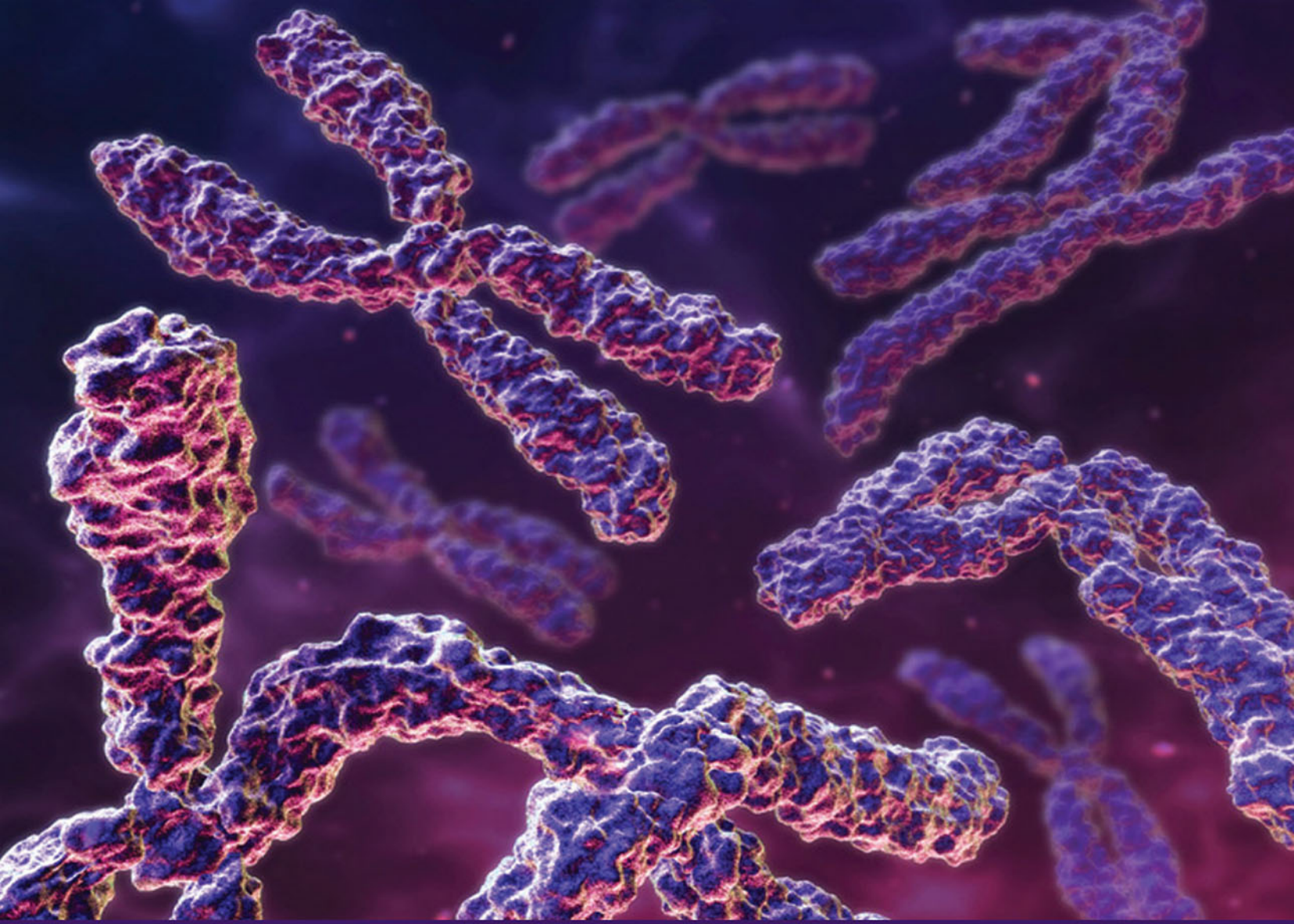

Manual of Cytogenetics *in* Reproductive Biology

Editor **Pankaj Talwar**

JAYPEE

Contents

Section 1 • Basics of Genetics and Genetics Laboratory

1. Structure of DNA 3
MS Ahuja
• DNA Packaging 3 • Forms of DNA 4 • Replication of DNA 4 • Ribonucleic Acid 5
• Gene Structure 5 • Gene Expression 6 • Genetic Code 7

2. Chromosome Nomenclature and Cell Division 10
Manisha Vajpayee
• Nomenclature 11 • Description of Human Chromosomes 13 • Karyotype Designation 13
• Designation of Chromosomal Abnormalities 14

3. Microscopes in Assisted Reproductive Technology 19
Rajvi H Mehta
• Important Terminology in Microscopy 19 • History of Microscopes 21
• Basic Optical Principles of Light Microscopy 21 • Application of Microscopes in ART 26
• Maintenance of Microscopes 27

4. The Cell Cycle and Cell Division 28
Manisha Vajpayee
• Stages and Types of Cell Division 28 • Gametogenesis 31

5. Cell 35
Kuldeep Mohanty, Swetasmita Mishra, Kranthi Vemprala, Tarranum Hassan, Rima Dada
• Types of Cells 35 • Structure 36 • Cell Division 41

Section 2 • Investigative Cytogenetics

6. Cytogenetics 47
Rima Dada, Manoj Kumar, Jhumur Pani, Dinesh Tomar
• History of Cytogenetics 47 • Cytogenetics: Principle and Methods 48 • Basics of Tissue Culture 51
• Cytogenetic Analysis of Chromosomes 52 • Banding Techniques 54 • Specialized Techniques to Visualize Chromosomes 56 • Drawbacks of Karyotyping Techniques 57 • Molecular Cytogenetics 57

7. Polymerase Chain Reaction 59
Rima Dada, Swetasmita Mishra, Kuldeep Mohanty, Manoj Kumar, Kranthi Vemprala
• Basic Principle 59 • PCR Methodology 60 • PCR Cycle 60 • Reagents and Instrumentation 61
• Optimizing the PCR Reaction 63 • Fidelity of PCR Reaction 63 • Do Errors in PCR Matter 63
• Types of PCR 63 • Drawbacks of Conventional PCR 65 • Quantitative PCR 65
• Primer Modifications 67 • PCR Optimization 68 • Clinical Applications 69

8. Human Chromatin **71**
Indu Chawla
• Functions of Chromatin 71 • Structure of Human Chromatin 71
• Chromatin Organization 71 • Types of Chromatin 72

9. Molecular Techniques in Preimplantation Genetic Diagnosis **73**
Nikhil Moorchung
• Structure of the Eukaryotic Chromosome 73 • Classification of Chromosomes 74
• Visualizing Individual Chromosomes 74 • Chromosomal Abnormalities 75
• Fluorescent *in situ* Hybridization 77 • Microarrays 79 • Comparative Genomic Hybridization 81 • Combining CGH with Microarrays: The Development of Array CGH 81
• Whole Genome Amplification 83

Section 3 • Applied Cytogenetics

10. DNA Fragmentation and Pregnancy Loss **87**
Vijayakumar Chelur Narayanamurthy
• Human Sperm Chromatin Structure 87 • Etiology: Origin of Sperm DNA Fragmentation 88 • Methods of Detection 88 • Ambiguity among the Methods of Detection 89 • Implications of DNA Fragmentation on Cycle Outcome 89 • Role of Sperm DNA Fragmentation on Pregnancy Loss 89
• Future Prospects for Research 92

11. Cytogenetics of Infertile Women **94**
Sarabpreet Singh
• Female Infertility 94 • The X and Y Chromosomes 94
• Structural Abnormalities of the X Chromosome 98

12. Cloning **105**
Sarabpreet Singh
• Background 105 • How is Cloning Different from Embryo Splitting? 106
• Events in Cloned Embryos 106 • How is Somatic Cell Nuclear Transfer Different from Asexual Reproduction? 107 • Methods of Cloning 108
• What We have Learned from Cloning? 108 • Genetic Reprogramming 108
• Applications of Somatic Cell Nuclear Transfer 108 • Limitations of Somatic Cell Nuclear Transfer 109 • Advantages 109 • Concerns 110 • Effect of Cloning on Disruption of Human Lineage 110 • Cloning versus Assisted Reproduction Techniques 110 • Genealogical Bewilderment 111

13. Premature Ovarian Failure: A Chronic Debilitating Condition of Womanhood **113**
GD Maiti
• Epidemiology 113 • Etiopathogenesis 114 • Clinical Associations 115
• Histological Evidence for Autoimmune Damage in POF 116 • Premature Ovarian Failure and Addison's Disease 116 • Nonovarian Autoantibodies 116
• Ovarian Autoantibodies 116 • Immunogenetics in Premature Ovarian Failure 117
• Clinical Presentation 119 • Differential Diagnoses 121 • Diagnostic Studies 121
• Prognosis 122 • Treatment 123

14. Genetics and Male Infertility **128**
Prasad Lele
• Genetic or Molecular Causes of Male Infertility 128 • Chromosomal Abnormalities 128
• The Y Chromosome 129

15. Sperm DNA Damage Assessment: Techniques and Relevance in Male Infertility Diagnostics **135**
Rima Dada, Kumar BS, Manoj Kumar, Ajit Singh Oberoi, Monis Bilal Shamsi
• Tests for Sperm DNA Damage Assessment 136 • Etiology of Sperm DNA Damage 139
• Outcomes of Studies on Sperm DNA Damage 139

16. Patterns of Inheritance **143**
MS Ahuja
• Laws of Inheritance 144 • Mendelian Inheritance 144

17. Epigenetics **155**
Prajnya Ranganath
• Epigenetic Mechanisms 155 • Role of Epigenetic Mechanisms in Development 156
• Environmental Influences on the Epigenome 157 • Effect of Assisted Reproductive Technology on the Epigenome 157 • Epigenetic Alterations in Human Disease 157
• Prospects for Epigenetic Therapy 159

18. Inborn Errors of Metabolism **160**
Prajnya Ranganath
• Prevalence 160 • Classification of Inborn Errors of Metabolism 160
• Inheritance Patterns of Inborn Errors of Metabolism 160
• Clinical Manifestations 160 • Investigations 162 • Treatment 162
• Genetic Counseling 162 • Newborn Screening 162

19. Male Infertility and Cytogenetics **166**
Kuldeep Jain, Rashmi Sharma
• Classification of Chromosomal Abnormalities 166 • Infertile Men with Normal Karyotype 168
• Clinical Implications 169

20. Cytogenetics in Recurrent Miscarriages **171**
Kuldeep Jain, Rashmi Malik
• Definition of Recurrent Miscarriage—When to Investigate? 171 • Causes of Recurrent Miscarriage 171 • Role of Genetic Factors (Chromosomal Abnormalities) in Miscarriages 171
• Cytogenetic Studies in Couples with Recurrent Miscarriages 172 • Structural Chromosomal Abnormalities 172 • Sex Relation 173 • Past History 173 • Other Minor Chromosomal Rearrangements 173 • Numerical Aberrations in Parents 174 • Prognosis in Carriers of Balanced Translocations: Clinical Consequences 174 • Normal Pregnancy Outcome 174
• Risk of Fetal Structural Chromosomal Anomaly 175 • Risk of Miscarriage 175
• Preimplantation Genetic Diagnosis 175 • Gamete Donation and *in vitro* Fertilization 175
• Chromosomal Studies in the Miscarriage Samples 175 • Techniques for Cytogenetic Studies 176 • Recommendations for Cytogenetic Studies in Recurrent Miscarriages 178
• Cytogenetic Studies of Miscarriage and Selective Parental Studies 178

21. Chromosomal Polymorphic Variants and Reproductive Outcome **181**
Arun Arora, Geetu Mahajan
• Clinical Applications 182

22. Oocyte and Maternal Inheritance **185**
Sohani Verma
• Oogenesis 185 • Oocyte Genome 185 • Nuclear Genome 185
• Ooplasm and Mitochondrial DNA 187 • Energy Production in the Oocyte 187
• Special Features of Mitochondrial Genetics 188 • Clinical Implications 189
• Prenatal Diagnosis and Emerging Technologies 190

Section 4 • Cytogenetics: Recent Advances

23. Cell Sorting in Genomics: Beginners' Guide **195**
SR Das
• Fluorescence Activated Cell Sorting 195 • Flow Cytometer Principles 196
• Fluorescence 196 • Optics and Data Collection 196 • Sorting 197

24. Gene Therapy **198**
Krishan Chugh, Neetu Talwar
• History 198 • Concept of Gene Therapy 198 • How does it Work? 198
• Types of Gene Therapy 199 • Different Approaches to the Treatment by Gene Therapy 200 • Choosing Targets 200 • Gene Delivery 200
• New Approaches 204 • Correct Approach in the Cases of Dominant, Negative, Mutated Genes 204 • Issues in Gene Therapy 204 • Research to Trials 205 • Challenges in Gene Therapy 205 • Preventive Gene Therapy 205
• Genetic Consultation 206 • Prognosis 206 • Future of Gene Therapy: Can we have Designer Babies? 206

25. Recombinant DNA Technology **209**
Jairam Yadav
• Uses for Recombinant Molecules 209 • Formation of Recombinant DNA 210
• Future Applications of Genetic Technologies in Treatments for Infertility 218

26. Blot Tests **219**
Surveen Ghumman Sindhu, Monika Gupta
• Southern Blot 220 • Northern Blotting 220 • Western Blotting 221
• Eastern Blotting 221 • Southwestern Blotting 222

27. Whole Genome Amplification and CGH: Recent Molecular Biology Techniques in Cytogenetics **223**
Raman Agrawal
• Whole Genome Amplification 224 • Comparative Genomic Hybridization 226

28. Soluble Human Leukocyte Antigen-G: Embryology in the Era of Proteomics **230**
Natachandra Chimote, Bindu Mehta, Nishad Chimote
• Proteomics and the Embryo 230

29. Role of Centrosome in Fertilization and Beyond in Assisted Reproduction **238**
Natachandra Chimote, Bindu Mehta, Nishad Chimote

• Fertilization and Early Embryogenesis 238 • Sperm and Oocyte Contributions 238 • Sperm Centrosome: Composition and Function 239 • Cytoskeletal Events during Fertilization 240 • Role of Centrosome Proteins in Fertilization 241 • When Fertilization Fails 242 • ICSI and Assays for Centrosome Functions in ART 243 • Conclusions and Future Perspectives 244

30. Human Genome Project **248**
Neetu Talwar, Krishan Chugh

• General Organization of the Human Genome 249 • DNA Sequencing 250 • Human Genome Project 252 • Who else is Involved with the Human Genome Project and Human Genome Research? 253 • Impact of Human Genome Project on Science, Genetics and Research 253

Section 5 • Preimplantation Cytogenetics

31. Preimplantation Genetic Diagnosis: A Review **259**
Pankaj Talwar

• Indications for Preimplantation Testing 259 • Techniques of PGS/PGD 260 • Timing of Biopsy 261 • Biopsy Procedure and Cell Extraction 261 • Number of Cells to Remove Safely 261 • Molecular Biology Techniques as Applied to PGD and PGS 261 • Basic Principles of PGD 262 • The Future: Toward a Full Chromosome Count 264 • Counseling the Couple for Preimplantation Genetic Testing 264 • Ethical Considerations 264

32. Preimplantation Genetic Diagnosis in Assisted Reproductive Technology **266**
Sujatha R, Ashraf CM

• Preimplantation Genetic Diagnosis and Preimplantation Genetic Screening 266 • Indications for PGS and PGD 267 • Molecular Diagnostic Techniques 267 • Samples for PGD 269 • Outcome 271

Section 6 • Prenatal Cytogenetics: Clinical Applications

33. Prenatal Cytogenetics **277**
Leena Wadhwa, Apoorva Kulshreshtha

• Indications 278 • Methods of Prenatal Cytogenetics 278 • Diagnostic Problems in Prenatal Diagnosis 282

34. Prenatal Diagnosis of Down Syndrome and other Chromosomal Disorders and Counseling for Abnormal Serum Marker Analytes **284**
Yoginder Singh

• Second-Trimester Serum Screening 285 • First-Trimester Combined Screen (Biochemical and Ultrasound) 285 • Combined First-Trimester and Second-Trimester Screening 286 • First-Trimester Ultrasound for Aneuploidy 287 • Noninvasive Prenatal Diagnosis 287 • Recommendations in Abnormal Serum Analytes 287

35. Common Genetic Syndromes in Clinical Practice **289**
Sheila S Mathai

• Causes of Genetic Disorders 289 • Modes of Inheritance 290
• Incidence of Genetic Disorders in India 291 • Clinical Terminologies 292
• Risks of Recurrence 292 • Common Chromosomal Anomalies 293
• Common Single Gene Defects 295 • Newborn Screening 297

36. Assisted Reproductive Technology and Genetic Counseling **298**
Koumudi Godbole

• Genetic Counseling 298 • Definition 298 • Process 298 • Providers 299
• Genetic Counseling in ART: Discussion Points 299 • Genetic Counseling: Specific Issues 299 • Genetic Counseling: General Issues 303 • Preimplantation Genetic Diagnosis 303 • Role of Maternal Aneuploidy Screening in Pregnancies Conceived by ART 304 • Newer ART Procedures and Genetic-Epigenetic Concerns 305
• Pregnancy Complications with ART 306

Index *309*

4 The Cell Cycle and Cell Division

Manisha Vajpayee

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INTRODUCTION

Development of any organism depends on its growth. At the time of conception, human cell zygote consists of a single cell and a mature human adult consists of approximately $1x10^{14}$ cells in total. This growth is a result of divisions leading to increase in cell mass by duplication of genetic material through rapid cell divisions. In this process, each progeny cell receives an equal compliment of the genetic material to ensure the perpetuation of cell line. This process of ordered progression of cell's life-span is called as cell cycle. Initially, a diploid cell (containing 2n chromosomes) undergoes a period of growth and increase in cell mass, replication of deoxyribonucleic acid (DNA) and after that a second growth phase takes place before actual division of the cell, this phase of the cell is called as interphase.

Chromosomes are not visible under the light microscope in non-dividing (interphase) cells. As the cell begins to divide, the threads of chromatin (DNA-protein complex) in the nucleus begin to condense into multiple levels of coiled structures recognizable as chromosomes. There are two modes of cell division: (1) mitosis and (2) meiosis. Mitosis is responsible for the proliferation of body (somatic) cells, whereas meiosis is responsible for the production of gametes. Because mitotic cells are easy to obtain, morphological studies are generally based on mitotic metaphase chromosomes.

STAGES AND TYPES OF CELL DIVISION

The transition of interphase to cell division (mitosis) and back to interphase is called the cell cycle. The average mammalian cell cycle lasts about 18–24 hours and is the transition of the cell from one interphase through cell division and back to interphase. Interphase of a dividing cell is divided into three stages: G1, S and G2, with G meaning gap. The stage in which cell actually undergo the division process is called as the mitosis phase.

Gap 1 stage is the longest stage and typically lasts about 9 hours. In this stage, cytoplasmic components, such as membranes, organelles, and ribosomes begin to proliferate and chromosomes exist as single chromatid. Cells are metabolically active in this stage and this is the stage when protein synthesis takes place. If a cell does not undergo further division, it may be permanently arrested at this stage and, at this instant, it is referred to as Gap zero (G0). G1 is followed by the S stage which lasts about 8–9 hours in mammalian cell, during which DNA synthesis occurs and the amount of DNA per chromosome is doubled, resulting in two sister-chromatids visible during prophase and metaphase. Some DNA replicates early in the S phase, and some replicates later. An interesting feature here is that if we analyze by standard G banding technique the light stained bands usually replicates early and contains higher portion of active genes, whereas the dark staining bands and the inactive X chromosome in female replicate late in the S phase.

Synthesis phase is followed by a second period of growth, the G2 stage. This stage lasts about 3–4 hours. During this stage, the cell prepares to undergo cell division. At the end of G2, the cell starts to divide and enters the M (mitosis) stage. When the cell is not cycling, interphase is said to be in G0. The cell cycle for human cells averages about 18–24 hours (8–10 hours for G1; 8–9 hours for S; 3–4 hours for G2; and 1 hour for M) (Fig. 1).

Mitosis

In the later part of 19th century, the process of cell reproduction was elucidated by Walther Flemming in animal cells

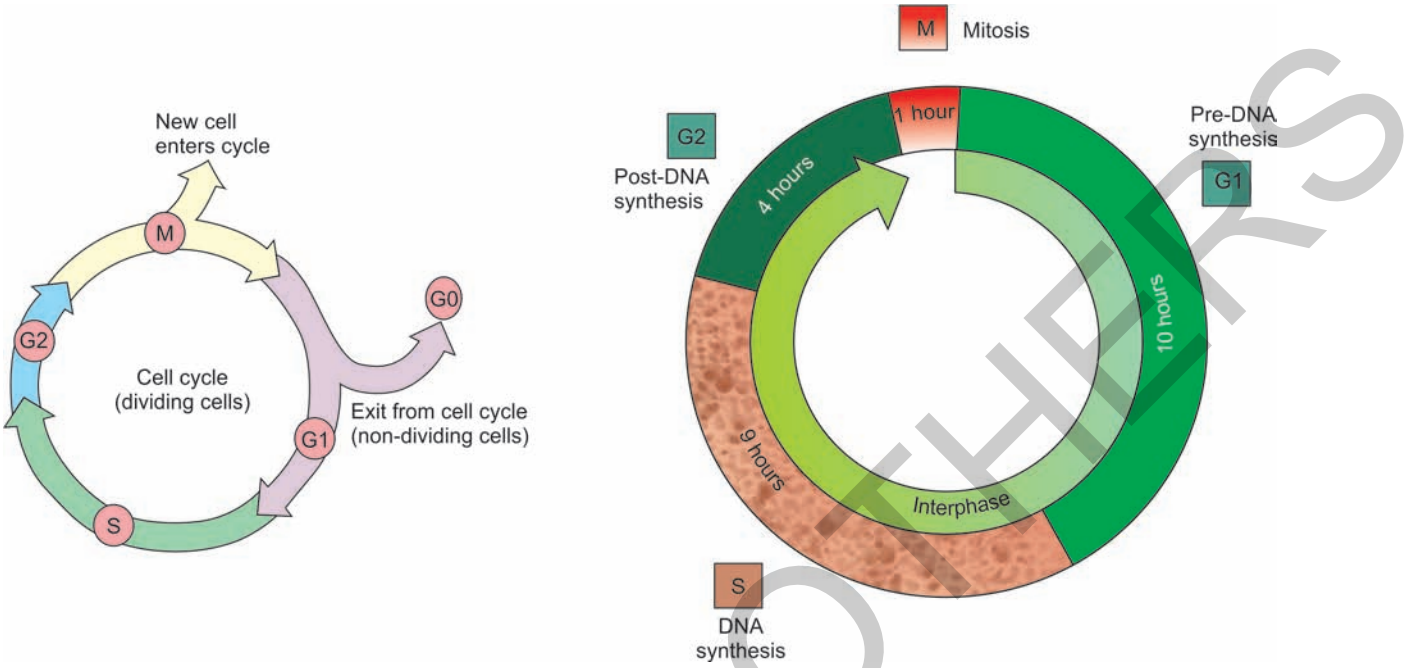

Fig. 1 The stages in the cell cycle of a typical mammalian cell (generation time 24 hours). Interphase is divided into G1, S and G2 stages. Mitosis (M) phase is divided into prophase (P), metaphase (M), anaphase (A) and telophase (T)

and by Edward Strasburger in plant cells (Gardner 1991). In the process of somatic cell division, two inter-related processes are involved: (1) mitosis, the nuclear division and (2) cytokinesis, the changes in the cytoplasm that include division of the cell proper.

Prior to entering in to mitosis, each chromosome consists of two identical sister chromatids, synthesized as a result of DNA replication taken place at S phase. In the process of mitosis, each of these pairs of chromatids separates and disperses into separate daughter cells. It is a continuous process, usually lasts for 1–2 hours. The initial indication regarding cell approaching to mitosis appears in cytoplasm of the interphase cell. A region of differentiated cytoplasm containing centriole starts to divide. The centriole is a reproducing organelle in the cytoplasm of the animal cells that initiate division and organize the mitotic apparatus. Mitotic apparatus is made up of two units: (1) asters and (2) spindle, which is a collection of spindle fibers and microtubules. Plant cells do not contain centriole. Mitosis can be divided into four phases: (1) prophase, (2) metaphase, (3) anaphase and (4) telophase.

Prophase

For better understanding, prophase can be divided in two substages: (1) early prophase and (2) late prophase.

In animal cells, during early prophase, the progeny centrioles move apart, chromosomes, consisting of thin uncoiled replicated two sister chromatids, condense and undergo progressive coiling. During the middle of the late prophase, the chromosomes can be seen as discrete structures, each with two chromatids and a constricted area called the centromere where the two chromatids are joined. Centromere is the region where spindle fibers attach. At this stage, centrioles now move to the opposite poles and continuous spindle fibers have connected it to the poles. The nuclear membrane and nucleolus disappear. Each chromatid gets attached with each spindle fiber at the centriole. This is the stage where each of the two sister chromatids becomes attached to the different poles of the spindle but the centromere remains together. The transitional period from late prophase to metaphase is called prometaphase, during which the nuclear envelope breaks down and the chromosomes move towards the equatorial plane (metaphase plate) of the cell.

Metaphase

At metaphase, the chromosomes are at their most condensed state, with spindle fibers attaching to the area of the centromere called the kinetochore, forming pole-chromosome fibers. The fibers which bypass the centromeres are called pole-pole fibers. At this stage, arms of sister chromatids are extended from the centromere, but chromatids are held together by centromere until the beginning of anaphase.

Anaphase

Anaphase begins with the division of the centromere and the separation of chromatids. Once separated, each chromatid has its own centriole and is known as a chromosome.

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Anaphase chromosome elongates somewhat by the relaxation of tight metaphase coiling and moves to respective poles of the mitotic spindle.

Telophase

Telophase marks the final stage of mitosis, during which the cell undergoes a reversal of prophase, including uncoiling of the chromosomes, disappearance of the spindle fibers, and reappearance of the nuclear envelope and nucleolus. At the same time, the cytoplasm is divided (cytokinesis) into two parts, forming two daughter cells.

The best mitotic stage for chromosome analysis is prometaphase or metaphase. A typical metaphase chromosome consists of two arms separated by a primary constriction or centromere. The diploid chromosome number is the number of chromosomes in the somatic cell and is designated by the symbol 2N. The gametes, which have one-half the diploid number, have the haploid number N. In humans, the diploid number is 46, with 23 inherited from each parent through the sperm or egg. Same (homologous) chromosomes form a pair with one member from each parent. Thus, there are 23 pairs of chromosomes in human cells. Of these, 22 pairs are not directly involved in sex determination, and are known as autosomes. The remaining chromosome pair consists of the sex chromosomes, and is directly involved in sex determination. In females, the two sex chromosomes are identical (XX), whereas in males, the two sex chromosomes are not identical (XY). The Y chromosome is smaller than the X chromosome. A gene which is responsible for switching the embryo to male characteristics was recently discovered on the Y chromosome (Fig. 2).

Meiosis

Meiosis is the nuclear division leading to the formation of gametes. It differs from mitosis in the following ways:

- During meiosis, unlike mitosis, diploid count is halved to haploid in each gamete
- Mitosis takes place in somatic cells and early cell division in germ cells while meiosis occurs in germ cells in gamete formation
- Mitosis occurs as single step process while meiosis occurs in two steps as meiosis I and meiosis II.

Meiosis I

This is also called as reduction division because chromosome number is halved here.

Prophase I: This is the longest and most important stage which is further subdivided in five substages. At this stage, chromosomes are already split longitudinally into two chromatids joined at the centromere. Homologous chromosome starts to pair.

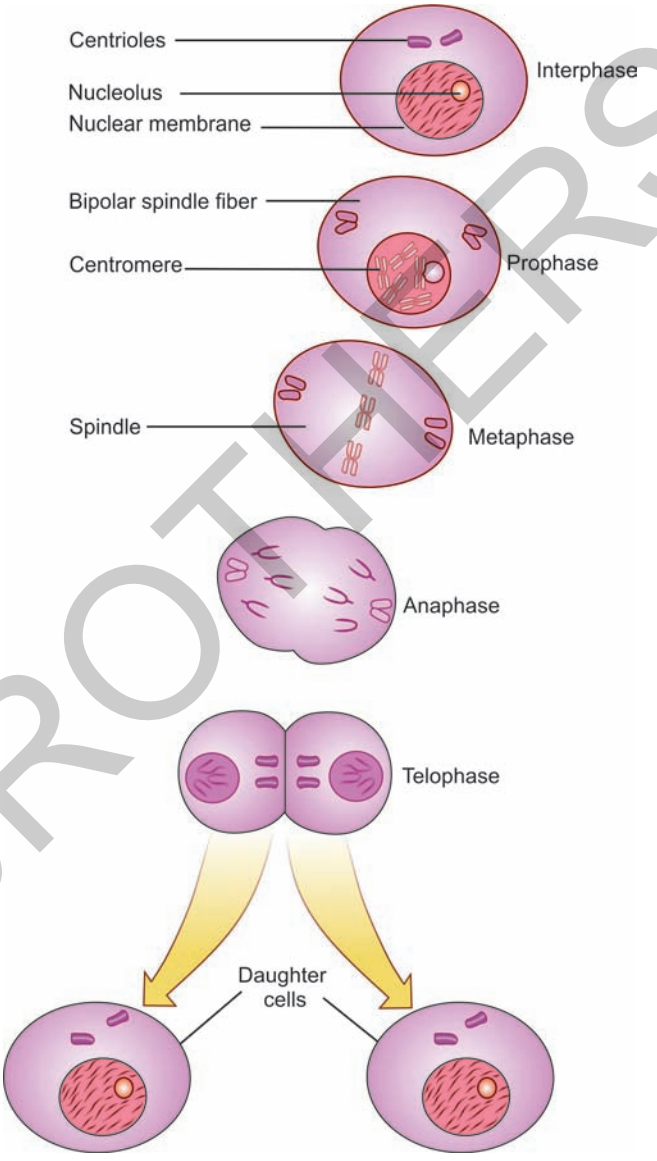

Fig. 2 Mitosis in a cell with three chromosomes

- Leptotene—chromosomes start the process to condense and become visible
- Zygotene—alignment of homologous chromosomes opposite to each other starts and the process is called synapsis through synaptonemal complexes
- Pachytene—here a pair of chromosome is known as bivalent. Exchange between homologous chromosomes at synaptonemal complex starts (crossing over). This formation is called chiasma. Actually, DNA is exchanged between chromatids. This stage is the main cause of genetic variations in each individual (Fig. 3)
- Diplotene—pair of chromatids start to repel each other causing strand to separate each other longitudinally

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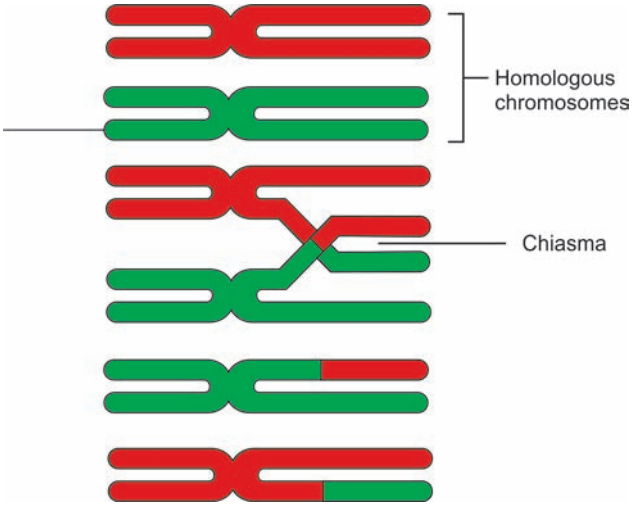

Fig. 3 Crossing over (chiasma formation) in prophase I (meiosis I)

but centromere is not split. Tetrads are held together at various places along their length because of the interchange between chromatids (chiasmata). One to several chiasmata may be observed depending on length of homologous chromosomes involved. Each chiasmata observed at this stage represents an exchange of DNA that occurred between non sister chromatin during pachytene stage.

- Diakinesis—separation of homologous chromosome pair takes place at this stage.

Metaphase I

The nuclear membrane disappears and chromosome aligns at cell equator and attached to poles through spindle fibers.

Anaphase I: The chromosomes separate to opposite poles through contraction of spindle.

Telophase I: Each set of haploid chromosome separates completely to opposite ends of cells, which cleaves into two new daughter gametes, so called secondary spermatocyte or oocytes.

Meiosis II

This is exactly similar to ordinary mitotic division. Each pair of chromatids becomes aligned along the equatorial plane, then splitting longitudinally, leading to the formation of two new daughter gametes called as spermatids or ova (Figs 4A and B).

GAMETOGENESIS

There are fundamental differences between oogenesis and spermatogenesis as depicted in Table 1.

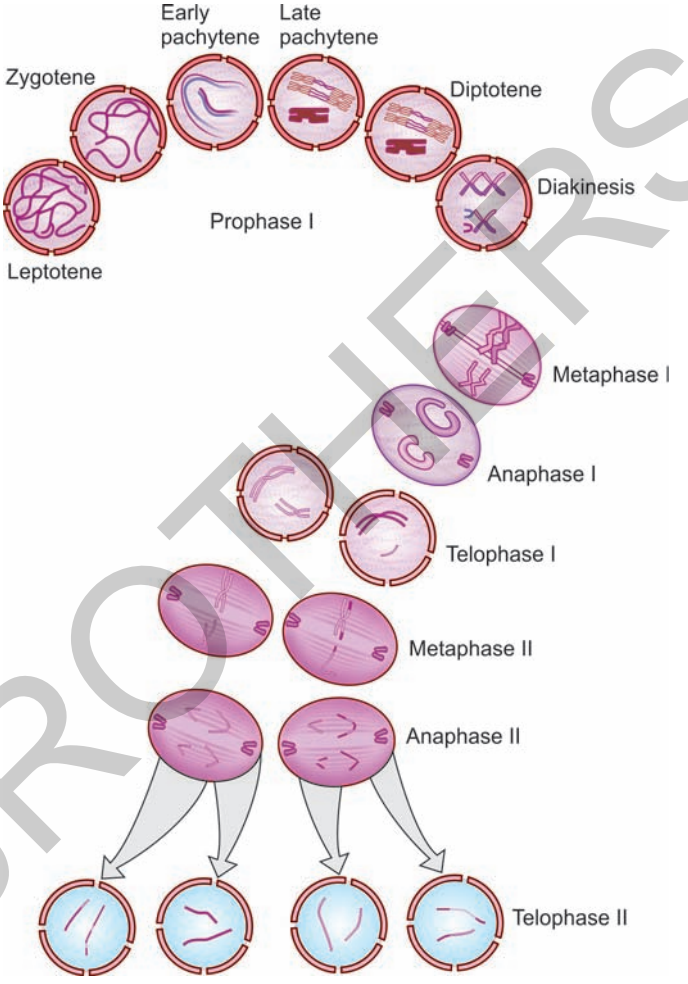

Fig. 4A Meiosis in a cell with two chromosomes

Table 1 | Differences between oogenesis and spermatogenesis

	Male	*Female*
Onset	Puberty	Early embryonic life
Duration	60–65 days	10–50 years
No. of mitosis in gamete formation	30–500	20–30
Gamete production per meiosis	4 spermatids	One ovum plus three polar bodies
Gamete production	100–200 million per ejaculate	1 ovum per menstrual cycle

Oogenesis

Development of mature ovum from oogonia begins in prenatal life. Ova develop from oogonia within the follicles in the ovarian cortex. This process involves 20–30 mitotic

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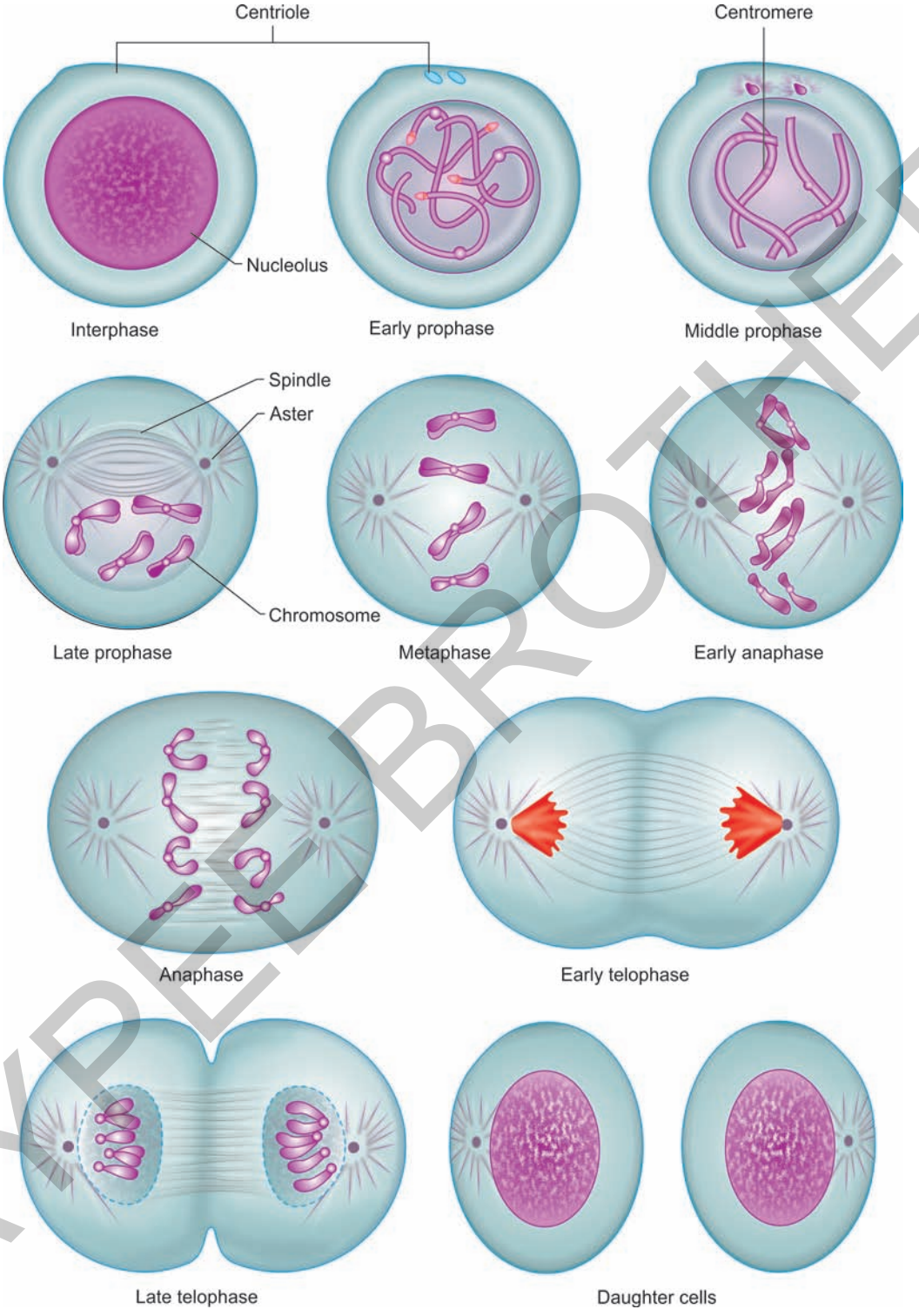

Fig. 4B Meiosis in a cell with four chromosomes

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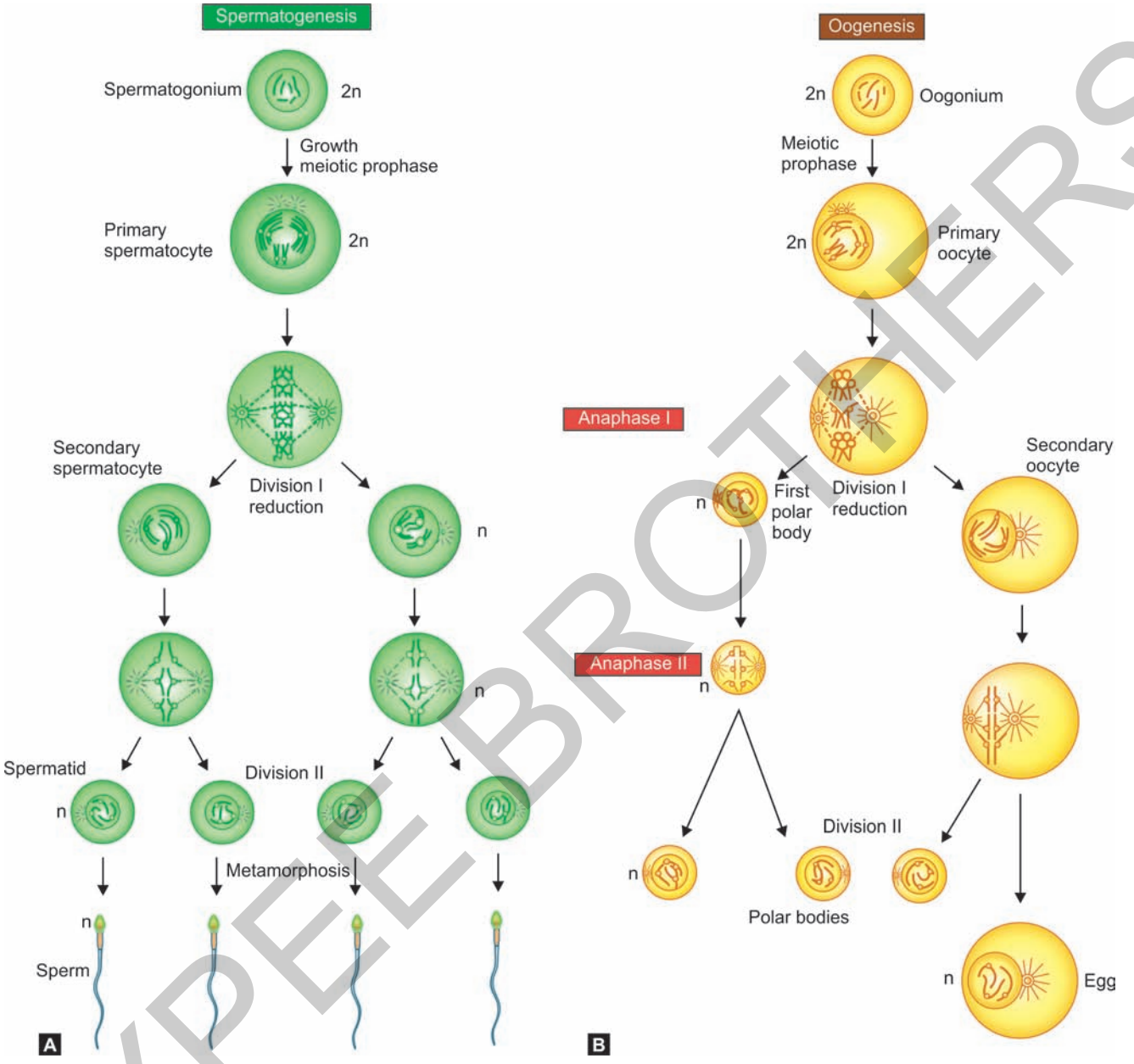

Figs 5A and B Meiotic sequence of a male and a female animal. (A) Spermatogenesis resulting in four sperms; (B) Oogenesis resulting into one ova and three polar bodies

divisions at about 3rd month of fetal life. The oogonia begin to develop into diploid primary oocyte that starts to undergo meiosis. Meiosis I continues to diplotene where it is arrested until sometime in the postpubertal reproductive life of woman. At birth, all the primary oocytes have entered in this phase of maturation arrest, here this suspended diplotene is referred to as dictyotene. Thereafter, at puberty, several follicles begin to mature with each menstrual cycle. Meiosis I occurs with an uneven distribution of cytoplasm in cytokinesis of meiosis I. Thereby, secondary oocytes are formed containing most of the cytoplasms along with first polar body. After ovulation, meiosis II begins in this secondary oocyte resulting into haploid ovum and second polar body. The first polar body may undergo meiosis II or degenerate.

At the time of birth, there are almost 2.6 million oocytes. The majority undergo apoptosis. Only 400 cells complete the first meiotic division and only fertilized cells complete meiosis (Duncan 2008).

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Spermatogenesis

In contrast to oogenesis, spermatogenesis is a relatively rapid process with an average duration of 60–65 days. Spermatogenesis takes place in seminiferous tubules of male testis. It begins with sexual maturity and occurs throughout the postpubertal life of a man. This process involves several mitotic divisions up to 20–25 per annum. Diploid spermatogonia give rise to primary spermatocyte through mitosis. At puberty, this diploid primary spermatocyte undergoes meiosis I or reduction division to give rise to a haploid secondary spermatocyte. This secondary spermatocyte undergoes meiosis II to produce spermatids. These spermatids differentiate into mature spermatozoa without any further cell division (Figs 5A and B).

Fertilization

Mature ova and sperm produced through meiosis contain haploid number of chromosomes in each. These chromosomes are surrounded by a nuclear membrane within the cytoplasm. These pronuclei fuse to form a diploid nucleus of the zygote. Thereafter first mitosis begins.

CONCLUSION

According to the cell theory, cells arise from the pre-existing cells. The process by which this occurs is called cell division. Any sexually reproducing organism starts its lifecycle from a single-celled zygote. Cell division does not stop with the formation of the mature organism but continues throughout its lifecycle. The stage through which a cell passes from one division to the next is called the cell cycle.

Cell cycle is divided into two phases: (1) Interphase—a period of preparation for cell division, and (2) Mitosis (M phase)—the actual period of cell division. Interphase is further subdivided into G1, S and G2. G1 phase is the period when the cell grows and carries out normal metabolism. Most of the organelle duplication also occurs during this phase. S phase marks the phase of DNA replication and chromosome duplication. G2 phase is the period of cytoplasmic growth. Mitosis is also divided into four stages namely prophase, metaphase, anaphase and telophase. Mitosis is the equational division in which the chromosome number of the parent is conserved in the daughter cell. In contrast to mitosis, meiosis occurs in the diploid cells, which are destined to form gametes. It is called the reduction division since it reduces the chromosome number by half while making the gametes. In sexual reproduction, when the two gametes fuse, the chromosome number is restored to the value in the parent.

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Manual of
Cytogenetics in Reproductive Biology

Salient Features

- Aims to discuss the relevance of science of Molecular Cytogenetics in modern-day medicine and assisted reproductive technologies (ARTs)
- All the chapters are dealt by the experts in their fields
- Principles and protocols pertaining to Cytogenetics and Molecular Biology have been dealt at length
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