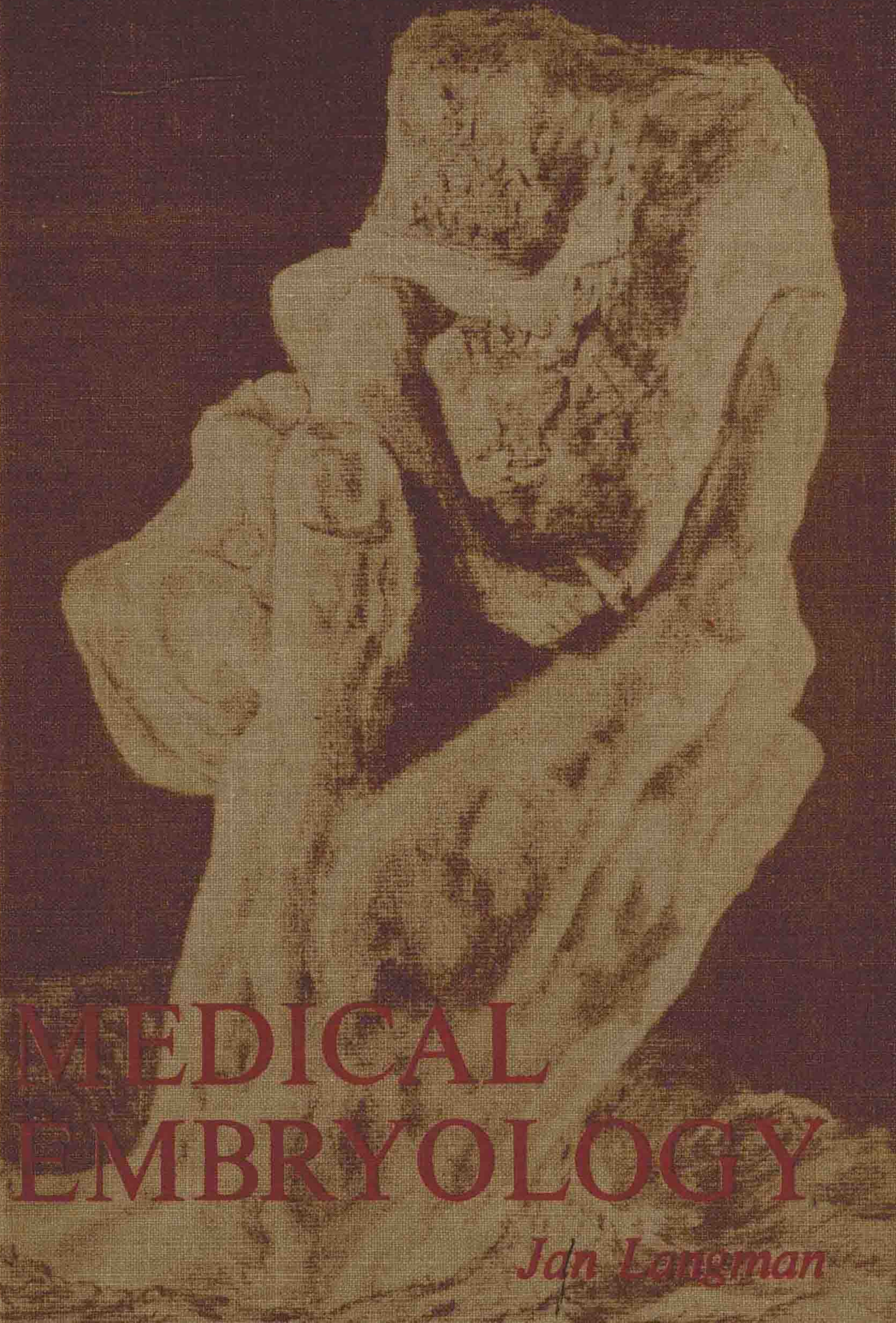

MEDICAL EMBRYOLOGY

Jan Langman

MEDICAL EMBRYOLOGY

Human Development — normal and abnormal

Jan Langman, M.D., Ph.D.

Professor of Anatomy, McGill University, Montreal

Illustrations by JILL LELAND

Baltimore

THE WILLIAMS AND WILKINS COMPANY

1963

428 E. Preston St., Baltimore, Md., 21202 U. S. A.
Made in the United States of America

First edition, June, 1963
Reprinted: February, 1964; May, 1964
Reprinted, July, 1965

Spanish Edition, December, 1963
French Edition (in preparation)
Russian Edition (in preparation)
German Edition (in preparation)

Library of Congress Catalog Card Number 63-19754

COVER ILLUSTRATION—"La Main de Dieu" (The Hand of God), by August Rodin, 1897. The hand is shaping a mass of formless matter, from which, as from a womb, emerge the bodies of Man and Woman. *Reproduced, with the permission of The Philadelphia Museum of Art, from a charcoal sketch of the bronze in its Rodin Museum.*

Composed and printed at
Waverly Press, Inc.
Mt. Royal & Guilford Aves.
Baltimore, Md., 21202 U. S. A.

MEDICAL EMBRYOLOGY

To my wife
INA
in appreciation of her great support during
the writing of this book

Preface

Recent advances in embryology, radioautography, and electron microscopy have been so overwhelming that the medical student often has difficulty in grasping the basic facts of development from the highly complicated picture presented to him. The aim of this book, therefore, is to give the future doctor a concise, well illustrated presentation of the essential facts of human development, clarifying the gross anatomical features without omitting the recent advances or changing concepts in the basic sciences. Furthermore, since embryology has become of great practical value because of the enormous progress made in surgery and teratology, each chapter on the development of the organ systems has been complemented by a description of those malformations important to the student in his further training. As a further reflection of the increased clinical importance of embryology an entire chapter has been devoted to the etiology of congenital defects.

Of the many colleagues who have been of help in the writing of this book, I particularly wish to thank Dr. C. P. Leblond for his continuous interest and encouragement; Dr. F. Clarke Fraser, for his help in discussing the various aspects of the congenital malformations; and my friends, Dr. Harry Maisel, Dr. Robert van Mierop, and Dr. Yves Clermont, who have spared no effort in assisting with the design of the drawings and the checking of the text.

I wish to express my sincere thanks to Miss Jill Leland, who prepared all the illustrations in this book, and to Mrs. E. Dawson, who has been of such excellent support to me in setting up the manuscript.

CONTENTS

Part I GENERAL EMBRYOLOGY

Part II SPECIAL EMBRYOLOGY

PART I

GENERAL EMBRYOLOGY

CHAPTER 1

Gametogenesis

- **PRIMORDIAL GERM CELLS**
- **OOGENESIS:** *oogonium; primary oocyte; first maturation division; secondary oocyte; second maturation division; mature oocyte*
- **SPERMATOGENESIS:** *spermatogonium; primary spermatocyte; first maturation division; secondary spermatocyte; second maturation division; spermatid*
- **SPERMIOGENESIS:** *acrosomic head cap; middle piece, body and tail*
- **MEIOSIS**
- **ABNORMAL GAMETES:** *multinucleated oocytes; abnormal spermatozoa*

The development of a new individual commences with fertilization. During this process two highly specialized cells, one from the male, known as the *spermatozoon*, and the other from the female, the *ovum*, unite to give rise to the *zygote*, the first cell of the new organism. In the male the germ cells or spermatozoa arise and mature in the testis; in the female the ova grow and ripen in the ovary.

In preparation for eventual fertilization, both male and female germ cells undergo a series of profound changes that involve the nucleus as well as the cytoplasm of the cells. The purpose of these changes is twofold:

1. To reduce the number of chromosomes in the germ cell to half that in the somatic cell, *i.e.*, from 46 to 23 chromosomes. Hence, the mature germ cells of both male and female contain 23 chromosomes. The reduction in the number of chromosomes is necessary for the maintenance of the species, as otherwise fusion of male and female gametes would give rise to an individual with twice the number of chromosomes of the parent cells. It is accomplished by two highly specialized divisions, known as *meiotic divisions* (see page 11).

2. To alter the shape of the germ cells in preparation for fertilization. The female germ cell, which initially approximates 30 μ in diameter,

enlarges greatly, because of the increase in cytoplasm. At maturity the ovum is about 120 μ in diameter. The male germ cell, on the contrary, loses practically all its cytoplasm, develops a tail, and becomes highly motile.

Since at present it is generally believed that the germ cells as found in the adult are direct descendants of the primitive germ cells as seen in early embryonic life, the discussion on the development of the spermatozoon and ovum will begin with that of the *primordial germ cells.*

Primordial Germ Cells

The primordial germ cells appear in human embryos at the end of the third week of development.[1] They are then located in the wall of the yolk sac near the caudal end of the embryo and from there migrate toward the developing gonads (primitive sex glands), where they arrive at the end of the fifth week.[1-8] (For further details, see Chapter 10.)

It was initially believed that the primordial germ cells died shortly after arrival in the gonads and that new germ cells were formed by the surface epithelium of the glands.[9-13] At present, however, it is evident from genetic, irradiation, and isotope studies that the mature germ cell is a direct descendant of the primordial germ cell in the embryo.[4-7, 14-18] This implies that the predecessors of the mature male and female germ cells produced during reproductive life are present in the embryo and it is thought that some of the primitive germ cells in the female, reaching maturity late in life, may have been dormant for 40 years or more.

Oogenesis

Once the primordial germ cells arrive in the developing female gonad, they divide rapidly and give rise to the *oogonia,* which are considered the most primitive female germ cells. By the third month of development the oogonia are located in the cortical part of the ovary, where they are arranged in clusters surrounded by a layer of flat epithelial cells (fig. 1-1*A*). It is thought that each cluster is formed by the descendants of a single primordial germ cell and that the surrounding cells originate in the surface epithelium. By the end of the third month some of the oogonia differentiate into the much larger *primary oocytes,* which immediately after their formation enter the prophase of the first meiotic division. By the seventh month, when practically all the oogonia have disappeared and the oocytes have started meiosis, each primary oocyte is surrounded by a layer of flat epithelial cells (fig. 1-1*B*).[19, 20] A primary oocyte, together with the surrounding epithelial cells, then forms the so-called *primordial follicle* (fig. 1-1*B*). At birth the primary oocytes have finished the prophase of the first meiotic division and have entered a resting stage (the *dictyotene stage*), in which they remain until sexual maturity is reached (fig. 1-1*C*).[20, 21]

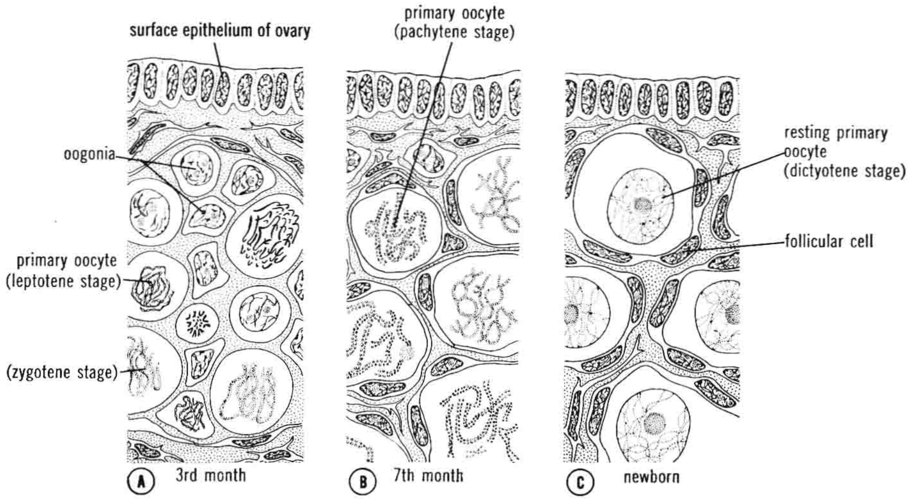

Figure 1-1. *Schematic representation of a segment of the ovary at different stages of development. A, At 3 months. The oogonia are grouped in clusters in the cortical part of the ovary. Some show mitosis; others have already differentiated into primary oocytes and have entered the prophase of the first meiotic division (leptotene and zygotene stages). B, At 7 months. Almost all the oogonia are transformed into primary oocytes, which show the pachytene stage of the prophase of the first meiotic division. C, At birth. No more oogonia can be detected. Each primary oocyte is surrounded by a single layer of follicular cells, thus forming the primordial follicle. The oocytes have entered the dictyotene stage in which they remain until maturation. Only then do they enter the metaphase of the first meiotic division (modified after Ohno et al.).*

Only then do they complete the first meiotic division. Although the total number of primary oocytes present at birth is estimated at 40,000 to 300,000, the majority degenerates during further life. After puberty, however, a number of oocytes begin to enlarge with each ovarian cycle, though usually only one achieves full maturity.

As a first indication of further development, the primary oocyte increases in size, while the follicular cells become cuboidal and begin to proliferate, thereby forming an increasingly thick covering around the oocyte (fig. 1-2). In addition, the follicular cells deposit some acellular material consisting of glycoproteins on the surface of the oocyte.[19, 22] This material gradually thickens and forms the *zona pellucida* (fig. 1-3*A*). Small processes of the oocyte and follicular cells extend into or across the zona pellucida and are thought to be of significance in the transport of materials from the follicular cells to the oocyte during its rapid growth.[19, 23, 24]

As development continues, irregular, fluid-filled spaces appear between the follicular cells. These spaces later coalesce to form the *follicular antrum*, which with time becomes crescent-shaped and filled

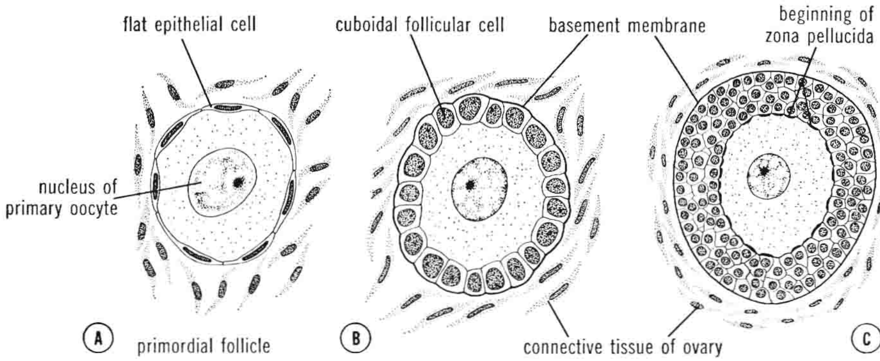

Figure 1-2. *A, Schematic drawing of a primary oocyte surrounded by a layer of flattened epithelial cells (primordial follicle). B, With increase in size of the primary oocyte the follicular cells become cuboidal and show a distinct basement membrane. C, With further growth of the oocyte, the follicular cells form an increasingly thick layer around it. The zona pellucida is visible in irregular patches between the surface of the oocyte and the columnar follicular cells (modified after Shettles).*

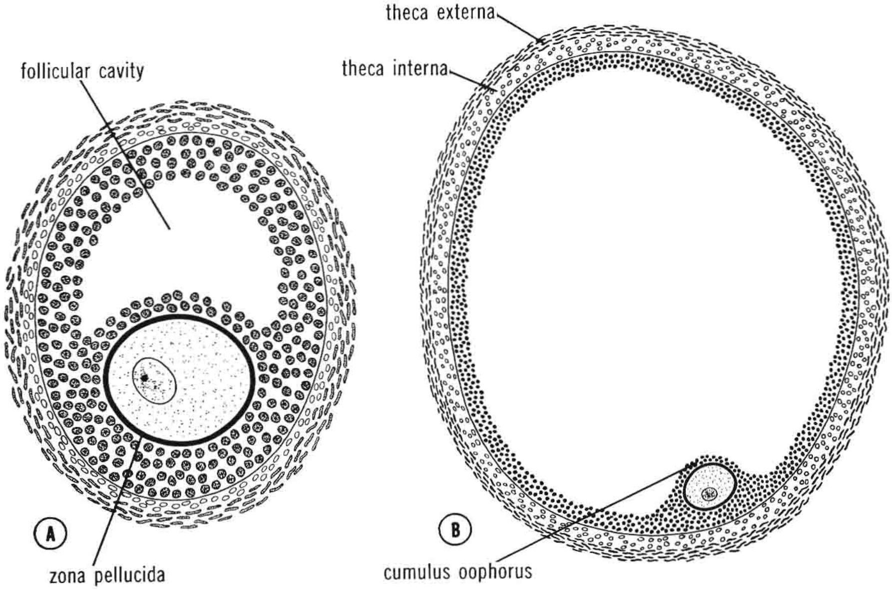

Figure 1-3. *Schematic representation of a maturing follicle. A, The oocyte surrounded by the zona pellucida is eccentrically located; the follicular antrum has developed by coalescence of intercellular spaces. Note the arrangement of the cells of the theca interna and the theca externa. B, Mature Graafian follicle The antrum has enlarged considerably, is filled with follicular fluid, and is surrounded by a layer of follicular cells. The oocyte is surrounded by a mound of follicular cells, the cumulus oophorus.*

with follicular fluid containing estrogenic hormones secreted by the follicular cells (fig. 1-3*A*). Those follicular cells massed around the oocyte itself are known collectively as the *cumulus oophorus* (fig. 1-3*B*). In its mature state the follicle is known as the *Graafian follicle*. It is then surrounded by two layers of connective tissue: an inner vascular layer, the *theca interna*, and an outer fibrous layer, the *theca externa* (fig. 1-3*B*). As the follicle nears maturity the cumulus oophorus becomes more elevated, until finally the oocyte is supported by a column of follicular cells.[24] The follicle then varies in size from 6 to 12 mm., and is found immediately adjacent to the surface of the ovary.

Toward the end of development of the primordial follicle into the mature Graafian follicle, the primary oocyte finishes its *first meiotic* or *maturation division*, which was started during prenatal life. The result of this division is the formation of two daughter cells, each with 23 chromosomes but of unequal size (fig. 1-4*A*, *B*). One receives almost all the cytoplasm of the mother cell and is known as the *secondary oocyte*; the other receives hardly any and forms the *first polar body*.[25] The latter lies between the zona pellucida and the cell membrane of the secondary oocyte (fig. 1-4*B*).

As soon as the first maturation division has been completed and before the nucleus of the secondary oocyte has returned to its resting stage, the cell starts a *second maturation division*. This division results in the formation of a large, mature oocyte and a second polar body. At the moment that the secondary oocyte shows the spindle formation, ovulation occurs and the oocyte is shed from the ovary (fig. 1-4*C*).[26] It is thought that the second maturation division is completed only if the

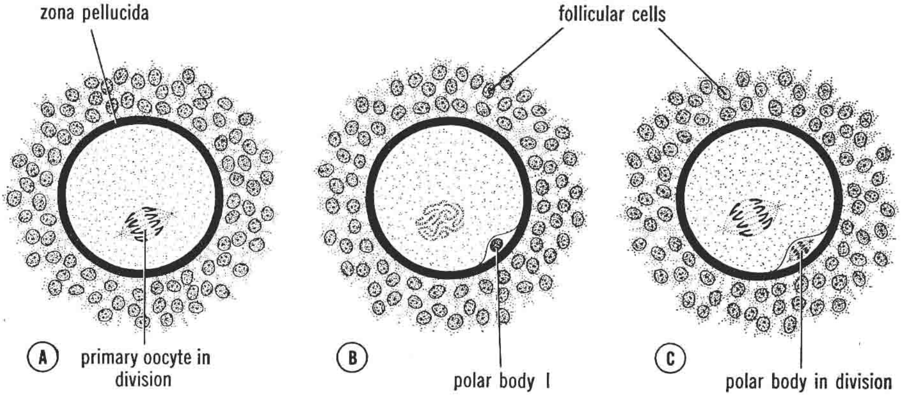

Figure 1-4. *Maturation of the oocyte. Although this process occurs inside the follicle, as shown in figure 1-3, in this drawing only a few layers of follicular cells are represented. A, Primary oocyte, showing the spindle of the meiotic division. B, Secondary oocyte and polar body I. C, Secondary oocyte, showing the spindle of the second maturation division. Polar body I likewise shows spindle formation (adapted from several sources).*

oocyte is fertilized, otherwise the oocyte degenerates approximately 24 hours after ovulation. Whether the first-formed polar body always undergoes a second division is not known for certain, but fertilized ova accompanied by three polar bodies have been observed.[24]

Spermatogenesis

During the fifth week of development the primordial germ cells enter the developing male gonad, where they are incorporated into the *primitive sex cords*. These irregularly shaped cords are composed of cells derived from the surface epithelium of the gland.[27]

At birth the sex cords are solid and contain two types of cells (fig. 1-5*A*). The larger of the two is located along the basement membrane and has a large, lightly staining, spherical nucleus with one or more nucleoli. These cells are believed to be the primordial germ cells.[18] The other cell type is likewise found along the basement membrane, but it is much smaller and characterized by nuclei with coarse chromatin granulations. These cells proliferate actively and are known as the *supporting cells*.[28] After birth they cease to divide and become typical *Sertoli cells* (*sustentacular cells*), a nonspermatogenic cell type derived from the surface epithelium (fig. 1-5*B*).

Recently it has been shown that some of the primordial germ cells die in the course of development but that the others develop into spermatogonia which later give rise to the spermatozoa.[18, 29-31]

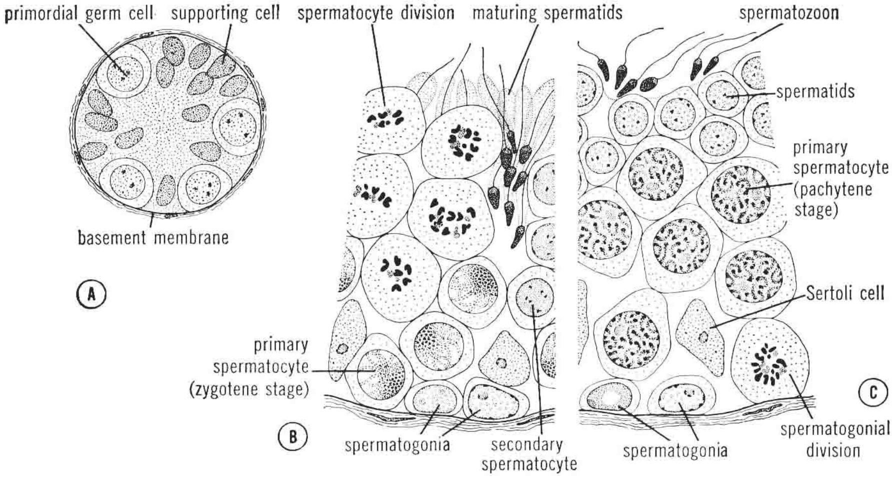

Figure 1-5. *A*, *Transverse section through testis cord in the newborn, showing the primordial germ cells and supporting cells surrounded by the basement membrane. B and C, Two different segments of the adult seminiferous tubule shown in transverse section. Each segment shows a different stage of the maturation of the male germ cells (derived from Clermont).*

In the course of postnatal development the sex cords obtain a lumen and become known as *seminiferous tubules*. The spermatogonia close to the basement membrane of the tubule then begin to divide and give rise either to new spermatogonia (the so-called type A spermatogonia which include the stem cells), or to a more differentiated type (type B), which develop into *primary spermatocytes* (figs. 1-5 and 1-6).[32-35] The latter have a spherical nucleus with fine chromatin granulations either free in the nucleoplasm or attached to the nuclear membrane. The primary spermatocytes then start the long lasting prophase of the *first meiotic* or *maturation division* (fig. 1-6). As in the case of the primary oocyte, this division is characterized by a reduction in the number of chromosomes. The primary spermatocyte thus gives rise to two *secondary spermatocytes*, each containing half the number of chromosomes of the mother cell. Contrary to the oocyte, however, both secondary spermatocytes receive an equal amount of cytoplasm (see fig. 1-9*B*).

The secondary spermatocytes have a very short life span and almost immediately after their formation start a *second maturation division*. The cells resulting from this division are called *spermatids* (figs. 1-5 and 1-6). Hence, each primary spermatocyte gives rise theoretically to four spermatids, which then develop into spermatozoa (fig. 1-9*B*).

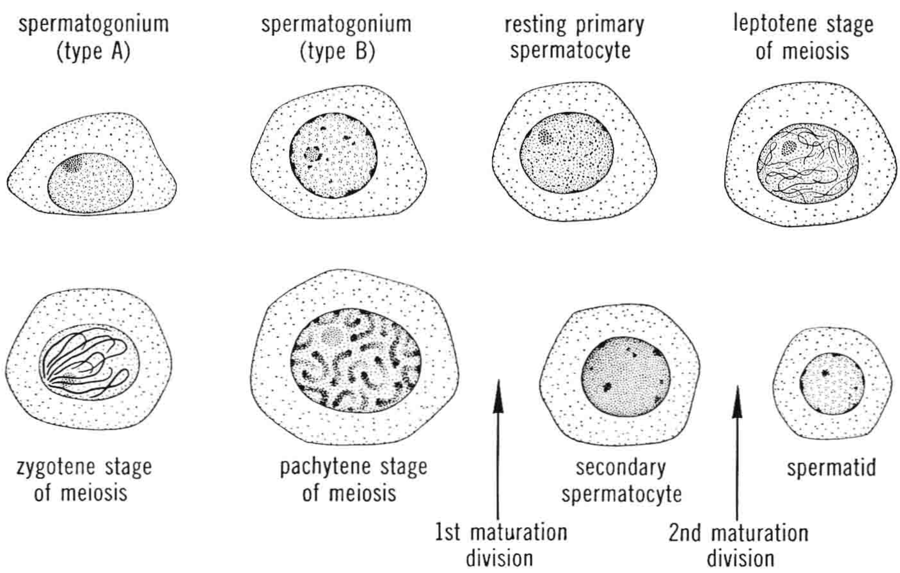

Figure 1-6. *Schematic representation of the spermatogenesis in man. Note the leptotene, zygotene, and pachytene stages of the prophase of the first meiotic division (derived from Clermont).*