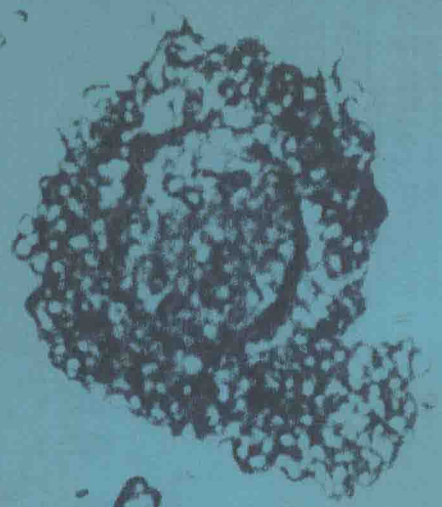
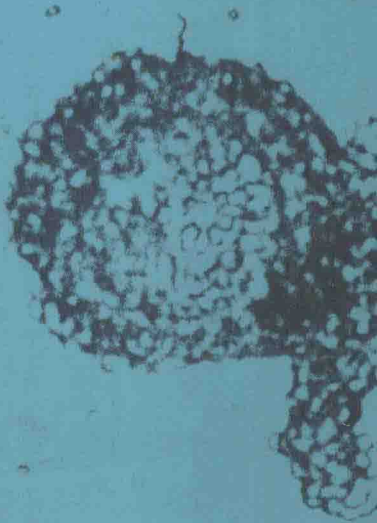
B.-M. Uebele-Kallhardt

Human Oocytes and Their Chromosomes

An Atlas





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In Cooperation with T. Trautmann

With a Foreword by K. Benirschke

With 72 Figures

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Foreword

The last decade has seen remarkable advances in human genetics. Once the correct chromosome number of the human genome was ascertained, a wide variety of diseases was recognized as due to numerical chromosome anomalies. There followed the discovery that spontaneous abortions are the result of chromosome errors, and specific band patterns of chromosomes allowed identification of minute lesions. The techniques of cell hybridization now allow specific gene assignment to chromosomes and even to distinct loci on their arms. All this was possible because of the ease with which metaphase chromosomes can be obtained and manipulated. The much older technique of analysis of meiotic chromosomes has taken a back seat in this exciting era. Being much less readily accessible, spermatogonial analysis is much less frequently undertaken and is less successful. Even more difficult for study is the female meiotic process. Not only is meiosis extraordinarily long, spanning from before birth to ovulation, the techniques for its study and the patience required for detailed inquiry have been significant obstacles. At the same time, the suspicion that female meiotic analysis should not only be rewarding but that it may be mandatory has been with us ever since it was recognized that a positive correlation exists between chromosomal nondisjunction and maternal age.

Before the intricacies of chromosomal behavior that are responsible for nondisjunction are understood, however, it is necessary that we comprehend the normalcy of the process. That is the aim of this presentation. A systematic inquiry of human oogonial maturation has been made in only two

or three laboratories. The cumulative descriptive results from one of these patient efforts now lie before us. Here are the detailed photographic records of the maturing oocyte, accompanied by descriptions which reflect the interpretation by the author. Having experience with an unusually large material she describes the initial meiotic prophases in fetuses after eighteen weeks of gestation to birth when the first phase is arrested. The continuation of meiosis is followed in biopsies of adult ovaries from which the oocytes are dissected and allowed to mature in tissue culture explants. A number of normal and abnormal chromosome sets could be identified in this tenacious study and will give us the background for comparison. A comprehensive citation of literature and succinct technical details are woven into the presentation to make the book more useful to future workers.

This is an unusual book. It is not meant to be read as other texts. It will be useful for the laboratory bench of cytogeneticists with an interest in exploring the borderline of knowledge and the wish to extend this imperfect understanding we now have of this important process. It is an atlas of beautiful photographs that sequentially depicts the meiotic progression and brings together all that is currently known of oogenesis. The author is to be congratulated for having persevered in so difficult a task as the accumulation and interpretation of this vast material. We also owe a special thanks to the publishers for presenting a book of this quality to a necessarily limited audience so that science may proceed at a more rapid pace. We wish that the book may find wide acceptance as a milestone in human cytogenetics.

San Diego, California K. Benirschke

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Acknowledgments

The author would like to express her gratitude to Professor K. Knörr, head of the Department of Obstetrics and Gynecology of the University of Ulm. His animating interest in genetic questions made it possible for me to carry out these investigations.
Thanks are due to all the members of this department, especially the surgical staff, for having provided me with the ovarian material.
Finally I am most grateful to Dr. R.G. Edwards, Physiological Laboratory, Cambridge University (U.K.), who, in 1969, introduced me to the intricate art of handling and culturing mammalian oocytes.

B.-M. Uebele-Kallhardt

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Contents

Introduction

Meiosis is by far the most essential part of oogenesis. It consists of two cell divisions, known as first and second maturation divisions, during which the nucleus and the cytoplasm undergo a number of changes. The highly specialized meiotic process causes an exchange of genetic material between pairs of chromosomes and provides the mature oocyte with half the number of chromosomes characteristic of the somatic cells.

Meiosis is of exceptionally long duration in the human oocyte. In the fetal ovary, oocytes enter the prophase of the first maturation division. At the time of birth all primary oocytes are arrested in a stage, known as dictyotene, that persists for many years. In the adult ovary this prolonged stage of development is terminated just before ovulation, when an individual oocyte resumes meiosis and begins its final maturation. The second maturation division is completed only if fertilization occurs.

Detailed knowledge of normal meiotic behavior of the chromosomes and its particulars (chromosome pairing, crossing-over, chiasma formation, separation and distribution of homologous chromosomes) is necessary for a full understanding of chromosomal abnormalities and their origins, problems which confront researchers in clinical genetics. As an example, a case of translocation heterozygosity will be treated extensively in this report.

Due to varying degrees of spiralization, the coiling and uncoiling of the chromosome threads, striking phenotypic changes are observable in the chromosomes during meiosis. The maximally despiralized and extended chromosomes represent the

functional form and are considered to be suggestive of intense transcriptional activity. The coiling cycle transforms the functional form into the transport form, in which the chromosomes are extremely spiralized and contracted. The preovulatory stages of meiosis are now available for study by in vitro maturation of oocytes. It seems worthwhile to present in its entirety the meiotic coiling cycle of the chromosomes from the prophase of meiosis up to the metaphase of the second maturation division. By means of microphotographs, a comprehensive picture of the sequential nuclear stages and the related chromosomal changes which occur in the human oocyte during meiosis in the fetal and adult ovaries is given.

Meiotic behavior of the human oocyte is generally in accordance with the observed basic rules of meiosis. Usually these rules are illustrated by schematic drawings. However, the simplification and subdivision necessary in such drawings is more or less arbitrary and does not do justice to the complex and dynamic process of meiosis. It is for these reasons, among others, that this report will show more life-like representations of meiosis and of the coiling cycle of the chromosomes within the human oocyte.

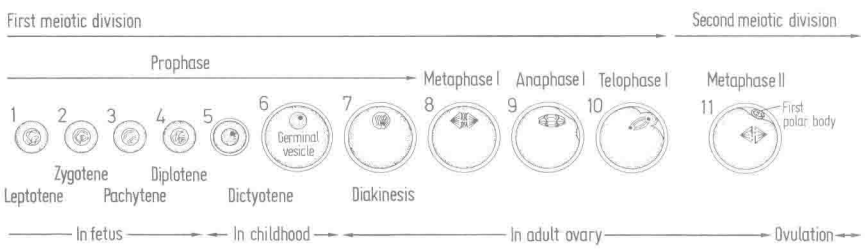

Fig. 1. Diagrammatic representation of the oocyte maturation process from the prenatal period to the preovulatory stage (modified from Edwards, R.G.: Mammalian eggs in the laboratory, Sci. Am. **215**, 73–81 (1966)

The micrographs on the following pages illustrate the sequence of maturational changes that human oocytes undergo during meiosis.

Oocytes of Fetal Ovaries: Prophase of First Meiotic Division

Between the 3rd and 7th month in the fetal ovary, there is not only an increase of germ cells by mitotic divisions, but also the transformation of oogonia into oocytes.

Having completed the last premeiotic interphase, during which DNA replication takes place, the germ cells, growing in size, enter the *preleptotene* stage of the first meiotic prophase. As has been shown in recent years, this phase of transition to the leptotene is characterized by profound changes in the chromosome shape, caused by increasing spiralization up to maximum condensation in the so-called prochromosomes and by the despiralization that follows.
The fine filaments of the *leptotene* nucleus emerge from this phase of despiralization. Subsequently the chromosomes once again contract and enter the *zygotene* stage, in which pairing of homologous chromosomes begins. In the next stage, the *pachytene*, the chromosomes pair completely (synapsis). These pairs are called bivalents, their number equal to that of half of the somatic chromosomes. Due to increasing spiralization, the chromosomes become shorter and thicker, and at this point a number of pairs can be identified. This is especially true of the acrocentric bivalents associated with nucleoli. At the end of the relatively long pachytene stage an exchange of genetic material takes place between the paired homologous chromosomes (crossing-over). In the subsequent *diplotene* stage, the oocyte's chromosomes once again despiralize. The homologues repel one another. Only the chiasmata, i.e., the sites of genetic exchange, hold the pairing partners together for the present.

At this stage in prophase, meiosis of the human female germ cell is suspended until sexual maturity and ovulation. The oocyte remains in a modified diplotene stage, the so-called *dictyotene*. The uncoiled, extremely extended bivalents, known as "lampbrush chromosomes," are difficult to observe even with the aid of an electron microscope. Their specific structure as well as the nucleoli, one to four per cell present throughout the entire prophase, are related to the intense metabolic and synthetic activity of the primary oocyte. By accumulation of nutrients, the oocyte increases its cytoplasm and expands greatly in size, finally reaching a diameter of 100–120 μ.
The suspension of meiosis in the dictyotene stage until the preovulatory phase of the oocyte's development probably occurs under the influence of epithelial cells, which together with the oocyte form the primary follicle at the end of the first meiotic prophase.

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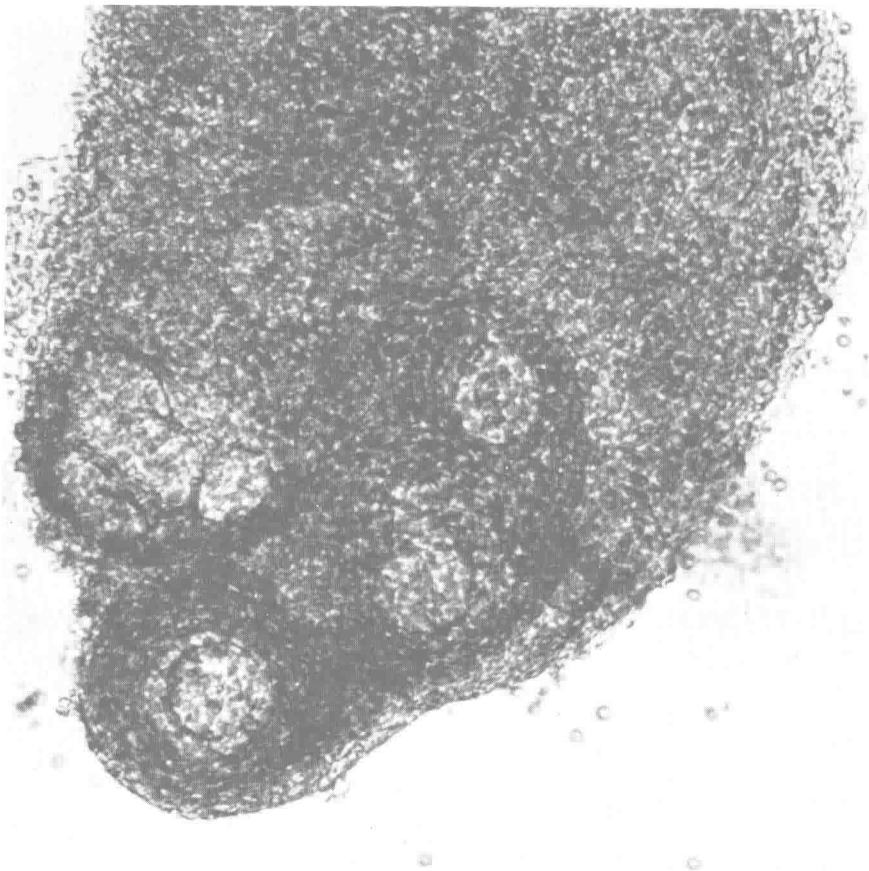

Fig. 2. Segment of an explanted fetal ovary. A group of germ cells, different in size, is present

Unstained, ×410

Fig. 3. Nucleus of an oogonium with its centrally situated nucleolus (*arrow*)

× 1,600

Oogonia, derived from primordial germ cells, undergo mitotic divisions, their number of chromosomes remaining at 46. At the end of the mitotic proliferation, oogonia become transformed into primary oocytes, when they enter the meiotic prophase.

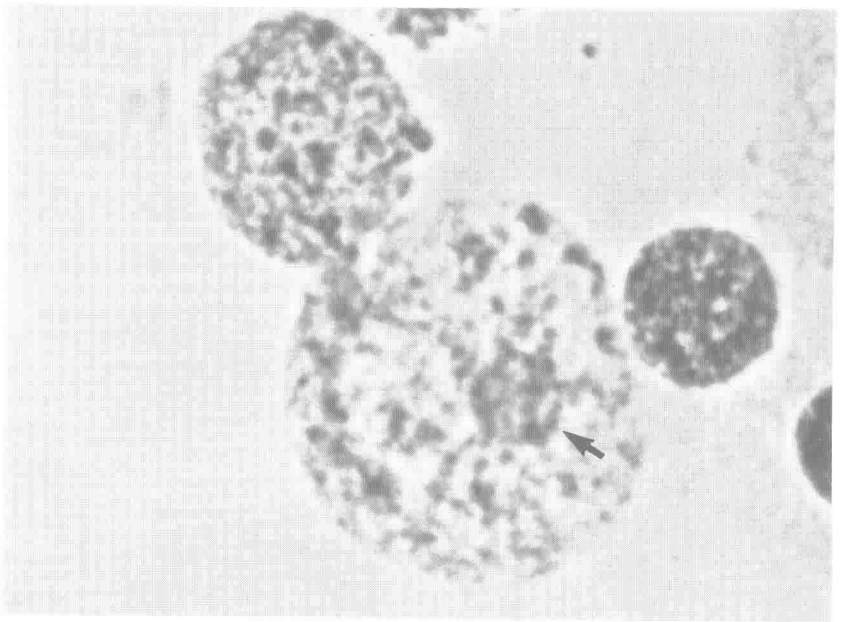

Fig. 3

Fig. 4. Nuclei of primary oocytes in different stages of the first meiotic prophase: preleptotene (prochromosomes), leptotene, pachytene. The smaller-sized nuclei are derived from somatic cells

× 600

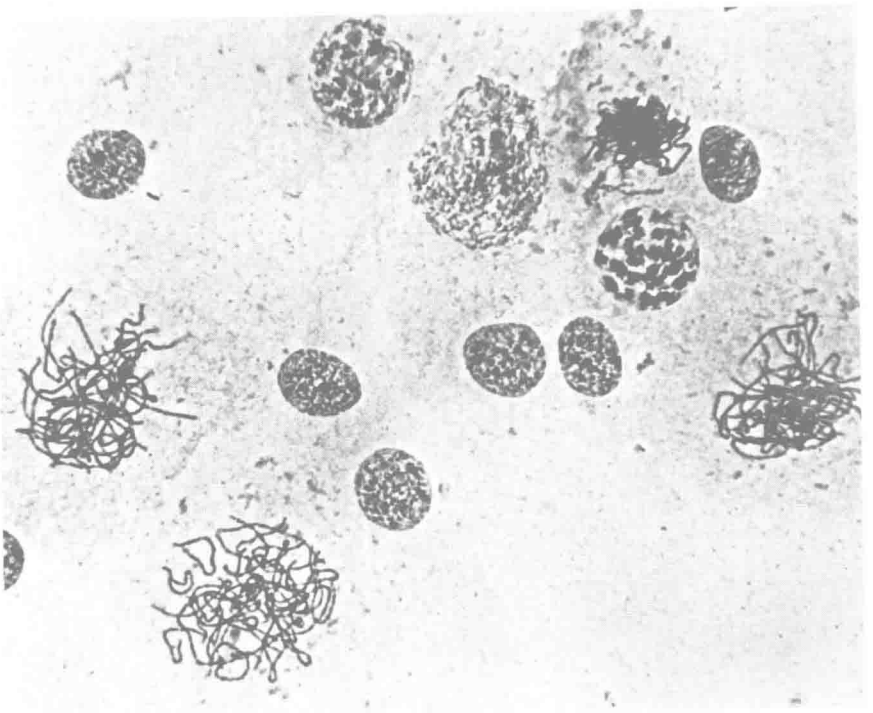

Fig. 4

The so-called preleptotene initiates the prophase of the first meiotic division. It represents a phase of transition between oogonium and leptotene oocyte. In recent years it has been shown that the preleptotene is characterized by a striking change of spiralization and despiralization of the chromosomes.

Fig. 5. Preleptotene. The spiralization starts with condensation of some chromosome segments

× 2,250

Fig. 6. Preleptotene. The chromosomes continue to shorten and thicken and the condensing segments increase

× 2,800

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