

Thaddeus Mann
Cecilia Lutwak-Mann

Male Reproductive Function and Semen

Themes and Trends in Physiology,
Biochemistry and Investigative
Andrology



Springer-Verlag Berlin Heidelberg New York

Thaddeus Mann and Cecilia Lutwak-Mann

Male Reproductive Function and Semen

Themes and Trends in Physiology,
Biochemistry and Investigative Andrology

With 46 Figures

Springer-Verlag
Berlin Heidelberg New York 1981

Thaddeus Mann, MD, ScD, PhD, FRS

Guest Scientist at the National Institute of Child Health and Human Development
(Endocrinology and Reproduction Research Branch), Bethesda, Maryland 20205,
USA,

Fellow of Trinity Hall and Emeritus Professor of Physiology of Reproduction
in the University of Cambridge, England

Cecilia Lutwak-Mann, MD, PhD

Guest Scientist at the National Institute of Child Health and Human Development
(Endocrinology and Reproduction Research Branch), Bethesda, Maryland 20205,
USA,

Formerly Principal Scientific Officer on the Staff of the Agricultural Research
Council Unit of Reproductive Physiology and Biochemistry in the University
of Cambridge, England

ISBN 3-540-10383-X Springer-Verlag Berlin Heidelberg New York

ISBN 0-387-10383-X Springer-Verlag New York Heidelberg Berlin

Library of Congress Cataloging in Publication Data. Mann, Thaddeus, 1908—Male reproductive function and semen. Bibliography: p. Includes index. 1. Generative organs, Male. 2. Human and animal reproduction. 3. Semen. 4. Andrology. I. Lutwak-Mann, Cecilia, joint author. II. Title. [DNLM: 1. Genitalia, Male—Physiology. 2. Semen. WJ 702 M282m] QP253.M36 612'. 80-25460
ISBN 0-387-10383-X (U.S.)

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically those of translation, reprinting, reuse of illustrations, broadcasting, reproduction by photocopying machine or similar means, and storage in data banks. Under §54 of the German Copyright Law, where copies are made for other than private use, a fee is payable to 'Verwertungsgesellschaft Wort', Munich.

©by Springer-Verlag Berlin Heidelberg 1981

Printed in Great Britain

The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Printed by The Lavenham Press Ltd., Lavenham, Suffolk. Bound by Mansell (Bookbinders) Ltd., Witham, Essex.

2128/3916-543210

Preface

To present a coherent and meaningful survey of scientific research endeavour in an area that has expanded as fast as physiology and biochemistry of reproduction in the male is no mean task these days. No less prodigious than the growth of knowledge of male reproductive function has been the rate at which the outpouring of publications on this subject has continued since the appearance of 'The Biochemistry of Semen and of the Male Reproductive Tract' in 1964. Since cyclopaedic treatment of this vast literature did not appeal to us, we have made no attempt either to rehash the material contained in that book or to enlarge the bibliography beyond the nearly 3500 references included in the present treatise. At the same time, whilst writing, we felt strongly that to advance, it is necessary to understand the past, and for this reason we have not hesitated to refer (especially in the introductory chapter) to a number of those fundamental early discoveries in which today's knowledge is deeply and firmly rooted. As regards progress since 1964, rather than attempt to tackle the research area as a whole, we have preferred to deal foremost with current trends and concepts, emphasizing the importance of topics that were the object of intensive study around the time of our writing, and in particular, we have tried to provide examples illustrating how the progress in male reproductive physiology and biochemistry is contributing, on a steadily mounting scale, to the development of investigative and diagnostic andrology. We have also assumed, correctly we hope, that a goodly proportion of our readers will take a direct interest in selected parts only, and not the whole of the book, and hence we did not hesitate to permit ourselves a certain amount of deliberate repetition and overlap between some of the chapters.

Because the comparative approach applied to biology of male reproduction proved to be very fruitful in the interpretation of various types of spermatogenic failure, hormonal disarray and malfunction of male accessory organs, and in view of the experience which we ourselves have gained over some 30 years, whilst studying and teaching comparative aspects of reproductive physiology and biochemistry at the University of Cambridge, we have described a certain number of findings made in this area of human and animal investigations. Reference has therefore, been made, sometimes rather briefly, to animal species as far apart as farm animals, laboratory rodents, insectivores, marsupials, birds, insects, echinoderms, and especially one large cephalopod mollusc, the North-Pacific Giant Octopus of the Puget Sound. This creature's impressively long spermatophores have been the study object of happy collaboration with Drs. Arthur Martin and John Thiersch at the University of Washington, Seattle, for several memorable years. We hope that by choosing the comparative approach we shall have succeeded in extending the readership of the present book, so as to attract not only our scientific colleagues and clinicians, but also environmentalists, sociologists, historians of medicine, and perhaps even those members of the public who evince nowadays a keen interest in matters relating to male fertility and sterility, often in conjunction with problems such as industrial health, population growth and adolescent sexual development.

In a large measure, much that has been achieved lately is due to highly specialized new techniques and refinement of older methods, and this prompted us to give in two chapters (II and III) certain general methodological guidelines for the inspection of male reproductive organs, and the collection, quality appraisal and preservation of human and animal semen.

Four chapters (IV-VII) are devoted, respectively, to exocrine and endocrine testicular function leading to the formation of testicular semen; the role of the epididymis in sperm maturation and storage, and the formation of epididymal semen; the physiology of the vas deferens and some of the hazards of vasectomy; and the secretory processes in the prostate, seminal vesicle, Cowper's gland and other male accessory organs, leading to the formation of seminal plasma.

A notable trend in modern research on semen has been the shift of emphasis from studies on intact spermatozoa to attempts at defining the structure, chemical make-up and function of separated sperm organelles, such as the plasma membrane, acrosome, nucleus, mitochondrial sheath and the axoneme of the flagellum. This is reflected in the treatment which we have accorded in two chapters (VIII and IX) to the biochemistry of spermatozoa and the seminal plasma, in which we have also dealt with the application of chemical methods of semen analysis to andrological problems. Finally, in the last chapter (X) we have outlined the adverse pharmacological effects upon male reproductive function of certain chemosterilants, anti-androgens, and antispermatogenic and spermicidal substances.

The task of writing the book has occupied a great deal of our working time for about 4 years. The initial work was undertaken with the support of the Agricultural Research Council and the Leverhulme Trust in Great Britain; during the last 3 years its continuation has depended entirely on the magnanimous support of the National Institutes of Health and the Lalor Foundation, in the United States of America. We owe an immense debt of gratitude to our many American friends and colleagues, but most of all to Drs. C. Lalor Burdick, Kevin Catt, Philip Corfman, Maria Dufau and Richard Sherins, who together with their families, have made our stay in Bethesda a memory that we shall always treasure. We thank Dr. Roy Jones for his valuable cooperation and Mrs. Carmen Frankl for the preparation of figures; to Mrs. Jennifer Constable goes out our joint gratitude for the excellent work done in the typing and assembling of the manuscript, and especially of the extensive bibliography. We also wish to put on record the assistance received from the staff of Springer-Verlag, and to acknowledge with thanks the permission granted by various individuals and publishing houses to reproduce material from certain journals, namely our colleagues Drs. Winston Anderson (Washington DC), David Brooks (Adelaide, Australia), Hector Dott and David Cran (Cambridge, England) and Don Fawcett (Boston, Mass), and the following publishers: The Royal Society of London, Biochemical Journal, Fertility and Sterility, Journal de Microscopie, Journal of Endocrinology, Journal of Reproduction and Fertility, S. Karger Publishing House, Messrs Methuen & Co. (Associated Book Publishers) and Nature Macmillan Journals.

November 15, 1980

T. Mann
C. Lutwak-Mann

Contents

Chapter I

Male Reproductive Function and the Composition of Semen:

General Considerations 1

1. Functional Dualism of the Testis 2

 The beginnings: conceptual formulation of testicular function.

 Exocrine and endocrine activity.

2. Male Reproductive Tract: Main Characteristics 4

 Representative accessory organs in mammals. *Prostate gland.*

Seminal vesicle. Bulbo-urethral (Cowper's) gland. Preputial and

urethral (Littre's) glands. Accessory organs in marsupials. Accessory

 organs in birds, frogs, reptiles, fishes and invertebrate animals.

3. Coordination of Male Reproductive Function by Extragenadal

Hormones and Environmental Factors. 11

 Control of male reproductive function by gonadotrophins (FSH and

 LH) and the hypothalamic gonadotrophin-releasing hormone

 (GnRH). Sexual dimorphism of the hypothalamus and other parts

 of the brain. Prolactin and the pineal antigonadotrophic factor.

 Regulatory hormonal mechanisms in invertebrate animals. Influence

 of nutrition on male fertility.

4. Cardinal Properties of Spermatozoa 23

 Exploratory observations on sperm structure, physiology and

 chemistry. Sperm passage in the male and female genital tracts.

 Correlations between motility and fertilizing ability.

5. General Features of the Seminal Plasma 28

 Species differences. Peculiarities of chemical composition. Role in

 male reproductive performance. Pheromonal properties. Effects on

 spermatozoa.

6. Spermatophores and Spermatophoric Reaction 34

 Delivery of semen by spermatophores. Spermatophore of the Giant

 North-Pacific Octopus. Spermatophoric reaction.

Chapter II

Methodological Guidelines in the Study of Male Reproductive

Organs 39

1. Andrological Examination of the Testis and Androgen Assays 39

 Gross inspection of the male gonad. Testicular biopsy. Quantifiable

techniques for the analysis of biopsy specimens. Evaluation of testicular function by hormone assays. Evaluation of the potency of androgens.

2. Cannulation, Micropuncture, Perfusion and Transplantation Techniques	43
Sampling of testicular lymph. Withdrawal of testicular and epididymal semen. Perfusion of the testis and epididymis. Perfusion of the prostate and superfusion of prostatic tissue slices. Transplantation of testicular and accessory gland tissues.	
3. Isolation of Seminiferous Tubules and Disaggregation of Germinal Cells and Sertoli Cells	48
Separation of seminiferous tubules from testicular interstitium. Functional characteristics of isolated seminiferous tubules. Disaggregation of different types of germinal cells. Sertoli-cell-enriched preparations.	
4. Cell and Organ Cultures	51
Androgen secretion in fetal testis culture. Culture techniques in the study of spermatogenesis. Biochemical events in Sertoli cell cultures. Maturation of spermatozoa in cultured epididymal tubules. Prostate explants.	

Chapter III

Collection, Examination, Quality Rating and Storage of Ejaculated Semen	55
1. Collection of Whole and Split Ejaculates, and Separation of Spermatozoa from Seminal Plasma	55
Methods for collecting whole and split ejaculates. Separation of spermatozoa from seminal plasma in ejaculated semen. Removal of seminal debris and seminal gel.	
2. Separation of Motile from Immotile, and Male-determining from Female-determining Spermatozoa	59
Methods for separating motile from immotile spermatozoa. Separation of male- and female-determining spermatozoa and manipulation of sex ratio. The fluorochrome test in human chromosomal aberrations.	
3. Examination of Spermatozoa and Isolated Structural Components ...	63
Dissection of spermatozoa. Spatial relationships between sperm head, cytoplasmic droplet, axial filament complex, mitochondrial sheath, dense fibres and fibrous sheath. Mechanical and chemical separation of sperm structure components.	
4. Quality Rating of Semen in Andrological Practice	69
Criteria used in semen evaluation. Devices for the appraisal of sperm density and motility, and differentiation between live and dead	

spermatozoa. Sperm abnormalities and polymorphism. Microbiological inspection of semen. The cervical mucus penetration and postcoital tests. Other methods for quality rating of semen.

- 5. Storage of Semen for Artificial Insemination** 78
 Prolongation of sperm viability by storage of semen. Storage techniques. Species-linked and individual differences in the keeping quality of semen. Assessment of damage in stored spermatozoa.

Chapter IV

Testis and Testicular Semen..... 83

- 1. Spermatogenesis** 83
 General characteristics of seminiferous tubules. Normal and abnormal spermatogenesis. Sertoli cells and the hormonal control of spermatogenesis. Inhibin. Biosynthesis of nucleic acids and proteins in the germinal epithelium. Enzymes as biochemical markers of differentiating germ cells.
- 2. Steroidogenesis** 106
 Leydig cells as providers of testicular androgen. Biosynthesis of testosterone in the testis. Pattern of testosterone release; episodic, circadian and seasonal fluctuations; effect of sexual arousal. Testosterone binding to target cells and reduction to dihydro-testosterone. Male gonad, skin and brain as androgen-sensitive organs. Male oestrogens. 16-Androstenes as olfactory sex stimulants.
- 3. Testicular Semen**..... 130
 General characteristics of testicular semen. Production of spermatozoa by the testes in relation to the sperm output in ejaculated semen. Testicular plasma as a secretory product of the testis. Entry of substances into testicular semen. Metabolic properties of testicular spermatozoa. Pathological accumulation of fluid in the testis; spermatocele and hydrocele.

Chapter V

Epididymis and Epididymal Semen 139

- 1. Functional Characteristics of the Epididymis**..... 139
 Epididymal duct as conduit for spermatozoa. Resorptive properties of the epididymal epithelium. Role of the epididymis in relation to spermatozoa. Effect of androgen withdrawal on epididymal function. Androgen transport in the epididymis.
- 2. Epididymal Spermatozoa**..... 145
 Functional and structural changes in spermatozoa undergoing epididymal maturation. Physicochemical and biochemical events associated with the passage of spermatozoa in the epididymis. Other aspects of sperm maturation.

3. Epididymal Plasma	150
Main biochemical features of the epididymal plasma. Characteristic constituents of the epididymal plasma: glycerylphosphorylcholine, carnitine, certain mucoproteins and enzymes.	
4. Metabolism of the Epididymis and Epididymal Semen	156
Oxidative metabolism of lipids. Glycolysis. Role of nucleotide coenzymes.	

Chapter VI

Vas Deferens and Vasectomy	161
1. Structural and Functional Features of the Deferent Duct	161
The human vas. Varicocele and spermatocele. The vas in animals. The vas as a conduit for spermatozoa. Response to noradrenaline and enkephalin. Secretory and absorptive function. Aplasia attributable to agenesis and cystic fibrosis.	
2. Vasectomy and Vasoligation	166
Andrological hazards and consequences of vasectomy, vasoligation and vasocclusion. Sperm granuloma and the appearance of sperm-agglutinating and -immobilizing antibodies. Postvasectomy reconstruction of the deferent duct.	

Chapter VII

Secretory Function of the Prostate, Seminal Vesicle, Cowper's Gland and Other Accessory Organs of Reproduction	171
1. Secretory Mechanisms	172
2. Androgen-dependent Maintenance of Growth, Metabolism and Secretory Activity in Male Accessory Organs	173
Androgen indicator tests. Accessory organs as targets for long-lasting testosterone action. Relationship between androgen levels and the functional state of the normal, hypertrophied and cancerous prostate in man.	
3. Overall Pattern and Mechanism of Hormonal Regulation	176
Activation of target cells by testosterone and formation of the dihydrotestosterone-receptor complex. Interaction of the androgen-receptor complex with chromatin and the ensuing synthesis of RNA, protein and enzymes. Metabolic events triggered by androgen-evoked enzymatic activity. Relative efficiency of androgenic steroids. Effects of hormones other than testicular androgens on accessory organs.	
4. Comparative Andrological Aspects	183
Man. Bull. Ram and billygoat. Boar. Stallion and jackass. Dog and cat. Laboratory animals. Wildlife.	

Chapter VIII

Biochemistry of Spermatozoa: Chemical and Functional

Correlations in Ejaculated Semen, Andrological Aspects	195
1. Chemical and Metabolic Characteristics of Ejaculated Spermatozoa; Comparative Viewpoint	195
Fructolysis and respiration. Pyruvate dismutation and carbon dioxide fixation. Sperm lipid chemistry and metabolism. Lipid peroxidation.	
2. Sperm Plasma Membrane; Permeability and Binding Properties	217
Role of sulphhydryl groups. Regional differentiation of plasmalemma. Ionic gradients and electric charge. Membrane-bound enzymes and substance-specific binding sites. Carboglutelin.	
3. Acrosome and Lysosomal Enzymes.	225
Constituent structures of the acrosome. Acrosome reaction. Acrosome as a specialized lysosome. Acrosin and its proteolytic activity. Acrosin inhibitors in seminal plasma. The kinin-kallikrein system. Glycosidases, hyaluronidase, neuraminidase, arylsulphatase, phosphatases and other acrosomal enzymes. Bindin. Lysosomal features of the cytoplasmic droplet.	
4. Sperm Nucleus: Nucleic Acid and Nuclear Proteins.	233
Haploid nucleus. Deoxyribonucleic acid, protamines and histones in normal and defective spermatozoa. Structure of mammalian sperm chromatin. The question of DNA-polymerizing activity in the sperm nucleus. Nucleoproteins of non-mammalian spermatozoa. Questionable occurrence of ribonucleic acid in the nuclei of mature spermatozoa.	
5. Mitochondria and their Role in Sperm Metabolism and Energetics.	242
Mitochondrial sheath of the middle piece. Sperm-specific lactate dehydrogenase. Other mitochondrial enzymes and the cytochrome-cytochrome oxidase system. Use of isolated sperm mitochondria in metabolic studies. Energy-rich phosphorus compounds and the adenylate energy charge. Link-up between the redox state of NAD and energy-yielding dehydrogenase-dependent oxidoreductions. Energy derived from fructolysis. Superiority of respiration and oxidative phosphorylation over glycolysis as a potential source of energy to spermatozoa.	
6. Flagellum and the Mechanochemical Basis of Motility.	252
Motility as the major energy-requiring process in spermatozoa. The ATP-controlled movement-generating mechanism of the flagellum. Tubulin, dynein and other axonemal proteins. Deficiency of dynein and protein carboxyl-methylase in immotile spermatozoa.	
7. Cyclic Nucleotides and Other Promoters of Sperm Activity	258
Cyclic AMP and cyclic GMP. Adenylate cyclase and guanylate cyclase. Protein kinase and phosphodiesterase. Cyclic AMP, caffeine and theophylline as promoters of sperm motility and metabolism. Other sperm activity enhancing agents.	

Chapter IX

Biochemistry of Seminal Plasma and Male Accessory Fluids;

Application to Andrological Problems.....	269
1. Chemical Analysis of Seminal Plasma and Interpretation of Results..	269
General observations on analytical methods. Post-ejaculatory changes in the seminal plasma in vitro. Other factors influencing the composition of seminal plasma. The importance of genotype.	
2. Ions, Free and Bound	273
Electrolytes in seminal plasma. Electrolytes in spermatophoric plasma.	
3. Proteins and Enzymes	276
Electrophoretic pattern of proteins in seminal plasma and accessory fluids. Calcium-binding proteins. Zinc-binding proteins. Lactoferrin and transferrin. Protein hormones. Proteolytic and lipolytic enzymes. Nucleases, nucleotidases and other nucleolytic enzymes. Seminal phosphatases. Glycosidases and glycoprotein-glycosyltransferases. Sulphydryl oxidase.	
4. Peptides, Amino Acids and Nitrogenous Bases	288
Peptides. Free amino acids. Preponderance of glutamic acid. Hypotaurine. Spermine, spermidine and putrescine. Choline, phosphorylcholine and glycerylphosphorylcholine. Carnitine and acetylcarnitine. Ergothioneine, 5-hydroxytryptamine, adrenaline and other nitrogenous bases.	
5. Fructose, Other Sugars, Polyols and Bound Carbohydrate	299
Fructose as the principal sugar of seminal plasma. Glucose, other saccharides and free acetylaminosugars. Sorbitol, inositol and other polyols. Glycerylphosphorylinositol. Bound sugar, aminosugar and sialic acid.	
6. Lipids, Cholesterol and Steroid Hormones	306
Comparison of the lipid composition and distribution in the seminal plasma and spermatozoa. Cholesterol. Patterns of steroid hormones in the seminal plasma. Metabolic conversions and effects of seminal steroids.	
7. Prostaglandins and Other Organic acids.....	312
Biosynthesis of prostaglandins in the seminal vesicle. Prostaglandins in the seminal plasma and their relation to male fertility. Citric acid. Ascorbic acid. Uric acid. Lactic acid and pyruvic acid.	
8. Biochemical Basis of Interactions between the Male Accessory Secretions, and between the Seminal Plasma and Spermatozoa	319
Coagulation and liquefaction of human semen. Copulatory plug formation in rodents. Gelation of boar semen. Coating and decoating of spermatozoa by seminal plasma constituents. Sperm-coating antigens and sperm-inactivating antibodies in seminal plasma. Ionic and metabolic exchange reactions between seminal plasma and spermatozoa.	

9. Examination of Whole Seminal Plasma and Split Ejaculatory Fractions as a Diagnostic Aid in Reproductive Disorders	326
Anatomical defects in the male reproductive tract. Inflammatory conditions. Appraisal of the male's androgenic state, and hormonal effects. Diabetes. Nutritionally conditioned changes in the composition of seminal plasma. Disturbances in the ejaculatory process. Absorption of seminal constituents from the female reproductive tract. Release of enzymes by damaged spermatozoa; correlations between quality of semen and the activity of transaminases and certain other enzymes in the seminal plasma.	

Chapter X

Effects of Pharmacological Agents: Andrological Aspects.

Drug Abuse, Therapeutic Agents, Male Contraceptives,

Occupational Hazards	337
1. Psychomimetic and Psychotherapeutic Drugs	337
Narcotics and hallucinogens. Antipsychotic, antianxiety and antidepressant drugs.	
2. Amphetamines, Cocaine and Alcohol	339
3. Passage of Drugs and Other Substances into Semen	341
4. Control of the Ejaculatory Process by Sympathomimetic, Parasympathomimetic and Autonomic-blocking Agents	343
Contractile responses of the male reproductive tract during ejaculation. Use of accessory organs for monitoring pharmacological effects in vitro.	
5. Chemosterilants as Potential Male Contraceptives	345
6. Dietary Factors, Food Additives and Antimetabolites	347
Detrimental effects of certain dietary factors and food additives. Metabolic analogues as potential antifertility agents.	
7. Cadmium-induced Damage in the Testis and Countereffect of Zinc and Selenium	349
8. Steroids and Other Suppressors of Spermatogenesis Acting via the Pituitary Gland	350
Rebound phenomenon. Testosterone enanthate and danazol. Other steroidal and nonsteroidal suppressors of gonadotrophic activity.	
9. Antiandrogens	352
Cyproterone acetate, methylnoretestosterone and flutamide. Spironolactone.	
10. Antimitotic and Antimeiotic Chemicals; Colchicine, Alkylating Agents, Heterocyclic Compounds	354
Colchicine. Nitrogen mustards (haloalkylamines), ethyleneimines and sulphonxyalkanes. Nitrofurans, nitropyrroles, nitroimidazoles and indazole derivatives.	

11. Chemotherapeutic Drugs, Industrial Chemicals and Pesticides	357
Win. 13,099. Niridazole. Cyclophosphamide and other cystostatic drugs. Cimetidine. Organochlorine compounds. Dibromochloropropane. Dibromopropanol, Tris-BP and dibromoethane. Ethylene oxide cyclic tetramer. Organophosphates. Carbamates. Paraquat.	
12. α-Chlorohydrin	360
13. Biochemical Basis of Spermiostatic and Spermicidal Activity	361
Enzyme inhibitors. Sulphydryl-binding substances. Surface-acting agents.	
References	365
Subject Index	477

CHAPTER I

Male Reproductive Function and the Composition of Semen: General Considerations

"Now, when a man is unable to beget children by his wife, although his virility is unimpaired, he is said in common parlance to have a cold nature. To my mind, however, it would be more apt to say that no living animalcules will be found in the seed of such a man, or that, should any living animalcules be found in it, they are too weakly to survive long enough in the womb."

Antoni van Leeuwenhoek 1685

The modern era of the physiology of reproduction in the male is commonly, and rightly so, accepted as having been ushered in by Leeuwenhoek's sensational letter to the Royal Society, dated November 1677, reporting the first-ever demonstration in semen of motile spermatozoa. From another of his famous communications, cited above and submitted 8 years later, it is evident that Leeuwenhoek intuitively associated the existence of spermatozoa with male fertilizing ability, by recognizing that even though a man may be keenly interested in the opposite sex, this alone is not enough to guarantee the birth of offspring. He anticipated, moreover, yet another basic concept of male reproductive biology, by proclaiming that for the act of procreation to be fulfilled, the spermatozoa, as well as being motile, must also be sufficiently energetic to survive in the female tract for a certain period, presumably to attain their full potential. The precise duration of that critical timespan he was, of course, unable to back up with experimental evidence.

A long time was to pass before spermatogenesis was discovered in all its intricacy and became generally recognized as the prerequisite for the formation of spermatozoa; how this came about is fully and lucidly recapitulated by Roosen-Runge (1977). It took a great deal more patient scientific effort before it became clear that the differentiation of the fetal gonad into a testis depends on several determinants, of which the H-Y antigen is a major one. Although it was clear by 1970 that the undifferentiated gonad of a mammalian fetus with an XX sex chromosomal complement is destined to become an ovary, and the XY complement is necessary if the gonad is to develop into a testis, it was still uncertain at that time how the Y chromosome directs the fetal gonad to become a testis. During the succeeding years convincing evidence accumulated to support the concept that the male sex chromosome acts on testicular organogenesis through a Y-linked gene locus which mediates the production of the H-Y antigen (Ohno 1979; Wachtel et al. 1975; Wachtel 1980). Even now the idea that the H-Y antigen is the principal evocator of testicular function still has to account for clinical observations on patients with various problems of sexual differentiation in whom the expression or non-

expression of the H-Y antigen does not seem to tally with the presence or absence of testicular development (Nagai et al. 1980; Winters et al. 1979d). Another important sex determinant is the Müllerian tract-inhibiting factor ('anti-müllerian hormone') of Jost (1947), which enables the genital tract to acquire male characteristics (Josso et al. 1980; Jost et al. 1977). Only within the recent past has due recognition been accorded to certain other factors controlling testicular function, such as the vascular and nervous supply network of the gonad and scrotum, the blood-testis barrier, testicular thermoregulation, and the mechanism of fluid secretion and entry of substances into the seminiferous tubules (Fawcett 1979; Setchell 1978, 1980; Setchell et al. 1980).

Another area in which progress has been spectacular concerns the endocrine function of the testis and the ways in which the gametogenic and hormonal activity of the male gonad proceed side by side in a manner that ensures a coordinated formation of both parts of semen, that is, the spermatozoa and the seminal plasma. Our early knowledge concerning the influence the testis exerts on the accessory organs, and thereby on the formation of seminal plasma, stems from John Hunter's famous experiments (1786) on the postcastrate regression of the prostate gland and seminal vesicles. Over a century later conclusive evidence was provided that the involutional changes can be reversed by parenterally administered male sex hormone; the latter was applied at first as a rather crude testicular extract and subsequently in its pure form, following the successful chemical isolation of testosterone (David et al. 1935). It was largely as a direct result of this achievement that it became possible at last to quantitate the action of testosterone upon the growth and secretory activity of the male accessory organs of reproduction and hence on the production of seminal plasma.

Technical modifications and improvements in quantitative analysis of testosterone soon followed, enabling better insight into the mechanism whereby testosterone promotes the growth and secretory activity of male accessory organs. Another important development has been the discovery of other major testosterone-dependent functions, such as promotion of the male phenotype during embryogenesis, initiation and maintenance of spermatogenesis in the pubescent male, and control of gonadotrophin secretion by the hypothalamus-pituitary system, among others. A direct outcome of these advances in male reproductive physiology was the formulation of new concepts concerning the pathogenesis of certain endocrine disorders, such as the syndrome of androgen resistance in male pseudohermaphrodites and the demonstration that male infertility is frequently the result of a combination of hitherto unrecognized genetic, phenotypic, endocrine and enzymatic defects. Reviews giving comprehensive coverage of this rapidly widening research area are available (Griffin and Wilson 1980; Steinberger and Steinberger 1980).

1. Functional Dualism of the Testis

The beginnings: conceptual formulation of testicular function

Brown-Séquard (1889) was the first to formulate the idea of functional duality of the testis, when he wrote:

"Je considère les glandes spermatiques, ainsi que les autres principales glandes (foi, reins, etc.), comme douées, en outre de leur puissance sécrétoire, d'une influence spéciale sur le sang, à la manière des glandes

sans sécrétion extérieure, comme la rate, la thyroïde, etc. Conduit par cette idée, j'ai déjà fait des expériences avec le sang revenant des testicules."

In these sentences Brown-Séquard (then 72 years old) was alluding to experiments in which he had injected himself with blood and juices pressed out of animal testicles, to overcome a feeling of physical and mental fatigue. Leaving aside judgement on the efficacy of such treatment on lassitude, its more important impact was that the concept of testicular dual function was taken up by others, and in particular Regaud (1899), who suggested, tentatively at first, that the interstitial or Leydig cells act primarily as a source of nutrients for the seminiferous epithelium, but in addition they are also representative agents "de cette sécrétion interne du testicule si nettement mise en évidence par Brown-Séquard." A subsequent, more precise formulation (Regaud and Policard 1901) of the dual role of the testis was expressed thus:

"Nous croyons pouvoir conclure que la fonction sécrétoire des cellules interstitielles s'établit bien avant la fonction spermatogénétique (testicule impubère), et qu'elle persiste lors même que la fonction spermatogénétique ne s'est jamais établie (testicule ectopique).

Il y a donc une indépendance relative, anatomique et fonctionnelle, entre les cellules interstitielles et les tubes séminifères; et il est permis de rattacher à une sécrétion interne particulière, depuis longtemps soupçonnée, les phénomènes sécrétoires dont les cellules interstitielles sont le siège."

Soon thereafter Bouin and Ancel (1903) quite boldly expressed their conviction that the interstitial tissue is endowed with an internal secretory activity:

"La glande interstitielle nous apparaît donc comme un organe qui élabore probablement des matériaux pour la glande séminale, et qui, par sa sécrétion interne, tient sous sa dépendance l'ardeur génitale et le déterminisme des caractères sexuels secondaires."

The notion that male genital ardour depends in the first place on the testes dates back a long time, and has had among its scientific proponents keen observers such as John Hunter (1786, 1792) and Berthold (1849).

Exocrine and endocrine activity

The groundwork on testicular function gradually clarified the dual mechanism whereby the testes control semen production. Testicular exocrine activity associated with the seminiferous tubules, tubuli recti, rete testis, and efferent ducts was decisively proved to result in the formation of testicular semen (a suspension of spermatozoa in testicular plasma) which is ultimately released into the epididymis. On the other hand, testicular endocrine activity residing in the interstitial tissue was shown to be responsible for the synthesis of several steroid hormones, first and foremost testosterone, which is carried from the testes to the target tissues mainly in the bloodstream but partly also via the lymphatic system and, to a minor extent, the testicular semen. On further study it also became apparent that much of the testosterone released by the testes is carried to the target organs not in the free form but bound to a special type of transport protein.

Testosterone, as we now know, influences a wide range of biological functions, and hardly any organ in the male body can be said to be unaffected by it. In the testis itself it plays a pivotal role in the initiation and maintenance of spermatogenesis. In the pituitary gland, testosterone coordinates the process of gonadotrophin formation and release. Its anabolic effects manifest themselves in the response of various organs, including musculature (maintenance of a positive nitrogen balance), kidney, liver, skin and hair follicles (Chap. IV). Each end-organ reacts to the

androgenic stimulus in a specific way. The reason for this behaviour is that upon arrival at the target cells the androgen becomes bound to organ-specific high-affinity protein receptors, which facilitate interaction with the chromatin of the cells and thus enable the hormone to induce its specific action in the target organ. In relation to semen formation, the most outstanding feature is the stimulatory influence which testosterone exerts on the secretory function of the male accessory glands. The end-result of the modulating influence of androgen receptors in the various accessory organs is the stimulation by androgens of cellular growth, metabolism and secretory activity, a process which in its entirety leads to the appearance of organ-specific secretory products in the seminal plasma.

2. Male Reproductive Tract: Main Characteristics

Representative accessory organs in mammals

On emerging from the testis, testicular semen in the form of a thin suspension of as yet immotile and infertile spermatozoa enters the epididymis, and having completed their passage and maturation in the epididymal duct, mammalian spermatozoa pass into the vas deferens. In the course of the ejaculatory process they encounter secretory fluids produced by several accessory organs of reproduction located along the male tract. At the time of semen emission these secretions blend into seminal plasma, which is the native element for the spermatozoa at this stage. The accessory

Table 1. Species differences in volume and sperm density of ejaculated semen

Species	Volume of single ejaculate		Sperm density in semen	
	Normal variations (ml)	Average value (ml)	Normal variations (sperm/ μ l)	Average value (sperm/ μ l)
Ass	10-80	40	100 000- 600 000	300 000
Bat		0.05	5 000 000- 8 000 000	6 000 000
Blue Fox	1.5-2.5	2	100 000- 230 000	150 000
Boar	150-500	250	25 000- 300 000	100 000
Buffalo	0.5-4.5	2.5	200 000- 800 000	600 000
Bull	2-10	4	300 000- 2 000 000	1 000 000
Camel	4-12	8	100 000- 700 000	400 000
Cat	0.02-0.12	0.03	100 000- 2 600 000	1 700 000
Cock	0.2-1.5	0.8	50 000- 6 000 000	3 500 000
Dog	2-15	9	60 000- 300 000	300 000
Drake	0.34-0.45	0.4	7 000 000-11 000 000	9 500 000
Fox	0.2-4	1.5	30 000- 250 000	70 000
Goat	0.2-2.5	1	1 000 000- 5 000 000	3 000 000
Goose	0.4-1.3		400 000- 1 500 000	
Guinea Pig	0.4-0.8		5 000- 17 000	10 000
Man	2-6	3	50 000- 150 000	80 000
Pigeon	0.002-0.04	0.016	800 000- 3 800 000	2 000 000
Rabbit	0.4-6	1	50 000- 350 000	150 000
Ram	0.7-2	1	2 000 000- 5 000 000	3 000 000
Red Deer	2-20	4	100 000- 1 300 000	200 000
Stallion	30-300	70	30 000- 800 000	120 000
Turkey	0.2-0.8	0.3		7 000 000