

---

## Contents

### Clinical Aspects of Male Infertility

Csilla Krausz and Gianni Forti

1	Introduction . . . . .	1
1.1	Definition of Couple and Male Infertility . . . . .	1
1.2	Assisted Reproduction and Clinical Andrology . . . . .	3
2	The Elements of Standard Medical Workup . . . . .	4
2.1	Medical and Familial History . . . . .	4
2.2	Physical Examination . . . . .	4
2.3	Diagnostic Tests . . . . .	4
3	Aetiology of Male Infertility . . . . .	6
3.1	Infertility Due to Antispermato-genic Agents . . . . .	6
3.2	Infertility Due to Endocrine Disorders (Hypogonadotrophic Hypogonadism) . . . . .	7
3.3	Infertility Due to Impairment of Sperm Transport and/or Accessory Gland Infections . . . . .	7
3.4	Autoimmune Infertility . . . . .	8
3.5	Infertility and Varicocele . . . . .	9
3.6	Infertility Due to Coital Disorders . . . . .	9
3.7	Infertility and Cryptorchidism . . . . .	9
4	Infertility Due to Genetic Disorders . . . . .	10
4.1	Chromosomal Abnormalities . . . . .	10
4.2	Klinefelter Syndrome . . . . .	11
4.3	Other Chromosomal Abnormalities . . . . .	12
4.4	Male Infertility from Defect in Meiosis . . . . .	12
5	Monogenic Diseases . . . . .	12
5.1	The Kartagener Syndrome or Immotile Cilia Syndrome . . . . .	12
5.2	Androgen Insensitivity Syndromes . . . . .	13
5.3	The Infertile Male Syndrome . . . . .	13
5.4	X-Linked Spinal and Bulbar Muscular Atrophy (Kennedy Disease)	14
5.5	Persistent Mullerian Duct Syndrome . . . . .	14
5.6	Inactivating FSH Receptor Mutation . . . . .	15
6	Clinical Considerations of Genetic Abnormalities . . . . .	15
7	Treatment of the Infertile Male . . . . .	16
	References . . . . .	17

**The Cell Biology and Molecular Genetics of Testis Determination**

Craig A. Smith and Andrew H. Sinclair

1	Introduction . . . . .	23
2	Human Sex Determination is Chromosomally Based . . . . .	24
2.1	Sex Reversal . . . . .	24
3	Gonadal Sex Differentiation . . . . .	25
3.1	Testicular and Ovarian Morphogenesis in Human Embryos . .	25
3.2	The Importance of the Supporting Cell Lineage . . . . .	28
3.3	The Contribution of the Mesonephros . . . . .	30
3.4	Genes Involved in Formation of the Gonadal Primordium . . .	30
4	The Testis-Determining Factor (TDF) . . . . .	31
4.1	<i>SRY</i> is TDF . . . . .	32
4.2	The <i>SRY</i> Protein and Its Targets . . . . .	33
4.3	Is <i>SRY</i> a Negative Regulator? . . . . .	35
5	The <i>SOX9</i> Gene and Testis Determination . . . . .	36
5.1	Campomelic Dysplasia, Sex Reversal and <i>SOX9</i> . . . . .	36
5.2	Embryonic Expression of <i>Sox9</i> . . . . .	38
5.3	Where is <i>SOX9</i> Placed in the Testis-determining Cascade? . . .	39
6	Orphan Nuclear Receptors and Sex Determination . . . . .	39
6.1	Steroidogenic Factor 1 (SF1) . . . . .	39
6.2	<i>DAX1</i> and Gonadal Differentiation . . . . .	41
7	Summary: A Genetic Cascade for Testis Determination . . . . .	44
	References . . . . .	46

**The Sertoli Cell-Germ Cell Interactions and the Seminiferous Tubule Interleukin-1 and Interleukin-6 System**

B. Jégou, J. P. Stéphan, C. Cudicini, E. Gomez, F. Bauché,  
C. Piquet-Pellorce, and A. M. Touzalin

1	Organisation of the Testis . . . . .	53
1.1	Spermatogenesis . . . . .	53
1.2	The Sertoli Cell . . . . .	54
1.3	The Interstitial Tissue . . . . .	54
2	Endocrine Regulation of Testicular Function . . . . .	55
3	Paracrine Regulation of Testicular Function . . . . .	55
3.1	The Place of the IL-1/IL-6 System in the Sertoli Cell-Germ Cell Communication Network . . . . .	56
3.1.1	IL-1 and IL-6 . . . . .	56
3.2	Sertoli Cell-Germ Cell Interactions . . . . .	57
3.2.1	The Role of the Sertoli Cell . . . . .	57
3.2.2	The Action of Germ Cells . . . . .	58
3.3	Sources of Seminiferous-Tubule IL-1 and IL-6 . . . . .	59

3.3.1	Tubular IL-1 . . . . .	59
3.3.2	Sertoli Cell IL-6 . . . . .	60
3.4	Testicular IL-1 and IL-6 Receptors . . . . .	60
3.5	Testicular Effects of IL-1 and IL-6 . . . . .	61
3.6	The Regulation of Sertoli Cell IL-1 and IL-6 by Germ Cells and the Synchronisation of the Seminiferous Epithelium Cycle	61
3.6.1	Residual Bodies and Production of Sertoli Cell IL-1 and IL-6 .	62
3.6.2	Control of Sertoli Cell IL-1 and IL-6 Production by Germ Cell Cytokines . . . . .	63
4	Conclusion . . . . .	63
	References . . . . .	64

## Leydig Cell Function and Its Regulation

M. P. Hedger and D. M. de Kretser

1	Introduction . . . . .	69
2	Leydig Cell Morphology and Endocrine Function . . . . .	70
2.1	Morphology of the Leydig Cell . . . . .	70
2.2	The Hypothalamo-Pituitary-Leydig Cell Axis . . . . .	70
2.2.1	Hypothalamo-Pituitary Activity and Androgen Secretion . . .	70
2.2.2	The Role of the Testicular Vasculature . . . . .	72
2.2.3	Androgen Metabolism, Action and Negative Feedback Regulation . . . . .	72
2.3	Leydig Cell Steroidogenesis . . . . .	73
2.4	Non-Steroidal Products of the Leydig Cell . . . . .	75
3	Leydig Cell Development . . . . .	76
3.1	Species Variation in Leydig Cell Development . . . . .	76
3.2	Fetal, Perinatal and Prepubertal Development of the Leydig Cell in the Human . . . . .	76
3.3	Pubertal Development of the Leydig Cell . . . . .	77
3.4	The Ethane Dimethane Sulfonate Recovery Model . . . . .	79
3.5	Hormonal Regulation of Adult Leydig Cell Development . . .	79
3.6	Local Factors and Leydig Cell Development . . . . .	80
4	Molecular Regulation of the Leydig Cell . . . . .	81
4.1	Luteinizing Hormone and the LH Receptor . . . . .	81
4.2	Intracellular Signalling Events and cAMP . . . . .	83
4.3	Cholesterol Mobilization . . . . .	84
4.3.1	Cholesterol Transport Proteins . . . . .	84
4.3.2	Steroidogenic Acute Regulatory Protein . . . . .	84
4.3.3	The Role of the Cytoskeleton . . . . .	85
4.4	Regulation of the Steroidogenic Enzymes . . . . .	85
4.4.1	Chronic Regulation of the Steroidogenic Machinery . . . . .	85
4.4.2	Transcriptional Regulation of Steroidogenesis . . . . .	86

4.5	Other Transducing Mechanisms . . . . .	86
4.5.1	Calcium . . . . .	86
4.5.2	Chloride . . . . .	87
4.5.3	Protein Kinase C . . . . .	87
4.5.4	Arachidonic Acid and Its Metabolites . . . . .	88
5	Extrinsic Regulation of the Leydig Cell by Factors Other than LH . . . . .	88
5.1	Anterior Pituitary Hormones: FSH, Prolactin, and Growth Hormone . . . . .	88
5.2	Regulation by the Seminiferous Tubules . . . . .	89
5.3	Cytokines and Growth Factors . . . . .	90
5.4	Autocrine Regulation . . . . .	91
5.4.1	Androgen-Mediated Autoregulation . . . . .	91
5.4.2	Leydig Cell Desensitization . . . . .	91
5.5	Glucocorticoids . . . . .	92
5.6	Neuropeptides . . . . .	92
5.7	Other Factors . . . . .	93
6	Leydig Cell Function and Infertility . . . . .	93
	References . . . . .	94

## Post-Transcriptional Control and Male Infertility

Robert E. Braun

1	Introduction . . . . .	111
2	The Need for Translational Control . . . . .	113
3	Regulatory Elements in Untranslated Sequences . . . . .	114
4	The Protamine mRNA Is Stored in a Ribonucleoprotein Particle Sequence-Specific RNA Binding Proteins . . . . .	117
5	Premature Translation of <i>Prm1</i> mRNA . . . . .	118
6	Activation of Translationally Repressed mRNAs . . . . .	120
7	Orphan RNA Binding Proteins . . . . .	121
8	Perspectives . . . . .	122
9	References . . . . .	124

## An Integration of Old and New Perspectives

### of Mammalian Meiotic Sterility

Terry Ashley

1	Introduction . . . . .	131
1.1	The Meiotic Cell Division . . . . .	132
1.2	Meiotic-Specific Structures . . . . .	133
1.3	Identified Protein Components of Meiotic-Specific Structures . . . . .	135

1.3.1	Components of the Synaptonemal Complex . . . . .	136
1.3.2	Meiotic Nodules . . . . .	138
2	Sterility from a “Process-Oriented” Perspective . . . . .	144
2.1	Errors in Synapsis . . . . .	144
2.1.1	The Asynaptic Phenotype and Sterility . . . . .	144
2.1.2	Theoretical Links Between Asynapsis and Sterility . . . . .	147
2.1.2.3	Mismatch Repair and Mammalian Meiotic Sterility . . . . .	150
2.2	Errors in the Meiotic Divisions (Metaphase I Through Anaphase II) . . . . .	153
3	Sterility from the Perspective of Cell Cycle Checkpoint Control . . . . .	154
4	Summary and Conclusions . . . . .	162
	References . . . . .	163

### **Mutations of the Cystic Fibrosis Gene and Congenital Absence of the Vas Deferens**

Pasquale Patrizio and Debra G. B. Leonard

1	Introduction . . . . .	175
2	CF and CBAVD: A Common Genetic Background . . . . .	176
2.1	Mutation Analysis Results and the 5T-Tract Variant . . . . .	179
3	Pathogenesis of CBAVD . . . . .	180
4	Spermatogenesis and Epididymal Length . . . . .	181
5	Remaining Questions . . . . .	182
6	Conclusions . . . . .	184
	References . . . . .	184

### **Mitochondrial Function and Male Infertility**

Thomas Bourgeron

1	Introduction . . . . .	187
2	Mitochondrial Diseases . . . . .	188
3	Mitochondrial Function and Aging . . . . .	191
4	Mitochondrial Biogenesis During Spermatogenesis . . . . .	192
5	Mitochondrial Organization in the Spermatozoon . . . . .	193
6	Regulation of Oxidative Phosphorylation in Mitochondria . . . . .	195
7	Abnormal Mitochondria and Infertility . . . . .	198
8	Mitochondrial Respiratory Chain, mtDNA and Infertility . . . . .	199
9	Reactive Oxygen Species Generation and Human Spermatozoa . . . . .	201
10	ATP Concentration, Creatine Kinase Activity and Infertility . . . . .	203
11	Mitochondrial Inheritance . . . . .	204
12	Conclusion . . . . .	206
	References . . . . .	206

## The Human Y Chromosome and Male Infertility

Ken McElreavey, Csilla Krausz, and Colin E. Bishop

1	Structure of the Human Y Chromosome . . . . .	211
1.1	Pseudoautosomal Regions . . . . .	211
1.2	Non-Recombining Region . . . . .	212
2	Functions Associated with the Non-Recombining Region of the Human Y chromosome . . . . .	214
2.1	Sex Determination . . . . .	214
2.2	Turner Syndrome . . . . .	214
2.3	Histocompatibility Y Antigen (H-Y) . . . . .	215
2.4	Gonadoblastoma . . . . .	215
2.5	Male Infertility . . . . .	216
3	Yq-Specific Genes and Gene Families . . . . .	217
4	Function of Y-Specific Genes in Spermatogenesis . . . . .	219
4.1	<i>RBMY</i> . . . . .	219
4.2	<i>DAZ</i> . . . . .	220
5	Which Genes Underlie the AZF Phenotypes? . . . . .	222
6	Frequency of Yq Microdeletions . . . . .	222
7	Microdeletions and Genotype/Phenotype Relationships . . . . .	223
8	Mechanism of Y Chromosome Microdeletions . . . . .	225
9	Y Chromosome Susceptibility Haplotypes . . . . .	226
10	Perspectives . . . . .	228
	References . . . . .	228

## Spermatogenesis and the Mouse Y Chromosome: Specialisation Out of Decay

Michael J. Mitchell

1	The Unique Y Chromosome . . . . .	233
2	The Functions of the Mouse Y Chromosome . . . . .	234
2.1	Somatic Functions of the Mouse Y Chromosome . . . . .	234
2.2	Germ Cell Functions . . . . .	235
3	The Molecular Genetics of the Mouse Y Chromosome . . . . .	236
3.1	Overview . . . . .	236
3.2	The Long Arm . . . . .	237
3.2.1	Molecular Structure . . . . .	237
3.2.2	Deletion of the Long Arm . . . . .	238
3.3	The Pericentric Region . . . . .	240
3.3.1	Molecular Structure . . . . .	240
3.3.2	Deletion of the Pericentric Region . . . . .	241
3.3.3	Deletion of the Long Arm and the Pericentric Region . . . . .	241
3.4	The Short Arm . . . . .	242

3.4.1	Molecular Structure . . . . .	242
3.4.2	Deletion of the Short Arm . . . . .	243
3.4.3	Genes in the <i>Sxr<sup>b</sup></i> Deletion Interval . . . . .	243
3.5	The Mouse Y Chromosome in Spermatogenesis – Conclusions	245
4	Comparison of the Mouse and Human Y Chromosome Maps .	246
4.1	Distinct Gene Organisation . . . . .	246
4.2	A Block of Syntenic Homology . . . . .	248
4.3	Implications for Spermatogenesis . . . . .	248
5	Evolution of the Y Chromosome . . . . .	250
5.1	Sex Chromosome Evolution Theory . . . . .	250
5.1.1	The Origin of the Non-Recombining Y Chromosome (NRY) .	250
5.1.2	The Decay of Genes on the Non-Recombining Y Chromosome (NRY) . . . . .	250
5.1.3	Accumulation of Male-Enhancing Mutations . . . . .	251
5.2	Evolution of Y Genes and Spermatogenesis . . . . .	252
5.2.1	X-Y Homologous Genes . . . . .	253
5.2.1.1	The Ubiquitin Activating Enzyme . . . . .	254
5.2.1.2	Dosage Compensation . . . . .	254
5.2.1.3	Restriction of Expression to the Germ Line . . . . .	255
5.2.2	Y-Autosomal Genes . . . . .	257
5.2.2.1	<i>DAZ</i> . . . . .	257
5.2.2.2	<i>RBMY</i> . . . . .	258
5.2.3	Genes of Unknown Origin . . . . .	259
5.2.3.1	<i>TSPY</i> . . . . .	259
5.2.3.2	<i>Ssty</i> . . . . .	259
5.2.4	Y Chromosome Gene Evolution and Function . . . . .	260
6	General Conclusions . . . . .	262
7	The Future . . . . .	263
	References . . . . .	263

## The Comparative Genetics of Human Spermatogenesis: Clues from Flies and Other Model Organisms

Ron Hochstenbach and Johannes H. P. Hackstein

1	Introduction . . . . .	271
2	Model Organisms for Studying the Genetic Causes of Subfertility in Man . . . . .	272
2.1	Mendelian Genetics and Male Subfertility . . . . .	272
2.2	Spermatogenesis: An Ancient, Conserved Process of Cellular and Subcellular Differentiation . . . . .	272
2.3	Model Organisms . . . . .	275
2.3.1	Yeast . . . . .	275
2.3.2	<i>Chlamydomonas</i> . . . . .	276

2.3.3	<i>Caenorhabditis elegans</i> . . . . .	277
2.3.4	Mouse . . . . .	277
2.3.5	Zebra Fish . . . . .	278
2.3.6	<i>Drosophila</i> . . . . .	278
2.3.6.1	In Flies, the Y Chromosome Carries Only a Few Genes Essential for Spermatogenesis . . . . .	279
2.3.6.2	Hundreds of Genes on the X Chromosome and Autosomes Are Involved in Spermatogenesis of <i>Drosophila</i> . . . . .	280
2.3.6.3	Phenotypic Analysis of Sterile Male Flies Suggests That Most of These Genes Are Expressed in the Male Germ Cells . . . . .	281
2.2.6.4	Sperm Components Differentiate by Independent Programs in <i>Drosophila</i> . . . . .	283
2.3.6.5	Genetic Switches Operating During Male Germ Cell Development in <i>Drosophila</i> . . . . .	284
2.3.6.6	Many Male Sterile Mutations in Flies Are Pleiotropic . . . . .	285
3	The Comparative Genetics of Male Germ Cell Differentiation in Flies and Man . . . . .	285
3.1	How Many Male Fertility Genes Exist in Man? . . . . .	286
3.2	Why Does Such a Large Fraction of All Genes Participate in Spermatogenesis? . . . . .	288
4	Population Studies and Mutations Affecting Male Fertility in Flies and Man . . . . .	290
5	Concluding Remarks . . . . .	291
	References . . . . .	292
<b>Subject Index</b> . . . . .		299



The Genetic Basis of Male Infertility

McElreavey, K. (Ed.)

2000, XIV, 306 p., Hardcover

ISBN: 978-3-540-66264-8