GYNECOLOGIC PATHOLOGY

Frederick T. Kraus

GYNECOLOGIC PATHOLOGY

Frederick T. Kraus, M.D.

Associate Pathologist, St. Luke's Hospital;
Instructor in Pathology,
Washington University School of Medicine,
St. Louis, Missouri

With 488 illustrations

The C. V. Mosby Company

Saint Louis 1967

Printed in the United States of America

Library of Congress Catalog Card Number 67-14719

Distributed in Great Britain by Henry Kimpton, London

GYNECOLOGIC PATHOLOGY

To my parents

Who provided the background that made study a pleasure and recording the study its own reward.

Preface

This textbook is the outgrowth of my attempts to separate from the voluminous literature on gynecologic disease those pathologic observations that have proven to be useful in establishing diagnoses, selecting the most appropriate therapy, and evaluating prognosis.

The scope of the book is limited to a discussion of the morbid anatomy of the female genital organs and the placenta. A brief discussion of certain nongenital lesions of the female pelvis is included, because they may be encountered first by the gynecologist and must be considered in the differential diagnosis of female genital tract disease.

When confronted with conflicting points of view I have presented the concepts that seem most consistent with my personal experience and represent a consensus at the present time. References to alternate ideas are cited but not enlarged upon. It is hoped that this design will prove sufficiently concise to provide the student with an uncluttered view of gynecologic disease.

For the resident or pathologist desiring a more detailed and varied exposure to individual subjects, a lengthy list of references has been provided for each chapter. Most of these references are cited in the text in support of specific ideas or observations; most are recent. I have read or consulted all of them during the preparation of this text. I believe that these extensive lists may prove useful to the many pathologists who find themselves increasingly involved in the preparation of clinical conferences.

In emphasizing pathologic findings of clinical importance I hope to demonstrate to the gynecologist the sort of information he should expect to receive from a pathologist who has been given sufficient material, properly prepared, to examine.

Greater space has been devoted to the discussion of common diseases. However I have attempted to characterize and illustrate rare lesions sufficiently to show how they are identified and indicate what sort of behavior may be expected of them. This is important in order to avoid overdiagnosis or rare malignancies and perhaps to stimulate the recognition of some lesions that may not be as rare as we think.

The pertinent aspects of normal anatomy, embryology, physiology, exfoliative cytology, and cytogenetics have been included where necessary to make

pathologic changes more understandable. These short discussions are in no way intended to supplant the excellent texts that exist for each of these fields. It is hoped that they will emphasize the dependence of gynecologic pathology upon other disciplines.

The illustrations are based in large part upon tissues that I have personally dissected in the pathology laboratory of St. Luke's Hospital, St. Louis. A number of excellent specimens and slides have been obtained from the abundant material graciously made available to me by Dr. John E. Hobbs, St. Louis Maternity Hospital, and by Drs. Richard L. Kempson and Lauren V. Ackerman, Barnes Hospital. Certain photographs have been kindly supplied by other physicians whose generosity is acknowledged in the captions.

I am greatly indebted to Dr. Herbert B. Taylor, Chief, Breast, Obstetric and Gynecologic Branch, Armed Forces Institute of Pathology, Washington, D. C., who read the entire manuscript; his suggestions have led to many corrections and improvements. For the mistakes that remain, the responsibility is mine.

Shortly after the writing of this book was begun, Dr. Robert E. Scully of Boston, Massachusetts reviewed the manuscript of Chapter 2, The vulva; his detailed suggestions not only resulted in a clarified presentation of the problems in this area, but also aided significantly in the organization of the chapters that follow.

Dr. Virgil R. Bleisch, Director of Snodgrass Laboratory, St. Louis City Hospital, provided illustrative material and numerous suggestions for the chapter on the placenta.

I have greatly appreciated the advice and comments of many practicing gynecologists at St. Luke's Hospital who have contributed to my understanding of gynecologic problems and principles. The frequent informal discussions with Drs. Carol Williams, William F. McGinnis, A. J. Meagher, and Joe E. Belew have been especially helpful to me. I wish to thank particularly Dr. John E. Hobbs, Clinical Professor of Gynecology and Pathologist to St. Louis Maternity Hospital, who introduced me to the subject of gynecologic pathology.

My colleagues in the Pathology Department of St. Luke's Hospital, Drs. R. W. Ogilvie and L. S. N. Walsh have given much useful advice and much appreciated encouragement and have done more than their share of the work while this writing was in progress.

The photomicrographs owe their technical excellence to the skill and meticulous attention to Mr. K. Cramer Lewis, Department of Medical Illustration, Washington University School of Medicine. The gross and clinical photographs, except as otherwise credited, have been made either by Mr. Lewis or by Mr. Walter J. Coerver

The diagrams and line drawings were made by Miss Marilyn J. Harris, Department of Medical Illustration, Washington University School of Medicine.

To my wife, Madeleine Veron Kraus, who typed much of the manuscript and whose comments have contributed to its readability, I am most grateful.

My debt to my teacher, Dr. Lauren V. Ackerman, will, I hope, be apparent. Whatever is good about this book stems from my attempt to emulate his emphasis of the importance of careful pathologic study in determining what is best for the patient.

Frederick T. Kraus, M.D.
St. Louis, Missouri

Contents

Chapter 1

Embryology: Genesis and dysgenesis of the female genital tract

Most structural abnormalities of the female genital tract are caused by failure to complete a developmental sequence, persistence of a transient organ or tissue, or incomplete suppression of male genital organs.

In some instances it has been possible to relate anatomic mishaps to improper transmission of the female sex chromosome.

These anomalies of development can be described and understood best by comparison with the normal embryologic and cytogenetic sequence.

THE ZYGOTE AND ITS ANOMALIES: CYTOGENETICS

The ultimate constitution of an individual is determined by the chromosomes of the sperm and ovum destined to unite and form the zygote from which the organism develops. Some pathologic conditions undoubtedly have their beginning at the time of formation of gametes or in the earliest divisions of the zygote, as a result of unequal division of the nuclear chromatin material. As the consequent chromosomal deficiency, or excess, is passed on in subsequent cell divisions, it is sometimes possible to identify the abnormality in the randomly obtained dividing cells of the abnormal individual. Present technical limitations require that a relatively gross alteration of chromosomal size, shape, or number be present. Various anomalies of clinical importance have now been correlated with specific abnormalities of chromosome number or constitution. At least a superficial knowledge of the mechanics of cell division and current techniques is useful in understanding these anomalies of development. The recent monographs and texts reviewing this field by Eggen[8], Yunis[16], and by Sohval[13] provide a more detailed background of modern cytogenetics.

Composition of nuclear chromatin

Each human cell nucleus contains strands of genetic material composed of deoxyribonucleic acid (DNA), arranged in the shape of a coil or helix. Two

complete (homologous) sets of *genes,* are arranged parallel to one another along these strands, one set from each parent. Each somatic cell, regardless of its function, has the same complete double set; for instance a kidney cell contains the genes determining color of hair or eyes, and an abnormal gene affecting the structure of the ovary will be present in a lymphocyte or vaginal epithelial cell. One gene of a pair is *dominant* in determining a particular characteristic of the individual. The *diploid* human somatic cell has twenty-three chromosome pairs, each pair composed of two homologous chromosomes, one contributed by each parent.

Cell division

Mitosis. During *interphase* the cell makes an exact duplicate of both sets of its nuclear complement of DNA. The *prophase,* or beginning stage of cell division, is occupied by contraction of the DNA helices, which separate into twenty-three pairs of chromosomes. Each chromosome is composed of two identical *chromatids.* At *metaphase* the forty-six chromosomes are aligned in the equa-

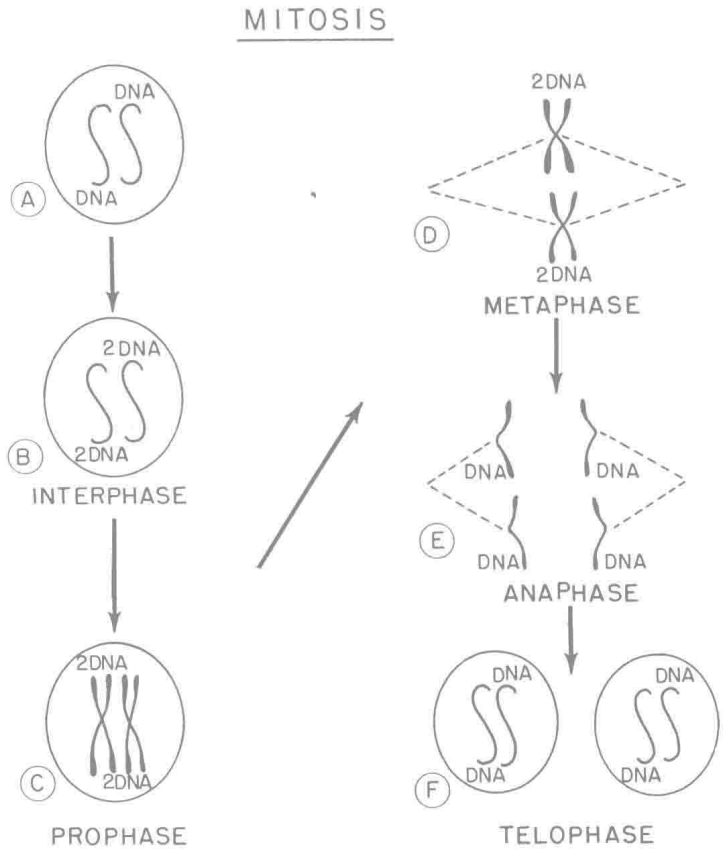

Fig. I-1. Diagrammatic summary of mitosis. This hypothetical cell has one pair of chromosomes. Each chromosomal strand **(A)** duplicates itself **(B)**; the old and new strands (chromatids) separate except at centromeres **(C)**. In metaphase **(D)** the chromosomes align at the equator and become attached to filaments of the spindle; in anaphase the chromatids separate **(E)** to supply a complete set of genetic characteristics to each daughter cell **(F)**.

torial plane at the center of the cell. The nuclear membrane has lysed. Each original chromatid and its duplicate are attached to one another at the constriction, the centromere. During *anaphase* the centromeres dissolve and the chromatids separate: *Disjunction* is accomplished. In *telophase* the two new cells reconstitute cytoplasmic and nuclear membranes and become separate structures. A new *interphase* then begins for each cell (Fig. 1-1).

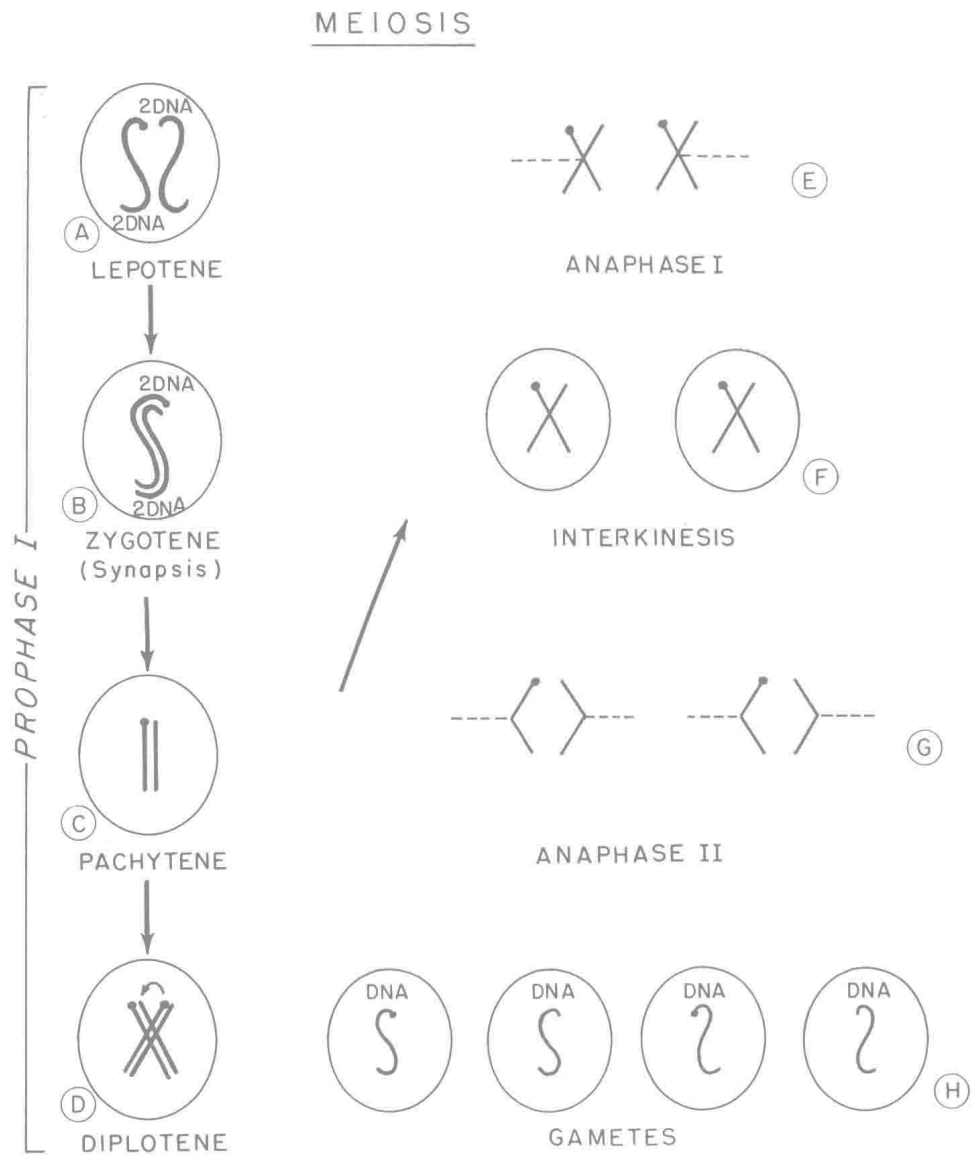

Fig. 1-2. Diagrammatic summary of meiosis. This hypothetical germ cell also has one pair of chromosomes. The homologous chromosomes are exactly aligned in synapsis (**B**). The chromosomes divide into chromatids, but remain closely aligned, forming a tetrad, and an exchange of genetic material takes place (**D**); then the two *chromosomes* separate (**E**). In the second anaphase (**G**) the *chromatids* finally separate to form four gametes, each with only one set of genetic determinants.

Meiosis. The specialized type of cell division called meiosis occurs only in germ cells in the formation of gametes, the ova and sperm. Two successive cell divisions are required to complete the process. In the first division twenty-three homologous chromosomes separate; the daughter cells therefore have only half as much chromatin material and are said to be *haploid*. Before this division is completed an interchange of genetic material occurs between homologous chromosomes, so that the daughter cells have some genetic material from each parent but only one gene for each characteristic. In the second meiotic division, after reduplication of the chromatin material, the chromatids separate as in mitosis. Thus, four gametes are formed, each with a single gene for each somatic characteristic.

When fertilization occurs, the zygote again has two sets of genetic determinants, one from each gamete (Fig. 1-2). Were it not for this specialized form of

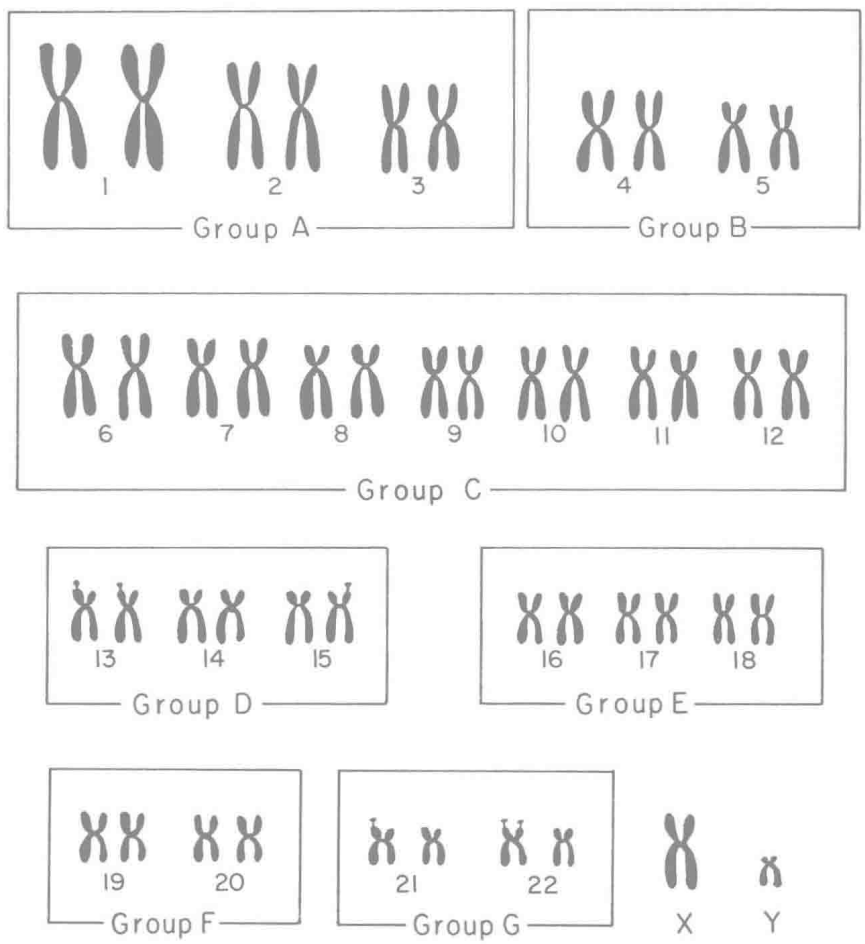

Fig. 1-3. Diagrammatic representation of human metaphase chromosomal pairs. The divisions are arbitrary, according to size and position of the centromere binding the chromatids together. Separation into groups is reliable in good preparations; complete identification of individual chromosomes is not possible in ordinary preparations and may be debatable in the best. This 46XY karyogram represents the normal male chromosomal pattern.

cell division for gametogenesis, the chromosomes would double with every generation.

Techniques and classification

Dividing cells growing in a culture of peripheral blood leukocytes, bone marrow, or other tissue are spread upon a microscopic slide, which is then stained and photographed under high magnification. Greatly enlarged photographic prints are made; the chromosomes are cut out and arranged in groups according to size and position of centromere (Fig. 1-3). The resulting standardized arrangement is called a *karyogram*, or *idiogram*.

The two sex chromosomes can be identified with regularity. In the female, two X chromosomes are found in each karyogram; in the male, one X and the much smaller Y chromosome are present. The other chromosomes, called autosomes, are separated into seven groups (A through G) with some confidence; an exact matching of each chromosome with its number as indicated in the karyogram usually represents an unattainable accuracy.

The customary notation used to designate both number of chromosomes and sex chromosome constitution gives first the total number of chromosomes, then one X for each X chromosome found, and a Y for each Y chromosome found. Thus the normal female chromosomal constitution is 46XX and the normal male, 46XY. Absence of the second sex chromosome (X or Y) is designated 45XO.

Female sex chromatin determination

The presence of female sex chromatin can be further established by the nuclear morphology of interphase cells in tissue sections or in stained smears. The nuclear membrane of the normal female cell bears a small mass of chromatin material intimately attached to its inner surface (Fig. 1-4). It is sometimes called the Barr body, after the investigator who first demonstrated its significance. Its

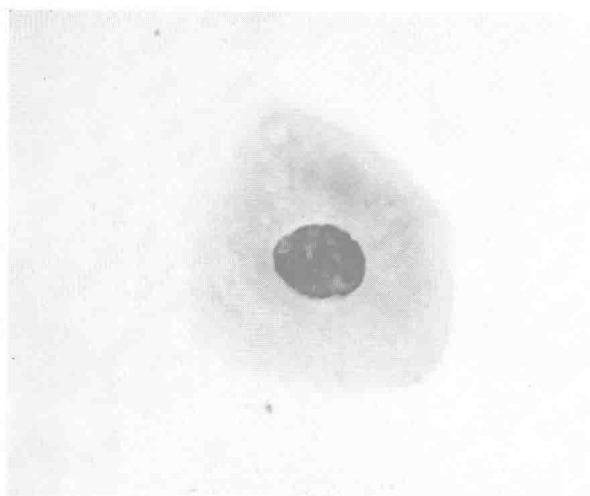

Fig. 1-4. Parabasal cell from a vaginal smear showing a dark chromatin mass inseparable from the inner surface of the nuclear membrane (at left). This "sex chromatin body" indicates the presence of a second X chromosome; the person is female. ×1250, W. U. Neg. 65-506.

presence indicates the existence of a second X chromosome in the nuclus and in most instances, therefore, is a reliable basis for identifying an individual as female. But note that the apparently male individual with Klinefelter's syndrome and 47XXY chromatin distribution also has two X chromosomes, and the nuclei of his cells, too, will have the "female" chromatin body. It is absent in cells from the normal male (46XY) but is also lacking in the vaguely female individual with Turner's syndrome (45XO). The distinction between male and female is at present sometimes hazy, and many a trusted landmark is proving to be unreliable.

A third X chromosome in the nucleus (47XXX) is manifest in smears or sections as a second sex chromatin body. The number of sex chromatin bodies identified in each cell is especially useful to the cytogeneticist confronted with the task of classifying a superfluity of chromosomes in group C, all of which resemble the X chromosomes to some extent.

As a tangential view of the nuclear membrane surface bearing the sex chromatin body is required to bring it into relief, it will not be recognizable in all cells. In smears of vagina or buccal mucosa of normal women it may be seen in approximately one-half of the cells having good nuclear detail. Confusion with overlying bacteria is to be avoided.

Pathologic cell division

Several mechanisms may cause abnormal distribution of chromatin material or loss of whole chromosomes. A whole chromosome may simply be lost during cell division. An entire chromosome pair may be drawn to one daughter cell,

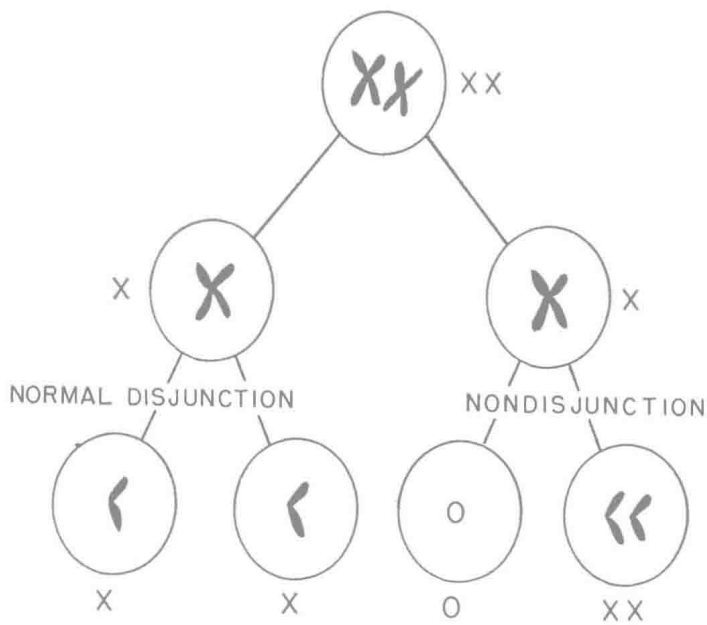

Fig. 1-5. Diagrammatic representation of the effect of nondisjunction in the division of X chromosomes during meiosis. This occurrence in one of the second meiotic divisions would produce two normal gametes, one gamete with no sex chromatin material, and one gamete with two sex chromosomes.

which will then have one extra chromosome—the other daughter cell will lack one chromosome. This process occurs when the two chromosomes fail to separate; it is called *nondisjunction* (Fig. 1-5). Part or all of one chromosome may become attached to another, an anomalous event called *translocation*.

If the pathologic cell division occurs during the formation of a sperm or ovum, the abnormal chromatin distribution of the zygote will be passed on in an identical fashion to all cells in the developing individual. Some possible combinations are shown in Fig. 1-6. If the first division of the zygote is abnormal, the daughter

Ovum	X	O	XX	X
Sperm	Y	Y	Y	O
Genotype of Zygote	XY	OY	XXY	XO
Phenotype of Individual	Normal	Lethal	Klinefelter's Syndrome	Turner's Syndrome

Fig. 1-6. Table showing the results of fertilization by various normal and abnormal gametes produced by the mechanism shown in Fig. 1-5.

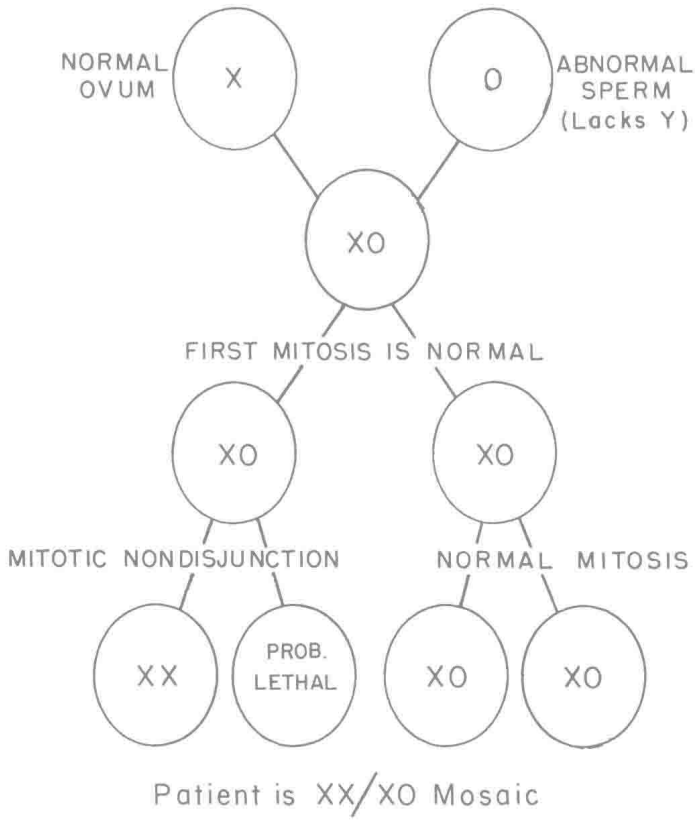

Fig. 1-7. Diagrammatic explanation of a possible mechanism in the production of the mosaic karyogram shown in Fig. 1-8.

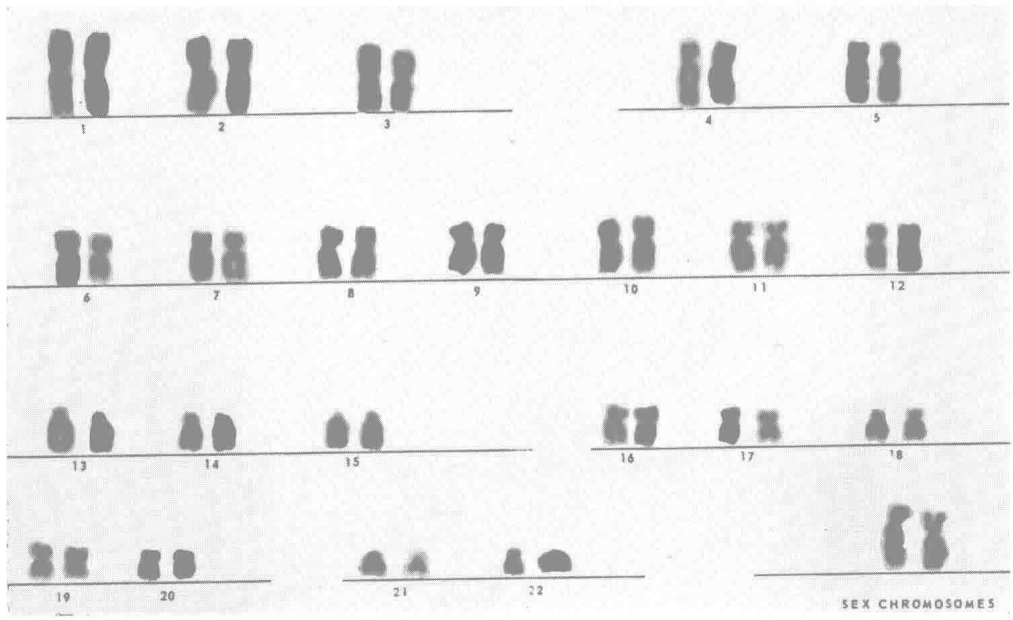

Fig. 1-8. Normal female karyotype, XX, one of the cell types of an XO/XX mosaic patient with some of the features of Turner's syndrome. W. U. Neg. 66-6422.

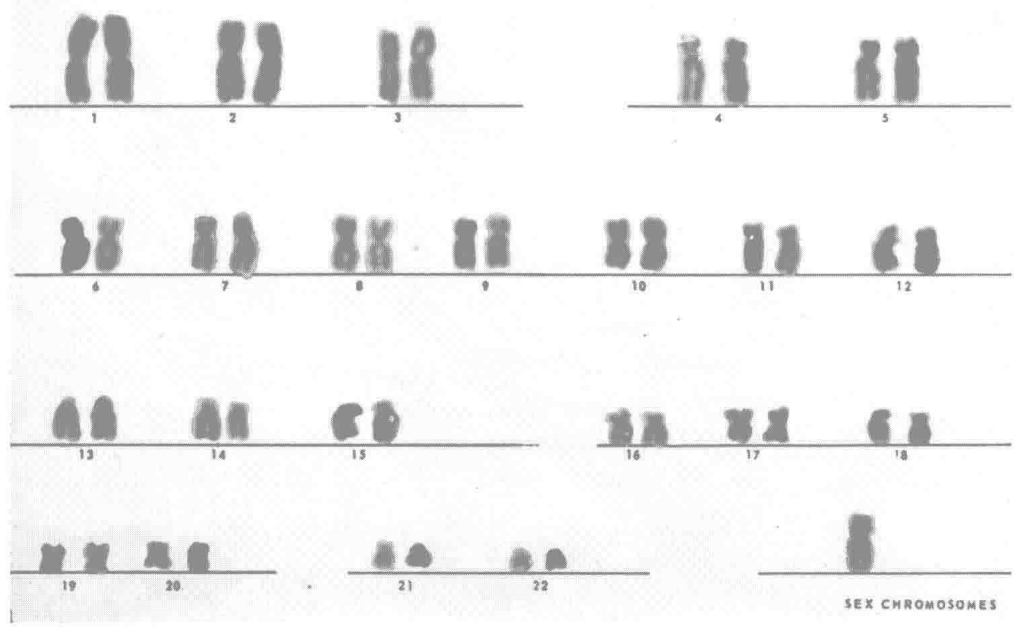

Fig. 1-9. Abnormal XO karyotype, involving approximately one-third of the cells in a peripheral blood culture of the same patient as in Fig. 1-8. W. U. Neg. 66-2423.

cells may be both abnormal and different, and two different cell lines will be formed. The presence of two or more cell lines is called a *mosaic* (Fig. 1-7). The notation designating chromosome number and sex chromosome complement of the cell lines in a mosaic lists the composition of each cell line. For instance, some individuals with some but not all of the features of Turner's syndrome have mosaics with two cell lines, designated 45XO/46XX (Figs. 1-8 and 1-9).

Clinicopathologic correlation

Most of the abnormalities of cell division ultimately affecting the female genital tract involve the absence, duplication, or malformation of one or both sex chromosomes. Some anomalies of sex chromatin distribution correlate well with certain clinical syndromes: 45XO with Turner's syndrome, and 47XXY with Klinefelter's syndrome. These and the mosaics that occur with some varieties of *gonadal dysgenesis* are discussed later. Total absence of sex chromatin in vaginal or buccal smears of an apparent female may suggest the syndrome of *testicular feminization*, if secondary sex characteristics are well developed, and Turner's syndrome, if they are not. A low percentage of chromatin-positive cells may be found in mosaics when only one line of cells has a 46XX constitution. Some very gross chromosomal abnormalities have been found in the trophoblastic tissue cultured from early abortions by Szulman,[14] indicating that the more bizarre departures from the norm are lethal.

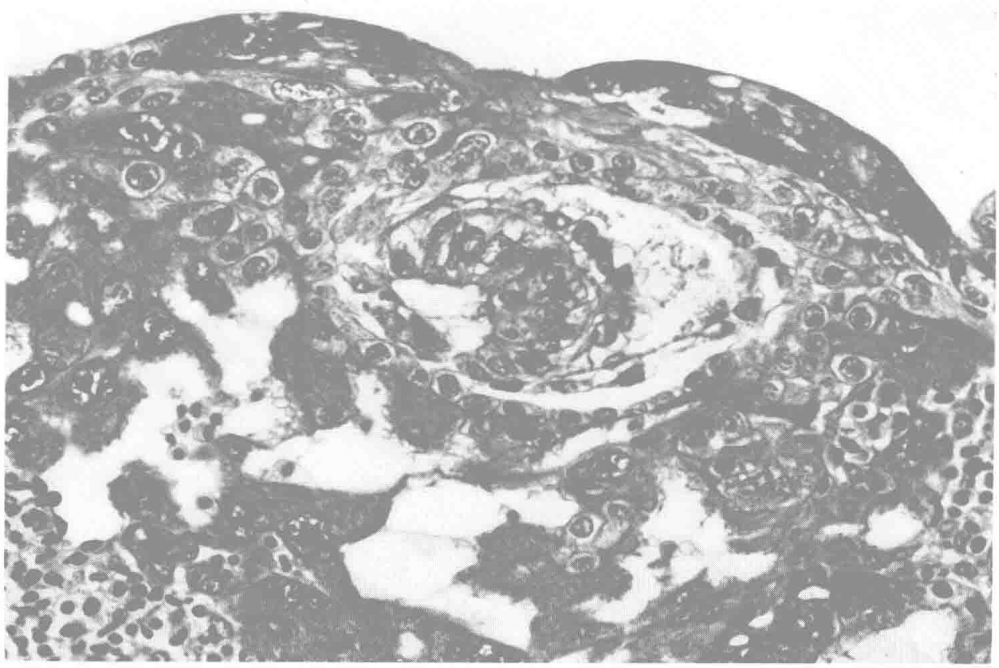

Fig. 1-10. A 9-day-old ovum showing differentiation into germ disc (center) surrounded by previllous trophoblast. The darker syncytiotrophoblast contains intracytoplasmic spaces, which will coalesce to form the future intervillous space. Carnegie 8171, Section 3-2-11, ×300. (Courtesy Dr. A. T. Hertig, Boston, and Carnegie Institution of Washington, Baltimore, Md. From Hertig, A. T., Rock, J., and Adams, E. C.: A description of 34 human ova within the first 17 days of development, Am. J. Anat. **98**:435-493, 1956.)