Normal Sex Development

The processes that result in a male or a female individual are:

1) sex determination, the genetic phenomenon that results in the sex genotype (the “constitutional” or “genetic” sex), and 2) sex differentiation, the process, governed by hormonal factors, that results in the phenotype sex (visible sex characteristics).

1. Sex Determination

The genetic sex of the embryo is determined by chromosomal pairing, which occurs upon meeting of sperm and ovum. The normal female inherits the chromosome pair XX; the normal male, the chromosome pair XY. All tissue cells of the female, at subsequent stages of development, are normally characterized by the presence of the XX chromosome pair; all tissue cells of the male contain the XY chromosome pair.

2. Sex Differentiation

Sex differentiation involves two groups of factors: a) gonadal and b) hormonal.

a. Fetal gonadal factors. The primordial gonad, according to Witschi,1 is sexually undifferentiated. It consists of a cortex and a medulla. In the female, the cortex develops into the ovaries, while the medulla degenerates. In the male, the cortex degenerates and the medulla develops into the testes.

b. Hormonal factors (fetal and maternal). The testis, after it has developed from the medulla of the primordial gonad, produces hormones that contribute to the differentiation of the male sex organs; the hormonal function of the fetal ovary is less well defined. The influence of the maternal hormones has been demonstrated by removing the gonads early in the fetal life of rabbits: all fetuses from which the gonads have been removed develop as females, with female secondary sex characteristics, presumably in response to the activity of the placental hormones.2 The testis of the male fetus is believed to produce hormones that counteract the maternal female hormones, to permit male sex differentiation.3

Aberrations from the normal path of sex development may occur at any of the three major periods implied by the above: the chromosomal pairing stage, the phase of

—Arthur Klatsky, Editor
gonadal differentiation, or as a result of hormonal changes at any period of life.

Abnormal Sex Determination

The clinical test for determining chromosomal sex, developed in 1953 by Moore and Barr, made possible a new phase in the investigation of states characterized by abnormal sexual development. These workers observed that in normal female subjects, the cells of many tissues (not of gonadal tissue alone) contained a chromatin body which they believed to represent an XX chromosome. The tissue cells of normal male subjects which contain the XY chromosome, do not contain the chromatin body. Buccal mucosal cells are used most frequently for the clinical test of “chromosomal sex” based on this observation.

Chromosomal sexing has been used in the investigation of states characterized by intersexuality. When chromatin bodies were found, the individual was said to be of the “female chromosomal sex”; when none were present, of “male chromosomal sex.” Wilkins noted in 1954 that chromatin bodies were absent from the nuclei of a majority of a series of apparent females with ovarian agenesis (Turner's syndrome), and considered these persons to be chromosomal males. In a majority of a group of patients with Klinefelter's syndrome (hypogonadism, gynecomastia, azoospermia, eunuchoid body build, hypergonadotropinism), chromatin bodies were found in the tissue cell nuclei, and the subjects were judged chromosomal females.

Commentary by Edgar J Schoen, MD

As someone who has “been there, done that,” I have been following with interest the comments of today’s PMG physicians on the publications of their predecessors in the pioneering, though long defunct, Kaiser Foundation Medical Bulletin. I was particularly intrigued by a surgical article written by one of our founders, Cecil Cutting, 50 years ago and analyzed by my current Physician-in-Chief, Tom McDonald. Tom pointed out that he was born the month the article was written. Similar commentaries on other articles were written by current physicians who were anywhere from toilet training to kindergarten when their PMG ancestors were publishing in the Kaiser Foundation Hospitals journal. Art Klatsky, a Permanente Journal Editor, sensed a unique variation on this theme. How about a current PMG physician commenting on his own article written more than four decades ago? Although this approach is unusual from the standpoint of history, individual endurance, and longevity, it is highly unlikely that the commentator will find great fault with the original author. But here goes.

In 1959, when I wrote an article on sexual differentiation in the Kaiser Foundation Medical Bulletin, I was a 30-something Brooklyn wiseguy trained in Boston. Now, as a 70-something California wiseguy with a 48-year TPMG career, my viewpoint on the topic is not radically different than it was four decades earlier. The principles of sexual differentiation, just as with personal sexual function, remain the same—it’s just the details that have changed.

As I looked back at my old article, I was surprised at how much we knew about sexual differentiation in the late 1950s. There had been great advances in both genetics and endocrinology in the previous decade. We had a rough clinical test for chromosomal sex—the buccal smear for “sex chromatin.” A chromatin body in the buccal cells on the smear indicated more than one X sex chromosome. This was considered to be a “female sex chromatin” pattern—later amended to “chromatin-positive” when it was realized that men with Klinefelter’s syndrome had more than one X chromosome in addition to the Y. And women with XO Turner’s syndrome were chromatin-negative though obviously not males. This chromosomal confusion became a lot clearer early in 1959, when a practical technique was developed for viewing chromosomes directly. Up until that time, whether humans had 46 or 48 chromosomes

(Continued on page 60)
Commentary
(Continued from page 59)

was not known for sure. Not only did it become apparent that 46 chromosomes was normal but that there was a logical explanation for the discrepancies in chromatin bodies. This realization was best illustrated by a reported case of a patient with both Down syndrome and Klinefelter’s syndrome and with 48 chromosomes—an extra chromosome 21 for Down syndrome and an extra X chromosome courtesy of Klinefelter’s syndrome.

Some exciting things happened in the 1950s with hormones as well. It was known that for the first six weeks or so of fetal life, the gonads were undifferentiated, after which they developed into a testis or ovary with the testes secreting testosterone. This fetal testosterone was found to be essential for further male sexual development. Studies from France showed that if fetal gonads were removed before differentiating, all the fetuses developed as females. On the other hand, presence of fetal androgens in the first two months of gestation, as occurs in the adrenogenital syndrome as a result of an enzymatic block in steroid formation, leads to virilization of the female fetus and development of ambiguous genitalia (clitoral hypertrophy and formation of a urogenital sinus).

Well, that was then. How about now? What we’ve done is filled in some of the blanks in the sexual differentiation process. We know, for instance, that the change from the undifferentiated gonad to a testis requires a gene called SRY, which is located on the short arm of the Y chromosome. Fetal testosterone stimulates the Wolffian structures (epididymis, vas deferens, and seminal vesicles), whereas a substance called antimüllerian hormone suppresses development of the fallopian tubes, uterus, and vagina. We now know that the active metabolite of testosterone is dihydrotestosterone and that, in a condition known as “testicular feminization,” an XY male with plenty of testosterone being formed by a fetal testis develops as a female because of an enzyme defect that prevents testosterone being converted to dihydrotestosterone. We know the gene locus for many enzymes and syndromes owing to new sophisticated techniques, and, with characterization of the human genome, there is more to come.

The scientific advances continue at an accelerating rate in both genetics and endocrinology, but, from the clinical standpoint, management of disorders of sexual differentiation in 2002 would still be recognizable by a 1959 pediatric endocrinologist. Plus ça change, plus c’est la même chose. Except when I look in the mirror, of course. ❖

other anomalies of sex development, resulted from abnormal evolvement of the germ cells of the gonads. A defect in the cortex of the primordial gonad of a chromosomal female might result in the formation of a testis in the female fetus, producing a “pseudomale” (Klinefelter’s syndrome). A defect in both cortex and medulla of the primordial gonad might result in an agonal state, whereupon the individual, whether a chromosomal male or a chromosomal female, would evolve as a female under the influence of maternal hormones. These hypothetical considerations were supported by experimental work cited by Witschi.1

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Moore,7 in 1959, reported his study of buccal mucosal smears from 3715 infants, 1804 of whom were female. Although the buccal smears of all of the female infants indicated chromosomal female sex, the tissue cells of five of the 1911 male infants contained chromatin bodies characteristic of the female. These five cases he considered to be instances of “sex reversal”, but recent work indicates that the chromatin bodies may not represent the normal female sex chromosome pair (XX), and that lack of chromatin bodies does not necessarily represent the normal male chromosome pair (XY). Ford, Jacobs, and their co-workers8,12 using techniques permitting direct visualization of chromosomes in human cells, demonstrated that the tissue cells of a patient with Klinefelter’s syndrome contained abnormal chromosomes in the grouping XXY, and that the tissue cells of a patient with Turner’s syndrome contained abnormal chromosomes in the distribution XO. In the light of these studies, the terms “chromosomal female” and “chromosomal male” were discarded by these and other investigators, and were replaced by the descriptive terms, chromatin positive and chromatin negative.

In addition, these workers found an important abnormality in the total number of chromosomes present in the tissue cells of the intersexes studied, and in patients with certain diseases, which appear to be connected with chromosomal abnormalities that were hitherto unsuspected. The observations were made possible by the technique developed by Ford, Jacobs, and Lajtha9: marrow cells are grown in tissue cultures: hypotonic saline or citrate is added to expand the cell and to separate the chromosomes, and mitosis is stopped in the metaphase by means of colchicine. A “squash preparation” is made from the cell suspension, which has been stained by Feulgen’s method, and the chromosomes can then be counted and paired. Prior to the application of this technique, the normal human tissue cell was believed to contain 48 chromosomes. It was now learned that such cells normally contain 46 chromosomes, in 23 pairs; one of the pairs consists of sex chromosomes, an XX pair in the female and an XY pair in the male. The cells of persons with Klinefelter’s syndrome (which are chromatin positive) contained 47 chromosomes instead of the normal 46; they had three sex chromosomes (XXX) instead of the normal “chro-
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