied.

DISCUSSION

The etiology of intersexuality is protean in nature, ranging from disorders of karyotype to production, synthesis and receptor sensitivity to androgen, rendering genitalia inadequately or overly virilized. Incidence ranges dramatically for different disorders (see Appendix).[9] These disorders have historically been addressed with feminizing genitoplasty or, less commonly, reconstructive surgery to normalize male genitalia.[10] The goal was to provide comfortable identity with appearance concordant with assigned sex.

A population specific interview technique was designed to address the physical, psychological and social issues that impact the intersexual condition. Existing instruments were considered. The Klein Sexual Orientation Grid,[11] Body Image Scale,[12] Gender-Role Assessment Schedule,[13] and Zucker Gender Identity Interview[14] address specific populations but not the unique qualities of the intersexual. Input from those intersexuals interviewed facilitated our formatting questions and modifying terminology.

In our study patients regarded general body appearance as satisfactory but expressed varying degrees of satisfaction with those body areas with sexually identifying characteristics. Some patients expressed complete dissatisfaction with specific genital appearance, including absent testes, absent inner labia, unnatural appearance of the clitoris and a penis deformed by chordee and fistula. This finding may be why satisfaction is difficult to assess with questions designed for

typical male/female anatomy. Some intersexuals expressed complete satisfaction although the genitalia were atypical. Most had surgical alteration. The interplay of gender identity and sexual orientation with genital anatomy and function may have impacted satisfaction of genital appearance. Although appearance may be part of gender identity in our subjects adjustment to bodily differences, particularly genital differences, did not seem to deter participation in sexual activities. Although we cannot know the full potential of sexual capacity, sexual activity was reported as satisfactory by all but 2 subjects.

Humans may follow the same basic principles demonstrated by other mammalian species in brain development and sexual differentiation. Males deprived of testosterone during the critical time of brain differentiation will exhibit a female pattern of sexual behavior. Conversely, females exposed to testosterone during prenatal or perinatal development exhibit male sexual behavior in adulthood.[15] Mammalian sexual behavior is not completely dimorphic but represents behavior components more typical of 1 sex or the other.[16]

Humans possess cognitive abilities that may influence sexual outcomes. Sexuality may be expressed early in gender role behaviors (toy, activity and playmate preferences), but whether these predict gender identity and orientation is unknown. Individuals with congenital adrenal hyperplasia (CAH) have been best studied in relation to behavior differences in toy play, aggression and playmate preference in childhood.[17,18] Psychosexual development of women with CAH suggests that excessive prenatal androgen exposure predisposes to more cross-gender role behavior and less comfort with femininity, shifting typical female behavior patterns toward male behavior patterns. However, no increased incidence of homosexuality has been reported.[19] Some data suggest increased rates of homosexuality (gynecophilia) in female raised XXY patients.[1]

In our study we considered childhood patterns of gender role behaviors and their continuity to later adulthood behaviors. Subjects were questioned about childhood toy and activity preferences. Masculine behaviors, activity and toy preferences were demonstrated by 8 of our subjects. These masculine preferences and activities suggest permanent organizational effects on the brain, possibly imposed by prenatal and perinatal androgen exposure. Of those exhibiting masculinized behavior in childhood all but 1 exhibited gender orientation to females. One was sexually oriented to men. Only 1 patient who had feminine toy and activity choices was sexually oriented to females. Interestingly, despite masculinized behavior in childhood, most (80%) chose intersexual over a male gender identity. Of the 2 intersexuals who were actually gender assigned and raised male, 1 chose an intersexual and 1 a male gender identity. In our study all intersexuals knew their diagnoses. Only 2 subjects believed they identified appropriately with male and female assignment, respectively, 2 felt dysphoria strongly enough to request male reassignment, although 1 wishes to be identified as intersexual, and 8 preferred identity as intersexual in true accordance with their acceptance of their dimorphic condition.

CONCLUSIONS

Based on this albeit small sample, feminizing choices for intersexual diagnosis may be less successful than desired. Despite feminization, masculine behavior and orientation continue to persist. Sexual debut with a partner opposite the intersexual assigned sex may represent an effort to maintain accepted societal patterns of heterosexual behavior rather than be a reflection of true sexual orientation that is manifested as a final partner choice.

Population specific interview techniques revealed discordance in gender assignment in all but 2 intersexuals. In this study most subjects were assigned female, and gynephilic (female) sexual orientation was evidenced in this study group, despite female assignment by surgery and rearing. Patterns of masculinized behavior were evident in the majority of subjects and may reflect prenatal and perinatal androgenization.

The majority of these adults are not expressing dysphoria. They recognize their diagnoses and differences in anatomy. They have been successful in partnering and in most cases have satisfying sexual function. Their personal input may lead us to realize that hormonal and neural factors influence behavior more than correct anatomical appearance. Recognition of possibilities for androgenized (masculinized) behavior and orientation may change the expectations of physicians, parents and caregivers, and increase the comfort level and satisfaction of our intersexual patients.

APPENDIX: INTERSEX DIAGNOSES AND INCIDENCE[9]

Chromosomal mozaic	1/1,666 births
Klinefelter (XXY)	1/1,000 births
Androgen insensitivity syndrome	1/13,000 births
Partial androgen insensitivity syndrome	1/130,000 births
Classical CAH	1/13,000 births
Vaginal agenesis	1/6,000 births
Idiopathic	1/110,000 births
Iatrogenic (caused by medical treatment for example progestin administered to pregnant mother)	No estimate
5-α reductase deficiency	No estimate
Mixed gonadal dysgenesis	No estimate

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Intersexuality and Gender Identity Differentiation

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People born with physical intersex conditions (often better known as hermaphroditism) remind us that the ordinary or "normal" process of physical sex differentiation is by no means automatic.[1] Throughout the course of human history, all cultural groups have had to make multiple decisions about newborns with physical hermaphroditism (at least for those who did not die from medical complications inherent to, or associated with, their condition) and their subsequent place within the fabric of social life. At times, this matter has been expressed in an almost urgent manner: Tuffier and Lapointe (1911), for example, wrote that "For hermaphrodites as well as for normal subjects, the possession of a [single] sex is a necessity of our social order" (p. 256, cited and translated in Dreger, 1995a).

Over the past 2 centuries, there have been considerable advances in developing a more accurate scientific taxonomy of physical intersex conditions, although Shearman (1982) quipped that one way to tax a

[1]The word normal is intentionally surrounded by quotation marks to alert the reader to one of the current controversies in the literature on physical intersex conditions, namely whether they should be considered "abnormal" or simply variants of typical or normal physical sex differentiation in ordinary biological males and females (see, e.g., Blackless et al., in press). I believe that physical intersex conditions are "abnormal," or, to use Money's (1994) descriptor, "sex errors of the body." I reach this conclusion by following King's (1945) definition of normal: "that which functions in accordance with its design." Given our understanding of the processes that govern normal physical sex differentiation and the processes that go awry in the differentiation of physical intersex conditions, it is hard to argue that such conditions are simply variants from the norm. In using the term abnormal, however, it is important, particularly from a moral point of view, to distinguish between the condition and the person who has the condition. In the 19th century, for example, hermaphroditism was viewed as a teratologic monstrosity and, at least for some people, the hermaphrodite was viewed as a "monster." The term teratology is of Greek origin (*teras*: monster or marvel). A less pernicious definition is that of an abnormality or serious deviation in the growth or structure of an organism. It is the blurring of the person and the person's condition that is particularly problematic. Of course, the psychological struggles that some people with physical intersex conditions experience cannot be comfortably distanced by referring to the past. Chase (1998a), the founder of a contemporary support group for intersexuals, the Intersex Society of North America, lucidly describes her efforts in adulthood to overcome the feeling of being a "freak" (see also Holmes, 1994).

taxonomist is to "ask him to classify intersexes" (p. 325). Over the past 50-60 years, there has also been a great deal of interest in human hermaphroditism from a behavioral and psychological point of view, particularly with regard to what it can teach us about normative or typical psychosexual development and differentiation. Along parallel lines, many researchers in the field of animal sexology have relied on the experimental induction of "pseudohermaphroditism" in order to understand better the mechanisms and processes underlying normative sexdimorphic behavioral differentiation (e.g., Baum, 1979; Dixson, 1998; Goy & McEwen, 1980; Wallen, 1996). Indeed, the study of hermaphroditism has been generally guided by the assumption that understanding atypical sexual differentiation (from both a physical and behavioral point of view) will enhance understanding of more typical sexual differentiation. In this respect, research on hermaphroditism is a prototype example of the interface between the study of normal and abnormal development (cf. Cicchetti, 1993; Sroufe, 1990).

At present, the clinical and scientific literature on physical intersex conditions is in a state of great debate and controversy. One might even go so far as to say that the field is in a sort of crisis. There are, for example, considerable concerns and objections about the use of surgical interventions to "normalize" the ambiguous genitalia of people with physical intersex conditions (see, e.g., Chase, 1998a; Diamond & Sigmundson, 1997a; Schober, 1998a, 1998b, 1999; Wilson & Reiner, 1998), and some critics have even gone so far as to call for a "moratorium" on surgical interventions until the status of previously treated patients are followed-up with greater precision (e.g., Diamond, 1999; Kipnis & Diamond, 1998; cf. American Academy of Pediatrics, 1996; Glassberg, 1998). Indeed, in May and August 1999, the Constitutional Court of Colombia in South America provided a potentially landmark ruling on what constitutes informed consent for surgical interventions for infants and children with physical intersex conditions (Intersex Society of North America, 1999; see also Greenberg, 1999). Although guidelines for psychological counselling have been available for some time (e.g., Money, 1965, 1994; see also Green, Stoller, & MacAndrew, 1966; Meyer-Bahlburg, 1982, 1993; Stoller, Garfinkel, & Rosen, 1962), there has been a resurgence of discussion about the uneven quality of psychological counselling that is available to people with physical intersex conditions and their families (e.g., Preves, 1998). Some of the current controversy has also been fueled by adults with physical intersex conditions who are quite critical about the care that they received as children and adolescents (see, e.g., Chase, 1998b; Holmes, 1994). Other aspects of the current debate have been stimulated by critics of the "medical model," who

utilize a "social constructionist" approach in appraising the extant literature (e.g., Dreger, 1995a, 1995b, 1998a, 1998b, 1998c; Fausto-Sterling, 1993; Findlay, 1995; Kessler, 1990, 1998; Lee, 1994). Indeed, many of these issues were recently discussed and debated at a 1999 conference in Dallas, Texas entitled "Pediatric Gender Reassignment: A Critical Reappraisal" (see Zderic, Canning, Snyder, & Carr, in press).

In this article, I will begin by providing a brief overview of relevant terminology. I will then review one specific aspect of the contemporary literature on intersexuality, namely what is known about gender identity formation and differentiation. I have chosen to focus the review on this specific topic for a couple of reasons. First, there has been, over the years, periodic debate regarding the question of the "appropriate" sex assignment and subsequent gender of rearing of infants and children with physical intersex conditions (see, e.g., Diamond, 1965; Imperato-McGinley, Guerrero, Gautier, & Peterson, 1974; Zuger, 1970), primarily in relation to the formulation originally introduced and then later amplified by the work of John Money and his colleagues at Johns Hopkins Hospital beginning in the 1950s (e.g., Money, 1952; Money, Hampson, & Hampson, 1955). Second, over the last few years, this debate has re-surfaced, with even greater force and intensity, following the publication of long-term psychosexual follow-up data pertaining to a specific case claimed to have especially important relevance to this issue (Diamond & Sigmundson, 1997b).

As it has in the past, much of this debate continues to revolve around the relative roles of nature and nurture in gender identity formation in particular and psychosexual differentiation in general. Although many scholars in the field have long rejected the nature-nurture axis as a false dichotomy (see, e.g., Bancroft, 1991; Money, 1985; Wallen, 1996), the fact remains that in practice the debate carries on. It is timely, therefore, to provide a critical summary of the empirical database on gender identity formation in people with physical intersex conditions and then to evaluate the candidate explanations that best account for the pattern of results.

Terminology

Webster's Seventh New Collegiate Dictionary (1963) defines an intersexual as a person who is "intermediate in sexual characters between a typical male and a typical female" (p. 443). A hermaphrodite is defined a bit more narrowly as "an animal or plant having both male and female reproductive organs" (p. 389). According to Dreger (1995a), it was Goldschmidt (1923) who first used the term intersexuality as part of an effort to describe a range of physical sex ambiguities. Over time in

the medical literature, intersexuality has become the preferred term used to encompass the diverse class of syndromes characterized by some abnormality or anomaly in the process of physical sex differentiation (Haqq & Donahoe, 1998; Shearman, 1982; Sizonenko, 1993). Thus, the term intersexuality can be understood to represent a broader class of syndromes than those that have been traditionally subsumed under terms like true hermaphroditism, female pseudohermaphroditism, and male pseudohermaphroditism, which were used in one of the first taxonomic efforts to classify physical intersex conditions (Klebs, 1876).

Efforts to devise accurate taxonomic systems are, of course, dependent on our knowledge of the multiple parameters that constitute biological sex (Table 1). Thus, for example, in Klebs' time, sex chromosome abnormalities were not part of any system of classification as it was only in the 1950s that reliable techniques were developed to karyotype the sex chromosomes (Moore & Barr, 1955). Klebs' proposed system of classification placed great emphasis on the importance of certain diagnostic techniques, including clinical microscopy, laparotomy, and biopsy (Dreger, 1995a). The insistence on histologic analysis appeared to have

Table 1
Parameters of Biological Sex

1. Chromosomal Sex
2. Gonadal Sex[a]
3. Hormonal Sex
4. Internal Reproductive Structures
5. External Genitalia
6. "Brain" Sex[b]

Note. From Migeon and Wisniewski (1998).

[a]Although it has long been surmised that the presence of the Y chromosome was necessary for the gonads to differentiate along male lines (i.e., testicular differentiation), it was only in 1990 that the "testis-determining factor" (TDF) was identified (Vilain & McCabe, 1998). As described by Haqq and Donahoe (1998), the TDF is located on the short arm of the Y chromosome, with subsequent identification of SRY (the sex-determining gene region of the Y chromosome) (Donahoe & Schnitzer, 1996). In addition, Mullerian inhibiting substance is another protein involved in the temporal sequence of events that leads to male sex differentiation, as it results in the regression of the Mullerian duct, the anlagen of the uterus, fallopian tubes, and the upper vagina. It is well-known, however, that even in the presence of a normal SRY and normal production of testosterone from the fetal gonad, the fetus must also have operative androgen receptors; otherwise, the external genitalia will differentiate along female lines although the vaginal canal lacks depth and there are no internal female organs.

[b]Over the past couple of decades, there has, of course, been great interest in the possibility that the human brain has certain sex-dimorphic characteristics. The existence of such putative anatomic and functional properties has not, however, been part of any formal taxonomic system of physical intersex conditions. Ironically, however, the assumption that there is some kind of CNS sex-dimorphism has played a great role in the current debate about gender identity differentiation among people with physical intersex conditions.

resulted in the nature of the gonads becoming the final arbiter in deciding upon the "true sex" of the hermaphrodite, a development that had substantial implications. As noted by Meyer-Bahlburg (1998), among others, the notion of a "true sex" in intersexuality is problematic. Given that a person's physical sex is multidimensional in nature, there is no reason to insist that one parameter should necessarily hold precedence over another. Thus, from a descriptive point of view all that is required is an accurate delineation of the physical sex parameters that are affected in particular intersex syndromes.

Which Sex? Which Gender?

A common aspect of several physical intersex conditions involves the differentiation of ambiguous external genitalia. When this occurs, there is often uncertainty whether the neonate's *sex assignment* should be that of a male or a female and the *gender assignment* that of a boy or a girl. Not surprisingly, such uncertainty causes anxiety in parents and in the professional involved in determining a newborn's sex, whether that professional is a physician or nurse working in the modern hospital delivery room or a midwife working in some remote "third world" community far removed from the postmodern Western scene. Perhaps reminiscent of Tuffier and Lapointe's (1911) remark quoted above, many contemporary physicians characterize this uncertainty as a "medical" and "psychosocial" emergency that requires immediate attention and resolution (e.g., Izquierdo & Glassberg, 1993; Pagon, 1987).

That the visible physical markers of biological sex are psychologically salient has even been documented by some empirically minded scientists. In one study of parental behavior shortly after the birth of a newborn, Woollett, White, and Lyon (1982) observed that the majority of the verbal comments pertained to the infant's sex. In another study, Intons-Peterson and Reddel (1984) had "parent-collaborators" call their friends following the birth of their babies. Overall, 80% of the initial questions were about the baby's sex. The single most frequently asked question was "Is it a boy or a girl?"

In an interesting analogue study, Delk, Madden, Livingston, and Ryan (1986) showed that perceptions of a toddler's behavior were affected by labeling it as a male, a female, or a hermaphrodite. Several hundred health professional trainees (e.g., medical and psychology students) viewed an 8-minute videotape of a 22-month-old infant engaged in various activities. Every 15 seconds, the trainees were asked to rate the toddler's last activity as masculine, feminine, or neutral. Activities were more likely to be rated as masculine than feminine when the toddler was labeled a male, whereas the converse occurred when the toddler was

labeled a female. When the toddler was labeled a hermaphrodite, a similar proportion of the activities was rated as masculine and feminine.

Sex and gender assignment at birth are believed to be the first of a cascade of events that fall under the rubric of gender socialization (Ruble & Martin, 1998); nowadays, with the development of techniques such as amniocentesis and ultrasound, parents can acquire information about fetal sex, which likely generates a variety of specific feelings and thoughts about their future child (e.g., Birnholz, 1983; Fletcher & Evans, 1983; Winestine, 1989). Following these first events, whether they occur prenatally or after parturition, parents often select a name for their newborn that has a stereotypical masculine or feminine connotation. Many books are available to aid parents in these selections, the popular press routinely reports on the most common given names of boys and girls (Hartocollis, 1999; Roberts, 1996), and there are scholars who actually study the psychology and sociology of naming (Lieberson & Bell, 1992).

It is also common for parents to dress male and female infants in sex-stereotypical ways, including the North American tradition of sex-dimorphic "color coding" in pink or blue that began in the 1920s (Paoletti & Thompson, 1987). Shakin, Shakin, and Sternglanz (1985) observed infants at a shopping mall in Long Island, New York, and found that about 75% of the females had at least some pink in their clothing, compared to 0% of the males, and that 79% of the males had at least some blue in their clothing compared to only 8% of females.

Sex assignment and subsequent "rearing" as a boy or girl have long been viewed as powerful socialization influences that account for sex differences in psychosexual differentiation. Thorne (1993), for example, writes that

> While many still see gender as the expression of natural differences, the women's movement of the 1970s and 1980s launched a powerful alternative perspective: notions of femininity and masculinity, the gender divisions one sees on school playgrounds . . . the idea of gender itself—*all* are social constructions. . . . Parents dress infant girls in pink and boys in blue, give them gender-differentiated names and toys, and expect them to act differently. . . . peer groups . . . also perpetuate gender-typed play and interaction. In short, if boys and girls are different, they are not born, but *made* that way. (p. 2, italics in original)

In stark contrast to this view, theorists with a biological bent also emphasize single-factor influences. For example, Swaab, Gooren, and Hofman (1992) asserted that gender identity is very difficult to change, "probably because . . . [it is] fixed in the brain" (p. 52).

But because the rearing of an infant as a boy or a girl is usually perfectly confounded with biological sex, researchers have long made the

point that it is actually difficult to disentangle the relative contribution of biological and psychosocial influences. For some researchers, it was this methodological and interpretive dilemma that led to the study of children with physical intersex conditions in the hope of providing at least a partial resolution to this problem.

Initial Empirical Studies: The Work of Money and Colleagues

Beginning in the 1950s, Money and colleagues began to report data on the psychosexual development of children born with physical intersex conditions. Money, Hampson, and Hampson (1957) noted that since hermaphrodites are "neither exclusively male or female, [they] are likely to grow up with contradictions existing between the sex of assignment and rearing, on the one hand, and various physical sexual variables, singly or in combination, on the other" (p. 333). Thus, Money et al. asked "whether the gender role and orientation[2] that a hermaphrodite establishes during the course of growing up is concordant with the sex of assignment and rearing, or whether it is predominantly concordant with one or another of the . . . physical sexual variables" (p. 333).

In their study of 105 hermaphrodites, Money et al. (1957) found that only 5 of 105 patients had a "gender role and orientation [that] was ambiguous and deviant from the sex of assignment and rearing" (p. 333). Thus, Money et al. concluded that "the sex of assignment and rearing is consistently and conspicuously a more reliable prognosticator of a hermaphrodite's gender role and orientation than is the chromosomal sex, the gonadal sex, the hormonal sex, the accessory internal reproductive

[2]The terms "gender role and orientation" require some explication. Two years prior to the Money et al. (1957) article, Money (1955) had coined the term *gender role*, which was defined as "all those things that a person says or does to disclose himself or herself as having the status of boy or man, girl or woman, respectively. It includes, but is not restricted to, sexuality in the sense of eroticism" (p. 254). As I have noted in detail elsewhere (Zucker & Bradley, 1995, pp. 2-6), over the past several decades, Money's original use of the term gender role has been decomposed into three conceptually distinct component parts that are identified by the terms *gender identity, gender role,* and *sexual orientation.* Briefly, gender identity refers to a child's basic sense of self as a boy or as a girl; gender role refers to a child's preferential adoption of behaviors stereotypically associated with masculinity and femininity (e.g., in the domains of toy play, role play, peer preference, and so on), and sexual orientation refers to a person's responsiveness to sexual stimuli, of which the sex of one's partner is probably the most salient dimension. It should also be noted that the construct of sexual orientation needs to be further distinguished from the construct of *sexual identity,* which refers to a person's self-labeling as, for example, heterosexual, homosexual, or bisexual. Although often congruent with each other, sexual orientation and sexual identity are not always so. In this article, I will, where appropriate, attempt to use the more differentiated terms of gender identity, gender role, and sexual orientation when discussing the extant data on psychosexual differentiation in people with physical intersex conditions.

morphology, or the ambiguous morphology of the external genitalia" (p. 333). This conclusion echoed that of Ellis (1945), who had previously reviewed the available literature on 84 cases of hermaphroditism:

> The hermaphrodite assumes a heterosexual libido and sex role that accords primarily not with his or her internal and external somatic characteristics, but rather with his or her masculine or feminine upbringing . . . . heterosexuality and homosexuality in hermaphrodites are primarily caused not by directly hormonal or other physiological factors but by environmental ones. (p. 120)

Money et al. (1957) offered one additional finding for the relative importance of socialization factors in determining gender identity differentiation among children with physical intersex conditions:

> The clinching piece of evidence concerning the psychologic importance of the sex of assignment and rearing is provided when, among persons of identical physical diagnosis, some are reared as boys, some as girls. It is indeed startling to see, for example, two children with female [congenital adrenal hyperplasia] in the company of one another in a hospital playroom, one of them entirely feminine in behavior and conduct, the other entirely masculine, each according to upbringing. (p. 334)

Given such evidence for the apparent malleability and plasticity in gender identity differentiation (see also Money, 1991), it became necessary to replace the reliance on identifying the patient's "true sex" with a different model for guiding decisions about gender assignment.

As summarized by Meyer-Bahlburg (1998), the model developed by Money and the Johns Hopkins school of pediatric endocrinology can be characterized as the *optimal gender* policy of psychosocial and medical management. This policy aimed to result in the best possible prognosis with regard to six variables, which are listed in Table 2.

Is There A Critical Period for Gender Identity Formation?

Money et al.'s (1957) conclusion about the relative salience of sex of rearing[3] had one important caveat, namely the advisability of an early decision about sex assignment. They recommended that when there was uncertainty about the appropriate sex of assignment, the final decision about it should certainly be made no later than 18-24 months, and argued that "uncompromising adherence to the decision is desirable" (p. 334). Otherwise, it was claimed that the child would be vulnerable to

[3]"Gender of rearing" would be the preferred description, but I will retain Money's use of the descriptor "sex of rearing" for the sake of historical continuity. But the reader should keep in mind that "rearing" really refers to putative gender-specific socialization techniques of the infant as a boy or a girl.

Table 2
Parameters of the Optimal Gender Policy of Psychosocial and Medical Management of Infants and Children with Physical Intersex Conditions

1. Reproductive potential (if attainable at all)
2. Good sexual function
3. Minimal medical procedures
4. An overall gender-appropriate appearance
5. A stable gender identity
6. Psychosocial well-being

Note. Derived from Meyer-Bahlburg (1998).

"psychologic nonhealthiness" (p. 334), which presumably was related to a more conflicted or ambiguous gender identity, which Stoller (1964) later referred to as a "hermaphroditic" gender identity. In part, Money et al.'s (1957) recommendation of an early sex assignment was based on the observation that among intersexed children who experienced a sex reassignment after the neonatal period, 11 of 14 children adjusted to the change without complications if the reassignment occurred prior to 27 months, in contrast to only 1 of 4 children who adjusted to the change without complications if it occurred after 27 months (Fisher's exact test, $p = .0379$, one-tailed, my analysis).

Money et al. (1957) interpreted this age effect as evidence for a process akin to the phenomenon of imprinting, or a critical period, that had been described by ethologists with regard to other behavioral characteristics, such as attachment formation (e.g., Bowlby, 1969). Thus, the first 2 years or so of life were deemed to represent a critical period for gender identity formation (see also Money & Annecillo, 1987).

Since the 1950s, the critical-period construct has been subject to a great deal of general empirical scrutiny, and the concept of a "sensitive" or an "optimal" period was introduced in order to expand the window of time in which certain environmental experiences might exert their greatest impact, but without implicating the irreversibility that was believed to occur in the case of critical periods (e.g., Bornstein, 1987, 1989; Hess, 1973).

The existence of a sensitive period for gender identity formation suggests a certain malleability or plasticity, in which gender identity differentiation can more readily move in one direction or another but, after some imprecisely defined window of time, this becomes more difficult.

Even if we put the concept of a sensitive period aside, normative data that have accrued over the past several decades on gender identity formation certainly suggest that important developments occur in the first 2 or 3 years (e.g., Fagot, 1995; Ruble & Martin, 1998). Let us

consider what is known about the development of the capacity to correctly self-label one's gender.

There is now some evidence that infants under the age of 12 months are able to perceptually discriminate males from females, relying on cues such as hair-style and voice quality. Although it is unlikely that infants have any conscious or reflective understanding of these distinctions, the data suggest that phenotypic markers that commonly distinguish males from females are salient to the infant. Between the second and third year of life, nonverbal techniques (e.g., sorting tasks) indicate that toddlers can correctly self-label their own gender and that of others and, by age 3, can answer correctly the question "Are you a boy or a girl?" Thus, the corpus of extant normative developmental data certainly support Money's original observations that signs of gender identity differentiation can be detected by age 2 years. Interestingly enough, however, it is not clear to what extent children rely on the configuration of the external genitalia in making judgments about their own gender. Indeed, some have argued that children pay more attention to markers such as hair-style and clothing style than they do to the configuration of the external genitalia, perhaps because they have more comparative cue exposure to the former than to the latter (de Marneffe, 1997; McConaghy, 1979), and it is only later in childhood that the external genitalia are used more systematically in the correct gender labeling of self and others (McConaghy, 1979).

In any case, the data suggest that a gender reassignment after the age of 2 or 3 years would require that the typical toddler unlearn his or her original gender self-label and learn another one. It is not clear how difficult such a task might be. For example, Kohlberg (1966) argued that although toddlers and preschoolers display a rudimentary cognitive understanding of gender, they do not truly appreciate its invariance: "the child age two to four is very uncertain of the constancy of his [gender] identity, and the label 'boy' is for him as arbitrary as the label 'Johnny'" (p. 87). In Kohlberg's (1966) now classical cognitive-developmental account of *gender constancy* development, the child's eventual understanding that gender is an invariant part of the self is attained only with the development of concrete-operational thought (around 5-7 years of age), which permits the child to appreciate the principle of invariance in the face of "superficial" or surface transformations in gender-related behavior, such as activity preferences or clothing style (for reviews of the gender constancy literature, see Ruble & Martin, 1998; Zucker et al., in press). It is unlikely that one could conduct an experiment in which, for example, parents of ordinary toddlers try to teach males that they are girls, not boys, and females that they are boys, not

girls, after they have acquired an initial correct self-labeling. Perhaps one could try a re-labeling experiment around something more innocuous (e.g., to re-teach a toddler that his nose is really his ear and vice-versa). To this, of course, one also has to add the cognitive complexity required of parents to change sets around their child's sex and gender. One would imagine that this would become a more difficult task after raising a child as one gender for a couple of years, rather than the issue being settled in the first few days or months after birth.

Appraisal of the Gender Identity Formation Data

To what extent have the original Money et al. (1957) data, as well as Ellis' (1945) earlier conclusion, been substantiated by subsequent research on gender identity formation in children with physical intersex conditions? To answer this question, one can take advantage of the increased precision in identifying physical intersex conditions on a syndrome by syndrome basis. Moreover, one can consider the nature of the syndromes themselves and which aspects of physical sex differentiation are affected in each.

As a point of departure, it should be noted that certain physical intersex conditions do not result in any substantive uncertainty about sex assignment and gender of rearing at the time of birth. Let us consider two such examples. In genetic males born with the complete form of the androgen insensitivity syndrome (cAIS) (Morris, 1953; Morris & Mahesh, 1963; Perez-Palacios, Chavez, Mendez, Imperato-McGinley, & Ulloa-Aguirre, 1987; Rutgers & Scully, 1991), which is inherited as an X-linked recessive trait (for recent accounts of molecular genetic studies, see Brown et al., 1993; Griffin, 1992; Quigley et al., 1995; Radmayr et al., 1997), the external genitalia differentiate as female because of a defect in androgen receptors. Accordingly, the baby is assigned to the female sex and reared as a girl. At puberty, there is relatively normal breast development (induced by testicular estrogens), but there is a lack of certain secondary sex characteristics, such as axillary hair and pubic hair. The testes remain undescended and the vagina is blind-ended. There is no cervix, uterus, or fallopian tubes. Clinical presentation often occurs for the first time during adolescence because of the absence of menarche.[4]

In the case of cAIS, the available empirical studies and case reports indicate an unequivocal female gender identity (e.g., Costa et al., 1997;

[4]Occasionally, the diagnosis is made in childhood (e.g., if there is notable swelling in the perineum because of the undescended testes). On rare occasions, the diagnosis is suspected when the karyotyping of the sex chromosomes taken from amniotic fluid appears to contradict the genital configuration observed during fetal ultrasound.

Hampson, Hampson, & Money, 1955; Imperato-McGinley, Pichardo, Gautier, Voyer, & Bryden, 1991; Masica, Money, & Ehrhardt, 1971; Slijper, Drop, Molenaar, & de Muinck Keizer-Schrama, 1998; see also Money, Ehrhardt, & Masica, 1968; Slob et al., 1993). Indeed, Meyer-Bahlburg (1999b) has pointed out that the literature does not appear to contain any report of a person with cAIS raised as a female who later voluntarily changed her gender to that of a male. Thus, a female gender identity differentiates in a person with XY chromosomes and testicular gonads.

From a psychosocial standpoint, one might infer that cAIS individuals who are assigned unequivocally to the female sex and reared as girls are subject to the same gender socialization influences as are unaffected girls. From a biological standpoint, it has been argued that the androgen resistance results in female-typical brain differentiation, which also plays a putative role in sex-dimorphic psychosexual differentiation (Collaer & Hines, 1995). Taken together, then, the putative psychosocial and biological mechanisms that produce "normal" or typical psychosexual differentiation act in concert among newborns with cAIS.[5]

The second example concerns males born with hypospadias, a genital anomaly. In this condition, the opening of the urethra appears at various levels on the undersurface of the penis and its position is used to classify the nature of the hypospadic anomaly (e.g., glandular, penile, penoscrotal, and perineal). The typical corrective surgery aims at reconstructing the distal urethra, which permits voiding in the standing position, facilitates sexual functioning in adolescence and adulthood, and "normalizes" the appearance of the penis. Unless the anomaly co-occurs with other abnormalities in genital differentiation (e.g., as in the micropenis syndromes), there is usually little uncertainty about sex or gender assignment at birth. In boys born with "pure forms" of hypospadias, the literature suggests an unequivocal male gender identity (Mureau, Slijper, Slob, & Verhulst, 1997; Sandberg, Meyer-Bahlburg, Aranoff, Sconzo, & Hensle, 1989; Sandberg et al., 1995).

From a psychosocial standpoint, one might infer that boys born with hypospadias are subject to the same gender socialization influences as

[5]Money (1991, Chapter 2, Case 2) reported on one patient, whose testes were discovered at 18 months (see also Crawford, 1970). A physician recommended gender reassignment on the grounds that physical masculinization could occur with exogenous hormone treatment. Unfortunately, the reassignment occurred during an era in which the natural history of cAIS was still unknown. The patient's body never masculinized. Although gender identity differentiated as male, the patient was extremely isolated socially, and eventually committed suicide in adulthood. To my knowledge, this is the only case in the literature of male gender identity differentiation in a patient with cAIS albeit with a tragic outcome.

are unaffected boys. From a biological standpoint, to the extent that some type of prenatal androgen insufficiency contributes to the condition, it would appear that such effects are relatively weak, in the sense that the penis is relatively well-differentiated, and there is no compelling evidence to believe that the putative androgen insufficiency has affected sex-dimorphic brain differentiation (Collaer & Hines, 1995). Taken together, the putative psychosocial and biological mechanisms that produce "normal" psychosexual differentiation appear to be relatively intact among boys born with hypospadias.

It is with regard to those physical intersex conditions in which there might be some uncertainty at birth regarding sex assignment that the relative importance of gender socialization can best be evaluated. In genetic females, the syndrome of congenital adrenal hyperplasia (CAH) is most relevant; in genetic males, the relevant syndromes include steroid 5α-reductase 2 deficiency (5-ARD), partial androgen insensitivity syndrome (pAIS), micropenis, penile agenesis (aphallia), and cloacal exstrophy. Regarding gender identity differentiation, these syndromes share two characteristic features: (a) there may be some uncertainty regarding sex assignment at birth, in part because the configuration of the external genitalia is severely affected and, as a result, there may be some uncertainty regarding the "optimal" gender in which the child should be reared; (b) either the prenatal hormonal milieu or the configuration of the external genitalia (and sometimes both) can be atypical in relation to the gender in which the child is reared.

Congenital Adrenal Hyperplasia in Genetic Females

In genetic females with CAH, the overproduction of androgenic steroids during fetal development, which has been documented from amniotic fluid assays in at-risk pregnancies (Carson et al., 1982; Forest, 1985), causes genital masculinization ranging from mild clitoral enlargement to complete fusion of the labioscrotal folds with a phallic urethra (New, Ghizzoni, & Speiser, 1996). It is this aspect of the syndrome that, at times, creates uncertainty with regard to sex assignment at birth. When the condition is properly diagnosed, several medical interventions typically ensue, including surgical "feminization" of the enlarged clitoris (Allen, Hardy, & Churchill, 1982; Donahoe & Schnitzer, 1996; Randolph, Hung, & Rathlev, 1981) and cortisol-replacement therapy to control or eliminate postnatal virilization (New & Josso, 1988; Wilkins, Lewis, Klein, & Rosemberg, 1950). Under these conditions, a female sex assignment is made and the infant is, invariably, raised as a girl. For further details on the syndrome itself, including recent understanding of its molecular genetic basis, see Pang (1997),

Wedell (1998), and Wilson, Mercado, Cheng, and New (1995).

Gender Identity Differentiation in Childhood

What do we know about the gender identity development of girls with CAH raised under these conditions? Ehrhardt, Epstein, and Money (1968) compared 15 girls with CAH and 15 control girls with regard to a variety of sex-dimorphic behaviors (*M* age, 10.5 years; range, 5-16 years). Based on interview data regarding gender identity, 7 (47%) of the CAH girls were classified as "content or prefers to be a girl," 5 (33%) were classified as "ambivalent," and 3 (20%) were judged to "[desire] expressly to be a boy." The corresponding percentages for the controls were 93%, 0%, and 7%, respectively. Thus, there was some evidence that girls with CAH were less content with their gender identity than were the controls; however, Ehrhardt et al. remarked that only one of the CAH girls appeared to be severely gender dysphoric and whose general psychosocial functioning was markedly impaired. In a similar study, Ehrhardt and Baker (1974) asked their youngsters whether it was better to be a girl or a boy. Of 17 girls with CAH (age range, 4.3-19.9 years), 6 (35%) indicated that they were undecided or thought that they might have chosen to be a boy if such a choice had been possible. In contrast, only 1 (9%) of 11 sisters gave a similar response. Ehrhardt and Baker noted, however, that "none of the [CAH] girls had a conflict with her female gender identity or was unhappy about being a girl" (p. 43).

The gender identity of girls with CAH has also been evaluated in two more recent studies. Slijper et al. (1998; Slijper, personal communication, April 18, 1999) assessed 18 girls with CAH (*M* age, 13.5 years; range, 2-27 years). Of these, 10 were assigned to the female sex at birth, but 8 others were initially assigned to the male sex (and subsequently reassigned to the female sex no later than age 6 months). Of the 18 girls, 2 (11%) were judged to meet the DSM-IV criteria for gender identity disorder (GID) (American Psychiatric Association, 1994). The remaining 16 girls were deemed reasonably content with their female gender identity.

Berenbaum and Bailey (1998) studied 31 girls with CAH, an ad-recruited group of 7 "tomboys" without known somatic intersexuality, and 22 unaffected sisters of both CAH girls and boys, and of the tomboys (*M* age, 10.9 yrs). A 9-item interview schedule assessed what was termed "continuous gender identity" (p. 9). On this measure, there was little evidence that the girls with CAH were uncomfortable being female. Item analysis indicated that the girls with CAH were more similar to the sister-control group, but different from that of the tomboys. For the continuous measure, the girls with CAH had a mean score that

was in between that of the other two groups. Berenbaum and Bailey concluded that their data confirmed earlier reports that girls with CAH "have female-typical gender identity" (p. 12).

Gender Identity Differentiation in Adulthood

Adult follow-up of women with CAH provides a more definitive picture with regard to gender identity differentiation. Over the years, there have been several follow-up reports pertaining to the gender identity development of women with CAH; in addition, inferences about gender identity development in adulthood can be gleaned from reports in which there is cursory mention of gender identity (typically, in the context of medical or surgical aspects of CAH).

In one study, Zucker et al. (1996) assessed the gender identity of 31 women with CAH (*M* age, 24.4 years) and 15 sister/female cousin controls (*M* age, 25.6 years). Gender identity was assessed via a semistructured interview and by a Gender Dysphoria/Identification self-report questionnaire.

At the time of assessment, all of the probands were living, in the broadest sense, as women (i.e., they were known to others as females and were registered as such on legal or other official documents). For the interview ratings of current and lifetime gender dysphoria, the proband-control comparisons were not significant. On the self-report questionnaire, the two groups did not differ on the factor labeled Gender Dysphoria.

Although these data did not provide any clear evidence for gender dysphoria or discontent among the CAH probands, it should be noted that there were 10 additional potential probands who refused to participate in the study and 13 others could not be traced (including one who had died, and two who were raised as boys from infancy by parental decision). To test for selective attrition factors, we examined three variables: current age, sex assignment at birth, and salt-wasting status.[6] The participants did not differ from the nonparticipants with regard to current age and the percentage assigned to the female sex at birth; however, the refusers were

[6]In many individuals with CAH, there is a deficiency in aldosterone, which causes low serum sodium levels, high serum potassium levels, and vascular collapse—the so-called "salt-wasting" crises in severe cases (New et al., 1996). Among patients with classical CAH, it has been traditional practice to classify them as either simple virilizers (SV; i.e., with no salt-wasting) or salt-wasters (SW). Although it is beyond the scope of this article to review the matter in detail, the SW-SV distinction is important from a psychosexual perspective because there is some evidence that the SW group is, on average, more severely physically masculinized genitally (Prader stages) at birth (for review, see Zucker et al., 1996), which likely indicates greater prenatal androgenization, and there is corresponding evidence for greater behavioral masculinization (see, e.g., Dittmann et al., 1990; Meyer-Bahlburg et al., 1999; Slijper, 1984; Zucker et al., 1996).

all classified as salt-wasters compared to 61% of the participants (Fisher's exact test, p = .0412, two-tailed). The untraced probands did not differ from the participants on this variable (46% vs. 61%).

By virtue of an independent clinical referral, one of the refusers (age, 19 years) had been previously assessed by me (in another hospital setting) because of extreme gender dysphoria. This proband was diagnosed with Transsexualism (with a homosexual sexual orientation) using the criteria in the DSM-III-R (American Psychiatric Association, 1987). It will be recalled that two CAH females (siblings) had been raised as boys by their parents, who had declined medical treatment for both of them in infancy/early childhood. Thus, of the 53 potential probands (excluding the one who had died in infancy), 3 (6%) were currently living as men.

This percentage was compared to one prevalence estimate of female-to-male transsexualism in genetic females, 1 in 30,400 (0.0000329%) (Bakker, van Kesteren, Gooren, & Bezemer, 1993). Using this baseline prevalence value, the odds ratio was 1823.70:1 that a genetic female with CAH in our sample was living, as an adult, in the male social role compared to genetic females in the general population living in the male social role (if we exclude the two CAH patients reared as boys from infancy, the odds ratio was 607.9:1).

Our group data appear to be comparable with other reports on the gender identity status of adult females with CAH. All of these studies indicate (or imply) that the vast majority differentiated a female gender identity (e.g., Dittmann, Kappes, & Kappes, 1992; Kuhnle & Bullinger, 1997). One early study of women with CAH is of particular interest. Ehrhardt, Evers, and Money (1968) studied 23 CAH women (M age, 33 years) who were "late-treated," (i.e., they did not receive early corticosteroid replacement therapy and thus had lived for many years with the "stigma of heavy virilization, sometimes uncorrected genital morphology and lack of feminine secondary sexual development" [p. 117]). The mean age of treatment with cortisone was 26 years (range, 8-47 years). Although Ehrhardt et al. did not directly assess the gender identity of these patients, all were living as women and none were judged to be severely gender dysphoric.

In some cohorts of patients, a percentage of genetic females with CAH were assigned to the male sex at birth (invariably due to the extreme masculinization of the external genitalia) and subsequently raised as boys without apparent complications. For example, in one large cohort, Mulaikal, Migeon, and Rock (1987) reported that 9 (6%) of 158 genetic females with CAH were assigned to the male sex and reared as boys. This cohort appeared to include at least some patients born prior to the availability of treatment with corticosteroids (see also

Abdullah et al., 1991; Chan-Cua, Freidenberg, & Jones, 1989; Hinman, 1951a, 1951b; Kandemir & Yordam, 1997; Money & Dalery, 1976; Sripathi, Ahmed, Sakati, & Al-Ashwal, 1997; van Seters & Slob, 1988; but also see Hochberg, Gardos, & Benderly, 1987). Given the gradual improvement in the early diagnosis and detection of CAH, it is likely that, in more contemporary cohorts, the percentage of genetic females declared to be males will decrease (Frank, 1997).

Genetic females with CAH reared as boys is interesting in its own right because it tells us that a male gender identity can differentiate in a person who, for example, has female sex chromosomes and internal reproductive structures. It is likely that the masculinization of the external genitalia, which go "uncorrected," work in concert with masculine gender socialization. Moreover, socialization as boys may well augment the putative prenatal androgenization of the CNS that predisposes such youngsters to behavioral masculinity.

More interesting, however, are the cases of gender change from female to male that occur gradually over the life course at the instigation of the person with CAH, not others. Recently, Meyer-Bahlburg et al. (1996) reviewed this aspect of the CAH literature and presented data on four new patients in which this type of transformation occurred (see also Hinman, 1951b, Money, 1991, Chapter 9, Case 2). Meyer-Bahlburg et al. identified four factors that appeared contributory: (a) lack of surgical feminization or delay beyond infancy; (b) poor adherence to glucocorticoid replacement therapy, resulting in progressive physical virilization; (c) markedly masculine childhood gender role behavior; and (d) sexual attraction to females.

Summary

In summary, the data on gender identity differentiation among genetic females with CAH generally support the Money et al. (1957) argument that gender identity differentiates primarily in accordance with gender of rearing. Nonetheless, there appears to be variability in the extent to which females with CAH are satisfied or content with their gender identity, and this variability appears to be greater than what is observed among control females.

To some extent, the assessment of gender identity in CAH females has been less adequately appraised than other aspects of their psychosexual development, including assessment of gender role behavior and sexual orientation, for which better psychometric measures have been utilized (e.g., Berenbaum & Hines, 1992; Meyer-Bahlburg et al., 1999; Zucker et al., 1996). Future studies on both girls and women should attempt to rely on more rigorous assessment techniques, such as the Gender Identity Interview for Children (Zucker et al., 1993) and the DSM-IV criteria

for the assessment of GID. Regarding the latter, although Slijper et al. (1998) reported relying on the DSM-IV criteria, it was not clear from their study the precise symptoms that were present, and it would be useful in subsequent studies to report on the actual manner in which the DSM-IV criteria were rated and the percentage of patients who met criteria for each of the symptoms that contribute to the overall diagnosis.

Recently, Diamond and Sigmundson (1997a) have suggested that genetic females with CAH with marked genital masculinization at birth be raised as males, in contrast to those with less marked genital masculinization (e.g., with a hypertrophied clitoris). It is not clear if the extant data provide direct support for this recommendation. On the one hand, it is likely the case that the CAH females who change gender later in life generally come from the subgroup with the most marked genital masculinization at birth. On the other hand, it is unlikely that this variable alone accounts for the gender change (see, e.g., Meyer-Bahlburg et al., 1996). To adopt the Diamond and Sigmundson (1997a) recommendation, one would like to see evidence that the quality of life of markedly masculinized genetic females with CAH who would be raised as males would be in any way superior to that of those reared as females, who receive the corresponding surgical feminization of the genitalia, regulation of the condition with cortisol-replacement therapy, and retain the potential for fertility (see, e.g., Meyer-Bahlburg, 1999c; Zacharin, 1999).

5-Alpha-Reductase Deficiency

In genetic males, this syndrome often, among other things, results in marked ambiguity of the external genitalia at birth. In the absence of a proper work-up, the genital configuration is often judged female (see, e.g., Opitz et al., 1972; Simpson, New, Peterson, & German, 1971). Prior to the discovery of the underlying metabolic defect (see below), the condition was characterized descriptively (Nowakowski & Lenz, 1961) and was subsequently called pseudovaginal perineoscrotal hypospadias (Opitz et al., 1972; Simpson et al., 1971).

During fetal development, an impairment of steroid 5α-reductase activity leads to an underproduction in plasma dihydrotestosterone (DHT), which causes the incomplete masculinization of the external genitalia (Russell & Wilson, 1994).[7] Because testos-terone production is unaffected, masculinization of the internal reproductive structures is normal.

[7]Prior to the discovery that two enzymes were involved in the pathophysiology, the syndrome was described simply as 5α-reductase deficiency. Over the past few years, the syndrome has been called 5α-reductase 2 deficiency. In genetic females with 5-ARD, it appears to have no substantive role in endocrine physiology and has no known adverse effects (Milewich et al., 1995; Wilson, Griffin, & Russell, 1993).

Moreover, at puberty, there is relatively normal physical masculinization—both primary and secondary sex characteristics develop along male lines (e.g., the phallus enlarges to become, in some instances, a functional penis; the testes descend, if they had not done so already; the voice deepens; and there is an increase in muscle mass). Although affected patients may have normal sperm counts, many are infertile or have azoospermia or oligospermia associated with undescended testes. Fertility is often impaired secondary to a rudimentary prostate and underdeveloped seminal vesicles, which results in highly viscous semen and a low volume of ejaculate (see, e.g., Cantu et al., 1976); however, a recent case report described a successful conception via intrauterine insemination (Katz et al., 1997). For further details on the syndrome itself, including recent understanding of its molecular genetic basis, see Fratianni and Imperato-McGinley (1994), Imperato-McGinley et al. (1974), Thigpen et al. (1992), Walsh et al. (1974), and Wilson et al. (1993).

Gender Identity Differentiation

In behavioral sexology, 5-ARD began to receive a great deal of attention about 25 years ago. At that time, Imperato-McGinley et al. (1974) described a cohort of affected individuals from the Dominican Republic, in which the prevalence of the condition was unusually high because of in-breeding (Imperato-McGinley, Gautier, Peterson, & Shackleton, 1986), showing a gradual change in gender identity from female to male (i.e., they "switched" from living as girls/women to boys/men).[8] Imperato-McGinley et al. (1974) noted that newborns with 5-ARD were often assigned to the female sex and subsequently "raised as girls." At puberty, the girls' physical masculinization was so striking that they became known locally as "guevedoces"—penis at 12 (years of age). Imperato-McGinley et al. (1974) commented that after puberty "psychosexual orientation" was male in all of the 18 individuals who had been reared as females (i.e., they perceived themselves as male, adopted a masculine gender role, and were sexually attracted to females). Imperato-McGinley et al. concluded that the

> male sex drive appears to be testosterone related and not dihydrotestosterone related . . . and the sex of rearing as females . . . appears to have a lesser role in the presence of two masculinizing events—testosterone exposure in utero and again at puberty with the development of a male phenotype. (p. 1215)

[8]According to Wilson et al. (1993), the 19th-century French hermaphrodite, Herculine Barbin (Barbin, 1980), who changed her legal sex from female to male, but, because of a series of complex social events, committed suicide in adulthood, may well be the first published case in the literature of an individual with 5-ARD.

In a subsequent article, Imperato-McGinley, Peterson, Gautier, and Sturla (1979) provided additional details about their subjects, including a description of the community's social life, the community's behavioral expectations for children, and the gender role tasks of the community's adults. They interviewed affected individuals and significant others (e.g., parents, siblings, neighbors) "to discern any sexual ambiguity in the rearing of subjects raised as girls and to determine in these subjects the validity of the change to a male . . . gender identity and male . . . gender role" (pp. 1233-1234). Of 18 subjects "unambiguously raised as girls . . . 17 of 18 changed to a male . . . gender identity and 16 of 18 to a male . . . gender role [during or after puberty]" (p. 1233). They summarized their data as follows:

> The 17 subjects who changed to a male . . . gender identity began to realize that they were different from other girls in the village between 7 and 12 years of age, when they did not develop breasts, when their bodies began to change in a masculine direction and when masses were noted in the inguinal canal or scrotum. These subjects showed self-concern over their true gender. A male . . . gender identity gradually evolved over several years as the subjects passed through stages of no longer feeling like girls, to feeling like men and, finally, to the conscious awareness that they were indeed men. (p. 1234)

Since these initial reports, similar accounts of gender change from female to male have been described in cohorts of subjects from Papua New Guinea (Imperato-McGinley, Miller, et al., 1991), Mexico (Mendez et al., 1995; cf. Perez-Palacios et al., 1984), Brazil (Mendonca et al., 1996), and the Middle East (Al-Attia, 1996; Elsayed, Al-Maghraby, Hafeiz, & Taha, 1988; Hochberg et al., 1996; Taha, 1994), as well as in single case or small series reports (e.g., Cantu et al., 1976; Deslypere, Coucke, Robbe, & Vermeulen, 1985; Imperato-McGinley et al., 1980; Kuttenn et al., 1979; Nordenskjöld, Magnus, Aagenaes, & Kundtzon, 1998; Price et al., 1984; Savage et al., 1980). Moreover, there are two other syndromes—3β and 17β-hydroxysteroid dehydrogenase deficiency—that have an endocrinological natural history very similar to that of 5-ARD, and several reports have described the same type of gender change from female to male (Imperato-McGinley, Peterson, Stoller, & Goodwin, 1979; Mendonca et al., 1987; Rosler & Kohn, 1983; see also Gross et al., 1986).

In some quarters, the reaction to the reports by Imperato-McGinley and colleagues was not to dispute the veracity of the gender change, but the explanation for it (see Zucker & Bradley, 1995, pp. 208-212). Here, I will summarize and provide an update on the empirical status of the literature and of the conceptual issues.

Regarding the Imperato-McGinley cohort, the initial commentaries contained a great deal of discourse about the nature of the gender assignment at birth, particularly among post first-generation probands. For these probands, the family and community had acquired some knowledge about the natural history of the condition, including the physical masculinization that occurred at puberty. Thus, for these probands, it was argued that they were not assigned unambiguously to the female sex and reared as girls, but that the culture created both "third sex" and "third gender" categories (cf. Herdt, 1994) that would guide postnatal socialization. Money (1976), for example, commented on the psychological significance of the "folk prognosis" of guevedoces. Money argued that since the parents rapidly became aware of the impending physical masculinization at puberty that they

> could not confidently assign a newborn hermaphroditic baby as a girl. Even if the birth certificate was assigned female, the parents would know they were rearing a guevedoce who would not look feminine after childhood. Even in the first generation in which hermaphrodites appeared in two families in the family tree . . . before they could be defined as guevedoces, parents would rear their child as one of ambiguous sex, not knowing what to expect at puberty. (p. 872)

Subsequently, Herdt (1990; Herdt & Davidson, 1988) made similar arguments with regard to the social environment of 5-ARD individuals from Papua New Guinea.

The rebuttal to Money by Imperato-McGinley, Peterson, and Gautier (1976) was, quite interestingly, equivocal. On the one hand, they argued that

> Money obviously does not know how the parents raised these children. Our interviews with some of the affected males and their parents indicate that in the first generation, the affected subjects . . . were raised as girls and there was no ambiguity on the part of the parents as to the sex of the child at birth or in early childhood. They believed they were raising a little girl. (p. 872)

On the other hand, Imperato-McGinley et al. (1979) also observed that because the condition had become better recognized, the

> villagers now either raise the subjects as boys from birth, rear them as boys as soon as the problem is recognized in childhood or raise them ambiguously as girls. Now that the villagers are familiar with the condition, the affected children and adults are sometimes objects of ridicule and are referred to as *guevedoce, guevote* (penis at 12 years of age) or *machihembra* (first woman, then man). (p. 1235)

How are we to best interpret the phenomenon of gender change among individuals with 5-ARD? On the one hand, some have read the

data as suggestive of a strong main effect (to use the language of the factorial design) of biological influences on gender identity differentiation. On the other hand, it has been argued that the evidence is more supportive of interaction effects: that is, genetic males with 5-ARD have, despite their ambiguous genitalia at birth, male-typical prenatal masculinization, including putative CNS effects, that predisposes to postnatal behavioral masculinity. The response in the social environment augments this biological predisposition, which is augmented even further by the spontaneous physical masculinization that occurs at puberty. Among 5-ARD individuals raised from infancy as boys, the social environment certainly appears to work in concert with the putative prenatal masculinizing CNS effects (e.g., Farkas & Rosler, 1993; Ivarsson, Neilsen, & Lindberg, 1988; see also Forti et al., 1996; Maes, Sultan, Zerhouni, Rothwell, & Migeon, 1979; Ng et al., 1990; Odame, Donaldson, Wallace, Cochran, & Smith, 1992; Opitz et al., 1972, Cases 6-8; Sinnecker et al., 1996, Cases 5-6, 8-9).

How best to resolve these competing explanations? Here, it would be extremely useful to have natural history data on individuals with 5-ARD who are treated differently, both medically and psychosocially, than in the cultural groups noted above. For example, in the United States and Europe, it is possible that at least some 5-ARD individuals would be raised as girls on the grounds that the external genitalia will not masculinize sufficiently to permit comfortable (heterosexual) sexual functioning (but see Ivarsson et al., 1988). Thus, in accordance with the optimal gender policy (see Table 2), such individuals would be castrated in infancy, receive surgical feminization of the genitalia, and be placed on feminizing hormones at puberty (see, e.g., Opitz et al., 1972; Simpson et al., 1971; Walsh et al., 1974). In this respect, then, the situation would be comparable to the usual course of surgical, hormonal, and psychosocial events for girls with CAH.

Unfortunately, the psychosexual development of 5-ARD individuals treated in this manner has been described rather poorly. The relevant case reports are scattered widely throughout the biomedical literature and reference to gender identity differentiation is often described rather briefly within the context of more detailed accounts of the syndrome itself. To my knowledge, only one prior review has made an effort, albeit in a cursory manner, to describe such individuals systematically (Wilson et al., 1993, pp. 586, 589; see also Carpenter et al., 1990; McCauley, 1990). Because of the importance of such individuals to the debate about gender identity differentiation, I will summarize these reports in more detail here.

In two early reports, both Walsh et al. (1974) and Saenger et al.

(1978) each described two patients with 5-ARD, born in the United States, who were all reared as girls (all were gonadectomized anywhere from infancy to early adolescence); however, no detailed information was provided about their psychosexual differentiation (see also Hodgins, Clayton, & London, 1977; Wieacker, Flecken, & Breckwoldt, 1992). Perhaps the absence of any commentary implies that their gender identity was female.

Donahoe, Crawford, and Hendren (1977, Case 2) described another case, in which the child was first evaluated at 10 days, reassigned to the female sex, and received orchiectomy and surgical feminization of the phallus at around 4 months. At age 6 years, the patient was said to have "no problem with social or psychologic adjustment" as a girl (p. 1049).

Fisher et al. (1978) reported on two sisters, ages 13 and 12 years. The "gender orientation" of the older patient was said to be "definitely female" although she was "very athletic and . . . nicknamed 'superwoman' at school" (p. 654). It was not clear from the report if this patient's nickname derived from her sex-typed behavior, physical masculinization, or both. Information about the younger sibling's gender identity was not provided, but there was no apparent evidence of gender dysphoria. Both sisters were treated surgically and placed on feminizing hormones. Money (1979) anecdotally described another patient so treated who "in teenage . . . is . . . consistently female in gender identity/role" (p. 771). Dewhurst, Chapman, Muram, and Donnison (1983) reported on two sisters, ages 9 and 10 years, respectively, who were reared as girls and who were "well adjusted," presumably with regard to gender identity differentiation in particular and psychosocially in general. Both were gonadectomized at the time of evaluation.

Cantu et al. (1980) reported on an 18-year-old patient from Mexico, reared as a girl, who was referred because of primary amenorrhea, lack of breast development, and postpubertal masculinization. Even in the prior absence of feminizing hormone therapy and bilateral orchiectomy, the patient was reported to have differentiated a female gender identity.

Several other case reports have described patients in adolescence or young adulthood referred for similar reasons. Okon et al. (1980) described two sisters, ages 18 and 17 years, respectively, who were reared as "normal females." At the time of evaluation, both were gonadectomized and the younger sibling's enlarged clitoris was amputated. Presumably, both patients were placed on feminizing hormones, but this was not specifically mentioned in the report. Mauvais-Jarvis, Kuttenn, Mowszowicz, and Wright (1981) reported on two patients, ages 25 and 20 years, respectively. The first patient's "psychosexual orientation" was said to become "definitely male at puberty" (noted above in Kuttenn et al., 1979) whereas

the second patient "remained female" (p. 460). Corrall et al. (1984) reported on a 21-year-old patient, reared as a girl, who "possessed an unequivocally female gender identity" (p. 538). Bartsch, Decristoforo, and Schweikert (1987) reported on a 16-year-old patient, reared as a girl, who was reported to have differentiated a female gender identity. Subsequent to feminizing hormonal therapy and surgery, the patient was reported to have married and to have "regular sexual intercourse" (p. 387). Hurtig (1992) described the psychosexual development of two sisters with 5-ARD, but with scant detail, both of whom received urogenital surgery and estrogen therapy. One of the two girls made a "satisfactory adjustment to her status as a female," but the other girl "rejected her female identity and has taken on the identity of a male, including sexual attraction and orientation to women" (p. 24). Boudon et al. (1995) reported on four patients from three families. All were said to develop a "female sexual identity," of whom three were not treated medically prior to puberty. Lastly, Sinnecker et al. (1996, Cases 2-4) described three patients who also appeared to differentiate a female gender identity, of whom two had had no medical treatment prior to puberty.

Further evidence for variability in gender identity differentiation among patients with 5-ARD comes from a recent study of 16 patients from 10 families in Brazil (Mendonca et al., 1996). In this series, the age at diagnosis ranged from 4-33 years, the majority (12/16) being diagnosed in adolescence or adulthood. Of the 15 assigned to the female sex at birth, 12 requested a change to the male gender, but three did not (for similar variability, see also Al-Attia, 1996; Elsayed et al., 1988). Two of the three patients living as women did not receive feminizing hormonal and surgical treatments until late adolescence and transpired at the patients' request. Of the three living as women, follow-ups were anywhere between mid-adolescence and adulthood (range, 15-32 years). All of these latter patients also reported a heterosexual sexual orientation and had sexual relationships with men.

From an interpretive standpoint, one could argue that a female gender identity differentiated in these patients because the social environment vis-a-vis gender identity (along with the corresponding surgical feminization of the genitalia, etc.) overrode the prenatal hormonal masculinization and its putative CNS effects. But even this argument may not be strong enough because in the Fisher et al. (1978), Cantu et al. (1980), Okon et al. (1980), Mauvais-Jarvis et al. (1981, Case 2), Corrall et al. (1984), Bartsch et al. (1987), and Mendonca et al. (1996) cases, a female gender identity differentiated in the absence of any hormonal or surgical intervention prior to early adolescence or young adulthood. Thus, even under the circumstance of a masculinizing body habitus at

puberty, if not earlier, these patients retained a female gender identity, a finding reminiscent of the female gender identity among late-treated women with CAH (Ehrhardt, Evers, & Money, 1968).

Summary

In summary, the data on gender identity differentiation among patients with 5-ARD are strikingly complex. On the one hand, the phenomenon of gender change first reported on by Imperato-McGinley et al. (1974) has been verified in several additional cohorts of patients, thus constituting an important replication of the original observation (Wilson et al., 1993). On the other hand, differentiation of a female gender identity also occurs in a minority of patients, even in cultures in which there is strong external pressure for the patient to change from living as a female to a male (see, e.g., Al-Attia, 1996; Mendonca et al., 1996; Perlmutter, 1994). To some extent, this latter finding appears to challenge the now prevailing perspective in the literature on the psychosexual natural history of patients with 5-ARD (i.e., that gender change is inevitable subsequent to the masculinizing events that occur around the time of puberty).

There are, however, some important caveats that must be borne in mind. First, the evidence for female gender identity differentiation in some patients with 5-ARD is presented in a rather informal manner, with little information provided about the clinical assessment, and there is a virtual corresponding absence of any formal psychometric assessment tools. Second, little is said about these patients' gender role behavior (which, one might predict, would be shifted in a male-typical direction). Third, the sexual orientation of patients living as women has been poorly described and none of the reports that described this parameter relied on formal interview techniques or psychometrically sound self-report questionnaires.

To account for this variability in gender identity outcome, what are the best candidate explanations? One possibility is that variation in gender identity differentiation is related to the degree of prenatal hormonal masculinization of the CNS and, perhaps, to the degree of postnatal physical masculinization at the time of puberty and beyond (see Sinnecker et al., 1996). A second possibility is that the variation is accounted for by the classical sex of rearing hypothesis originally advanced by Money et al. (1957): For those patients who are unequivocally reared as females, a female gender identity ensues; for those reared ambiguously (along with the corresponding pubertal physical masculinization), a gender change ensues; for those reared as males from infancy onwards, a male gender identity ensues. Unfortunately, as

I have argued elsewhere (Zucker & Bradley, 1995), this interpretation has been hampered by the absence of good prospective data and the reliance on post hoc interpretations of the eventual outcome. As I also argued elsewhere (Zucker & Bradley, 1995), what is urgently needed is a psychometrically sound method of assessing the sex-of-rearing construct, in which observers can agree whether the affected individual is being raised unequivocally as a girl or as a boy or, alternatively, somewhere in between these two traditional modes of gender rearing.

Here, I would like to introduce a third interpretation of the data, based on Bem's (1996) recent theoretical analysis of the developmental factors involved in the differentiation of sexual orientation, which considers both between-sex and within-sex variation in sexual orientation development. In the model, Bem argues against a purely biological or "essentialist" account of sexual orientation development (i.e., in accounting for the fact that most men are attracted sexually to women and most women are attracted sexually to men—a between-sex difference—as well as for within-sex variation in sexual attraction). Rather, Bem argues for a biological account that predisposes individuals to show variation in aspects of temperament (e.g., activity level and aggression) which, in turn, is associated with some of the most common sex-dimorphic behaviors that distinguish boys from girls (e.g., playmate preferences, gender role interests, and so on).

Regarding within-sex variation in sex-dimorphic behavior, it is now well-established that, on average, homosexual men and women show more childhood cross-gender behavior than heterosexual men and women (Bailey & Zucker, 1995). Bem argued that for children who grow up in cultures that emphasize the differences in gender role behavior between boys and girls (most cultures? all cultures?), those with "deviant" gender role behaviors experience themselves as feeling different from same-sex peers. Similarly, children with more ordinary gender role behavior experience themselves as feeling different from opposite-sex peers. In Bem's analysis, by middle childhood, heightened nonspecific autonomic arousal occurs in relation to that class of peers from whom one feels different which, in turn, eventually becomes sexualized: "the exotic becomes erotic." Thus, in this model, it is the pattern of gender role behavior that is the mediating variable that accounts for whether a particular child will eroticize same-sex or opposite-sex conspecifics.

Can we extend this model to variations in gender identity differentiation in individuals with 5-ARD (and to other intersex conditions)? I believe that we can in the following manner. From a phenomenologic perspective, it is clear that many 5-ARD patients reared as girls show masculine role interests during childhood. Like the behavioral mas-

culinity of girls with CAH, many authors attribute this gender role preference to the influence of prenatal androgens. Such gender role interests likely contribute to the 5-ARD patient's sense of being different from other "girls," which may be accentuated by any corresponding awareness of genital differences. It is also clear that this sense of being different is accentuated further by the physical masculinization that occurs with the onset of puberty.

The corresponding nascent awareness of sexual feelings towards other "girls" likely further augments the 5-ARD patient's sense of being different. In cultures, or subcultures, in which homoerotic feelings are taboo, then a reasonable solution is to change genders, which would then "normalize" the sexual attraction to same-sex peers: one is heterosexual, not homosexual. My reading of the literature on 5-ARD suggests that there has been an underappreciation of the role of what is commonly referred to in other literatures as internalized homophobia. In other words, there may well be a complex transactional interaction between the 5-ARD patient's sense of difference with regard to both "deviant" gender role behaviors and sexual feelings, and both contribute to the gradual change in gender identity from female (or an ambiguous gender identity) to male. One prediction that follows from this analysis is that, for 5-ARD patients who do not grow up in a culture in which homoerotic feelings are subject to strong sanctions, they will not necessarily feel the "need" to change their gender, but rather will adopt a homoerotic sexual orientation. In this regard, it would be important to better ascertain the sexual orientation of 5-ARD patients who appear to have differentiated a female gender identity. Unfortunately, these data are sorely lacking in the case reports described earlier, and we do not have a clear sense if the proportion of 5-ARD patients living as women are disproportionately homoerotic in their sexual orientation. If they are, it would suggest that the relatively normal prenatal masculinization in such patients has a stronger influence on sexual orientation development, perhaps mediated by the mechanisms proposed by Bem (1996), than it does on gender identity development.

Partial Androgen Insensitivity Syndrome

According to Perez-Palacios et al. (1987), partial androgen insensitivity syndrome (pAIS) is apparently the least common of the androgen resistance syndromes. As the name implies, there is only partial resistance to androgens at the cellular (or postcellular) level; hence, there is a partial masculinization of the external genitalia (see, e.g., Assael, Lancet, & Shani, 1976; Mark et al., 1983). Because there is variation in the degree of androgen resistance, the appearance of the genitalia

varies and, therefore, so does gender assignment. Even in so-called familial pAIS (Reifenstein's syndrome), the severity of the condition varies, so some newborns are assigned as boys, others as girls (Money & Ogunro, 1974). Because of familiality in pAIS, the condition is sometimes anticipated in subsequent births and decisions about gender assignment may thus be influenced by the course of events in affected older siblings (see, e.g., Beheshti, Hardy, Churchill, & Daneman, 1983).

Like cAIS, pAIS shows an X-linked pattern of inheritance, although it has been noted that the two conditions never occur in the same pedigree (Morris & Mahesh, 1963; Perez-Palacios et al., 1987), which is one reason that the two conditions have been considered to be distinct entities. Other studies have reported that cAIS and pAIS have distinct underlying molecular abnormalities, which likely account for the variation in androgen action at the cellular level (see, e.g., Brown et al., 1993; Medina, Chavez, & Perez-Palacios, 1981; Quigley et al., 1995) although Warne and Zajac (1998) have argued that this is not always the case. Regarding differential diagnosis, it has been further established that pAIS is, in fact, distinct from 5-ARD. For example, in patients with pAIS, administration of human chorionic gonadotropin does not induce phallic growth despite normal testosterone synthesis, normal 5-α reductase activity in the genital skin fibroblasts, and normal DHT levels in blood (e.g., Mark et al., 1983).

Gender Identity Differentiation

What do we know about the gender identity development of patients with pAIS? Morris and Mahesh (1963) reported on one patient, age 19 years, reared as a girl, and noted to have a "female . . . psychological orientation" (p. 732; presumably, meaning a female gender identity and a heterosexual sexual orientation), but no details were provided. Teter and Boczkowski (1966) reported on another patient, age 21 years, with a hypertrophied clitoris who was reared as a girl. Gender identity was female and sexual orientation was apparently heterosexual. Madden, Walsh, MacDonald, and Wilson (1975) reported on a third patient, age 26 years, also reared as a girl. Details about her gender identity development were not provided and no information was given about her sexual orientation. Assael et al. (1976) reported that their patient was reared as a girl and differentiated a female gender identity; in adulthood, however, the patient became psychotic, which apparently remitted following orchiectomy and after the physical signs of marked virilization (e.g., facial hair) were reduced. Lastly, Quattrin, Aronica, and Mazur (1990) reported on a 21-year follow-up of one patient, initially assigned male but changed to female at age 13 days, with subse-

quent surgical feminization and gonadectomy at 4 months. The patient and parents had fairly regular counselling throughout childhood and adolescence. Although the patient apparently displayed elements of girlhood tomboyism (p. 706), a female gender identity differentiated. No information was provided about the patient's sexual orientation.

In contrast to these five case reports, Gooren and Cohen-Kettenis (1991) reported on a patient assigned at birth to the male sex because of an enlarged clitoris, but reassigned five days later and "reared as a girl." At age 30, their patient requested sex reassignment following a long history of masculine gender role interests and behavior and a "heterosexual" sexual orientation (i.e., an attraction to biological females).

To my knowledge, there are only two group studies of patients with pAIS. Money and Ogunro (1974) reported on a series of 10 patients—eight were reared as boys, one as a "hermaphroditic girl," and one as a girl. In this series, the medical diagnosis was not made until adolescence or adulthood. At the time of last follow-up, the median age was 24 years (range, 13-39 years). Based on a variety of descriptive and qualitative data, gender identity was judged to differentiate in accordance with the gender of rearing.

Slijper et al. (1998) assessed eight patients with pAIS, with a mean age of 11.5 years (range, 6-23 years). In contrast to the sex assignment pattern in Money and Ogunro's (1974) series, seven were assigned to the female sex at birth. This appears largely a result of the Slijper et al. clinic team following the optimal gender policy described earlier (Table 2). Of the seven patients assigned to the female sex, three were reported to display "deviant" gender role behavior (cf. Crawford, 1970), at least by their parents, including one who met criteria for GID. Details on the assessment of the girls' gender role behavior was not provided; however, Slijper et al. commented that the girls' "boyish conduct [cross-gender behavior] was perceived as an indication that the decision to assign the female sex had been wrong. In particular, the wild, rough play of these [girls] was difficult for their parents to regulate" (p. 137).

Summary

Compared to the psychosexual literature on genetic females with CAH, the psychosexual data on pAIS are surprisingly sparse. The case report literature is patchy at best, with minimal information provided about the patients' psychosexual differentiation. The two group studies had very different distribution patterns regarding gender assignment, which was likely due to cohort effects in terms of the policy of psychosocial and medical management (Money & Ogunro, 1974; Slijper et al., 1998).

For patients reared as girls, one can glean from the available cases

evidence for a common pattern of girlhood tomboyism, which appears comparable to the data on genetic females with CAH. Unfortunately, the behavioral data are much poorer in quality for patients with pAIS than with CAH. Nonetheless, in both syndromes, prenatal androgenization may well be the active biological mechanism that accounts for the behavioral masculinity (Collaer & Hines, 1995). In CAH, prenatal androgenization is clearly elevated compared to unaffected females. In pAIS, it is not clear if prenatal androgenization would be comparable to unaffected males, but it is, no doubt, greater than in biologically normal females.

The data on gender identity suggest a mixed pattern, with some patients differentiating an uncomplicated female gender identity, but others developing a conflicted gender identity, including a change to the male gender later in life. If the Slijper et al. (1998) data are valid, the presence of a formal GID in one of seven patients in childhood is obviously well above the likely prevalence of GID in the general population.

In my own clinical experience, I have assessed three youngsters with the diagnosis of pAIS, all of whom were assigned to the female sex in infancy—in two cases, the assignment was made after a brief trial of exogenous testosterone treatment, which did not result in adequate phallic growth. These youngsters likely represent a biased sample because they were referred, in part, because of concerns about their gender identity development. Moreover, in two of the three cases, the parents remained uncertain about the "correctness" of the gender assignment.

On standardized assessment measures, these youngsters generally showed evidence for masculine gender role preferences, illustrated in Table 3 with results from a sex-typed behavioral free play task. These youngsters also expressed some confusion about their gender identity. For example, one 8-year-old girl (Verbal IQ, 100; Performance IQ, 126) provided the following responses on a structured gender identity interview schedule (Zucker et al., 1993):

Interviewer (I): Are you a boy or a girl?
Child (C): Girl.
I: Are you a boy?
C: No.
I: When you grow up, will you be a mommy or a daddy?
C: Mommy.
I: Could you ever grow up to be a daddy?
C: No.
I: Are there any good things about being a girl?
C: Yes.
I: Tell me some of the good things about being a girl.

C: Don't be shy, wear dress, cut your hair long.

I: Are there any things that you don't like about being a girl?

C: Yes.

I: Tell me some of the things that you don't like about being a girl.

C: I can't play with Nintendo. I can't play with boys.

I: Do you think it is better to be a boy or a girl?

C: Boy.

I: Why?

C: Because you get to play with Nintendo, get to play with Sega and get to play with guns.

I: In your mind, do you ever think that you would like to be a boy?

C: Yes.

I: Can you tell me why?

C: Because you could play lots more things than girls, you can buy whatever you want, when you get married you don't need to do anything.

I: In your mind, do you ever get mixed up and you're not really sure if you are a boy or a girl?

C: Sometimes.

I: Tell me more about that.

C: No thanks.

I: Do you ever feel more like a boy than like a girl?

C: Yes . . . a little bit more and . . . because I could drink Coke [Coca-Cola™] and more, I could eat lots of chips.

I: You know what dreams are, right? Well, when you dream at night, are you ever in the dream?

C: Yes.

I: In your dreams, are you a boy, a girl, or sometimes a boy and sometimes a girl?

C: A boy. . . . Well, I dream about the Power Rangers and the Mystery Knights. I dream about when I was in the Power Rangers, I was Silver Ranger, I could beat everyone up.

I: Do you ever think that you really are a boy?

C: A little bit, not too much.

I: Tell me more about that.

C: No thanks.

Thus, on this interview, this youngster could correctly identify herself as a girl, not a boy, but showed evidence of some desire to be a boy, which, at least on the surface, was closely intertwined with her masculine gender role preferences and the belief that boys could do more things. There was also evidence, both from the interview schedule and additional information, that being a boy was associated with more power. Unfortunately, her

parents' continued ambivalence and resistance to understanding how their daughter felt about herself precluded further clinical evaluation.

The Money, Devore, and Norman (1986) Study

A study by Money et al. (1986), which likely included cases of 5-ARD and pAIS, needs to be described separately because the sample was initially generated "prior to the era of diagnostically subtyping male hermaphroditism" (pp. 179-180) on the basis of specific endocrine profiles or other parameters. Money et al. studied 32 genetic male patients assigned to the female sex in infancy and then followed-up at a mean age of no younger than 18 years (range not specified). Of these, 26 patients were deemed "regular" referrals (i.e., they were seen through the Johns Hopkins pediatric endocrine clinic for routine long-term care and follow-up). The remaining six patients were deemed "special" referrals, as they came from other clinics or hospitals because the patient was requesting a sex reassignment (age of request not specified).

Money et al. (1986) examined several variables as potential correlates of the request for sex reassignment and/or a homosexual/bisexual sexual orientation. Across both types of referrals, nine patients were requesting sex reassignment and had a homosexual or bisexual sexual orientation (in relation to the patient's genetic sex) and six others were homosexual or bisexual but were not gender dysphoric. These two types of "gender transpositions" were associated with three variables: presence of a childhood history of stigmatization (both at home and in the community) pertaining to the physical intersex condition and age at which feminizing surgery and gonadectomy occurred. In the gender transposed group, feminizing surgery of the genitalia occurred at 3

Table 3
Proportion of Masculine (M) and Feminine (F) Play on a Free Play Task for Three Girls with Partial Androgen Insensitivity Syndrome

		Trial 1		Trial 2		Trial 3	
		M	F	M	F	M	F
Subject 1 (5.8 years)		.92	.06	.17	.04	.99	.00
Subject 2 (9.4 years)		.76	.05	.00	.75	.95	.04
Subject 3 (8.1 years)		.99	.00	.99	.00	.99	.00
Control Males	*M*	.83	.06	.67	.10	.82	.06
(*N* = 85)	*SD*	.19	.13	.29	.16	.24	.12
Control Females	*M*	.24	.66	.13	.62	.26	.57
(*N* = 15)	*SD*	.26	.25	.18	.22	.26	.28

Note. Task modified from Rekers and Yates (1976), as described by Zucker, Doering, Bradley, and Finegan (1982). Trial 1 (5 min) contains masculine and feminine toys; Trial 2 (5 min) contains masculine and feminine dress-up apparel; Trial 3 (10 min) contains both sets of stimuli simultaneously.

years or later. The presence of gender transpositions was not associated with other variables, such as initial uncertainty about the infant's sex and the presence of gross family behavioral pathology.

In interpreting the pattern of findings, Money et al. (1986) considered in particular the delay of surgical feminization, both with regard to its potential impact on gender self-representation and on the reaction of significant others, such as parents and peers (cf. Meyer-Bahlburg et al., 1996):

> Stigmatization is more closely related to postponement of surgical feminization . . . so that the child looks genitally abnormal. She becomes subject not only to stigmatization by others, but also to self-stigmatization. In a world dichotomized by sex, if she does not look completely like a girl, then the only other alternative is that she must look like a boy, or a half-boy, half-girl. Self-stigmatization leads the way to a self-generated development of a gender transposition, masculinizing all aspects of the girl's gender-identity/role. (pp. 178-179)

Micropenis Syndromes

According to Feldman and Smith (1975), the mean stretched length of a newborn male's penis is 3.5 cm (*SD* = .35). The diameter is 1.1 cm (*SD* = .10). How does one decide that a penis should be called a micropenis? Money, Mazur, Abrams, and Norman (1981) used the criterion of a stretched length as no longer than 2 cm (i.e., 4 *SD* below the mean, which corresponds to a percentile value at or below the 3rd percentile).

As noted by Smith (1977) and Lee et al. (1980), a micropenis (or, at least an underdeveloped one) occurs in several known syndromes (e.g., pAIS), but it can also be idiopathic. Apart from etiological considerations, the birth of a newborn infant with a tiny penis, particularly when it does not enlarge in response to exogenous testosterone treatment, results in debate about whether the infant should be raised as a boy or a girl (Van Wyk & Calikoglu, 1999).

In this section, I will review data on gender identity differentiation among XY patients with micropenis that is not associated with other forms of intersexuality, such as pAIS or 5-ARD. The extant literature indicates marked inconsistency in psychosexual management: Some of these babies have been raised as boys, others as girls. For those reared as girls, the management plan includes surgical feminization of the genitalia and administration of feminizing hormones at puberty.

Gender Identity in Patients Reared as Boys

Hinman (1972) reported on 20 cases, noting that "in all cases directly under the author's control the decision was for repair rather than sex

conversion" (p. 501); however, details on psychosexual development, including gender identity differentiation, were not provided.

Money and Mazur (1977) reported on one patient, who was referred at age 9 months for micropenis (1.5 cm) and undescended testicles. The patient was then lost to follow-up until the age of 23 months, at which time the stretched penis remained at 1.5 cm. During this period, the child was adopted, and there had been some responsiveness to exogenous testosterone cream. It appeared that the infant had been raised as a boy, as the adoptive parents "were habituated to treating the child as a boy, and his gender identity/role was already well advanced in its differentiation, as illustrated in the application of gender dimorphic nouns and pronouns in self-reference" (p. 192). Continued exposure to testosterone application resulted, after 2 months, in a stretched penis length of 2.4 cm, but it did not enlarge thereafter. At age 9, the boy was receptive to wearing a prosthetic phallus made of nontoxic, flexible plastic, which was judged to enhance the youngster's "self-esteem and self-confidence as a male" (p. 193).

Money (1984b) provided a particularly detailed case report through young adulthood on another patient reared as a boy. In childhood, the patient tended to affiliate with girls and avoided competitive sports although, in other respects, there were no gross signs of behavioral femininity. This patient struggled for years with feelings of inferiority related to his small penis, which was associated for a considerable period of time, beginning in late childhood, with fantasies of sex-reassignment and then later on with severe depression and suicidal urges. As this patient lucidly described, "If you ever let parents who have a baby with a microphallus raise their kid as a male, you're a damn fool" (p. 363). After a period of heterosexual behavior in late adolescence, the patient reported stronger homoerotic attractions and, by young adulthood, had differentiated a homosexual sexual identity and greater sexual satisfaction in having sex with other men than with women.

Money, Lehne, and Pierre-Jerome (1985) reported adult follow-up (*M* age, 25 years; range, 22-31) of nine youngsters with micropenis (of diverse etiology) raised as boys. Money et al. noted that topical application of testosterone propionate resulted in a "partial and localized pubertal-type of growth spurt," but, by adolescence and adulthood, "the penis permanently resume[d] a disproportionately small dimension relative to the rest of the body" (p. 29). Thus, boys "with a micropenis [grow] up to be confronted with the teenaged and young-adult challenges of coping with a micropenis erotosexually and with respect to overall behavioral health" (p. 29).

Five patients appeared to differentiate an uncomplicated male gen-

der identity, with a corresponding childhood history of male-typical behavioral masculinity, and all had a heterosexual sexual orientation. The remaining four patients, including the one described above (Money, 1984b), were less conventionally masculine and/or feminine during childhood, but appeared to have a male gender identity. Three of these four patients differentiated a homosexual sexual orientation; the one with a heterosexual sexual orientation had a co-occurring sadomasochistic paraphilia.

Reilly and Woodhouse (1989) provided follow-up data on 20 patients with micropenis of diverse etiology, including 6 who also had hypospadias: 8 were still prepubertal (2 of whom were severely mentally retarded) and 12 were between 17 and 43 years old. An additional 30 patients were unavailable for follow-up.

Based on Schonfeld's (1943) age-graded norms, the penile length of the prepubertal group at follow-up was at or below the 10th percentile (range, 2-5 cm), except for one with a stretched length of 7.2 cm. It was reported that "all parents in this group considered their children as normal boys . . . . but they expressed concern about [the] size of the penis, wondering if sexual function in adulthood would be a problem" (p. 569). One additional patient, lost to follow-up, was reported to have a lot of psychosocial difficulties secondary to the micropenis and nonpalpable testes.

Of the 12 postpubertal patients, stretched penile length was below the 10th percentile (range, 4-10 cm) although "the 3 largest penises look normal for body size and only measurement revealed the deficiency" (Reilly & Woodhouse, 1989, p. 571). Half of these patients recalled childhood experiences of being teased; the other half did not. All patients "felt male" although one was reported to lack "total confidence about it" (p. 571). Nine of the patients had had sexual intercourse and seven were married or co-habitating. It was noted that "the group was characterized by an experimental attitude to positions and methods" (p. 571) in order to accommodate the constraint imposed by the size of the penis.

Reilly and Woodhouse (1989) argued that parental attitudes were associated with how well this subgroup adapted to having grown up with a small penis although no formal statistics were used to demonstrate this putative relation (for a similar study, see Bin-Abbas, Conte, Grumbach, & Kaplan, 1999).

Gender Identity in Patients Reared as Girls

Money et al. (1981) provided descriptive data on the initial decision-making process in assigning 14 newborns with micropenis to the female sex. Follow-up data (range, 10-25 years) on 3 patients showed that a female gender identity had differentiated without known complications.

Subsequently, Money (1984a) provided a particularly detailed case report through young adulthood on another patient reared as a girl. Gender identity was female and sexual orientation was heterosexual.

Money and Norman (1988) reported on four patients with micropenis reared as girls (age at last follow-up ranged from 10-18 years). In this series, there was a co-occurring history of either learning disability or the CHARGE syndrome (coloboma, heart disease, atresia choanae, retarded growth, genital hypoplasia, and ear anomalies). Eight other patients reared as girls were lost to follow-up. All four patients appeared to differentiate a female gender identity, although their general psychosocial adaptation was complicated by their co-occurring developmental problems.

Summary

The data on gender identity differentiation among patients with micropenis suggest a great deal of variability and, if these reports are accurate, largely a function of the gender of rearing. There are, however, several limitations to these reports. First, it should be recognized that the number of reports is relatively few in number if one compares them to some of the other syndromes, such as CAH and 5-ARD (Meyer-Bahlburg, 1999a). Second, cases of "pure" micropenis are relatively rare, as the condition often occurs in concert with other signs of physical intersexuality, rather than in isolation. Third, the rigor of assessment is rather poor in these studies, with reports of outcome largely confined to clinical description, rather than reliance on standardized psychometric assessment instruments or structured interview schedules. Lastly, several of these reports had a very high selection bias, with many patients unavailable or lost to follow-up (e.g., 60% in Reilly & Woodhouse [1989] and 67% in Money & Norman [1988]). Thus, generalization about outcome must be made with great caution.

Penile Agenesis

Penile agenesis (aphallia) is an intersex condition in which the penis fails to differentiate, although the scrotum is normally formed and contains the testicles (Kessler & McLaughlin, 1973; Richart & Benirschke, 1960). Prenatal androgenization, including putative CNS effects, is apparently normal. The condition is quite rare although conjectures about prevalence have varied wildly, from 1 in 50,000 (Young, Cockett, Stoller, Ashley, & Goodwin, 1971) to 1 in 10-30 million live births (see Kessler & McLaughlin, 1973)! Mortality is high because of associated urinary and gastrointestinal tract abnormalities (see, e.g., Farah & Reno, 1972; Kirshbaum, 1950). Accordingly, it is not surprising that

there are very few studies of affected patients with regard to psychosexual differentiation.

Gender Identity Differentiation

The literature suggests that, when reared as a boy, a male gender identity differentiates, albeit at times with complications. Stoller (1965), for example, reported on two cases in some detail. At age 4, the first patient was judged to have a male gender identity, with typically masculine gender role interests. The patient's mother described his behavior as follows:

> He likes to wrestle and box. He likes all kinds of sports . . . and he told me that he wants to be a wrestler . . . when he is big. He plays with dolls, but when he does, he is the father and his sister is the mother. . . . You can give him a little stick and send him out to play, and he can make everything out of that stick you can imagine. . . . [Other children] know he has a catheter on. They have seen it and they accepted it and treat him like he was a boy. . . . He dislikes anything that looks girlish to him . . . he wants everything boy's. . . . Sometimes he is Superman. (pp. 209-210)

The boy's step-father noted that his favorite game was "Gas Station" (mimicking the father's occupation as a manager of a gas station), using a "cat's tail as a gasoline pump." The youngster was also quite attached to his indwelling catheter, which he often displayed proudly to others.

In the second case, first seen at age 15 years, the patient was also reared as a boy, but in a family environment in which his parents were gauged to be distant and indifferent. Since the age of 1.5 years, he had numerous surgical procedures, including a phalloplasty described as a "monstrosity of unearthly appearance." Although the patient had differentiated a male gender identity, he was severely paranoid, particularly when under stress, describing himself as "the grandson of God and maybe I am the Messiah." Since age 7, he was reported to have engaged in sadistic homosexual activity, including a game called "the Pull," in which each of the two partners pulled forward on the other's penis in order to produce pain (the patient himself, however, did not experience pain and was known by his friends to be faking it). The patient was also reported to be preoccupied with knives.

Drury and Schwarzell (1935) reported on a 13-year-old boy who appeared to have a male-typical gender identity. Kessler and McLaughlin (1973) reported on two cases also reared as boys. By late childhood, the first patient was judged to have "no problem with gender identity" (p. 228). In the second case, the patient at age 22 years was judged to have a male gender identity, but with severe psychiatric problems and was reported to be homosexual. Lisa et al. (1973) reported on an 11-year-

old boy, whose "role as that of a boy was clearly defined" (p. 328). Gautier, Salient, Pena, Imperato-McGinley, and Peterson (1981) reported on two cases, but only one was old enough to assess gender identity which, at age 6 years, was judged to be male. Oesch, Pinter, and Ransley (1987) reported on six cases, one of whom was reared as a boy. At age 9 years, there was no mention of gender identity problems, but the result of numerous surgical attempts at phalloplasty was described as "not very satisfactory cosmetically and functionally" (p. 172). In a remarkable case, Rosenblum and Turner (1973) reported on a 45-year-old male who grew up on a farm in rural South Carolina. He was seen medically for the first time at this age complaining of dysuria. Upon physical examination, the patient was noted to lack a penis. The patient was married and appeared to be exclusively heterosexual.

The optimal gender management policy has been prescribed in other cases, in which a female gender reassignment was made. Pohlandt, Kühn, Teller, and Thomä (1974) reported on one patient, first seen at 2.5 years, at which time the sex assignment was changed from male to female. Follow-up at age 5.5 years indicated that "the sex identification was female" (p. 2166). Skoog and Belman (1989) reported on another patient reared as a girl from the age of 14 days. At age 8, the patient was described as "an apparently well adjusted . . . girl" (p. 589). Two other patients were too young to report on their psychosexual differentiation. Young et al. (1971) reported on two cases in which the decision was made to raise the infants as girls (ages not specified), but follow-up data were not reported. Oesch et al. (1987) reported on four patients reared as girls. Cases 3 and 6 appeared to be too young to report information on gender identity development; Case 2 at age 9 years was apparently normal (nothing in the report indicated otherwise), whereas Case 4 was described as having "severe behavior problems" (p. 172) at the time of puberty, but details were not provided. Stolar et al. (1987, Case 2) reported on a 13-year-old patient, with an apparent female gender identity. Evans, Erdile, Greenberg, and Chudley (1999) reported on four patients, only one of whom survived. At age 8 years, there was no mention of any problems in the patient's gender identity development although the youngster was noted to be of "borderline low-normal intelligence" and had been recently diagnosed with attention deficit disorder. Several other case reports noted that there was a female gender assignment, but there was no information on follow-up (e.g., Azpiroz, 1971; Bruch, Meuli, & Harrison, 1996; Glüer, Fuchs, & Mildenberger, 1998; Johnston, Yeatman, & Weigel, 1977; Stolar et al., 1987, Case 1; Talwar & Kapoor, 1988).

Dittmann (1998) provided a particularly detailed case report in which the patient was given a female name at the age of 2 months. At age 4

months, however, the patient was given a boy's name because of his genetic sex and, at age 16 months, was legally registered as a male. At age 3, it was suggested by referring physicians that the patient might better be raised as a girl, and the patient was admitted to hospital for further evaluation. During this evaluation, a gender re-assignment was recommended, which occurred shortly before the patient turned 4, at which time gonadectomy was also performed. Prior to age 7, the patient was judged to be "content with her female role" (p. 259). Shortly thereafter, however, the patient was noted to have "serious doubts" (p. 260) about her female gender identity. Yet, as late as age 15 years, the patient was said to be "convinced . . . that the decision to rear her as a girl had been correct . . . [and] she . . . does not wish to be a boy" (p. 260). By late adolescence, however, the situation changed, and the patient began to live as a man, which maintained itself through the last follow-up at 27 years. The patient was attracted sexually to females and married a woman at the age of 24 years.

Summary

It is obvious that the literature on penile agenesis and psychosexual differentiation is quite patchy, both with regard to standardized assessment during childhood and long-term follow-up. The extant data suggest the following provisional conclusions: (a) Like the other intersex syndromes reviewed so far in which there are either male-typical levels of prenatal androgen exposure (e.g., as in 5-ARD) or levels of prenatal androgen exposure that, at minimum, are greater than in normal females (e.g., as in CAH in genetic females), childhood gender role behavior is shifted in the direction usually observed in unaffected males; (b) A male gender identity can differentiate in the absence of a penis, particularly when the parents appear to have no uncertainty that the decision to raise the child as a boy was the correct one (e.g., Stoller, 1965, Case 1). Regarding this observation, the conclusion is similar to what was reached in cases of micropenis in which the gender assignment was that of a boy; (c) The long-term implications of growing up without a penis remain unclear. It would not be surprising that self-esteem issues related to one's sexual competence during adolescence and adulthood will be variable, as occurs in other conditions, such as hypospadias (e.g., Mureau, Slijper, Nijman, et al., 1995; Mureau, Slijper, Slob, & Verhulst, 1995; Mureau, Slijper, Slob, Verhulst, & Nijman, 1996). In this regard, assessment of general psychological functioning and social support networks will likely be of great importance in accounting, at least in part, for variations in sexual adjustment.

Unlike the situation with 5-ARD and in the micropenis syndromes, in which there are some long-term follow-up data regarding "successful"

gender identity differentiation as a female, none of the case reports of patients with penile agenesis raised as girls have provided information on gender identity status in adulthood, with the exception of Dittmann's (1998) case report, in which there was a patient-initiated change from female to male.

Cloacal Exstrophy

Cloacal exstrophy, which occurs in both genetic males and females, is a complex disorder of embryogenesis involving the genitourinary and intestinal tracts (Howell, Caldamone, Snyder, Ziegler, & Duckett, 1983). It includes exstrophic bowel of the ileocecal region, imperforate anus, two exstrophic hemibladders, omphalocele, vertebral anomalies, and anomalies of the external genitalia. Myelomeningocele and scoliosis are common associated anomalies. Prior to 1960, surgical interventions were usually not attempted and the affected newborn was left to die (Rickham, 1960). Over the past 4 decades, advances in pediatric surgery have resulted in a more optimistic approach to management and survival rates now exceed 80% (Howell et al., 1983).

In genetic males with cloacal exstrophy, the configuration of the external genitalia is often poorly differentiated or grossly anomalous (e.g., the penis is split and the two halves are widely separated), if not entirely absent. In bladder exstrophy, the external genitalia are less severely affected, and penile reconstruction is the usual course of medical management, although not always (see, e.g., Mesrobian, Kelalis, & Kramer, 1986; Reiner, Gearhart, & Jeffs, 1999). Although such youngsters appear to differentiate a male gender identity without notable complications, there is some evidence, not particularly surprising, that during adolescence and adulthood, such individuals experience a great deal of uncertainty about their sexual functioning and in initiating intimate sexual relationships (e.g., Reiner et al., 1999).

When the reconstruction of the genitalia is impossible, particularly in the case of cloacal exstrophy, the most common management policy has been to recommend a female sex assignment (Tank & Lindenauer, 1970; Zwiren & Patterson, 1965). Thus, from a psychosexual perspective, this strategy is of interest because, like in penile agenesis, prenatal androgenization, including putative CNS effects, is apparently normal.

Gender Identity Differentiation

What do we know about the gender identity development of genetic males with cloacal exstrophy or bladder exstrophy who have been raised as girls? Unfortunately, not very much; for example, several reports in the literature make mention of sex and gender reassignment, but no informa-

tion on psychosexual outcome was provided (e.g., Howell et al., 1983).

Hayden, Chapman, and Stevenson (1973, Case 1) reported on a genetic male sex-reassigned right after birth, with removal of the left gonad at 7 months. At around age 3, the right gonad descended, which was removed just prior to age 5 years, a time when the youngster was physically well enough to begin kindergarten. At age 5, Hayden et al. commented on the parents' apparent ambivalence in adapting to the gender assignment:

> The psychosocial problem causing the most difficulty at the present time is the parents' adjustment to the arbitrary sex assignment for their child. When the mother called to describe the descent of the testis, her confusion was evident. The multiple determinants of sex, including chromosomal, gonadal, hormonal, and psychological had been discussed with the parents, and they seemed to intellectually understand the plan to override the cellular and gonadal maleness of this child by rearing her as a female with plastic surgery and hormonal intervention as she grew older. That emotionally they have not been able to do this is evident from an increasing tendency to dress the child in boyish clothes and to call her by a masculine nickname. At the time of the removal of the remaining gonad this whole problem was reviewed with the parents, and hopefully with continued counseling they will be able to adjust to a pattern of rearing this child as a girl. Retrospectively, it may have been an error to inform these parents about the chromosomal and gonadal findings. The difficulties that have arisen in this area are in part iatrogenic and point to the hazard that the multiple disciplinary approach may compound confusion unless one member of the team is responsible for relaying and interpreting the mass of information gained. (p. 883)

Although Hayden et al. provided a nice illustration of parental uncertainty, it would have been helpful to know even more, including whether or not the child's gender role behavior itself was contributing to parental uncertainty. On this point, no information was provided.

In another report, Stein et al. (1994) noted that one male (out of a total of 31) with bladder exstrophy, with multiple other malformations and a "lower IQ," had been castrated at age 4 years and "raised as a girl." After puberty, "the patient decided to change his sexual identity and name legally but no further operation was performed" (p. 1414). Feitz, Van Grunsven, Froeling, and de Vries (1994) reported on another male (out of a total of 11) with bladder exstrophy who

> was kept home since birth and . . . raised as a girl. At the age of 52 years he presented for treatment after the death of both parents. After extensive psychological examinations he underwent urinary diversion . . . and reconstruction as a man. He presently demonstrates male behavior. (p. 1418)

In both reports, no further details were provided about the life histories of the two patients, including information relevant to their psychosexual rearing.

Reiner (1997c) reported preliminary impressions on a cohort of 15 genetic males castrated at birth "who are reared unequivocally as females" (p. 225; see also Reiner, 1997a, 1997b). Prior to the age of 12 years, two patients "declared themselves to be males" and three others "spontaneously described themselves as the most masculine girl they know" (1997c, p. 225). No other details were provided.

In another report, Montagnino et al. (1998) reported on the general adjustment of 29 exstrophy patients (*M* age, 7.8 years; range, 3-18), including 10 genetic males, 4 of whom were raised as girls. Although these four patients did not differ in their general adjustment from the other patients, no specific information was provided regarding their psychosexual adaptation. Perhaps it is reasonable to conclude that if any of these four patients were severely gender dysphoric, it would have been commented on. To my knowledge, there are two additional series of cloacal exstrophy patients, in which a subgroup of genetic males were sex-reassigned but, in both cases, detailed information about psychosexual differentiation is lacking (Kodman-Jones & Zderic, 1999; Mitchell, 1999) although Mitchell alluded to the fact that some of the patients reared as females were unhappy living as girls/women.

Lastly, Meyer-Bahlburg, Ehrhardt, Pinel, and Gruen (1989) reported on two genetic males (ages 8 and 12 years) with cloacal exstrophy who were sex-reassigned shortly after birth. Based on standardized psychometric tests, both patients were reported to have "marked shifts in gender-role behavior" (i.e., in the masculine direction), but "current gender identity appeared female."

I have also assessed one 12-year-old genetic male with cloacal exstrophy (IQ = 100), who was sex-reassigned in the newborn period. Because of co-occurring physical anomalies, the patient was confined to a wheelchair. Her various physical problems had necessitated about 18 different surgical procedures during her growing-up years. Although my patient knew a great deal about her various physical problems, it should be noted that she did not know that she was a genetic male and that a decision had to be made about her gender assignment in infancy. I was asked to see this youngster for a couple of reasons. First, she had recently had a dream in which she was a boy, and her mother wondered if this had any prognostic implications. Second, this youngster was ambivalent about starting feminizing hormone therapy to induce puberty. Clinically, it was unclear if this reluctance was related specifically to gender identity issues or if it was related to more general anxieties about growing up.

Like the patients provisionally described by Meyer-Bahlburg et al. (1989) and Reiner (1997c), my patient had a childhood history of girlhood masculinity. Her current phenotypic appearance (e.g., very short hair and a gender neutral clothing style) often resulted in naive observers perceiving her as a boy, in a manner very similar to that which occurs in girls with GID without somatic intersexuality (see Fridell, Zucker, Bradley, & Maing, 1996; McDermid, Zucker, Bradley, & Maing, 1998). In her local community, however, she was known to her peer group as a girl, and she never made explicit efforts to pass as a boy or to intentionally deceive anyone.

Like Meyer-Bahlburg et al.'s (1989) two patients, my patient did not, at age 12, show any signs of gross gender dysphoria, at least as could be inferred from clinical interview data and a structured interview schedule (Zucker et al., 1993):

Interviewer (I): Are you a boy or a girl?

Child (C): Girl.

I: Are you a boy?

C: No.

I: When you grow up, will you be a mom or a dad?

C: Mom.

I: Could you ever grow up to be a dad?

C: No.

I: Are there any good things about being a girl?

C: Yes.

I: Tell me some of the good things about being a girl.

C: Everything, I don't know, stuff. . . . I don't know.

I: Are there any things that you don't like about being a girl?

C: No.

I: Do you think it is better to be a boy or a girl?

C: I don't really care. . . . Because it's basically the same thing.

I: In your mind, do you ever think that you would like to be a boy?

C: No.

I: In your mind, do you ever get mixed up and you're not really sure if you are a boy or a girl?

C: No.

I: Do you ever feel more like a boy than like a girl?

C: No.

I: You know what dreams are, right? Well, when you dream at night, are you ever in the dream?

C: Yes.

I: In your dreams, are you a boy, a girl, or sometimes a boy and sometimes a girl?

C: Usually a boy.
I: Tell me about the dreams in which you're a boy.
C: I forget. . . . don't remember any of my dreams.
I: Do you ever think that you really are a boy?
C: No.

Summary

In many respects, the extant data on psychosexual differentiation for cloacal exstrophy patients suggest a pattern very similar to those with penile agenesis, so I will not repeat these observations. I will only emphasize here that it is obvious that more rigorous psychosexual assessments of such patients are required, including long-term follow-up.

Ablatio Penis

There is a final group of genetic male patients that has substantial relevance to the debate about gender identity differentiation, even though in these cases there is no presence of a physical intersex condition. These are patients who have experienced accidental or traumatic loss of the penis, as in cases of circumcision mishaps, amputation by a mentally ill parent, animal attacks, and motor vehicular accidents (e.g., Gearhart & Rock, 1989; Money, 1998; Ochoa, 1998). In one other rare situation involving conjoined male twins who share one set of genitalia, surgical separation results in penile and testicular loss for one of the twins (O'Neill et al., 1988). In these cases, there is, of course, no uncertainty about the patient's biological sex at the time of birth. These patients presumably experienced normal physical masculinization in utero, including putative CNS effects; in this regard, then, these patients are quite similar to those with penile agenesis and cloacal exstrophy.

As noted by Gearhart and Rock (1989; see also Jones, Park, & Rock, 1978), when there is total loss of the phallus, there are two main management options: (a) a gender re-assignment with immediate surgical feminization and subsequent hormonal feminization at puberty or (b) continued rearing of the infant or child as a boy, with eventual surgical reconstruction of the penis or phalloplasty. From a surgical point of view, the latter option is very difficult and complicated to execute during infancy or childhood. Such procedures become more viable by adulthood, and the procedures used would be along the lines that are performed in phalloplasty in female-to-male transsexuals (Dickey & Steiner, 1990).

Regarding the gender reassignment option, the theoretical and practical rationales (vis-a-vis the optimal gender policy) should by now be apparent: (a) the apparent malleability in gender identity differentiation that Money and colleagues had observed in children with physical

intersex conditions; (b) the timing of the accident and gender re-assignment (within the window of the putative sensitive period for gender identity formation); (c) the medical and psychosocial difficulties that a young boy growing up without a penis would experience; and (d) the relative ease of surgical feminization (see Table 2).

Regarding gender identity differentiation, recall Money's emphasis on the importance of rearing; for example, Money et al. (1955) had argued that "in place of a theory of instinctive masculinity or femininity which is innate, the evidence of hermaphroditism lends support to a conception that, psychologically, [gender identity][9] is undifferentiated at birth and that it becomes differentiated as masculine or feminine in the course of the various experiences of growing up" (p. 308), which Diamond (1965) later characterized as a psychosexual "neutrality-at-birth" theory.

If this model is taken to its logical conclusion, then one could posit that a child with perfectly "normal" biological attributes could be successfully assigned and reared as a member of the opposite sex. Of course, an ideal test of this hypothesis would be to conduct a randomized control trial with a series of biologically normal newborn males, the particulars of which I have facetiously described elsewhere (Zucker, 1996). Of course, it is doubtful that such an experiment would be able to recruit volunteers or to pass an institutional ethics review committee. For obvious reasons, then, it is unlikely that such an "experiment of nurture" will ever be conducted. Thus, tests of the hypothesis have had to rely on special cases, and it is likely that cases of ablatio penis are the prototype in this regard.

In the early 1970s, Money and Ehrhardt (1972) (see also Money, 1975) reported on a case of ablatio penis that received widespread attention. This case involved a pair of monozygotic male twins, in which the penis of one twin was accidentally ablated (flush with the abdominal wall) during a circumcision by electrocautery at the age of 7 months. It then necrosed and sloughed off. The decision about gender reassignment was made at 17 months, with surgical castration and initial genital reconstruction occurring at 21 months.

Money (1975) reported follow-up data on this child through 9 years of age, at which time the patient was described as having many "tomboyish traits, such as abundant physical energy, a high level of activity . . . and being often the dominant one in a girl's group" (p. 70). Money reported, however, that a female gender identity had apparently differentiated: "Her behavior is so normally that of an active little girl, and so

[9]I have inserted here the term gender identity in place of "sexuality," because the discussion focuses on a more specific aspect of psychosexual differentiation.

clearly different by contrast from the boyish ways of her twin brother, that it offers nothing to stimulate one's conjectures" (p. 71). Thus, Money concluded that "gender identity is sufficiently incompletely differentiated at birth as to permit successful assignment of a genetic male as a girl . . . and differentiates in keeping with the experiences of rearing" (p. 66). When Money first reported the case, it received widespread media attention (see "Biological Imperatives," 1973) and was noted in many pediatric, psychology, and sociology textbooks as a powerful proof of the importance of socialization influences on gender identity formation (see Diamond, 1982).

Subsequently, however, Diamond (1982) reported the further course of events for this patient. By early adolescence, the patient had rejected the female identity and began to live as a male at the age of 14 years (Diamond & Sigmundson, 1997b). Indeed, when interviewed in his early 30s, the patient's recall of his childhood gender development was that he had never felt comfortable as a girl, and his mother, father, and cotwin reported similar recollections (Colapinto, 1997, in press). At age 14, the patient received a mastectomy and began testosterone replacement therapy and surgical procedures for phallus construction were at ages 15 and 16. At age 25, the patient married a woman several years his senior and adopted her children. The patient reported an exclusive sexual attraction to females (Diamond & Sigmundson, 1997b).

The long-term psychosexual outcome of this patient, which also received recent widespread media attention ("A Tragedy Yields Insight Into Gender," 1997; Angier, 1997; Colapinto, 1997; Gorman, 1997; King, 1998), has been used as evidence against the importance of sex of rearing for gender identity formation and also as a general critique of the guidelines of psychosexual management that have been used in the care of infants with physical intersex conditions (e.g., Diamond, 1996a, 1996b, 1997, 1999; Diamond & Sigmundson, 1997a; cf. Benjamin, 1997; Glassberg, 1999; Schwarz, 1997).

There are several additional cases of ablatio penis with which to compare this case. O'Neill et al. (1988, Case 8) reported on a pair of male twins joined from the midthorax to the common perineum and who shared a single set of genitalia. The separated twin who retained the genitalia died from sequelae related to tight thoracic wall closure, but the twin who was sex-reassigned was reported, at age 10 years, to be "functioning well as a female" (p. 303). No other details were provided. However, Diamond (1999) has subsequently reported that this individual (at an unspecified age) now wishes to "transition as the male she believes she should be." Unfortunately, no further information on the course of events was described.

Several years ago, I evaluated another set of conjoined male twins who also shared one set of genitalia, one of whom was sex-reassigned at the time of surgical separation (5.5 years) (see Filler, 1988). Because of the twins' living conditions prior to surgery, they were both somewhat developmentally delayed at the time of surgery, but appeared to catch-up subsequently. At age 12, the sex-reassigned twin shared many "boyish" interests with her brother, but, based on interview data with the youngster and her father, appeared to have differentiated a female gender identity. Given the apparent course of events in the O'Neill et al. (1988) case, it would be premature to draw any firm conclusions about the ultimate gender identity of this patient.

Gearhart and Rock (1989) reported on four cases of ablatio penis secondary to circumcision accidents: at birth, two at 2 days postpartum, and one at 2 months of age (this last case will be described below). In the first three cases, surgical removal of the testis and the creation of a neovagina occurred at 6 months (in two cases) and at 23 months in the third.

The first case began feminizing hormone treatment at 12 years and received vaginoplasty at 17 years (the two other cases were not old enough to start feminizing hormone therapy or to receive vaginoplasty). Regarding the first patient, Gearhart and Rock (1989) reported that she was "well adjusted" and sexually active (presumably with males, but this was not specified). Details about the gender identity development of the other two cases were not provided, but there was no indication in the report for any apparent difficulties in this regard.

Ochoa (1998) reported on a 6-month-old boy who was apparently emasculated by a dog; however, it was noted that the wound edges "suggested that a knife had been used" (p. 1116). The family agreed to a gender reassignment. At 5 years of age, the patient was said to have a "normal feminine identity" (details not provided) and, as a result, surgical feminization was performed. In adolescence, however, the patient refused to continue taking feminizing hormones and requested re-reassignment as a boy. Unfortunately, Ochoa did not provide further details other than to note that "it was not difficult to identify psychosocial factors that explained the gender disorder" (p. 1119), that is, the patient's request for gender re-reassignment and, on this point, details were also not provided.

Ochoa (1998) described four other cases of penile loss during infancy (at 4, 6, 8, and 9 months, respectively): In one case, the testicles and scrotum were also "missing . . . as if made with a cutting instrument" (p. 1116); in the second case, the penis had been amputated by the infant's "mentally disturbed" mother; in the third case, the genitalia had been eaten by a dog; and, in the fourth case, the penis had been

"destroyed" by a pig.

In these cases, the recommendation of gender reassignment was either refused by the parents or deferred for legal reasons: one case was subsequently lost to follow-up, but in the other three, various methods of surgical repair, including corpora cavernosa phalloplasty, were carried out. Time of last reported follow-up was at ages 12, 17, and 8 years, respectively. Although no details on the patients' gender identity were provided, one might presume that a male gender identity had differentiated.

Bradley, Oliver, Chernick, and Zucker (1998) reported on a final case of ablatio penis, originally alluded to by Money (1975, p. 65), but for whom there had been no previously reported follow-up (this was the fourth case in Gearhart & Rock, 1989). During an electrocautery circumcision at the age of 2 months, the patient sustained a burn of the skin of the entire penile shaft, and the penis eventually sloughed off. Consequently, the patient was unable to void through the urethra, resulting in a suprapubic cystostoma. The patient was subsequently hospitalized for care of the surgical complications and at age 7 months was referred to Johns Hopkins Hospital, where the remainder of the penis and the testes were removed. The suprapubic cystostoma was eventually closed, and the patient was then able to void through the urethra. Sometime between the circumcision accident and the hospital admission, the decision was made to reassign the patient as a female and to raise the baby as a girl. This was formally recognized at the time the patient was admitted to Johns Hopkins, as the infant was designated on hospital records to be a female.

The patient was interviewed at 16 years and 26 years. On both occasions, the patient appeared to have differentiated a female gender identity. Although tomboyish as a child, the patient also reported her closest friends to be girls. In adulthood, the patient reported a predominant sexual attraction to biological females, but had been sexually active with both men and women, had lived with both men and women, and characterized her sexual identity as "bisexual."

The ablatio penis case reported by Money (1975) and then by Diamond (1982; Diamond & Sigmundson, 1997b) and Colapinto (in press) contains the greatest details in which to make direct comparisons with the Bradley et al. (1998) case vis-a-vis psychosexual differentiation. Obviously, the two cases differed with regard to long-term gender identity differentiation, but there were similarities with regard to childhood gender role behavior and adult sexual orientation. Both patients had strong elements of behavioral masculinity in childhood. The Money/Diamond-Sigmundson patient had an exclusive heterosexual sexual orientation (attraction to biological females); our patient

reported a bisexual sexual orientation, but a stronger attraction to biological females than to males. Lastly, the Money/Diamond-Sigmundson patient reported a heterosexual sexual identity whereas our patient reported a bisexual sexual identity (see also Meyer-Bahlburg, 1999a).

Summary

Because these cases are few and far between, it is difficult to reach any kind of definitive conclusion. In the Money/Diamond-Sigmundson case and in the case reported by Ochoa (1998), it would appear that the "experiment of nurture" vis-a-vis gender identity differentiation was unsuccessful. As in all experiments in which the null hypothesis cannot be rejected, it is difficult to ascertain why the experiment failed. Was it the result of the underlying normal prenatal masculine biology eventually overriding the efforts of gender socialization as a girl? Was it because the gender re-assignment occurred too late (i.e., because it was at the upper end of the putative age range for the sensitive period for gender identity formation)? Was it because of parental uncertainty regarding the appropriateness of the decision, thus resulting in the child receiving mixed messages in the arena of gender socialization?

These are some of the more common explanations that have been proffered in the extant literature. To these, we can add some additional possibilities. In the Money/Diamond-Sigmundson case, the patient was reported to have been relatively "tomboyish" in her childhood gender role behavior. Did such behavior cause the patient to see herself as more like a boy than like a girl, thus creating additional uncertainty regarding gender identity, along the lines that I have described earlier with regard to 5-ARD patients? As this patient approached adolescence, there was also evidence that the patient became aware of sexual attraction towards biological females. Is it possible that such attractions were experienced by the patient as intolerable (a variant of "internalized homophobia") and, in an effort to "normalize" such feelings, the patient began to consider even more strongly the idea of changing genders, again as in the case of some 5-ARD patients? In this regard, Colapinto (in press) provides some supportive evidence.

In the Bradley et al. (1998) case, the experiment of nurture vis-a-vis gender identity differentiation was successful, at least as judged by the follow-up data at the age of 26 years. The only plausible explanation of our patient's differentiation of a female gender identity is that sex of rearing as a female, beginning at around age 7 months, overrode any putative influences of a normal prenatal masculine sexual biology.

Although it is not possible to state with precision what constituted our patient's sex of rearing as a girl, it clearly included her parents agreeing to the sex reassignment decision (although this was easier for the mother than for the father), the provision of a stereotypical girl's name, and the patient being perceived as a girl by significant others in her social environment. In this case, then, the experiment of nurture was successful regarding female gender identity differentiation.

There are two likely reasons, perhaps related, why the gender identity development of our patient differentiated as a female, whereas it did not (at least in the long run) in the previous case. First, in our case, the decision to reassign the patient to the female sex occurred somewhere between ages 2 and 7 months; in the other case, it occurred only at 17 months, and surgical castration and vaginoplasty were done at 21 months. Second, it is possible that the parents of our patient, particularly the mother, had less ambivalence about the decision than the parents of the other patient, perhaps because the decision occurred earlier in life. Third, it is possible that our patient's awareness of sexual feelings towards biological females was not experienced as ego-dystonic (i.e., internalized homophobia), whereas such feelings were experienced in this manner by the Money/Diamond-Sigmundson patient.

General Summary

The aim of this article was to review what is known about gender identity differentiation among patients with selected physical intersex conditions. In particular, this review was focused on physical intersex conditions characterized by at least two common features: (a) the presence of ambiguous genitalia at birth, which might result in initial uncertainty as to the "appropriate" sex and gender assignment and (b) a prenatal hormonal milieu or external genital configuration (and sometimes both) that are atypical in relation to the gender in which the child is reared. In summarizing the review, I will first make some general comments pertaining to methodological matters and limitations of the extant database.

Methodological Considerations

1. Knowledge about gender identity differentiation varies considerably across syndromes. Thus, for example, there is a much larger database about the "natural history" of CAH and 5-ARD than for pAIS, micropenis, penile agenesis, and cloacal exstrophy. Thus, it is critical that the database itself be increased for these more poorly studied syndromes.

2. Within the extant databases for each syndrome, closer attention

must be given to selection biases at the time of follow-up. In particular, greater efforts need to be made to reduce the number of cases lost to follow-up, as it is possible that participants differ in important respects from nonparticipants (see, e.g., Zucker et al., 1996). For example, in two of the more important studies of patients born with a micropenis, 60% (Reilly & Woodhouse, 1989) and 67% (Money & Norman, 1988) of the patients were unavailable for follow-up.

3. The reliance on standardized assessment protocols varies considerably across syndromes, with some accounts of gender identity differentiation quite poorly described. Thus, it is important that future researchers of gender identity differentiation (and other aspects of psychosexual differentiation), particularly in the less well-studied syndromes, rely on more rigorous assessment methods and techniques.

4. The availability of long-term follow-up data also varies considerably across the different syndromes. Even among the better studied syndromes (e.g., CAH), adult follow-ups have generally been when the patients were in their early 20s (cf. Ehrhardt, Evers, & Money, 1968). Among gender dysphoric adults without known somatic intersexuality (and who have a homosexual sexual orientation), the decision to formally seek out sex-reassignment procedures often occurs in the mid-20s to early 30s (e.g., Blanchard, Clemmensen, & Steiner, 1987). Thus, among young intersex adults who may be struggling with gender identity issues, the "period of risk" may not have passed, so even longer term follow-up is likely required in order to gain a more accurate picture about gender identity differentiation. Overall, then, definitive conclusions about the natural history of gender identity differentiation are severely hampered by the variability in the quantity and quality of follow-up information.

5. For some of the syndromes reviewed in this article, it was noted that the gender assignment in infancy varies considerably. For example, among patients with 5-ARD, a minority of such individuals, particularly those living in Western countries, are assigned to the female sex and then proceed with surgical feminization of the genitalia, gonadectomy, and administration of feminizing hormones at puberty. Much less is known about the natural history of gender identity differentiation (and other aspects of psychosexual differentiation) among patients treated in this manner than among those from non-Western countries in which the treatment history is very different. Comparative data for these differing treatment histories are urgently needed and would greatly facilitate a more accurate understanding of the factors involved in gender identity differentiation.

Conclusions About Gender Identity Differentiation

The empirical database suggests the following broad conclusions:

1. Among the physical intersex conditions reviewed in this article, gender identity differentiation appears to be more variable than among individuals with apparently "normal" physical sex differentiation (cf. Meyer-Bahlburg, 1994, 1999b). In the latter population, the most relevant comparison condition is that of GID in children, adolescents, and adults (American Psychiatric Association, 1994). In GID, there is no ambiguity of the external genitalia at birth, and there is no evidence for a gross hormonal abnormality, as in the case of some of the physical intersex conditions, such as CAH in genetic females. Thus, GID occurs in individuals who are unambiguously assigned at birth to the male or female sex. The prevalence of GID in children is not known, but in adults it has been estimated to occur in 1:11,000-30,000 genetic males and 1:30,400-100,000 genetic females (American Psychiatric Association, 1994; Bakker et al., 1993). These figures are probably the most relevant since, among children with GID, prospective follow-up studies suggest that the majority of youngsters resolve their gender dysphoria and do not grow up to request sex-reassignment (Green, 1987; Zucker & Bradley, 1995).

2. Although gender identity differentiation appears to be more variable among individuals with the physical intersex conditions reviewed in this article, it is also apparent that there is significant and meaningful variability across syndromes. For example, although instances of gender change in genetic females with CAH appear to be more common than occurs in the general population (Meyer-Bahlburg et al., 1996; Zucker et al., 1996), it is noticeably less common than which appears to occur in 5-ARD, where the majority of cases reported so far appear to change genders. Thus, we need to account for two facts: (a) Why is gender identity differentiation more variable in general among people with physical intersex conditions than it is among people without such conditions? (b) How does one account for the cross-syndrome variability in gender identity differentiation?

Regarding the first question, there are two candidate explanations. The first explanation is that elements of the physical intersex condition itself serve as a predisposing factor for greater lability in gender identity differentiation (Hoenig, 1985). Thus, in genetic females with CAH assigned to the female sex and reared as girls, for example, the sex-atypical exposure to prenatal androgens increases the potential for cross-gender behavior, including gender identity differentiation (Collaer & Hines, 1995).

The second explanation is that elements of the gender specific rearing environment also serve as a predisposing factor for greater lability in gender identity differentiation. It is this second point for which the literature is most divided. For example, among patients with 5-ARD who are assigned to the female sex and "raised" as girls, there has been a great deal of debate regarding the extent to which the gender of rearing has been truly unambiguous or for which there is, in fact, some uncertainty. On this point, the matter is far from settled. Here, prospective studies would be particularly informative, in order to track better the developmental course of gender socialization and the entire literature on physical intersex conditions is particularly poor in this regard.

Regarding the second question, there are also two candidate explanations. The first explanation is that elements of the physical intersex conditions themselves vary in their predisposing "power" to increase the potential for cross-gender behavior, including gender identity differentiation. Appraisal of this hypothesis is, however, very difficult because of the manner in which physical intersex conditions are treated, both medically and socially. For example, in the case of CAH in genetic females, the typical medical treatment regimen is to block the excess production of adrenal androgens with corticosteroids and to surgically "normalize" the masculinized genitalia. In contrast, among patients with 5-ARD raised as girls, at least in some cohorts, there is no medical intervention at all: Thus, the girl grows up with ambiguous genitalia, and there is progressive physical masculinization at the time of puberty. Because of this kind of confound, it cannot be concluded with certainty that the influence of prenatal androgen exposure itself is more powerful among 5-ARD patients than it is among genetic females with CAH in accounting for the higher rate of gender change in the former group.

The second explanation is that the consistency (or lack thereof) of the gender-rearing environment varies across syndromes, and it is this variability that accounts for the varying rates of gender change or gender dysphoria that occur in the different syndromes. Apart from the inherent difficulty in specifying the nature of the gender-rearing environment, it is likely that the variation, if it actually occurs, interacts in complex ways in which the physical intersex condition itself is treated both medically and surgically.

3. Perhaps the most important conclusion from this review is to reiterate the importance of respecting the complexity of gender identity differentiation in particular and psychosexual differentiation in general. The gender specific social environment clearly matters, because there are so many instances of gender identity differentiating in accordance with the gender assignment. Perhaps the most striking illustration of

this comes from the Bradley et al. (1998) adult follow-up data on one genetic male with ablatio penis raised as a girl. It is hard to account for this patient's female gender identity without implicating some kind of environmental influence.

At the same time, biological factors also matter. For example, the shift towards masculinized gender role behavior seen in girls with CAH or pAIS are likely related, at least in part, to their exposure to prenatal androgens and the pattern is very similar to what has been observed in experimental studies of nonhuman primates (see, e.g., Goy, Bercovitch, & McBriar, 1988; Goy & McEwen, 1980). Although such effects on gender identity differentiation are likely more indirect, there is probably some alteration in the threshold, interacting with other factors, that results in an increased risk for gender change in some individuals (see Meyer-Bahlburg et al., 1996).

Despite the increasing recognition of the complex factors involved in psychosexual differentiation, the seductive lure of either psychosocial or biological reductionism remains a very strong temptation, to which many writers in the field succumb. Recent advances in the field of animal sexology point to the importance of paying serious attention to multifactorial models in our understanding of psychosexual differentiation in humans. For example, Juraska (1998) has shown how the typical sex difference in the number of neurons in the corpus callosum of rats is exquisitely sensitive to, and modified by, the rearing environment. In nonhuman primates, Wallen (1996) has recently summarized ways in which the social environment either attenuates or exacerbates typical sex differences in behavior, thus providing illustrations of how "nature needs nurture." Thus, it is in the more precise identification of the transactional nature of biological and psychosocial influences on gender identity differentiation in particular and psychosexual differentiation in general that future empirical inquiry must continue to invest its efforts.

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Gender Dysphoria in Adults

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Abstract

Gender dysphoria (GD), a term that denotes persistent discomfort with one's biologic sex or assigned gender, replaced the diagnosis of gender identity disorder in the *Diagnostic and Statistical Manual of Mental Disorders* in 2013. Subtypes of GD in adults, defined by sexual orientation and age of onset, have been described; these display different developmental trajectories and prognoses. Prevalence studies conclude that fewer than 1 in 10,000 adult natal males and 1 in 30,000 adult natal females experience GD, but such estimates vary widely. GD in adults is associated with an elevated prevalence of comorbid psychopathology, especially mood disorders, anxiety disorders, and suicidality. Causal mechanisms in GD are incompletely understood, but genetic, neurodevelopmental, and psychosocial factors probably all contribute. Treatment of GD in adults, although largely standardized, is likely to evolve in response to the increasing diversity of persons seeking treatment, demands for greater client autonomy, and improved understanding of the benefits and limitations of current treatment modalities.

Contents

INTRODUCTION

Gender dysphoria (GD) is a technical term that is familiar to specialist clinicians and researchers, but it is perhaps less familiar to clinicians who have little or no experience in this area. It is also a diagnostic term: In the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; Am. Psychiatr. Assoc. 2013), GD replaced prior diagnostic labels, including transsexualism and gender identity disorder.

In the past few years, GD has received an unprecedented amount of attention in all forms of media, perhaps under the broader rubric of the terms "transgender" or "transgenderism." In 2014, an essay in *Time* suggested that a "tipping point" had been reached with regard to "transgender visibility" (Gray 2014). In his State of the Union address on January 20, 2015, Barack Obama was the first US President to use the term "transgender" in public:

> As Americans, we respect human dignity.... That's why we defend free speech, and advocate for political prisoners, and condemn the persecution of women, or religious minorities, or people who are lesbian, gay, bisexual, or transgender. We do these things not only because they're right, but because they make us safer. (Steinmetz 2015)

On May 4, 2015, the *New York Times* launched a series of editorials, entitled "Transgender Today," and around the same time, the American public appeared captivated by the very public gender change from male to female, at the age of 65, of Olympic athlete Bruce (aka Caitlyn) Jenner, whose name yielded 79,500,000 "hits" on Google as of July 1, 2015 (Bissinger 2015).

TERMINOLOGY AND PHENOMENOLOGY

The term "gender dysphoria" was first introduced by Fisk (1974) to describe individuals who experience sufficient discomfort with their biological sex to form the wish for sex reassignment. In the DSM-5, GD is defined as "an individual's affective/cognitive discontent with the assigned gender [usually at birth and referred to as natal gender]" (Am. Psychiatr. Assoc. 2013, p. 451).

The specialist clinician will be well aware of the multitude of terms currently in use to describe individuals whose gender identity or gender role behavior does not match up with societal expectations or stereotypes associated with the (biological) male-female binary: apart from GD, there are many other terms, such as gender variant, gender nonconforming, gender queer, gender fluid, bigender, gender neutral, agender, and nonbinary, along with "trans*," transsexual, and transgender. And, cross-culturally, there are many terms used to label individuals whose behavior and subjective identity fall under the rubric of a "third gender" (Herdt 1994).

Developmental Trajectories

Table 1 shows the DSM-5 diagnostic criteria for GD in both children and adolescents/adults. It is important to include the criteria for children because the phenomenology of GD in adults, particularly in natal males, has at least two distinct pathways. Some adults with GD will recall a childhood pattern of sex-typed behavior that corresponds to the behavioral indicators of GD in childhood. In the contemporary literature, this is known as early-onset GD (Nieder et al. 2011) or an early-onset of cross-gender identification, which might be present in the absence of an explicit desire to be of the other gender. For other adults with GD, there is no clear evidence of childhood cross-gender identification; rather, the indicators of GD emerge at puberty, if not much later, which is called late-onset GD. An important methodological and interpretive issue pertains to what "counts" as early onset. On this point, the literature is quite variable: Some researchers consider early onset to be any time prior to puberty, whereas other researchers consider early onset to be during the toddler and preschool years, the developmental period in which both gender identity and gender role behaviors are first expressed (Lawrence 2010, pp. 531–532).

If age of onset is used as the independent variable, one can ask if it correlates with any other variables that might be of importance from a clinical perspective. One such variable is sexual orientation. Nieder et al. (2011) found that early-onset female-to-male (FtM) clients were more likely to be sexually attracted to females than were late-onset clients, and early-onset male-to-female (MtF) clients were more likely to be sexually attracted to males than were late-onset clients, particularly when it was the clinician who classified the client's sexual orientation.

If sexual orientation is used as the independent variable, one can also ask which, if any, variables it is correlated with. In the best-studied sexual orientation typological scheme, adults with GD are divided into two subtypes: in the case of males, the two subtypes are those who are sexually attracted to males versus those who are sexually attracted to females, both males and females, or neither males

Table 1 *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) criteria for gender dysphoria in children, adolescents, and adults

Criteria for gender dysphoria in children
A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least six months' duration, as manifested by at least six of the following (one of which must be Criterion A1):
1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender)
2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing
3. A strong preference for cross-gender roles in make-believe play or fantasy play
4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender
5. A strong preference for playmates of the other gender
6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities
7. A strong dislike of one's sexual anatomy
8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender
B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.
Specify if: with a disorder of sex development
Criteria for gender dysphoria in adolescents and adults
A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least six months' duration, as manifested by at least two of the following:
1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
3. A strong desire for the primary and/or secondary sex characteristics of the other gender
4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender)
5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender)
6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender)
B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Specify if: with a disorder of sex development
Specify if: posttransition, the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen—namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female)

nor females (Blanchard 1989). In the case of females, the two subtypes are those who are sexually attracted to females versus those who are sexually attracted to males, both males and females, or neither males nor females. Gender-dysphoric males who are not exclusively sexually attracted to males often have transvestic disorder (Blanchard 2010), in which there is sexual arousal associated with cross-dressing or autogynephilia, defined in the DSM-5 as sexual arousal associated with a man's thought or image of himself as a woman (for details, see Blanchard 2005, Lawrence 2013). Although this taxonomic scheme did not begin to receive empirical validation until the 1980s,

the importance of sexual orientation as a subtype goes back to some of the earliest writings by clinicians who worked with transsexual clients. For example, Harry Benjamin, an endocrinologist considered to be the father of transsexualism (Green 2009), described quite clearly male clients who could be classified as either homosexual or nonhomosexual (in relation to birth sex) (Schaefer & Wheeler 1995).

For natal females, the older literature suggested an almost complete predominance of the early-onset form of GD, with a corresponding sexual orientation toward females. More recently, however, a greater proportion of natal females with the late-onset form of GD have been described in the literature, with a sexual attraction to natal males and who from a subjective point of view identify as gay men (Bockting et al. 2009, Chivers & Bailey 2000).

In contemporary times, consideration of sexual orientation in relation to GD has been an extremely contentious issue. Some clinicians and transgender activists object to the idea that GD in males might be associated with autogynephilia because they worry that this might result in the GD being taken less seriously and viewed simply as a paraphilic sexual condition (Dreger 2008, Lawrence 2013).

There is a historical reason for this concern. When sex reassignment surgery (SRS), or what is now called gender-confirming surgery, for adults with GD began to receive more credence as a legitimate therapeutic option in the 1960s and 1970s (Meyerowitz 2002), clinicians were wary about recommending this treatment for late-onset males. For example, a male client who had a history of transvestic fetishism, was (or had been) married to a woman, had children, and had lived for a long time in the male gender role was viewed as a more dubious candidate for SRS in comparison with other male clients. And such male clients often present with the request for SRS at a later age than do early-onset males (Blanchard 1994, Lawrence 2010, Nieder et al. 2011). Indeed, Stoller (1968) considered such clients to be "secondary" rather than "primary" transsexuals. Other clinicians in this era noted that such clients had a more episodic history with regard to GD and the wish for sex reassignment, which was deemed to be a reason for caution in recommending an irreversible medical treatment (Wise & Meyer 1980). And perhaps there was good reason to be cautious, as there is evidence that instances of "regrets" after SRS are more common in this subgroup (Blanchard et al. 1989).

The primary-secondary classificatory scheme has now been largely abandoned, and eligibility for SRS takes into account different parameters, which are described more fully in the section on therapeutics, but it is noted here that the debate has remained a very political, contentious issue. In the seventh revision to the *Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People* (SOC-7) published by the World Professional Association for Transgender Health (Coleman et al. 2011), terms such as sexual orientation, transvestic fetishism, and autogynephilia are never mentioned. We would argue that this reflects a kind of intellectual erasure in the discourse on phenomenology, which may inadvertently (or, perhaps, intentionally) obscure the importance of these parameters with regard to theoretical issues, empirical research on causal mechanisms, and therapeutic care.

EPIDEMIOLOGY

Prevalence and Incidence

In the late 1970s, the epidemiology of psychiatric disorders was examined with the use of the Diagnostic Interview Schedule (DIS) (Robins et al. 1981), which was designed to assess DSM-III diagnoses. Interestingly, Robins and colleagues (1981) noted that the module pertaining to transsexualism was "omitted" because it "had not been cleared by NIMH for submission to [the] OMB

[the US Office of Management and Budget]" (p. 388). Thus, in the 1980s, the US studies on DIS prevalence did not contain any specific information on transsexualism. However, Hwu et al. (1989) reported on the prevalence of transsexualism in Taiwan for 11,004 adults ranging in age from 18 to 64+ years. Depending on geographic area, lifetime prevalence ranged from 0.3 to 2.0:1,000, with a higher prevalence for females than for males (range, 0.7–4.2:1,000 versus 0–0.4:1,000). One-year prevalence ranged from 0 to 1.0:1,000. Stefánsson et al. (1994) reported prevalence data on 862 Icelanders at the age of 55 to 57 years, who were all born in 1931: Lifetime prevalence was 0.1%, and point prevalence (one month to one year) was 0.0%.

Estimates of prevalence have also relied on less rigorous methods, such as the number of adults seeking clinical care at specialized gender identity clinics in a particular country or the number of such clients approved for or already receiving cross-sex or gender-affirming hormonal treatment. Zucker & Lawrence (2009) reviewed this quasi-epidemiological literature on prevalence and identified 25 relevant studies. Population-based data from European countries provided the best estimates of the prevalence of GD in Western societies. In Belgium, for example, the prevalence of transsexualism, defined as having undergone sex reassignment, was 1:12,900 for adult males and 1:33,800 for adult females; data from the Netherlands were similar: 1:11,900 adult males and 1:30,400 adult females.

Since the 2009 review, two new studies have been published. Dhejne et al. (2014) reported a point prevalence in December 2010 of 1:7,750 adult males and 1:13,120 females in Sweden who had applied for a legal name change, and Judge et al. (2014) reported a prevalence of 1:10,154 adult males and 1:27,668 adult females referred for hormonal treatment in Ireland. Arcelus et al. (2015) provided a meta-analytic review of 21 studies (many of which were included in Zucker & Lawrence 2009) and concluded that the prevalence of transsexualism in (predominantly) adult males was 1:14,705 and 1:38,461 in (predominantly) adult females.

Because these studies have relied on clients seen by gender identity specialists or clinics, it has been argued that the true prevalence of GD (transsexualism) could be underestimated because not all affected individuals might seek out such care at specialized centers. Veale (2008) gauged the prevalence of transsexualism in New Zealand on the basis of the number of individuals, 15 years of age and older, who requested, for example, an "X" on their passport instead of M (for male) or F (for female) after they had been living as a member of the opposite sex and had made a legal name change. On this basis, Veale reported a higher prevalence rate of 1:3,630 in males and 1:22,714 in females.

In the past few years, some novel data have emerged that also suggest higher prevalence rates; however, these studies have tended to use definitions of "caseness" that are looser than the definitions used for clients seen in specialty clinics. Conron et al. (2012) examined a probability sample of 28,176 adults (age range 18–64 years) who participated in a telephone health survey. They found that 0.5% of the adults considered themselves to be transgender (e.g., "a person born into a male body, but who feels female or lives as a woman") (see also Kuyper & Wijsen 2014, Van Caenegem et al. 2015). Although these new data should be interpreted with caution because of the less restricted definition of caseness, they may well reflect a bona fide increase in the prevalence of adults who self-identify somewhere along the transgender spectrum; some of these individuals may eventually seek out gender change with biomedical treatments.

Sex Ratio

From the clinic-based studies, it is apparent that the prevalence of male-to-female transsexualism is consistently higher than female-to-male transsexualism in adults. If these estimates reflect, even in a crude way, sex differences in true prevalence, one can ask why GD is more common in biological

males than in biological females. One explanation pertains to sex differences in the prevalence of subtypes of GD. As noted previously, the best-established evidence for a sex difference in subtypes pertains to sexual orientation. This sex × sexual orientation difference may well explain the higher prevalence in biological males (of course, the interaction itself also requires an explanation).

DIAGNOSIS

Placement in the Nomenclature

Transsexualism as a psychiatric diagnosis (for adolescents and adults) appeared for the first time in the DSM in 1980 (the corresponding diagnosis for children was gender identity disorder of childhood). In 1994, transsexualism and gender identity disorder of childhood were merged into one diagnosis, gender identity disorder (GID), with distinct criteria sets for children and adolescents/adults (Am. Psychiatr. Assoc. 1994). In the DSM-5 (Am. Psychiatr. Assoc. 2013), GID was renamed GD, with a chapter of its own.

Substantive Changes in the DSM-5

Zucker et al. (2013) outlined the key changes to the diagnosis of GID between DSM-IV and DSM-5. Before describing the changes relevant to adults, it should be noted that the subworkgroup on Sexual and Gender Identity Disorders reflected on a more fundamental matter, namely, whether to retain the diagnosis in the DSM-5 at all. Some transgendered activists and some clinicians wanted the diagnosis to be removed in its entirety, arguing that GID was not a mental disorder, and the arguments for removal drew on many of the same reasons that led homosexuality to be removed in 1973 from the DSM-II (Am. Psychiatr. Assoc. 1968) (Bayer 1981): Transsexualism or GID was nothing more than a normal variant of a cisgender identity, that its presence in the DSM contributed to stigma, and that there was nothing inherently "wrong" with a gender identity incongruent with one's natal sex (Ault & Brzuzy 2009, Vance et al. 2010). Two members of the DSM-5 subworkgroup wrote reviews that, in part, considered the question of whether to leave the diagnosis in the DSM or take it out (Drescher 2010, Meyer-Bahlburg 2010; see also Zucker & Duschinsky 2016).

The recommendation of the subworkgroup to retain the diagnosis was based on at least two key considerations: access to care and a reconceptualization of the diagnosis. If there were no psychiatric diagnosis, access to care, including insurance coverage for SRS, would be threatened. The argument that GID is a nonpsychiatric medical condition [e.g., a neural, central nervous system (CNS)-limited intersex condition] (Meyer-Bahlburg 2011) was considered, but it was deemed that the evidence for this was far from clear and could not be justified.

To retain the diagnosis in the DSM-5, a reconceptualization was articulated in which "identity" per se was not considered a sign of a mental disorder. Rather, it was the incongruence between one's felt gender and assigned sex/gender (usually at birth) leading to distress and/or impairment that was the core feature of the diagnosis. As a result, the subworkgroup argued for a change in name from GID to GD in order to better reflect this incongruence. Once a consensus within the subworkgroup was reached with regard to retention, five substantive changes were proposed and implemented:

1. The diagnostic criteria for adolescents and adults moved to a more detailed polythetic format (**Table 1**), replacing the rather vague criteria that were used in the DSM-IV. The threshold of two symptoms (out of six) was based, in part, on secondary data analyses, which indicated that the presence of at least two indicators yielded a sensitivity rate of 94.2% and a specificity rate of 99.3%.

2. A lower-bound six-month duration criterion was introduced based on clinical consensus, but, unfortunately, without formal empirical evidence. The inclusion of a duration criterion was, however, deemed important for clinical reasons, namely, to caution against a hasty diagnosis with the potential unintended consequence of inappropriate treatment for clients in which the symptoms might well prove to be transitory.
3. Whether or not individuals with a physical intersex condition, now termed a disorder of sex development (DSD), should be diagnosed with GD has had a back-and-forth history since the DSM-III (Kraus 2015; Meyer-Bahlburg 1994, 2010, 2015). Since the publication of the DSM-IV, considerable evidence has accumulated that some individuals with a DSD experience GD and may wish to change their assigned gender (Berenbaum & Meyer-Bahlburg 2015, Meyer-Bahlburg 2010, Pasterski et al. 2015, Richter-Appelt & Sandberg 2010). Although the percentage of DSD clients who develop GD is DSD syndrome dependent, such clients express a phenomenology that is both similar to and different from clients with GD with no known DSD, and similarities and differences also exist in developmental trajectories. Because the presence of a DSD suggests a specific causal mechanism that may not be present in individuals without a DSD, it was included as a specifier in the DSM-5.
4. For adolescents and adults, the DSM-IV specifier for sexual attraction (to males, to females, to both, to neither) was removed in the DSM-5. This was an issue that was debated intensely by the subworkgroup. On the one hand, there is considerable evidence, particularly for natal males, that sexual orientation in adults with GD is related to a whole host of variables, including developmental phenomenology and trajectories, and is likely related to somewhat distinct causal mechanisms. Indeed, sexual orientation (or sexual attraction) fits well with the DSM-IV definition of a subtype ("mutually exclusive and jointly exhaustive phenomenological subgroupings"), and there is considerable evidence for its validity as a subtype (Lawrence 2010). On the other hand, it can be argued that sexual orientation per se does not, in and of itself, constitute a symptom of GD ("symptom expression"), which is a cornerstone of the meaning of a specifier in DSM-5. As a result, the subworkgroup recommended that sexual attraction be removed as a specifier but described in the text as an important component of variations in developmental trajectories and with regard to research on causal mechanisms.
5. A posttransition specifier was added to the GD criteria for adolescents and adults. The addition of this specifier was deemed necessary because there are many individuals who, after a gender transition (social and/or biomedical), no longer meet the criteria set for GD; however, they continue to undergo chronic hormone treatment, further gender-confirming surgery, or intermittent psychotherapy/counseling to facilitate the adaptation to life in the desired gender and the social consequences of the transition. Although the concept of posttransition was modeled on the concept "in [partial or full] remission" as used for mood disorders, "remission" has implications in terms of symptom reduction that do not apply directly to GD. Cross-sex hormone treatment of gonadectomized individuals could, of course, be coded as treatment of hypogonadism, but this would not apply to individuals who have not undergone gonadectomy but receive hormone treatments. In the DSM-5 text, it is noted that the course specifier of "full remission" in its original meaning does apply to a small number of adults.

Gender Dysphoria and the ICD-11

The World Health Organization intends to publish the eleventh revision to its *International Classification of Diseases and Related Health Problems* (ICD-11) in 2018. Advisory groups have been assembled for the Mental and Behavioural Disorders section (First et al. 2015). Two members of the DSM-5 Work Group on Sexual and Identity Disorders, Cohen-Kettenis and Drescher,

served on a subgroup of three. A general proposal has been made to move the ICD-10 diagnoses pertaining to GD, the sexual dysfunctions, and the paraphilic disorders out of the Mental and Behavioural Disorders section to a new section provisionally entitled Conditions Related to Sexual Health (Drescher 2013, 2015; Drescher et al. 2012), with the DSM-5 "gender dysphoria" label replaced with the label of "gender incongruence." This proposal appears to be based in part on the argument that such a section would be agnostic with regard to whether or not gender incongruence is best conceptualized as a psychiatric or nonpsychiatric medical condition. Retention in the ICD-11 in this new section would, in theory, allow national health care systems or private insurance companies to continue to provide coverage and thereby not threaten access to care for clients unable to pay for medical care out of pocket.

ASSESSMENT

Psychological Assessment

Psychological assessment of GD, particularly dimensional evaluation, can be used to complement a detailed clinical history, including an appraisal of the symptoms that constitute the DSM-5 diagnosis. For example, the gender-related scales [masculinity-femininity, masculine gender, feminine gender (Mf, GM, and GF, respectively)] of the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) (Martin & Finn 2010) provide objective measures of clients' gender-typical or atypical attitudes and interests (Gómez-Gil et al. 2008). The Feminine Gender Identity Scale for Males (Freund et al. 1977) and the Masculine Gender Identity Scale for Females (Blanchard & Freund 1983) were developed, in part, to provide dimensional assessment of some indicators of transsexualism (both historic and concurrent) during the period when the diagnosis was either about to appear in the DSM-III or shortly thereafter.

More recently, the Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults (GIDYQ-AA) has been developed (Deogracias et al. 2007). The GIDYQ-AA consists of 27 items that pertain to gender identity and GD and are designed to capture multiple indicators of gender identity and GD, including subjective ($n = 13$ items), social ($n = 9$ items), somatic ($n = 3$ items), and sociolegal ($n = 2$ items) parameters. The GIDYQ-AA has parallel male and female versions. Each item is rated on a 5-point response scale ranging from 1 (never) to 5 (always) based on a time frame of the past 12 months. A total score is calculated by summing scores on the completed items and dividing by the number of marked responses.

The psychometric properties of the GIDYQ-AA were examined by Deogracias et al. (2007) with a sample of 462 participants that included both university students and gender identity clients. A principal factor analysis indicated a one-factor solution was the best fit, accounting for 61.3% of the total variance. The measure successfully discriminated gender identity clients from both heterosexual and nonheterosexual controls, with large effect sizes. Using a cut-point of ≤ 3.00, selected on the basis of visual inspection of the frequency distributions of mean scores, Deogracias et al. (2007) found the scale to have excellent sensitivity (90.4%) and specificity (99.7%). Similarly, using clinical controls, Singh et al. (2010) found a specificity rate of 100% and sensitivity rates of 93.3% and 87.3% for adolescents and adults with GID, respectively. These findings suggest that the GIDYQ-AA can be used to identify "caseness" in clients referred to a specialized gender identity clinic and that the questionnaire does not simply identify clinical problems in general. It has also been used to identify potential "cases" in client groups for whom it has been surmised contain an overrepresentation of individuals with GD, such as women with borderline personality disorder (Singh et al. 2011). Other contemporary dimensional measures of GD include the Utrecht Gender Dysphoria Scale (Schneider et al. 2015); however, one advantage of the GIDYQ-AA is

that it uses a specific time frame and has parallel items for males and females, whereas the Utrecht Gender Dysphoria Scale does not have identical items for the two sexes.

An important component of GD pertains to body image and body dissatisfaction. Although signs of body image dissatisfaction, including anatomic dysphoria, can be detected in some prepubertal children with GD, this becomes much more salient with the onset of puberty, which accentuates the incongruence between one's felt gender and somatic sex with the emergence of secondary sex characteristics (Feusner et al. 2015).

Several measures have been used to assess this body image dissatisfaction, including the Body Image Scale (Lindgren & Pauly 1975, van de Grift et al. 2015), the Body Uneasiness Test (Bandini et al. 2013), and the Hamburg Body Drawing Scale (Becker et al. 2015). Becker and colleagues found the expected elevation in body image dissatisfaction with regard to sex-specific body features, but they also found some elevations in more general aspects of body image. Along similar lines, Vocks et al. (2009) reported that gender-dysphoric adults showed impairment in body image related to eating disorders (e.g., restrained eating behavior). Body image is an important variable to assess because a reduction in dissatisfaction is an important metric in identifying improvement in psychosocial well-being following a gender social transition and corresponding biomedical treatments (Kraemer et al. 2008).

Biological Assessment

Physical examination and laboratory testing are generally viewed as having limited value for clients with GD. For adults who have a co-occurring DSD, this has invariably been documented prior to an assessment for GD. Almost all clients with GD have a normal sex chromosome karyotype (Auer et al. 2013a). Nonautosomal positive findings in males most commonly indicate the presence of Klinefelter syndrome (47,XXY) or an XYY karyotype (Auer et al. 2013a, Buhrich & McConaghy 1978). Only a few case reports in the literature have identified a sex chromosomal abnormality in females with GD (Auer et al. 2013a, Khandelwal et al. 2010).

ASSOCIATED PSYCHOPATHOLOGY

Understanding the nature and prevalence of psychopathologic conditions that occur in association with GD can potentially improve diagnostic precision, inform treatment planning, and provide insights into the causes and consequences of GD. A review of existing research in this area, however, reveals a wide range of inconsistent, confusing, and at times seemingly contradictory results. Many studies have significant limitations. These include the use of small and potentially unrepresentative samples and reliance on brief self-report measures rather than structured clinical interviews. Some investigators have combined male-to-female (MtF) and female-to-male (FtM) persons for purposes of analysis, and subtypes based on sexual orientation or age of onset have rarely been taken into consideration.

Increased Prevalence of Associated Psychopathology

Comorbid psychopathology is significantly more prevalent in adults with GD than in the general population. Mood and anxiety disorders are especially likely to occur in association with GD. Two large, recently published, methodologically strong studies illustrate these points; they also provide a standard against which the results of other investigations can be compared. These two reports are summarized in the first two rows of **Supplemental Table 1** (follow the **Supplemental Material link** in the online version of this article or at **http://www.annualreviews.org**).

Supplemental Material

Dhejne et al. (2011) reported the results of a longitudinal, population-based follow-up study of all persons who underwent SRS in Sweden between 1973 and 2003, a cohort consisting of 191 MtF and 131 FtM transsexuals. Data were obtained from several Swedish national registries, which contain information about births, deaths, hospital discharges and diagnoses, criminal records, etc. Each client was compared with 10 randomly selected, age-matched persons of both their birth sex and their reassigned or final sex. Dhejne et al. (2011) found that 19% of MtF clients and 17% of FtM clients had been hospitalized for psychiatric problems other than GD prior to undergoing sex reassignment, compared to only 3–4% of both birth-sex and final-sex matched controls. After SRS, clients with GD were 2.8 times more likely than controls to have been hospitalized for a psychiatric problem other than GD, even after adjustment for prior psychiatric comorbidity; they were 4.2 times more likely prior to this adjustment. After SRS, transsexual clients were 4.9 times more likely to have made a suicide attempt and 19.1 times more likely to have died from suicide, again after adjusting for prior psychiatric comorbidity. The prevalence of these conditions was similar in MtFs and FtMs. The multiple strengths of this study—longitudinal design, absence of selection bias, well-chosen control groups, and unusually long follow-up times—suggest that its findings are likely to be highly reliable.

Heylens et al. (2014a) described the prevalence of current and lifetime comorbid psychopathology in 305 clients with GD (182 MtFs, 123 FtMs) seen from 2007 through 2010 in gender clinics in Belgium, Germany, the Netherlands, and Norway that participated in the European Network for the Investigation of Gender Incongruence. Data were collected using the Mini International Neuropsychiatric Interview-Plus and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders. Approximately 38% of clients had a current Axis I disorder and about 69% had a lifetime Axis I disorder, with similar prevalence figures in MtFs and FtMs. The most common Axis I conditions were mood disorders (27% current, 60% lifetime) and anxiety disorders (17% current, 28% lifetime). Although this study did not employ a formal control group, these figures substantially exceed prevalence rates of comorbid psychopathology in the general population in Western European countries. For example, Alonso & Lépine (2007) used the Composite International Diagnostic Interview and found that, in a representative sample of adults from six European countries, only 26% reported a lifetime prevalence of any mental disorder. About 30% of both MtFs and FtMs had either attempted suicide or reported recent suicidal ideation. About 15% of GD clients had one or more DSM-IV Axis II disorders, a prevalence similar to that of the general population in the countries that participated in the European Network for the Investigation of Gender Incongruence. There were no significant differences in comorbid conditions between early-onset and late-onset GD groups, except for a higher prevalence of Axis II disorders in late-onset FtMs.

Eight other studies that used structured clinical interviews for data collection (Colizzi et al. 2015; Gómez-Gil et al. 2009; Guzmán-Parra et al. 2015; Haraldsen & Dahl 2000; Hepp et al. 2005; Madeddu et al. 2009; Mazaheri Meybodi et al. 2014a,b) reported generally similar results (see **Supplemental Table 1**): Most found about a 30–40% prevalence of current comorbid psychopathology and about a 50–80% prevalence of lifetime comorbid psychopathology in adults with GD, including a 20–60% prevalence of personality disorders. Another large study by Landén et al. (1998), which used data from Swedish national registries—the same method that Dhejne et al. (2011) subsequently employed—reported similar results, as did three smaller studies by Miach et al. (2000) and De Cuypere et al. (1995, 2006), all of which found a high prevalence of associated psychopathology despite the use of unstructured clinical interviews. The studies by Dhejne et al. (2011) and Heylens et al. (2014a) and these 12 other studies, summarized in the first 14 rows of **Supplemental Table 1**, probably provide the most reliable estimates of the prevalence of associated psychopathology in adults with GD.

Supplemental Material

Four other studies have used self-report screening instruments to assess current depression, anxiety, and psychological distress in large cohorts of US transgender adults, some of whom probably would not have met full diagnostic criteria for GD (Bockting et al. 2013, Budge et al. 2013, Clements-Nolle et al. 2006, Nuttbrock et al. 2013). All of these studies found that current depression and anxiety were significantly more prevalent in adults with GD than in the general population: about a 45–60% prevalence of current depression and about a 35–40% prevalence of current anxiety. The results of these studies are summarized in the final four rows of **Supplemental Table 1**.

Supplemental Material

Studies that Find Little or No Increased Prevalence of Associated Psychopathology

Some studies have identified no or little increased prevalence of associated psychopathology. These reports are sometimes cited to support the idea that GD is "usually an isolated diagnosis" (Cole et al. 1997, p. 13) or one that is "associated with a low level of psychopathology" (Fisher et al. 2013, p. 417). Few of these studies, however, employed structured clinical interviews. Hoshiai et al. (2010) observed that investigations that use structured clinical interviews typically report higher comorbidity rates than investigations that do not, and they suggested that the latter studies could easily underestimate the prevalence of comorbid conditions:

> Studies using the structured clinical interview revealed a relatively high comorbidity rate of Axis I disorders (30–67%), while studies without a structured interview showed a lower comorbidity rate of Axis I disorders (4–19%). The possibility that clinical diagnosis without a structured interview missed psychiatric comorbidity among GID patients cannot be denied. (p. 517)

Some reports that found a relatively low prevalence of comorbid psychopathology also have other methodological limitations that render their conclusions questionable.

Five studies that found little or no increased prevalence of associated psychopathology in adults with GD are summarized in **Supplemental Table 2** (follow the **Supplemental Material link** in the online version of this article or at **http://www.annualreviews.org**). The report by Fisher et al. (2013) is arguably the most detailed and methodologically sound; the prevalence figures it found for current and lifetime associated psychopathology (approximately 15–20% current, and approximately 30% lifetime) are lower than most of the studies listed in **Supplemental Table 1** and are not greatly different from general population estimates in Western countries. Fisher et al. found an especially low prevalence of personality disorders—lower than in the general population. The report by Colizzi et al. (2014) described the same client cohort as the report by Colizzi et al. (2015) in **Supplemental Table 1** but found much lower prevalence figures for associated psychopathology; the reasons for this difference are unclear, although it was noted that there were "several patients with substantial functional impairment that did not receive a standard diagnosis based on the DSM-IV-TR criteria due to an insufficient number/duration of symptoms" (p. 71).

The final three studies listed in **Supplemental Table 2** are methodologically less strong and may have underestimated the prevalence of comorbid psychopathology. The low prevalence figures reported by Hoshiai et al. (2010) are especially puzzling, given the very high prevalence of suicidal ideation, suicide attempts, and self-harm among their participants. Reports by Terada et al. (2011, 2012), which examined subsets of the larger client cohort described by Hoshiai et al. and which are not included in the table, found almost identical results: Comorbid psychiatric diagnoses were uncommon, but approximately three-quarters of clients reported suicidal ideation or suicide attempts.

Self-Report Measures of Associated Psychological Symptoms

Several investigators have used self-report measures, including the Symptom Checklist-90-Revised (SCL-90-R), MMPI, and MMPI-2, to examine psychiatric symptoms in adults with GD. Reports using the SCL-90-R have generally found that GD clients—at least prior to treatment—have significantly higher mean scores than healthy control subjects (Auer et al. 2013b, Davey et al. 2014, Haraldsen & Dahl 2000, Heylens et al. 2014b, Simon et al. 2011). Haraldsen & Dahl (2000) also found, however, that the GD clients had significantly lower mean scores than clinical clients with personality disorders. Differences between the mean SCL-90-R scores of GD clients and healthy control subjects, although statistically significant, were typically small and in most cases clinically unimportant. Unfortunately, investigators have not systematically examined differences in the percentages of clinically elevated SCL-90-R scores between GD clients and healthy control subjects.

Several studies have used the MMPI or MMPI-2 to assess psychopathology in adults with GD. Most investigations conducted prior to 2000, however, involved small numbers of participants, and their results have been inconsistent or contradictory (for reviews, see Gómez-Gil et al. 2008, Miach et al. 2000). In one of the larger pre-2000 studies, which involved 93 MtFs and 44 FtMs, Cole et al. (1997) found that mean MMPI clinical scale scores were in the normal range for both MtF and FtM participants, but more than 20% of participants had *T* scores ≥70 on at least one clinical scale, excluding the Gender Identity Scale (Mf). Miach et al. (2000) and Gómez-Gil et al. (2008) found similar results using the MMPI-2: Clients with GD had mean clinical scale scores in the normal range, but 28% of MtFs and 27% of FtMs had *T* scores ≥65 on one or more clinical scales (excluding Mf), especially those measuring depressive, psychopathic, paranoid, or schizophrenic traits.

Increased Prevalence of Suicidality and Self-Harm

Supplemental Material

Supplemental Table 3 (follow the **Supplemental Material link** in the online version of this article or at **http://www.annualreviews.org**) summarizes the results of 13 studies that investigated suicidality and self-harm in adults with GD. These studies suggest that about one in three adults with GD has experienced suicidal ideation, attempted suicide, or engaged in suicidal or nonsuicidal self-harm. The results described by Dhejne et al. (2011)—a greatly increased likelihood of attempted and completed suicide a decade or more after completion of SRS—are particularly disconcerting. Prevalence figures for suicide attempts, which usually reflect self-reports, vary widely between studies—probably a result of varying standards for what constitutes an attempt. Dhejne et al. (2011) found a 9.0% prevalence of documented suicide attempts in adults with GD over a minimum 10-year follow-up period, compared to a 1.4% prevalence in age- and sex-matched control subjects.

Explanations of Associated Psychopathology

Mental health professionals who agree that GD is a genuine mental disorder would probably consider the increased prevalence of associated psychopathology in adults with GD unsurprising, given that different types of mental disorders are significantly correlated with each other and that having one mental disorder greatly increases the probability of having one or more other mental disorders (Caspi et al. 2014, Newman et al. 1998). Mental health professionals who doubt that GD is a genuine mental disorder generally invoke other explanations to account for the increased prevalence of associated psychopathology; these include the psychological consequences of gender incongruence and especially the effects of minority stress (Meyer 2003), a term that refers to the

stressful consequences of the prejudice, discrimination, and victimization that persons with GD often experience.

Meta-analytic reviews (Pascoe & Smart Richman 2009, Pieterse et al. 2012) demonstrate that perceived prejudice and discrimination are associated with an increased prevalence of mental health problems in minority groups, although effect sizes are small to medium: typical correlations are about 0.20. Moreover, direction of effect cannot be conclusively determined (i.e., whether prejudice and discrimination lead to a greater likelihood of developing mental health problems, or whether mental health problems lead to a greater likelihood of experiencing—or perceiving—prejudice and discrimination).

Several studies have investigated the relationship between psychosocial variables and associated psychopathology or related symptoms (suicidality or self-harm) in persons with GD. Perceived prejudice and discrimination have been found to be positively associated with general mental health symptoms (Bockting et al. 2013), depression (Nuttbrock et al. 2013), suicidality (Clements-Nolle et al. 2006), and self-harm (Claes et al. 2015). One study with implications for direction of effect (Nuttbrock et al. 2013) found that gender-related abuse that had been experienced a year earlier was associated with current depression in MtFs age 30 or younger—but not in MtFs older than age 30. Bauer et al. (2015) found that greater social support was associated with less suicidality.

A number of studies have found that receiving treatment for GD, especially hormone treatment, is associated with lower levels of psychopathology (Colizzi et al. 2014, 2015; Gorin-Lazard et al. 2013; Heylens et al. 2014b; Murad et al. 2010; Newfield et al. 2006) and suicidality (Bauer et al. 2015). Conversely, anxiety and depression are more prevalent early in the transition process (Budge et al. 2013). Clients who have completed at least a year of hormone therapy and cross-living and are applying for SRS demonstrate less psychopathology than clients undergoing evaluation for hormone therapy (Gómez-Gil et al. 2008). In contrast to many of these findings, Dhejne et al. (2011) reported that even after successful completion of SRS—and after adjustment for pretreatment psychopathology—transsexuals exhibited much higher prevalence rates for psychopathology and suicidality than age- and sex-matched control groups.

Investigators have also reported a few findings that are not easy to reconcile with the hypotheses that gender incongruence and minority stress are causally related to a higher prevalence of psychopathology in adults with GD. For example, Bockting et al. (2013) found no significant association between self-reported GD (as a symptom, not a formal diagnosis) and symptoms of psychopathology in transgender adults. Moreover, Heylens et al. (2014a) and Terada et al. (2012) found no significant relationship between age of onset of GD and prevalence of comorbid psychopathology, which seems contrary to the expectation that an earlier onset of GD and a consequent lengthier exposure to experiences of prejudice and discrimination ought to be associated with more prevalent psychopathology. Interestingly, Terada et al. (2012) found that nonhomosexual orientation in MtFs and analloeroticism (lack of attraction to either men or women) in FtMs was positively associated with comorbid psychopathology.

CAUSAL MECHANISMS

Understanding the genesis of GD has relied on some general principles about "normative" or sex-typical psychosexual development. A simple model is that the mechanisms involved in normative sex-dimorphic psychosexual differentiation (including gender identity itself) are inverted in the development of GD. Thus, a normative sex differentiation model, not only as used in human studies but also in scores of animal studies (Wallen 2009), has guided much of the causal mechanism research on the development of GD, whether such research is biological or psychosocial. It is,

however, important to note that within-sex models have also been utilized; such models involve the identification of mechanisms that might explain a within-sex difference in a sex-dimorphic trait. An example of this would be the fraternal birth order effect, namely, the finding that gay men have more older brothers than do heterosexual men. Although there is an enormous sex difference in sexual orientation, the hypothesized mechanism regarding the fraternal birth order effect applies only to males (Blanchard 2004).

Biological Processes

In this section, we summarize research on biological mechanisms in two areas: genetics and the role of prenatal sex hormones, including their effects on putative sex-dimorphic neural structures.

Genetics. Family and twin studies have examined whether genetic factors contribute to the development of gender identity, GD, and related phenomena (Burri et al. 2011, Gómez-Gil et al. 2010, Heylens et al. 2012, Loehlin et al. 2005). Loehlin et al. (2005) examined the heritability of gender diagnosticity, a scale that predicts whether an individual is masculine or feminine based on gender-related interests: 25% to 47% of the total variance was explained by genetic factors. Recalled gender nonconformity was studied in adult twins, with heritability estimates ranging from 0.50 to 0.57 in men and from 0.37 to 0.40 in women (Bailey et al. 2000). Burri et al. (2011) examined recalled childhood gender typicality, sexual orientation, and adult gender identity. Heritability for the Adult Gender Identity Scale was only 0.11. A study in twins of which one was diagnosed with GID showed that 39.1% of the monozygotic twins were concordant for GID, whereas none of the dizygotic twins were concordant (Heylens et al. 2012).

Genes that are involved in either sex steroid biosynthesis or action have been investigated because it is known that sex steroids contribute to the sexual differentiation of the brain. Complete loss of function of the androgen receptor in XY individuals with complete androgen insensitivity syndrome almost invariably results in a female gender identity; therefore, it may be a candidate gene that affects gender identity development. In MtFs, a longer *CAG* repeat length polymorphism in the androgen receptor was found (Hare et al. 2009), but another study with a larger sample failed to replicate this finding (Fernández et al. 2014b). Estrogen receptor (*ER*) genes have also been studied. The prevalence of a long *CA* repeat in *ERβ* was found to be higher in MtF transsexuals than in control men (Henningsson et al. 2005). Because the *CYP19* is important for aromatization of androgens into estrogens, this gene may be another candidate, but none of the studies found support for this gene's involvement in the development of GD (Fernández et al. 2014b, Hare et al. 2009, Henningsson et al. 2005, Ujike et al. 2009). In FtMs, there was a link to the *CYP17* gene (Bentz et al. 2008) and to polymorphism of the *ERβ* gene (Fernández et al. 2014a), but another study did not find any associations with these polymorphisms (Ujike et al. 2009).

At present, no strong candidate gene has been found that can account for the development of GD. Many human traits and diseases have a polygenic architecture, where the phenotype is determined by variation in many genes. This is plausibly the case for GD, and future studies should determine if the architecture is polygenic or if there are specific loci with larger effects. In addition, gender identity is most likely a complex trait that results from a combination of multiple genetic and environmental factors. In twin, adoption, or family studies, these factors can be dissected. Furthermore, phenotypes should be carefully defined, and homogeneous groups should be compared. In neuroimaging studies (see below), attention has now been drawn to the importance of describing the phenotypes and taking into account sexual orientation and age of onset.

Prenatal sex hormones. Sexual differentiation of all somatic tissues has long been ascribed to exposure of androgenic hormones in the fetus (Bocklandt & Vilain 2007), resulting in masculine phenotypes in the presence of androgenic hormones and feminine phenotypes in the absence of these hormones. These early effects of sex hormones on the brain are denoted as organizing effects, as opposed to effects of circulating hormones later during life on the already organized neural system (Phoenix et al. 1959). It is hypothesized that feelings of gender incongruence may arise from atypical sexual differentiation of the brain under the influence of prenatal hormones (Swaab & Garcia-Falgueras 2009). Time windows for prenatal development of genitals and the brain are believed to differ; thus, exposure to atypical levels of prenatal hormones during a certain gestational period may have an effect on the brain but not the body.

Sex-dimorphic neural structures. In the search for neurobiological underpinnings of GD, brain structure and function have been studied to determine whether the brains of transgender individuals show atypical sexual differentiation. A series of Dutch studies fueled this line of research by showing female-typical hypothalamic nuclei in MtF transsexuals (Garcia-Falgueras & Swaab 2008, Kruijver et al. 2000, Zhou et al. 1995). The aim of subsequent imaging studies was to determine whether the brains of people with GD would show more resemblance to their experienced gender than their natal sex. **Supplemental Table 4** (follow the **Supplemental Material link** in the online version of this article or at **http://www.annualreviews.org**) summarizes imaging studies in adults with GD before the start of cross-sex hormone treatment.

Supplemental Material

Gray matter is one of the main components of the CNS and largely consists of neuronal cell bodies. Studies of nonhomosexual MtFs have shown that gray matter volumes were largely in line with their natal sex (Luders et al. 2009, Savic & Arver 2011). For homosexual MtFs, some differences have been observed: Like control women, homosexual MtFs showed larger gray matter volumes in comparison with male controls and FtMs in several cortical regions (Simon et al. 2013). Another measure of gray matter volume is cortical thickness (CTh). CTh is generally higher in women than in men. Homosexual MtFs showed CTh similar to that of female controls but increased CTh compared with male controls in the orbito-frontal, insular, and medial occipital regions of the right hemisphere (Zubiaurre-Elorza et al. 2013). Using this measure, nonhomosexual MtFs also showed higher CTh compared with control men (Luders et al. 2012).

The putamen, a nucleus that is part of the basal ganglia and mainly associated with motor regulation, is the only subcortical structure that has shown differences, although the findings are diverse: The right putamen of nonhomosexual MtFs was larger than that of control men and was in the female range in one study (Luders et al. 2009), but relatively smaller than that of male and female controls in another study (Savic & Arver 2011). In homosexual MtFs, the volume of the putamen was comparable to that of male and female controls (Zubiaurre-Elorza et al. 2013).

White matter mainly contains myelinated nerve fibers. Diffusion tensor imaging (DTI) is a technique that is used to visualize white matter microstructure. One DTI study found that homosexual MtFs had a pattern that was significantly different from control men and control women (Rametti et al. 2011b) and the values were in between male and female controls. A similar picture, but with another DTI measure, was found in MtFs (in both homosexual and nonhomosexual subgroups): Mean diffusivity values were increased compared to control males (Kranz et al. 2014b). Structural connectivity networks were also examined in the same participants (Hahn et al. 2014). A decreased hemispheric connectivity ratio in subcortical/limbic regions was found in mainly nonhomosexual MtFs compared to control men and women, which seemed to be related to an increased interhemispheric lobar connectivity.

With regard to the sexual differentiation hypothesis, the following picture now emerges, taking sexual orientation into account: Homosexual MtFs are dissimilar to their natal sex in gray matter

volume (Simon et al. 2013), CTh (Zubiaurre-Elorza et al. 2013), and white matter microstructure (Rametti et al. 2011b). For nonhomosexual MtFs, the picture is less clear: Their gray matter volumes were in line with their natal sex (Luders et al. 2009, Savic & Arver 2011), but they do show differences in white matter microstructure compared to control men (Kranz et al. 2014b). However, all groups in the Kranz et al. study were mixed with regard to sexual orientation, which may have affected the results. Overall, evidence supports the sexual differentiation hypothesis in homosexual MtFs, but not in nonhomosexual MtFs. Natal women with GD are more homogeneous with regard to sexual orientation (most are homosexual). FtMs (like control men) had larger gray matter volumes than female controls and MtFs in several areas (Simon et al. 2013), and similar CTh to control women (Zubiaurre-Elorza et al. 2013). Like male controls, they had a larger volume of the putamen than female controls (Zubiaurre-Elorza et al. 2013). White matter FA values of FtMs were significantly greater than those of female controls but similar to those of male controls in several fascicles (Rametti et al. 2011a). In one of the fascicles, the corticospinal tract, FtMs had values in between male and female controls. Kranz et al. (2014b) found a significant decrease in mean diffusivity values in FtMs compared with control females. Intrahemispheric connectivity between the right subcortical/limbic and right frontal and temporal lobes was decreased in FtMs compared with male and female controls and MtFs (Hahn et al. 2014). All structural studies in adult FtMs thus far render support for atypical sexual differentiation of their brains.

Neural functioning. Functional connectivity is a method to evaluate interactions between regions while performing a task (task-related functional connectivity) or while not performing a particular task (resting-state connectivity). While viewing erotic and nonerotic interactions of male-female couples, the functional connectivity of MtFs and FtMs (as a group) showed an increase between the ventral tegmental area and the anterior cingulate cortex subregions compared to controls (men and women together) (Ku et al. 2013). It was argued that because the ventral tegmental area is associated with dimorphic genital representation and the anterior cingulate cortex is central in conflict monitoring and social processing, the pattern could be a substrate of the psychological distress of transgender individuals. These findings should thus not be viewed in the realm of the sexual differentiation hypothesis, but rather are more suggestive of the brain's substrate for incongruence between body and identity.

Functional studies that focus on homosexual MtF adults do not exist, nor are there studies that compare homosexual with nonhomosexual MtF adults. In nonhomosexual MtFs, a female-like response in hypothalamic activation while smelling odorous steroids (Berglund et al. 2008) and brain activity while viewing erotic videos (Gizewski et al. 2009) were detected, arguing for sex-atypical reactions in these groups. Brain activation patterns during voice perception of a sexual-orientation mixed group of MtFs differed from those of men and, partly, also of women (Junger et al. 2014). Differences were shown in brain activation during a visuospatial task in MtFs with unknown sexual orientation in comparison with controls of their natal sex (Schöning et al. 2010).

While processing positive affective images, FtMs under gonadal suppression with gonadotropin-releasing hormone agonists (GnRHa) showed less activation in the right superior temporal lobe compared to control women (Soleman et al. 2016). The findings may well be related to their GD instead of the GnRHa treatment because no associations with hormonal levels were found.

Kranz et al. (2014a) studied the hemispheric asymmetry in the cerebral serotonin transporter system in males, females, and MtF transsexuals because lateralization of emotional processing has been shown. Serotonin is known to play an important role in emotional processing, and hemispheric asymmetry of the serotonin system has been reported as well. MtFs differed from

male controls in the midcingulate cortex (rightward asymmetry for male controls but not for MtFs and female controls) and from female controls in the calcarine gyrus. It was concluded that MtFs show asymmetries of the serotonin transporter system "that relate to both genetic sex, gender and a special feature of gender dysphoria" (p. 180).

In sum, findings indicate structural as well as functional alterations in the brains of transgender individuals, either as a consequence of atypical sexual differentiation or as a result of a mismatch between their anatomical sex characteristics and their gender identity. Brain changes may also be triggered by psychological distress. Future studies should carefully consider the phenotypes of participants, ideally combining genetic profiles with neuroimaging measures.

Psychosocial Processes

Nascent markers of gender identity emerge very early in development (Martin et al. 2002). To the extent that gender identity is a stable trait, psychosocial factors—to truly merit causal status—should be able to account for the emergence of a cross-gender identity in the first few years of life, when it is first expressed. Otherwise, psychosocial factors would be better conceptualized as having a perpetuating role. If psychosocial factors can also account for instances of a cross-gender identity that first manifest in adolescence or even later (the late-onset form of GD discussed previously), they should also be operative prior to the time of onset.

Given these assumptions, it is obvious that the study of causal psychosocial factors in adults with GD faces methodological barriers because it largely relies on retrospective methods, which are subject to many interpretive problems. As an example, Cohen-Kettenis & Arrindell (1990) had both MtF and FtM adult clients rate their parents on the *Egna Minnen av Barndoms Uppfostran* (My Memories of Upbringing) questionnaire with regard to three dimensions of behavior: rejection, emotional warmth, and overprotection (e.g., intrusiveness, strictness). Compared to a volunteer sample of male community controls, the MtF clients did not differ significantly in their recollection of maternal behavior; however, fathers were rated as significantly more rejecting, less warm, and more overprotective. The FtM clients rated their mothers as significantly more rejecting, less warm, and more overprotective than the female controls. They also rated their fathers as more rejecting and less warm.

Regarding the MtF data, it could be argued that there was no support for the maternal overcloseness hypothesis theorized to play a role in the development of GD (Stoller 1968); however, ratings of the fathers could be interpreted as support for a distance hypothesis (Green 1987). Regarding the FtM data, it could be argued that there was support for a maternal undercloseness hypothesis that has been theorized (Stoller 1975), but there was no support for an overcloseness hypothesis with the father, since the fathers were also rated as more rejecting and less warm.

Consider three challenges in interpreting these kinds of data. First is the direction-of-effect conundrum. For example, perhaps fathers of MtF clients were more rejecting because they themselves were alienated by the feminine-gendered behaviors of their son in childhood, so the direction of effect was from son to father, not father to son (Freund & Blanchard 1983). Second, the community controls were volunteers, so it is conceivable that this was a source of bias (e.g., perhaps they were more likely than a truly random sample to come from families that were more harmonious). Third, the study lacked a clinical control group. A control group would have been desirable to determine whether the adult clients with GD recalled patterns of parental behavior that were unique or simply characteristic of clinical populations in general (Garber & Hollon 1991).

One conceptual issue is the extent to which gender identity is a stable, within-person trait, almost impervious to external influences once it has become internalized. An ideal study would be to sample a representative cohort of young children who have a clear-cut identity as a boy or as

a girl and to assess their gender identity again much later in development (e.g., in adolescence or adulthood) in order to examine its stability. Although the data are limited, some evidence suggests that gender identity is likely a very stable trait. In Green's (1987) study of very feminine boys, a control sample of boys, who were all behaviorally masculine in childhood and presumably had a male gender identity, all had a male gender identity at follow-up in late adolescence. Steensma et al. (2013b) used data from a longitudinal study of 879 Dutch children to assess the stability in gender identity at two time points: any time between 4 and 12 years of age and then 24 years later (mean ages, 7.5 years and 30.9 years, respectively). On the Child Behavior Checklist, 818 parents indicated that their child did not express a wish to be of the other gender or to behave like the other gender. At follow-up, 98.8% of these now grown-up children did not self-report a desire to be of the other gender.

In clinical populations of children with GD, however, gender identity stability is less certain. A number of studies have shown that the majority of these children do not persist in their desire to be of the other gender when followed up in late adolescence or adulthood (Drummond et al. 2008, Green 1987, Singh 2012, Wallien & Cohen Kettenis 2008), particularly in samples in which a social transition to living as the desired gender has not occurred prior to puberty (Steensma et al. 2013a).

If children with GD shift their gender identity in a direction that is more congruent with their natal sex, and if there are some adults who initially identify as a sexual orientation minority (Diamond & Butterworth 2008) but then shift their gender identity so that it is no longer congruent with their natal sex, then it becomes important to understand the proximal factors that might contribute to this change. One such factor may involve an iterative matching process between surface expressions of gender role behavior and identity. Many children with GD show a diminution of their cross-gender role behavior over time, which may lead to a shift in their underlying gender identity or identification. Conversely, adults with a minority sexual identity and who have a history of marked gender-nonconforming behavior may eventually settle on a cross-gender identity that is more comfortable for them, as noted by Diamond & Butterworth (2008). Taken together, these data suggest that, for at least some individuals, gender identity may be a more dynamic, fluid process than previously thought.

THERAPEUTICS

The treatment of adults with GD is now largely standardized in developed countries, reflecting the influence of clinical guidelines promulgated by professional associations. The *Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Version 7* (SOC-7; Coleman et al. 2011) is the best known and most influential guideline; similar recommendations have been published by the Royal College of Psychiatrists (Wylie et al. 2014), a task force of the American Psychiatric Association (Byne et al. 2012), the Endocrine Society (Hembree et al. 2009), and other professional groups (for reviews, see Gooren & Asscheman 2014, Lawrence 2014, Monstrey et al. 2014). These guidelines represent the views of experienced clinicians and scholars, but many of their recommendations reflect a low quality of evidence (i.e., case-series reports and expert opinion) (Byne et al. 2012).

The following subsections examine recent developments and controversies related to the treatment of adults with GD. Two broad themes underlie these analyses. First, the contemporary emphasis on reducing barriers to care and promoting client autonomy and self-determination is not easily reconciled with some elements of current treatment guidelines. Second, the increasing diversity of adults who qualify for a GD diagnosis has not been matched by an expanded range of treatment options addressing this diversity.

Diagnosing GD and Comorbid Conditions and the Role of Mental Health Professionals

The SOC-7 rescinded the longstanding requirement that the diagnosis of GD and any associated psychopathology be made by mental health professionals (MHPs). Now, any "health professional who is appropriately trained in behavioral health and competent in the assessment of gender dysphoria" (Coleman et al. 2011, p. 181) may make these diagnoses and any contingent treatment recommendations. This change, intended to reduce barriers to care, may unintentionally result in underdiagnosis of comorbid psychopathology. As noted previously, even experienced MHPs tend to underdiagnose comorbid psychopathology unless they employ structured clinical interviews.

MHPs have historically served as gatekeepers as well as diagnosticians for adults with GD, because eligibility for hormone therapy and SRS has traditionally been contingent on assessments that only MHPs were considered qualified to make. Some clinicians believe that such gatekeeping functions are unnecessarily time consuming and potentially undermine individuals' autonomy and choice (Bouman & Richards 2013). The SOC-7 and other guidelines have deemphasized the role of MHPs in recommending hormone therapy: Physicians are now allowed to prescribe hormones without a MHP's recommendation, particularly for clients using hormones without medical supervision (Coleman et al. 2011, pp. 187, 191–192; Wylie et al. 2014, pp. 176–177). This approach to prescribing is sometimes referred to as the informed consent model (Coleman et al. 2011, Deutsch 2012).

This liberalized approach reflects contemporary clinical realities, particularly the widespread use of nonprescribed hormones by persons with GD. Gómez-Gil et al. (2009) reported that approximately 60% of Spanish MtF applicants for sex reassignment had taken hormones without medical supervision (see also Simonsen et al. 2015). Interestingly, some evidence indicates that adults with GD who disregard traditional treatment guidelines and undergo hormone therapy without the recommendation of a psychiatrist achieve psychosocial outcomes similar to those of more compliant clients and achieve them more quickly (Pimenoff & Pfäfflin 2011).

It is not always clear what the informed consent model means. Deutsch (2012), who surveyed 12 clinics that claimed to prescribe hormones using this model, found that whereas "only four of the 12 sites required any contact with a mental health provider" (p. 141), the average time clients spent with MHPs during the intake process was 2.4 hours. Five clinics required a minimum number of visits or imposed specified waiting periods before prescribing, suggesting a belief that meaningful informed consent cannot be obtained quickly. It remains unclear whether informed consent prescribing requires a formal diagnosis of GD or whether any transgender adult who is able to give consent can receive hormones, regardless of diagnosis. It is similarly uncertain whether informed consent requires that any comorbid psychopathology be satisfactorily controlled. A close reading of the SOC-7 suggests that the latter is required—and that the informed consent model is not very different from the standard model:

> The difference between the Informed Consent Model and *SOC, Version* 7, is that the *SOC* puts greater emphasis on the important role that mental health professionals can play in alleviating gender dysphoria . . . In the Informed Consent Model, the focus is on obtaining informed consent as the threshold for the initiation of hormone therapy . . . Less emphasis is placed on the provision of mental health care . . . unless significant mental health concerns are identified that would need to be addressed before hormone prescription. (Coleman et al. 2011, p. 188)

It appears that what one might intuitively consider "informed consent prescribing"—offering medically supervised hormone therapy without preconditions or delay to any transgender person

who requests it, is competent to consent (i.e., not psychotic or grossly mentally impaired), and has received basic information about risks and benefits—is not yet widely available. Given the prevalence of unsupervised hormone use, such a development is arguably overdue.

Counseling and Psychotherapy for Adults with Gender Dysphoria

In past decades, helping adults with GD find greater acceptance and comfort with their natal sex and assigned gender was considered a legitimate goal of counseling and psychotherapy, especially when undertaken at the client's request. Current guidelines, however, describe such efforts as both futile and unethical. According to the SOC-7:

> Treatment aimed at trying to change a person's gender identity and lived gender expression to become more congruent with sex assigned at birth has been attempted in the past (Gelder & Marks 1969; Greenson 1964), yet without success, particularly in the long-term (Cohen-Kettenis & Kuiper 1984; Pauly 1965). Such treatment is no longer considered ethical. (Coleman et al. 2011, p. 186)

The citations allegedly demonstrating that such treatment efforts are "without success" date from 30 to 50 years ago, when adults with GD were much less prevalent and diverse than today. It is recognized that GD can remit in some cases (Marks et al. 2000); perhaps psychotherapy could facilitate such remission—or a reduction in GD symptoms, with greater congruence between gender identity and expression and assigned sex—in some subset of the diverse group of adults whose gender problems now qualify for a diagnosis of GD. Unfortunately, these possibilities have not yet been investigated, and such investigations are strongly discouraged in the SOC-7. If a client with GD decided that overt cross-gender expression carried too great a risk of unacceptable consequences and requested a psychotherapist's help in trying to make their gender identity and gender expression more congruent with their assigned sex, would the therapist's participation always be unethical, as the SOC-7 seems to assert? If so, the SOC's position would seem to conflict with the client's right to autonomy and self-determination. Perhaps the overarching treatment goal of psychotherapy for GD—"long-term comfort in . . . gender identity expression, with realistic chances for success in . . . relationships, education, and work" (Coleman et al. 2011, p. 184)—could sometimes best be achieved by supporting clients in a decision to forego gender transition or overt public cross-gender expression. This psychotherapeutic aim, which was explicitly set forth in version 6 of the SOC [i.e., "acceptance of the need to maintain a job, provide for the emotional needs of children, honor a spousal commitment, or not to distress a family member as currently having a higher priority than the personal wish for constant cross-gender expression" (Meyer et al. 2001, pp. 19–20)], was expunged from the SOC-7.

These issues assume greater importance in light of recent evidence that sex reassignment is associated with more serious psychological sequelae and more prevalent regret than had previously been supposed. Two large population-based studies from Sweden (Dhejne et al. 2011, 2014) are particularly relevant. The 2011 study, discussed previously, described the greatly elevated prevalence of comorbid psychopathology, death by suicide, and suicide attempts in the cohort of clients who underwent SRS between 1973 and 2013. The 2014 study examined the prevalence of "regret applications" (applications for reversal of legal sex reassignment) in clients who underwent SRS during the 1960–2010 period. Only 2.2% of these clients submitted regret applications, over one-quarter of which came from the small cohort of clients who underwent SRS before 1972. But regret applications were made a median of eight years after SRS, so some clients who underwent SRS recently may yet submit such applications. Moreover, whereas only 10 clients who underwent SRS between 1972 and 2000 submitted regret applications, 10 others who underwent SRS between

1973 and 2003 died by suicide, and another 29 made documented suicide attempts (Dhejne et al. 2011). This suggests that regret applications underestimate the prevalence of genuine regret or dissatisfaction after sex reassignment. Moreover, 3.3% of applications for SRS were denied, sometimes due to comorbid psychopathology or failure to meet diagnostic criteria; had these applicants undergone SRS under more liberal standards, they might have contributed to a still greater prevalence of regret. Although a 2.2% prevalence of regret after SRS thus represents a conservative estimate, it substantially exceeds figures previously reported by Pfäfflin (1992; 1.0–1.5%) and Weitze & Osburg (1996; 0.4%). As Dhejne et al. (2014) noted, "This [difference] might be explained by the extensive follow-up time in the present study and by the fact that virtually all cases of regrets are captured in the Swedish registry system" (p. 1543).

A recent meta-analysis by Murad et al. (2010), examining outcomes of sex reassignment in 1,833 participants, confirmed both the benefits and limitations of this treatment. About 86% of FtMs and 71% of MtFs reported improvement in GD symptoms after sex reassignment; about 84% of MtFs and 78% of FtMs reported improvement in quality of life. Thus, it appears that about 20% of clients do not experience significant benefit from sex reassignment. Many adults with GD who now undergo sex reassignment would have been considered unsuitable or risky candidates in years past (Dhejne et al. 2014). Smith et al. (2005) observed that factors predictive of less satisfactory functioning after sex reassignment included nonhomosexual orientation relative to natal sex, greater dissatisfaction with secondary sex characteristics, and more comorbid psychopathology, yet adults with late-onset GD and nonhomosexual orientation, physical characteristics that are highly incongruent with the desired sex, and significant comorbid psychopathology increasingly request and undergo sex reassignment. Perhaps the SOC should reinstate its endorsement, at least in certain cases, of psychotherapy that aims to increase comfort with assigned sex and gender role and discourages sex reassignment.

Real-Life Experience in the Preferred Gender Role

It is now accepted that not all persons with GD will want or need all of the treatment elements available to them. Accordingly, the SOC-7 endorses hormone therapy, real-life experience (RLE), and SRS without psychotherapy; hormone therapy and RLE without SRS; and even RLE and SRS without hormone therapy in certain cases. The ordinary eligibility requirements in the SOC-7, however, do not allow SRS without a 12-month, full-time RLE, even when the client does not desire a RLE. This exception to the principle of client autonomy and self-determination has never been seriously challenged, despite a dearth of evidence supporting the value of RLE as an eligibility criterion for SRS (Lawrence 2013, Levine 2009). Recognizing that SRS has significant risks, the SOC-7 does not require adults with GD to undergo SRS if they can achieve satisfactory relief of GD with hormone therapy and RLE alone. But RLE also carries significant psychosocial risks, including loss of employment, impaired relationships with family and friends, and gender-based discrimination and physical and mental abuse. Given these risks, the SOC arguably should not require adults with GD to undertake a RLE if they can achieve satisfactory relief of GD with hormone therapy and SRS alone.

This issue will probably soon become moot in light of language in the DSM-5 specifying that adults with "a strong desire for the primary and secondary sex characteristics of the other gender" can qualify for a diagnosis of GD on the basis of "a strong desire to be of the other gender (or some alternative gender different from one's assigned gender)" (Am. Psychiatr. Assoc. 2013, p. 452). Consequently, adults with GD who want to undergo SRS to achieve the primary sex characteristics of the other gender but who identify with an "alternative gender" comprising both male and female elements could theoretically satisfy the eligibility requirement of living for

12 months in a gender role that is congruent with one's gender identity (Coleman et al. 2011) by living part-time in their original gender role (e.g., in public) and part-time in the gender role of the other sex (e.g., in private). When this option becomes more widely appreciated, the RLE will be recognized as no longer meaningful and will cease to be an eligibility requirement for SRS.

Hormone Therapy

Recent investigations have largely confirmed the opinion that hormone therapy is an effective and reasonably safe treatment in adults with GD. As noted previously, Murad et al. (2010) found that cross-sex hormone treatment, usually accompanied by SRS, was associated with improvement in GD, other psychological symptoms, and quality of life in about 80% of MtFs and FtMs. Cross-sectional studies have also shown that hormone-treated MtFs and FtMs who have not undergone SRS demonstrate significantly better quality of life (Gorin-Lazard et al. 2012), greater self-esteem, better mood (Gorin-Lazard et al. 2013), and less psychological distress (Heylens et al. 2014b) than persons who have not yet begun hormone treatment. But hormone therapy can be associated with significant medical complications. Wierckx et al. (2012) found that, in 50 MtF clients who had used feminizing hormones for a mean of 9.2 years, there were 3 (6%) thromboembolic events and 3 (6%) other cardiovascular complications, including 2 myocardial infarctions; moreover, about one-quarter of MtF clients had significant osteoporosis. Wierckx et al. (2012) could not, however, document any significant cardiovascular events or other serious complications in 50 FtM clients who had used masculinizing hormones for a mean of approximately 10 years. In a subsequent prospective study of 53 MtFs and 53 FtMs who received cross-sex hormone therapy for one year, Wierckx et al. (2014) found no evidence of serious complications.

Hormone therapy for adult males with GD has traditionally included testosterone suppression with spironolactone, cyproterone acetate (not available in the United States), or GnRH agonists. Although both the SOC-7 (Coleman et al. 2011) and the Endocrine Society guidelines (Hembree et al. 2009) mentioned the use of GnRH agonists in adult males with GD, the SOC-7 deemphasized GnRH agonists because of their expense and administration by injection or subcutaneous implantation; it described cyproterone and spironolactone as more cost effective. In contrast, the recent Royal College of Psychiatrists guidelines (Wylie et al. 2014) emphasized the problems associated with spironolactone and cyproterone acetate and recommended GnRH agonists as an "alternative and preferable" means of testosterone suppression in adult males with GD. GnRH agonists may soon supersede traditional antiandrogens in this role.

Sex Reassignment Surgery

Few controlled studies have examined the psychosocial outcomes of SRS per se. Mate-Kole et al. (1990) compared 20 MtFs who underwent vaginoplasty on an expedited basis with 20 wait-list control clients; SRS clients were more socially active and displayed less anxiety, depression, and obsessionality. Barrett (1998) examined psychological and social functioning in 40 FtMs who had undergone phalloplasty an average of four years previously and 23 FtMs who had been approved for, but were still awaiting, phalloplasty; there were no significant between-group differences in SCL-90-R scores. Udeze et al. (2008) studied 40 MtFs who completed the SCL-90-R before and six months after undergoing SRS, with each client acting as her own control; no significant differences in pre- and post-SRS scores were found. In a study discussed previously, Heylens et al. (2014b) compared SCL-90-R scores in 46 MtFs and 11 FtMs before treatment, after hormone therapy, and after SRS. Before treatment, clients' mean subscale scores were significantly higher than those of general population controls. After hormone therapy, clients' scores no longer differed from those of controls, but no further improvement was observed after SRS. Contemporary outcome

studies of SRS are therefore consistent with earlier ones: Although the great majority of adults with GD report improved subjective satisfaction, objectively measured psychological symptoms neither improve nor worsen after SRS.

SUMMARY

In this article, we have provided an overview of GD in adults, including terminology and phenomenology, epidemiology, diagnosis and assessment, associated psychopathology, causal mechanisms, and therapeutics. As transgender adults have attained increasing recognition, modern cultures have undergone a remarkable change with regard to acceptance and support of people with GD, including legal recognition and better access to health care. As more transgender adults "come out," we hope that this article will provide the contemporary clinician with a greater understanding of the research and clinical issues that will inform best practice in working with this underserved population.

DISCLOSURE

Dr. Zucker was the Chair of the DSM-5 Workgroup on Sexual and Gender Identity Disorders.

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