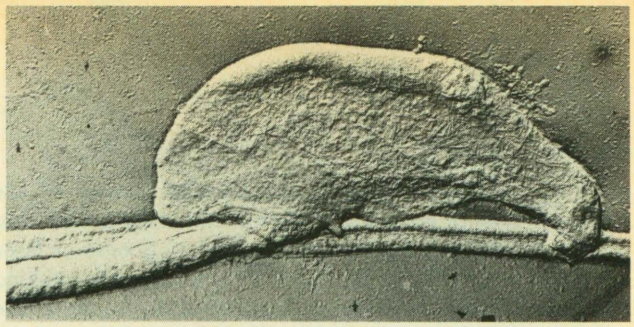
— file: Transsex.



The buck starts here. So do the boar, bull, billy goat, ram, tomcat—and man. On acrosomal cap of sperm (here, that of a mouse), sites of maleness-enforcing H-Y antigen are labeled by tiny hairlike tobacco mosaic virus particles in photo from Dr. Gloria Koo's lab at Sloan-Kettering. Tail of sperm shows no antigen.

GENES, GENDER, AND GENITAL REVERSAL

If embryos could talk, they might voice agreement with surgeons treating transsexuals: It's a lot harder to achieve maleness than femaleness.

"The development of maleness is a complex and precarious process—a continuing struggle against the basic trend toward femaleness," says Cornell endocrinologist Ralph E. Peterson. Science is now shedding a good deal of new light on how the male fetus' Y chromosome and its deputies direct their side of the struggle, convincing primitive gonads to give up their innate tendency to become ovaries, protecting the male wolffian duct from being overpowered by its female müllerian neighbor, and persuading the genital tubercle to forsake its clitoral destiny for that of a penis.

For each of these tissues, maleness appears as a detour, not the main road. Pediatricians are refining their ideas about what to do when the detours aren't all successfully negotiated—or are partially mimicked, in a genetically female fetus, by such influences as exogenous androgens.

And while clinicians still disagree about why some people

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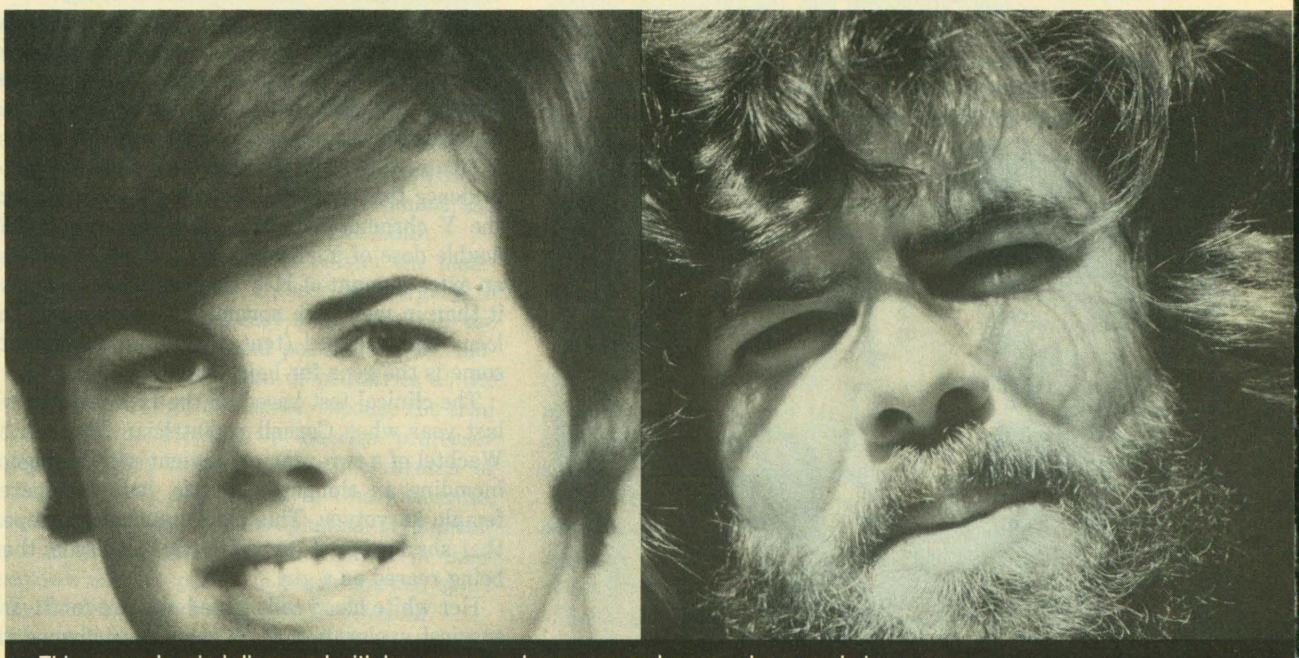

This woman's mind disagreed with her genes, so hormones and surgery have made her a man

grow up convinced that the sex identity success of the fetuses they once were was a big mistake, they are moving toward a consensus on what to do about it. Sooner or later every physician will be consulted by a transsexual seeking help, predicts Dr. Ira B. Pauly, professor of psychiatry at the University of Oregon in Portland—and in this issue MWN provides a directory of available referral services (page 57).

Until recently, no one knew how the Y chromosome enforces its insistence on masculinization. But immunologist Stephen S. Wachtel of New York City's Memorial Sloan-Kettering Cancer Center has apparently found its chief deputy enforcer: a Y-induced histocompatibility antigen, H-Y for short, that appears to occur on the surface of all male mammalian cells and in fact to be on the job determining sex throughout the vertebrate family tree, down at least to the bony fishes.

Its mission during embryogenesis, says Dr. Wachtel, "seems to be directing the indifferent gonad to develop toward the heterogametic sex"—in mammals, the male. He suggests that from its cell-surface perch it acts as a "cell recognition signal" that causes the bipotential gonad to turn into testes, thus launching the process of virilization. Columbia University cytogeneticist Orlando J. Miller calls the antigen "the ultimate determinant of maleness."

And the new antigen has already been put to work clinically to help decide in which direction ambiguous genitalia should be modified. It can also help determine whether laparotomy should be done to remove cryptic testicular tissue that may be cancer-prone.

A couple of years ago, Dr. Wachtel was studying why inbred female mice reject skin transplants from genetically identical male mice, whereas males accept female skin grafts. The only possible histoincompatibility, scientists reasoned, resided in their oppositeness of sex; the females were literally "allergic" to some cell-surface factor inherent in maleness. Hence, this factor must be related to the Y chromosome—the only one they did not share.

Dr. Wachtel's discovery of the sexually strategic H-Y antigen was sparked by a need to explain male-to-female graft rejection in genetically uniform strains of mice.

"If H-Y antigen is really the long-sought product of the mammalian testis-determining gene," Dr. Wachtel told a recent symposium in Albany, N.Y., on the genetic mechanisms of sexual development, "then its expression on the cell surface should always be associated with formation of at least rudimentary testes, regardless of phenotypic sex or apparent karyotype." Thus, if a woman's blood tests indicate that she has the Y antigen, she must be presumed to harbor cryptic testicular tissue despite her XX karyotype and normal female genitalia.

He found a striking verification of his hypothesis in a Scandinavian rodent, the wood lemming (*Myopus schisticolor*). This small creature has another claim to fame besides its reputed cyclic mass suicidal migrations to the sea: The female of the species is almost as likely to carry an XY karyotype as an XX. Despite this chromosomal "masculinity," XY female lemmings are anatomically quite female, and fertile. And Dr. Wachtel found that their Y-linked maleness gene yields no H-Y antigen. He presumes that some other gene, probably a mutation on the X chromosome, has switched off the Y, thus preserving the XY females from developing any occult testicular tissue in utero.

A similar X-linked mutation, suggests the Sloan-Kettering immunologist, perhaps explains some forms of gonadal dysgenesis in human females with an anomalous Y chromosome. Similarly, in a rare variant of Klinefelter's syndrome, there are human anatomic males with two X chromosomes and no apparent Y who test positive for H-Y antigen. They presumably have at least a fragment of the missing Y translocated to some other chromosome, from which it orchestrates the creation of testicular tissue during gestation. Alternatively, the elusive Y may exist as a mosaic, present in some but not all of the patient's somatic cells.

In California, cytogeneticist Susumu Ohno at the City of Hope Medical Center near Pasadena has apparently just clinched Dr. Wachtel's hypothesis about the H-Y gene's sex-determining role. Dr. Ohno smashes, separates, and interrupts the growth of the testes of newborn mice; in vitro the cells reaggregate to form testicular tubules. But when he blocks the H-Y antigen by adding specific antiserum to the culture, the cells from the demolished testes grow into ovarian follicular aggregates instead.

Meanwhile, Dr. Wachtel's group has lately adduced evidence that the testis-inducing gene really does reside on the Y chromosome. They showed that in XYY men, the double dose of Y chromosomes in cell nuclei is matched by an extra amount of H-Y antigen in cells—markedly more of it than in men with normal XY karyotypes. The only other locus ever mapped (tentatively) on the human Y chromosome is the gene for hairy ears.

The clinical test based on the H-Y antigen was first tried last year when Cornell pediatrician Maria I. New told Dr. Wachtel of a two-year-old patient with ambiguous genitalia, including an elongated clitoris, but an apparently normal female karyotype. This child's endocrine responses implied that she harbored cryptic testicular tissue, though she was being reared as a girl.

Her white blood cells tested positive for H-Y antigen, and surgical exploration at 26 months confirmed the suspected

diagnosis of true hermaphroditism: She had an ovary on the left side coexisting with an ovotestis on the right. Even after removal of all testicular tissue, she continued to test positive for H-Y antigen, showing the gene to be present in at least some of her somatic cells.

The new H-Y assay, says Columbia's Dr. Miller, is a better index of male-determining gene function than presence of the Y chromosome itself. The tiniest chromosome in the karyotype, a Y can easily be overlooked, especially if translocated to another chromosome.

Many factors can attenuate the Y chromosome's control over fetal sexual development, presenting pediatricians with a variety of perplexing problems. One of these, rare but controversial, was debated at the Albany symposium: microphallus. When a child is born with a fully formed but minuscule penis, "legitimate concern should arise" about whether the boy will be able to perform sexually as a male when he grows up, said pediatric endocrinologist Howard E. Kulin, chief of pediatric endocrinology at the Pennsylvania State University School of Medicine in Hershey.

Focus of the debate at Albany: testosterone versus sex reversal. "If you expose the infant to testosterone, you can get growth of the phallus. That's been shown conclusively," says Dr. Kulin.

A pioneer exponent of this approach has been Dr. David W. Smith, director of the dysmorphology unit in the University of Washington department of pediatrics in Seattle and author of a recent study establishing normal penis sizes for fetuses and neonates (*J Pediatr* 86:395, 1975). From 37 full-term newborns he derived a mean penile length of 3.5 cm and diameter of 1.1 cm. "A small penis," suggests Dr. Smith, "may provide a clue to fetal testosterone deficiency."

Over the years, Dr. Smith has given testosterone to a number of infants with diagnosed microphallus and has achieved catch-up growth of the organ to normal size-for-age. But he concedes that the future "capacity of the penis in such patients to respond to endogenous or exogenous testosterone during adolescence in order to provide the patient with a normal-appearing, functional adult phallus is yet to be determined."

The surgical alternative to that gamble removes phallus and gonads and fashions labia majora. With a neovagina created later and lifelong estrogen supplementation after puberty, "expectations for normal breast development and normal female identity are excellent," says Dr. Kulin.

The clinical predilection—hormones to bolster the maleness that the genes couldn't fully enforce, or surgery to remove it—tends to divide along east-west lines. On the West Coast, Dr. Smith in Seattle and pediatric endocrinologist Melvin M. Grumbach, chairman of pediatrics at the University of California in San Francisco, espouse the trial with testosterone. Johns Hopkins pediatrics professor Claude J. Migeon and Dr. Robert Blizzard, chairman of pediatrics at the University of Virginia in Charlottesville, emphasize the variable etiology of microphallus. Hypopituitarism is only one of several salient causes that in their experience forecloses the prospect of a penile growth spurt at puberty. They therefore favor surgical sex reversal.

Dr. Kulin cites another argument for surgery, that of clinical psychologist Anke Ehrhardt of Children's Hospital in Buffalo. She believes the prepubertal years are the ones crucial to the psyche's gender identity and that lack of a competent vagina then is not troublesome to a girl, whereas to a young boy a diminutive penis can be devastating.

Dominican involuntary transsexuals' Y chromosome-and-antigen system doesn't make itself much known (above, age eight) till puberty (right), when erection and intromission—though not insemination—become possible. Cornell investigators suggest thinking twice before changing any similar enzyme-deficient boys into girls.

The question of penile growth at puberty arises even more strikingly among a recently discovered group of involuntary transsexuals in a remote valley of the Dominican Republic. Until puberty, they seem like normal girls, but then they become psychologically and physically male.

In four tiny villages 150 miles southwest of Santo Domingo, the island republic's capital city, Cornell endocrinologists Julianne Imperato-McGinley and Ralph E. Peterson have identified 38 of these *guevedoces*—literally, penis-at-twelves. One in every 90 births in the area is thus affected; the 38, of whom 33 are still living, involve two dozen largely consanguinous families. The hitherto unreported form of male pseudohermaphroditism has been traced back seven generations to a single genetic "founder," a woman named Altagracia Carrasco. Inheritance, says Dr. Imperato, is autosomal recessive.

The *guevedoces* are born with a clitoris-like phallus (which has no urethral opening), a labial-like bifid scrotum, a urogenital sinus with blind vaginal pouch, and bilateral inguinal or labial testes. All have a normal male 46,XY karyotype and none has any müllerian structures.

At about age 12, their voices suddenly deepen, muscle mass increases markedly, testes descend into a scrotum that becomes rugous, and the phallus enlarges to a functional penis. They are capable of intromission and ejaculation, and only the perineal site of their urethral meatus prevents their normal sperm from inseminating a woman.

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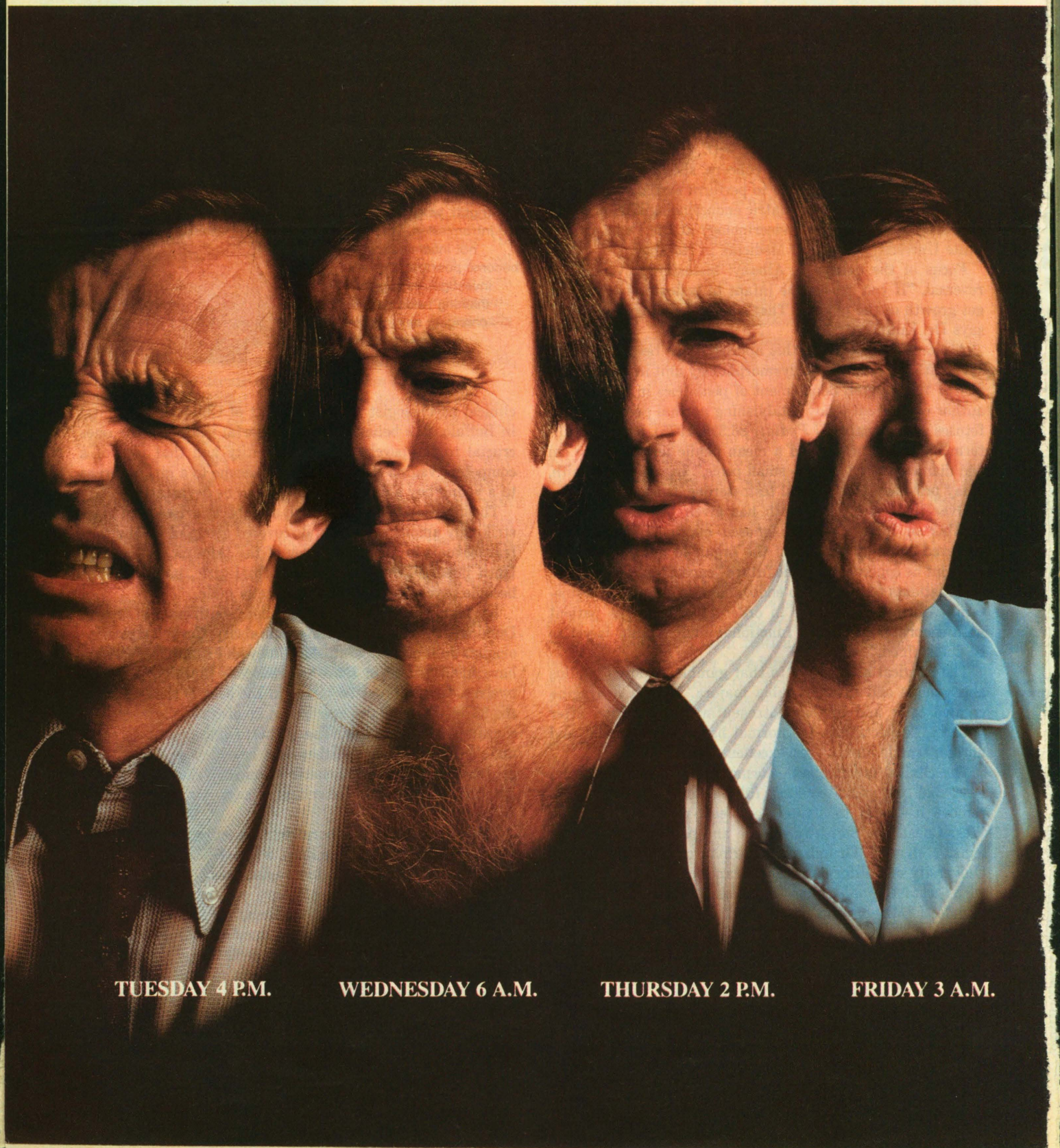
PERSISTENT



After exhaustive pedigree analysis and hormonal measurements, the Cornell team concludes that the bizarre defect is caused by drastic deficiency of a microsomal enzyme, 5 α-reductase, which converts testosterone to dihydrotestosterone (DHT) in utero, and again at puberty, in specific androgen-dependent target tissues. During normal embryogenesis, DHT impels the urogenital sinus and tubercules to evolve into external male genitalia; at puberty, this hormone produces facial hair, enlarges the prostate, and brings on male adolescent acne. The Dominican postpubertal men lack these secondary attributes, evidence that it is lack of DHT that has attenuated the Y chromosome's effects.

Dr. Peterson describes this new biochemical lesion as the first known inherited disorder of steroid metabolism. He regards it as a unique clinical model for delineating the little-understood roles of testosterone and dihydrotestosterone in sex differentiation and development. Its immediate pediatric payoff, he emphasizes, is to caution against too-hasty assignment of gender to infants born with ambiguous genitalia and diagnosed as pseudohermaphrodites.

"The inclination of pediatricians," notes Dr. Imperato, "would be to raise such a child as a girl, performing castration and corrective surgery at appropriate times." Two siblings in Texas—not related to the Dominicans—have been found with a similar disorder, and Drs. Imperato and Peterson recommend that such neonates be screened for 5 α-reductase deficiency to identify those with a good prospect of masculinization and virilization at puberty.

Despite their upbringing as girls, the Dominican involuntary transsexuals have unequivocally male psychosexual orientation and gender identity as adults, with libido directed toward women. As Oregon's Dr. Pauly points out, "Even in 1977 we know precious little of how little boys and girls grow up to be—and feel like—men and women."

Transsexuals of the more famous kind can also be studied as exceptions that may cast light on developmental rules. "They are giving us tremendous information about gender identity—what young parents need to know. It's information that's useful to every single human being in interacting with his or her own children," says Dr. Pauly.

He was one of more than three score psychiatrists and surgeons who took part several weeks ago in the Fifth International Gender Dysphoria Symposium, hosted by the Eastern Virginia Medical School in Norfolk. Some two dozen psychologists and social workers also attended the interdisciplinary gathering—as did two surgically switched transsexuals, one male-to-female, the other female-to-male.

Transsexual surgery burst publicly upon the world just a quarter-century ago when a 26-year-old American ex-G.I. underwent elective castration and penectomy in Denmark. The 25th anniversary was recalled at the Norfolk symposium by plastic surgeon Poul Fogh-Andersen of Copenhagen's Deaconess Hospital, whose patient it was—now Christine Jorgenson. Currently, the most publicized transsexual in the U.S. is Renee Richards, formerly a leading American eye surgeon named Richard Raskin and now a tennis pro (MWN, Sept. 6, '76, p. 26; Oct. 18, '76, p. 18), hoping that acceptance of her femaleness by European tournaments will help lower barriers against her in the U.S.

As a clinical entity, gender dysphoria—the ill from which transsexuals suffer—is unusual in several respects:

- It can be life-threatening or traumatic—though the patient's physique may be intact.
- Its diagnosis—the conviction of belonging to the opposite sex from that manifested by genitalia, gonads, and chromosomes—is determined by the patient, not the physician.
- Though seemingly a delusional state, it has almost never responded to psychotherapy.
- The only treatment—hormonal and surgical sex reversal—to which it yields is that prescribed by the patient, not the doctor.

Most doctors who encounter patients suffering from true gender dysphoria tend to discount its bizarre symptoms as a homosexual or transvestite perversion. Indeed, as Dr. Pauly notes of this "monosymptomatic psychosis," most naive transsexuals sensing the torment of inhabiting "the wrong body" initially mistake themselves for homosexuals.

Gender dysphoria's incidence and prevalence are matters of sheer guesswork. The statistic hazarded most often at the Norfolk meeting was one person in 50,000, or some 4,300 transsexuals in the U.S.

The Erickson Educational Foundation, a private eleemosynary fund with headquarters in Baton Rouge, La., that has fostered gender dysphoria research and public information for the past decade, lists 984 sex change operations (815 male-to-female; 169 female-to-male) done by clinics and individual surgeons in 18 states as of Nov. 1, 1976. The foundation has sponsored the biennial symposiums since 1969. It is phasing out its subsidy of gender dysphoria work, but its promotion of medical and social services to transsexuals will be carried on, for another year at least, at the Gender Clinic of the University of Texas Medical Branch at Galveston. Its director, psychologist Paul A. Walker, thinks the current estimate that there are four times as many male-to-female transsexuals as vice versa is changing with increased public knowledge of the phenomenon and that the real ratio is 50:50.

"To deal with this disorder clinically," says Dr. Pauly, "we

continued


FINAL DAILY NEWS 4¢
NEW YORK'S PICTURE NEWSPAPER

EX-GI BECOMES BLONDE BEAUTY

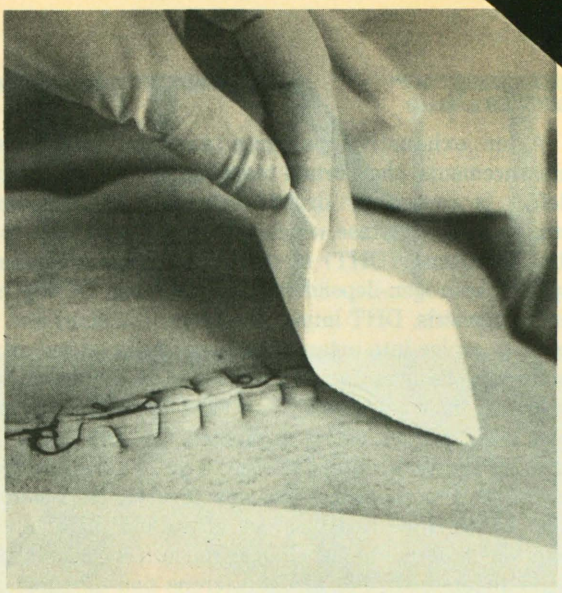
Operations Transform Bronx Youth

A World of a Difference

On Dec. 1, 1952, Christine Jorgenson faced a shock: her home-town paper told the world she'd been a man, and sex-change surgery was suddenly in the public's mind.

Surgical Menopause:

The sign...



The scar is obvious, but the chief concern of every premenopausal woman facing bilateral oophorectomy is that somehow, suddenly, she must face what might have been years away: the symptoms of the menopause.

For many women this fear is a real one, because surgical removal of the ovaries may bring about the abrupt onset of menopausal symptoms: hot flushes, sweats, palpitations, globus hystericus, and other symptoms due to estrogen deficiency. Moreover, such symptoms are often more severe than those that accompany the gradual estrogen decline of the physiological menopause.

Relief can be prompt. For most women, estrogen replacement with PREMARIN (Conjugated Estrogens Tablets, U.S.P.) can begin shortly after surgery—right in the hospital. PREMARIN can minimize the intensity and duration of vasomotor symptoms such as flushes and sweats, and help tide the patient over this distressing period of physiologic adjustment.

Relief can be long-term. Continued on a cyclic basis after discharge, at minimum effective doses, PREMARIN may help retard or prevent many of the long-term sequelae of estrogen deprivation, particularly genital tissue atrophy and osteoporosis*

PREMARIN. When the menopause is premature...and when it isn't.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis. See Prescribing Information.

must accept the transsexual in the gender role he or she assumes." A local community physician, he suggests, is logically the first medical practitioner to whom a newly aware transsexual will turn for help. A typical plea: "Doctor, I want a change-of-sex operation. I'm trapped in the wrong body, and I can't play masquerades any longer. I've got to get rid of this horrible thing hanging between my legs!"

Too often, adds the Oregon psychiatrist, the physician is taken off guard. He may react with "Get out of my office, you dirty queer!" To Dr. Pauly, what is needed is medical compassion. "The suffering of the transsexual is beyond belief," he declares.

"Transsexuals are not all hookers, panderers, and female impersonators," notes psychiatrist Norman Fisk of Stanford University's multidisciplinary gender dysphoria service—though some practice these occupations to amass the large sums of money needed for the hormonal and surgical treatment they crave. At the Stanford center, Dr. Fisk relates, "We've had as patients four MDs, several attorneys, and a corporate vice president from General Motors."

Is the lesion of gender dysphoria mental or genital? Is its etiology psychic or somatic? Psychiatrist K. Roy MacKenzie of the Calgary Faculty of Medicine in Alberta, Canada, considers the fundamental cause to be "biological, probably subcortical."

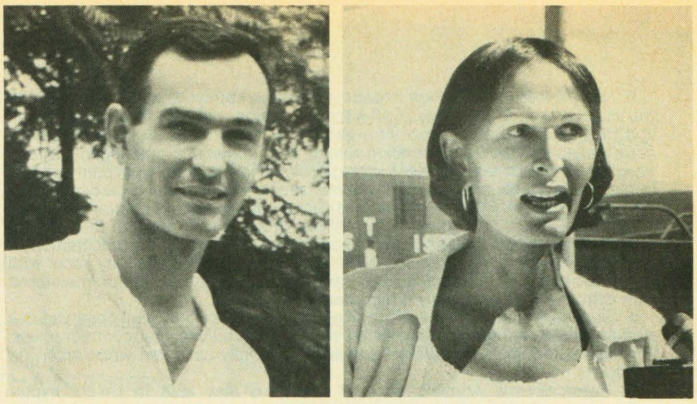
At the opposite pole is the psychoanalytic interpretation, which sees the dissonance between anatomic sex and psychosocial gender as caused by a disturbance in the mother-child bond early in life. In this scenario, a depressed mother binds her beautiful son too closely to her, in blissful symbiosis, and in the effective absence of a father figure. A spokesman for this school of thought is psychiatrist Robert J. Stoller of the University of California, Los Angeles, School of Medicine.

Psychiatrist Jon Meyer, who directs the Sex Behaviors Consultation Unit at Johns Hopkins, defends an alternative psychoanalytic etiology: not mother-child symbiosis but an early childhood defect in separation and individuation from the mother. Transsexuals, he believes, suffer from "a borderline personality disorder closely related developmentally to the sex perversions."

Dr. John Money, professor of medical psychology and associate professor of pediatrics at Johns Hopkins—where in 1966 the Erickson foundation financed the first gender identity clinic to evaluate and treat patients seeking sexual reassignment—says any either/or espousal of nature or nurture as the root cause of transsexualism represents an "utterly futile dichotomy." He told MWN that prenatal and postnatal influences both play a sequential and mutually essential role. "It takes a specifically programmed protoplasm subjected to special life circumstances to produce a transsexual," he concludes.

Once a comprehensive multidisciplinary medical and psychiatric workup has confirmed an applicant's contention that he or she is a bona fide transsexual in need of sex reassignment, patient management may proceed along one or more of several lines:

- Psychosocial—assuming the dress and the social and economic roles of the desired sex; "passing" or "cross-living" in the community; taking a new name.
- Hormonal—receiving the estrogens or androgens required to develop gynecomastia or facial hair, respectively, as well as other desired secondary sex characteristics.
- Secondary surgical—bilateral mastectomy and tracheal shaving, or breast prostheses and facial hair electrolysis.
- Primary surgical—castration, penectomy, and vaginoplasty, or oophorohysterectomy and phalloplasty.



New York eye surgeon Raskin, a top tennis amateur (left), is now a Californian, a woman, and a pro. She gave up anonymity to show the public that 'transsexuals are people, too.'

The longer one postpones irreversible genital surgery, the better, says Dr. Pauly, urging that the most reversible procedures be undertaken first. He regards hormone therapy and cross-living as an ideal clinical trial, affording transsexual patients a not-irrevocable foretaste of their heart's desire.

Most authorities prescribe cross-living for one or two years. Many physicians give hormones on demand, and some surgeons do the primary operation simply on request.

Unlike homosexuals, transsexuals do not club together. They see themselves as patients seeking a cure, not sociosexual variants pursuing a lifestyle. But in quest of therapy, they have formed a grapevine by which individual seekers tell each other where the longed-for surgery is available and at what cost in time, effort, and money. As they shop from team to team across the country, patients are now matching their personalities and capabilities with the psychiatrists and surgeons available to them.

Suicide and self-mutilation are real risks to frustrated transsexuals. Psychiatrist Don Angus of the Calgary Faculty of Medicine in Alberta recalls a 17-year-old boy who carried radioactive charges in his pockets to destroy his testicles. For five years his gender dysphoria made a shambles of his family life. But once encouraged to dress as a woman, "he turned around instantaneously, became a model citizen, and went on to hormones."

How many untreated, perhaps undiagnosed, transsexuals have taken their own lives is of course not known, nor how many have performed castration and penile amputation on themselves. Such self-mutilation forces a surgeon to intervene but denies him the time and tissue to achieve optimal genital transmutation.

Plastic and urologic surgeons are using inverted penile skin and scrotal flap grafts in various ways to create credible labia majora and vaginal introitus. Some, as in conventional corrective colpoplasty, divert the gracilis muscle and employ split-thickness grafts of thigh skin to complete a patent functional vaginal vault.

continued

b. *Hepatic adenoma.* Benign hepatic adenomas appear to be associated with the use of oral contraceptives.[38-40] Although benign, and rare, these may rupture and may cause death through intra-abdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestogen preparations but should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives.[39] The relationship of this malignancy to these drugs is not known at this time.

c. *Elevated blood pressure.* Increased blood pressure is not uncommon in women using oral contraceptives. There is now a report that this may occur with use of estrogens in the menopause[41] and blood pressure should be monitored with estrogen use, especially if high doses are used.

d. *Glucose tolerance.* A worsening of glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while receiving estrogen.

4. *Hypercalcemia.* Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS

A. General Precautions.

1. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed.

2. Fluid retention—Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor such as epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

3. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc.

4. Oral contraceptives appear to be associated with an increased incidence of mental depression.[24] Although it is not clear whether this is due to the estrogenic or progestogenic component of the contraceptive, patients with a history of depression should be carefully observed.

5. Preexisting uterine leiomyomata may increase in size during estrogen use.

6. The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

7. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving estrogen-containing oral contraceptive therapy. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.

8. Estrogens may be poorly metabolized in patients with impaired liver function and they should be administered with caution in such patients.

9. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

10. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.

11. Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following similar changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

B. Pregnancy Category X. See CONTRAINDICATIONS and Boxed Warning.

C. Nursing Mothers. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: (See Warnings regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, and adverse effects similar to those of oral contraceptives, including thromboembolism.) The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives:

1. *Genitourinary system:* Breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis; change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome.

2. *Breasts:* Tenderness, enlargement, secretion.

3. *Gastrointestinal:* Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice.

4. *Skin:* Chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.

5. *Eyes:* Steepening of corneal curvature; intolerance to contact lenses.

6. *CNS:* Headache, migraine, dizziness; mental depression; chorea.

7. *Miscellaneous:* Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: Numerous reports of ingestion of large doses of estrogen-containing oral contraceptives by young children indicate that serious ill effects do not occur. Overdosage of estrogen may cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

1. *Given cyclically for short-term use only:* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage ranges: Vasomotor symptoms—1.25 mg daily. If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding.

Atrophic vaginitis and kraurosis vulvae—0.3 to 1.25 mg or more daily, depending upon the tissue response of the individual patient. Administer cyclically.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Usual dosage ranges: Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily. The effectiveness of therapy can be judged by phosphatase determinations as well as by symptomatic improvement of the patient.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women. (See INDICATIONS)— Suggested dosage is 10 mg three times daily for a period of at least three months.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867—Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.

PHYSICIAN REFERENCES: 1. Ziel, H.K., *et al.*: N. Engl. J. Med. *293*:1167-1170, 1975. 2. Smith, D.C., *et al.*: N. Engl. J. Med. *293*:1164-1167, 1975. 3. Mack, T.M., *et al.*: N. Engl. J. Med. *294*:1262-1267, 1976. 4. Weiss, N.S., *et al.*: N. Engl. J. Med. *294*:1259-1262, 1976. 5. Herbst, A.L., *et al.*: N. Engl. J. Med. *284*:878-881, 1971. 6. Greenwald, P., *et al.*: N. Engl. J. Med. *285*:390-392, 1971. 7. Lanier, A., *et al.*: Mayo Clin. Proc. *48*:793-799, 1973. 8. Herbst, A., *et al.*: Obstet. Gynecol. *40*:287-298, 1972. 9. Herbst, A., *et al.*: Am. J. Obstet. Gynecol. *118*:607-615, 1974. 10. Herbst, A., *et al.*: N. Engl. J. Med. *292*:334-339, 1975. 11. Stafl, A., *et al.*: Obstet. Gynecol. *43*:118-128, 1974. 12. Sherman, A.I., *et al.*: Obstet. Gynecol. *44*:531-545, 1974. 13. Gal, I., *et al.*: Nature *216*:83, 1967. 14. Levy, E.P., *et al.*: Lancet *1*:611, 1973. 15. Nora, J., *et al.*: Lancet *1*:941-942, 1973. 16. Janerich, D.T., *et al.*: N. Engl. J. Med. *291*:697-700, 1974. 17. Boston Collaborative Drug Surveillance Program: N. Engl. J. Med. *290*:15-19, 1974. 18. Hoover, R., *et al.*: N. Engl. J. Med. *295*:401-405, 1976. 19. Boston Collaborative Drug Surveillance Program: Lancet *1*:1399-1404, 1973. 20. Daniel, D.G., *et al.*: Lancet *2*:287-289, 1967. 21. The Veterans Administration Cooperative Urological Research Group: J. Urol. *98*:516-522, 1967. 22. Bailar, J.C.: Lancet *2*:560, 1967. 23. Blackard, C., *et al.*: Cancer *26*:249-256, 1970. 24. Royal College of General Practitioners: J. R. Coll. Gen. Pract. *13*:267-279, 1967. 25. Inman, W. H. W., *et al.*: Br. Med. J. *2*:193-199, 1968. 26. Vessey, M. P., *et al.*: Br. Med. J. *2*:651-657, 1969. 27. Sartwell, P.E., *et al.*: Am. J. Epidemiol. *90*:365-380, 1969. 28. Collaborative Group for the Study of Stroke in Young Women: N. Engl. J. Med. *288*:871-878, 1973. 29. Collaborative Group for the Study of Stroke in Young Women: J.A.M.A. *231*:718-722, 1975. 30. Mann, J.I., *et al.*: Br. Med. J. *2*:245-248, 1975. 31. Mann, J.I., *et al.*: Br. Med. J. *2*:241-245, 1975. 32. Inman, W.H.W., *et al.*: Br. Med. J. *2*:203-209, 1970. 33. Stolley, P.D., *et al.*: Am. J. Epidemiol. *102*:197-208, 1975. 34. Vessey, M.P., *et al.*: Br. Med. J. *3*:123-126, 1970. 35. Greene, G.R., *et al.*: Am. J. Public Health *62*:680-685, 1972. 36. Rosenberg, L., *et al.*: N. Engl. J. Med. *294*:1256-1259, 1976. 37. Coronary Drug Project Research Group: J.A.M.A. *214*:1303-1313, 1970. 38. Baum, J., *et al.*: Lancet *2*:926-928, 1973. 39. Mays, E.T., *et al.*: J.A.M.A. *235*:730-782, 1976. 40. Edmondson, H.A., *et al.*: N. Engl. J. Med. *294*:470-472, 1976. 41. Pfeffer, R.I., *et al.*: Am. J. Epidemiol. *103*:445-456, 1976.

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REFERRAL CENTERS FOR GENDER DYSPHORIA

	Directors, Coordinators	Specialists[1]	Year started	Number of patients treated surgically (and total number) ♂→♀	♀→♂
WEST COAST					
Columbia Psychiatric Clinic 1345 S.E. Harney St. **Portland,** Ore. 97202	IRA B. PAULY, M.D. (503) 238-5580	ObG, Pla, Ps, Psg, Ur	1967	40	30
Gender Dysphoria Program Stanford University Medical Center **Stanford,** Calif. 94305	DONALD R. LAUB, M.D. NORMAN M. FISK, M.D. Coordinator: MARTHA NORBERG (415) 497-5824	End, Int, ObG, Pla, Ps, Psg	1968	122	47
MIDWEST					
Omaha Consultation Center, Inc. 2717 S. 88th St. **Omaha,** Neb. 68124	DUANE E. SPIERS, Ph.D. (402) 397-4880	FP, ObG, Ps, Psg	1970	12	4
Gender Dysphoria Program Division of Plastic and Reconstructive Surgery Cook County Hospital 1835 W. Harrison St. **Chicago,** Ill. 60612	BANGALORE JAYARAM, M.D. (312) 633-8910	Pla, Ps, 2Psg, Ur	1966	85	15
Case Western Reserve University School of Medicine 2040 Abingdon Rd. **Cleveland,** Ohio 44106	STEPHEN B. LEVINE, M.D. AARON BELLOWITZ, M.D. (216) 444-3426	End, Ps, 4Psg, Ur	1975	10	2
SOUTH CENTRAL					
Oklahoma Gender Identity Center P.O. Box 18912 **Oklahoma City,** Okla. 73118	DAVID W. FOERSTER, M.D. CHARLES L. REYNOLDS, M.D. Coordinator: CLAIRE L. ARTHUR (405) 848-3459	End, ObG, Pla, Ps, Psg, Ur	1973	27	5
Department of Community and Social Psychiatry University of Texas Medical Branch **Galveston,** Tex. 77550	PAUL A. WALKER, Ph.D. (713) 765-2326	End, ObG, Pla, 2Ps, 4Psg, Ur	1976	9 (50)	9 (15)
NORTHEAST					
Psychoendocrinology Program Children's Hospital **Buffalo,** N.Y. 14222	ANKE EHRHARDT, Ph.D. HEINO MEYER-EAHLBURG, Ph.D. (716) 878-7645	3Psg	1971	40	20
Gender Identity Service, Inc. 80 Boylston St., Room 860 **Boston,** Mass. 02116	CAROL Z. STEINMAN, M.S.W. (617) UN 4-8181	PC, 3Psg	1972	8 (250)	7
Gender Identity Clinic of New England, Inc. Mt. Sinai Hospital 500 Blue Hills Ave. **Hartford,** Conn. 06112	MICHAEL BAGGISH, M.D. (203) 242-4431, ext. 4283	End, ObG, PC, Pla, Ps, Psg	1974	29 (100)	6 (30)
MIDDLE ATLANTIC					
Gender Identity Pennsylvania Hospital Eighth and Spruce Sts. **Philadelphia,** Pa. 19107	A. JAMES MORGAN, M.D. Coordinator: LYNN HUBSCHMAN (215) 829-3577	End, Pla, 2Ps, Psg, Ur	1969	21	2
Gender Identity Clinic Johns Hopkins Hospital and Medical Institutions 605 N. Broadway **Baltimore,** Md. 21205	Coordinator: EILEEN HIGHAM, Ph.D. (301) 433-1588	End, ObG, Pla, Ps, 2Psg	1966	100	
SOUTHEAST					
Gender Identity Clinic University of Virginia Medical Center **Charlottesville,** Va. 22901	MILTON T. EDGERTON, M.D. Coordinator: BARBARA J. HAWKINS (804) 924-5801	ObG, 2Pla, Ps, Psg, 2Ur	1970	45	12
Gender Identity Team Eastern Virginia Medical School P.O. Box 1980 **Norfolk,** Va. 23501	PAUL SOLOFF, M.D. (804) 627-0211, ext. 203	FP, ObG, 2Pla, Ps, Psg, Ur	1974	12	7
Gender Identity Association 580 W. 8th St. **Jacksonville,** Fla. 32209	IRA M. DUSHOFF, M.D. (904) 355-0561	2ObG, PC, Pla, 2Ps, 2Psg	1967	34 (453)	38 (211)

Additional information—and assistance in obtaining local psychosocial counseling—may be obtained from ZELDA SUPLEE, director of the Janus Information Facility at the University of Texas Medical Branch, Galveston, Tex. 77550. Telephone: (713) 765-2361.

[1]Key: ***End*** *endocrinologist,* ***FP*** *family practitioner,* ***OBG*** *obstetrician-gynecologist,* ***PC*** *pastoral counselor,* ***Pla*** *plastic surgeon,* ***Ps*** *psychiatrist,* ***Psg*** *psychologist,* ***Ur*** *urologist.*

"The worst outcome," warns plastic surgeon David W. Foerster of Oklahoma City's Baptist Medical Center, "is an inadequate vagina. It can lead to deep depression in the patient."

Self-image more than libido seems to be the underlying motivation; transsexuals do not display unusually strong sex drives. Dr. Pauly's group in Oregon has devised a series of questionnaires to score patients' satisfaction after sexual reassignment; they find it approaches the baseline well-being of normal heterosexual controls.

Colorado surgeon Stanley H. Biber says that of the 130 patients on whom he has done a primary male-to-female reassignment, "follow-up shows a 95% orgasm rate," and 26% have married.

Exception to such optimism about postoperative orgasms was taken by Dr. Paul J. Fink, chairman of psychiatry and human behavior at Jefferson Medical College and Hospital in Philadelphia. "The thrill of being penetrated," Dr. Fink suggested, "may be sufficient to be called orgasm in one who had been having orgasm in an entirely different way."

The Calgary group reported that all their patients altered "in both directions" were using their new genitalia sexually, but Dr. Fisk of Stanford noted that only one third of theirs had achieved such success, and fully 50% suffered postoperative complications. Three had experienced a delayed change of heart and sought reversal to their previous male anatomical sex five to six years after surgery. But none of the surgically transformed transsexuals regretted their original switch, Dr. Fisk emphasized. All said they *had* to do it at the time.

This form of therapeutic failure—repentence or reversion—is "a dreaded nightmare" to surgeons in particular, the Stanford psychiatrist points out, and "devastating to their morale," since for the surgeon "it's hard enough to have to amputate or excise healthy tissue" without seeing the effort eventually repudiated by the patient.

Six postoperative transsexuals have committed suicide since 1962, notes New York University psychiatrist Arthur Zitrin. Dr. Zitrin also cites a 31-year-old male social worker with casual transvestite and homosexual associations who late last year "decided it would be cool to have a sex change." He took hormones for a couple of months and then presented himself to a surgeon's office. After "a perfunctory psychiatric examination, he was wheeled into the operating room. His last recollection before going to sleep was: "This is a terrible mistake!"

It was. As Dr. Zitrin relates, "He woke up reassigned and in a panic, which gave way to a serious depression." He now consoles himself by carrying around a reprint the surgeon gave him on phalloplasty.

Phalloplasty—the ultimate corrective that female-to-male transsexuals seek—is still far from perfected. Penile reconstruction was developed during World War I by the pioneer British plastic surgeon, Sir Harold Gillies. He would show his students slides of a convincing neopenis pieced together from abdominal skin flaps, with the umbilicus converted to a meatus, and exclaim: 'You see, gentlemen, a thing of beauty—but alas, no joy forever!"

Little progress has been made in phalloplasty since the Gillies classic tube-in-a-tube pedicle flap operation, declares plastic surgeon Charles Horton of the Eastern Virginia Medical School's gender identity team. Every attempt must choose or compromise between fashioning a pseudopenis long enough to look adequate and one short enough to permit passing the urethra through its middle to permit voiding standing up. Sensation and erectility, he states, continue to elude the surgeon.

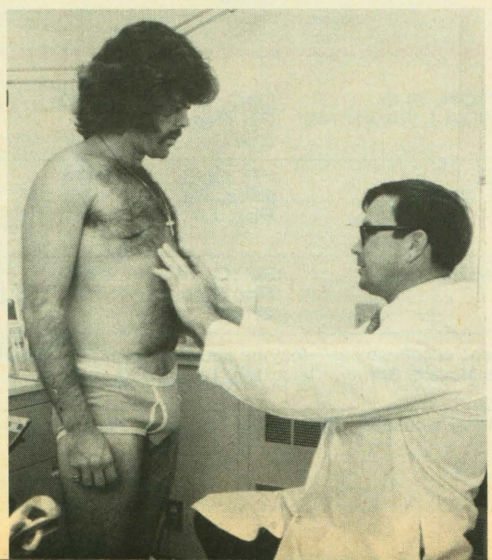
Stanford plastic surgeon Donald Laub, who has done 40 female-to-male reassignments, finds that phalloplasty follows rather than precedes "a happy person-to-person relationship" between the transsexual and her female partner in life. While an artificial vagina becomes part of the patient's body image, a neopenis typically remains an alien appendage.

One of the Stanford group's successful female-to-male transsexuals attended the Norfolk symposium with his wife. He told MWN: "I feel satisfied with the fact that my new penis is cosmetically good. I'm glad to have a penis after 32 years; if and when something better comes along, I'll be the first on the doorstep to get it."

Gender dysphoria will soon have its own subspecialty organization. The participants in the symposium at Norfolk resolved to constitute, at their sixth meeting two years hence in San Diego, the Harry Benjamin International Gender Association. Dr. Benjamin, a New York City endocrinologist now in his nineties, was among the first to give transsexualism medical respectability with his book, *The Transsexual Phenomenon*, published by Julian Press in 1966 and now out of print.

Preparing for the 1979 meeting is a six-man steering committee consisting of a plastic surgeon (Stanford's Dr. Donald Laub), an endocrinologist (Dr. Leo Wollman of New York Ciy), two psychiatrists (Drs. Jack C. Berger of Chicago and Richard Green of New York City), a psychologist (Dr. Paul Walker of Galveston), and a urologist (Dr. Charles L. Reynolds of Oklahoma City). This panel of clinicians, all long involved in transsexualism, will draft a code of standards for the diagnosis, care, and follow-up of gender dysphoria patients, as well as a charter for the future association.

—DAVID N. LEFF



'It's difficult to change one's mind to fit one's body,' notes Stanford's Dr. Laub. Here he examines the patient shown on page 45, whose body he changed to match the mind.