Standard Practice in Sexual Medicine

EDITED BY

Hartmut Porst
Chairman, ISSM Standards Committee
Neuer Junglernstieg 6a
20354 Hamburg
Germany

Jacques Buvat
Co-Chairman, ISSM Standards Committee
Centre ETPARP
3 Rue Carolus
59000 Lille
France

AND

The Standards Committee of the International Society for Sexual Medicine
Standard Practice in Sexual Medicine
ISSM STANDARDS COMMITTEE

Chairman: Hartmut Porst (Germany)
Co-Chairman: Jacques Buvat (France)

Sub-Committee: Preclinical Research and Animal Models in Sexual Medicine (Male and Female)
Chairman: François Giuliano (France)
Members: James G. Pfaus (Canada), Kevin McKenna (USA), Balasubramanian Srilatha (Singapore)

Sub-Committee: Psychobehavioral and Couple Aspects
Chairmen: Stanley E. Althof (USA), Raymond Rosen (USA)
Members: Eusebio Rubio-Aurioles (Mexico), Carolyn Earle (Australia), Marie Chevret-Measson (France)

Sub-Committee: Male Sexual Dysfunction
Medical Treatment in ED, Priapism and Peyronie’s Disease
Chairmen: Hartmut Porst (Germany), Ajay Nehra (USA)
Members: Ganesan Adaikan (Singapore), Hussein Ghanem (Egypt), Sidney Glina (Brazil), Wayne Hellstrom (USA),
Ira D. Sharlip (USA), Allen D. Seftel (USA)

Surgical Treatment of ED, Priapism and Peyronie’s Disease
Chairmen: John P. Mulhall (USA) and Michael Sohn (Germany)
Members: Antonio Martin-Morales (Spain), Sudhakar Krishnamurti (India)

Ejaculatory Disorders
Chairmen: Chris G. McMahon (Australia), Marcel D. Waldinger (The Netherlands)
Members: David L. Rowland (USA), Pierre Assalian (Canada), Alan Riley (UK), Young Chan Kim (South Korea),
Amado Bechara (Argentina)

Sub-Committee: Hormones, Metabolism, Aging, and Sexual Function
Chairmen: Jacques Buvat (France), Ridwan Shabsigh (USA)
Members: André Guay (USA), Louis Gooren (The Netherlands), Luiz Otavio-Torres (Brazil),
Eric Meulemann (The Netherlands)

Sub-Committee: Female Sexual Disorders
Chairwoman: Alessandra Graziottin (Italy)
Members: Linda Banner (USA), Annamaria Giraldi (Denmark), Lorraine Dennerstein (Australia), Beverly Whipple (USA),
Jeanne L. Alexander (USA)

Sub-Committee: Cardiovascular Issues in Sexual Medicine
Chairman: Graham Jackson (UK)
Member: Adolph Hutter (USA)

Members of the ISSM Standards Committee attending the preparatory meeting for Standard Practice in Sexual Medicine in Rüdesheim, Germany, 31st August–4th September, 2005.
Standard Practice in Sexual Medicine

EDITED BY

Hartmut Porst
Chairman, ISSM Standards Committee
Neuer Junglernstieg 6a
20354 Hamburg
Germany

Jacques Buvat
Co-Chairman, ISSM Standards Committee
Centre ETPARP
3 Rue Carolus
59000 Lille
France

AND

The Standards Committee of the International Society for Sexual Medicine
Contents

List of contributors, viii
Preface, xi
Foreword, xiii
1. Preclinical Research and Animal Models in Sexual Medicine, 1
François Giuliano, Kevin McKenna, Balasubramanian Srilatha, James G. Pfau
2. Psychologic and Interpersonal Aspects and their Management, 18
Stanley E. Althof, Raymond Rosen, Eusebio Rubio-Aurioles, Carolyn Earle, Marie Chevret-Measson
3. Anatomy and Physiology of Erection, 31
Hartmut Porst, Ira D. Sharlip
4. History and Epidemiology of Male Sexual Dysfunction, 43
Hartmut Porst, Ira D. Sharlip
5. Etiology and Risk Factors of Erectile Dysfunction, 49
Hussein Ghanem, Hartmut Porst
6. Diagnosis of Erectile Dysfunction, 59
Allen D. Seftel
7. Oral Pharmacotherapy of Erectile Dysfunction, 75
Hartmut Porst
8. Self-Injection, Trans-Urethral and Topical Therapy in Erectile Dysfunction, 94
Hartmut Porst, Ganesan Adaikan
Hartmut Porst
Wayne J.G. Hellstrom
11. Vacuum Constriction Devices, 121
Sidney Glina, Hartmut Porst
12. Surgical Treatment of Erectile Dysfunction, 126
   Vascular Surgery of the Penis, 126
   Michael Sohn
   Penile Prosthetic Surgery, 136
   Michael Sohn, Antonio Martín-Morales

13. Hypoactive Sexual Desire in Men, 149
   Eusebio Rubio-Aurioles

14. Peyronie’s Disease, 158
   Pathophysiology and Medical Management, 158
   Ajay Nehra
   Surgical Treatment of Peyronie’s Disease, 165
   John Mulhall

15. Priapism, 174
   Pathophysiology and Non-Surgical Management, 174
   Ajay Nehra
   Surgical Management of Priapism, 180
   John Mulhall

16. Ejaculatory Disorders, 188
   Chris G. McMahon, Marcel Waldinger, David Rowland, Pierre Assalian, Young Chan Kim,
   Amado Bechara, Alan Riley

17. Radical Pelvic Surgery-Associated Sexual Dysfunction, 210
   John Mulhall, Sidney Glina

18. Hormones, Metabolism, Aging and Men’s Health, 225
   Jacques Buvat, Ridwan Shabsigh, André Guay, Louis Gooren, Luiz Otavio Torres,
   Eric Meuleman
   Introduction to Female Sexual Disorders, 287
   Alessandra Graziottin

19. Anatomy and Physiology of Women’s Sexual Function, 289
   Alessandra Graziottin, Annamaria Giraldi

20. Classification, Etiology, and Key Issues in Female Sexual Disorders, 305
    Alessandra Graziottin, Lorraine Dennerstein, Jeanne L. Alexander, Annamaria Giraldi,
    Beverly Whipple

21. Sexual Desire Disorders in Women, 315
    Lorraine Dennerstein, Jeanne L. Alexander, Alessandra Graziottin

22. Sexual Aversion Disorders in Women, 320
    Linda Banner, Beverly Whipple, Alessandra Graziottin

23. Sexual Arousal Disorders in Women, 325
    Annamaria Giraldi, Alessandra Graziottin

24. Orgasmic Disorders in Women, 334
    Beverly Whipple, Alessandra Graziottin
<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Pages</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Sexual Pain Disorders: Dyspareunia and Vaginismus</td>
<td>342</td>
<td>Alessandra Graziottin</td>
</tr>
<tr>
<td>26</td>
<td>Iatrogenic and Post-Traumatic Female Sexual Disorder</td>
<td>351</td>
<td>Alessandra Graziottin</td>
</tr>
<tr>
<td>27</td>
<td>Hormonal Therapy after Menopause</td>
<td>362</td>
<td>Alessandra Graziottin</td>
</tr>
<tr>
<td></td>
<td>Female Sexual Disorders: Future Trends and Conclusions</td>
<td>374</td>
<td>Alessandra Graziottin, Beverly Whipple, Lorraine Dennerstein, Jeanne L. Alexander, Linda Banner, Annamaria Giraldi</td>
</tr>
<tr>
<td>28</td>
<td>Cardiovascular Issues in Male and Female Sexual Dysfunction</td>
<td>376</td>
<td>Graham Jackson, Adolph Hutter</td>
</tr>
<tr>
<td></td>
<td>Index</td>
<td>387</td>
<td></td>
</tr>
</tbody>
</table>
List of Contributors

Ganesan Adaikan MD, PhD, DSc, ACS
President, ISSM
Department of Obstetrics and Gynaecology
National University Hospital
Yong Loo Lin School of Medicine
National University of Singapore
5 Lower Kent Ridge Road
Singapore 119074
Singapore

Jeanne L. Alexander MD, ABPN, FRCPC, FAPA, FACPsych
Director, Northern California Kaiser Permanente Medical Group
Psychiatry Women’s Health Program
Assistant Clinical Professor of Psychiatry, Stanford Medical School, Palo Alto, California
Founder, Alexander Foundation for Women’s Health
1700 Shattuck Avenue, Suite 329
Berkely, CA 94709
USA

Linda Banner PhD
Health Psychologist
Research Consultant, Stanford Medical Center
2516 Samaritan Drive D
San Jose, CA 95124
USA

Pierre Assalian MD
Associate Professor, Department of Psychiatry, McGill University
Executive Director, Canadian Sex Research Forum
Director, Human Sexuality Unit, Montreal General Hospital
1650 Cedar
Montreal
Quebec H3G 1A4
Canada

Marie Chevret-Measson MD
Psychiatrist and Sexologist
283, Rue de Crêqui
69007 Lyon
France

Lorraine Dennerstein MBBS, PhD, FRANZCP, DPM
Director, Office for Gender and Health Department of Psychiatry
The University of Melbourne
Level 1 North, Main Building Royal Melbourne Hospital Victoria 3050
Australia

Carolyn Earle
Manager / Sexologist
Keogh Institute for Medical Research
3rd Floor, A Block
Sir Charles Gairdner Hospital
2 Verdun Street
Nedlands
Western Australia
Australia

Hussein Ghanem MD
Professor of Andrology, Sexology and STDs
Cairo University
139(A) El Tahrir Street
Dokki, Cairo
Egypt

Amado Bechara MD, PhD
Urologist
Director, Instituto Médico Especializado (IME)
Av. Santa Fe 3312 6to D (1425)
Buenos Aires
Argentina

Jacques Buvat MD
Past President, SFMS and ISSM
Centre ETPARP
3 rue Carolus
59000 Lille
France

Stanley E. Althof PhD
Professor of Psychology
Case Western Reserve University School of Medicine
Executive Director, Center for Marital and Sexual Health of South Florida
1515 N. Flagler Drive
Suite 540
West Palm Beach, Florida 33401
USA
Annamaria Giraldi MD, PhD
President Elect, ISSWSH
Specialist Registrar and Lecturer in Sexology
Division of Sexological Research
Rigshospitalet 7111
Blegdamsvej 9
Copenhagen 2100
Denmark

François Giuliano MD, PhD
Professor of Therapeutics, Urology AP-HP, Neuro-Urology-Andrology Unit
Department of Physical Medicine and Rehabilitation
Raymond Poincaré Hospital
104 bd Raymond Poincaré
92380 Garches
France

Sidney Glina MD, PhD
Past President, ISSM
Director, Instituto H. Ellis
Rua Almirante Pereira Guimarães, 360
01250-000 São Paulo-SP
Brazil

Louis Gooren MD, PhD
Professor, Department of Endocrinology
Vrije Universiteit Medical Center
PO Box 7057
1007 MB Amsterdam
The Netherlands

Alessandra Graziottin MD
Director, Center of Gynecology and Medical Sexology
Consultant Professor of Sexual Medicine, University of Florence and Parma
H. San Raffaele Resnati
Via E. Panzacchi 6
20123 Milan
Italy

Wayne J.G. Hellstrom MD, FACS
Chief, Section of Andrology and Male Infertility
Tulane University School of Medicine
Department of Urology
1430 Tulane Avenue, SL 42
New Orleans, LA 70112
USA

Adolph Hutter MD
Professor of Medicine, Harvard Medical School
Yawkey 5B
Massachusetts General Hospital
55 Fruit Street
Boston, MA 02114
USA

Graham Jackson MD, FRCP, FACC, FESC
Cardiothoracic Centre
St Thomas' Hospital
London SE1 7EH
UK

Young Chan Kim MD
Korean Sexual and Men's Health Center
3F. Han Central Bldg.
646-7 Yoksam-dong
Kangnam-ku 135-911
Seoul
Korea

Sudhakar Krishnamurti MD
Andromeda Andrology Center
1st Floor, Topaz
P.O. Box 1563
Greenlands Rd.
Hyderabad, 500 082 AP
India

Chris G. McMahon MBBS, FACHSHM
Professor, Genitourinary Physician and Director, Australian Centre for Sexual Health
Suite 2-4
Berry Road Medical Centre
1a Berry Road
St Leonards NSW 2065
Australia

Kevin McKenna PhD
Professor, Departments of Physiology and Urology
Northwestern University Feinberg School of Medicine
Tarry Building 5-755 (M211)
303 East Chicago Avenue
Chicago, IL 60611-3008
USA

Antonio Martín-Morales MD
Unidad Andrología, Servicio Urología Hospital Regional Universitario Carlos Haya
Plaza Hospital Civil s/n
Málaga, 29009
España

Eric Meuleman MD
Department of Urology
Free University Medical Center
PO Box 7057
1007 MB Amsterdam
The Netherlands

John Mulhall MD
Associate Professor, Department of Urology
Weill Medical College of Cornell University
Director, Sexual Medicine Programs
New York Presbyterian Hospital and Memorial Sloan Kettering Cancer Center
525 E 68th St
New York, NY 10021
USA

Ajay Nehra MD, FACS
Consultant, Department of Urology
Professor of Urology
Mayo Medical School
Mayo Clinic
Rochester
USA

James G. Pfaus PhD
Professor, Center for Studies in Behavioral Neurobiology
Department of Psychology
Concordia University
7141 Sherbrooke W.
Montreal, QC H4B 1R6
Canada


**List of Contributors**

**Hartmut Porst MD**  
Professor of Urology  
Urological Practice  
Neuer Jungfernstieg 6a  
20354 Hamburg  
Germany

**Alan Riley MSc, MBBS, MRCS, DRCOG, FFPM**  
Professor, Sexual Medicine  
Lancashire School of Health and Postgraduate Medicine  
University of Central Lancashire  
Preston PR1 2HE  
UK

**Raymond Rosen PhD**  
UMDNJ-Robert Wood Johnson Medical School  
671 Hoes Lane  
Piscataway, NJ 08854  
USA

**David Rowland MD, PhD**  
Professor of Psychology  
Office of Graduate Studies  
Valparaiso University  
Valparaiso, IN 46383  
USA

**Eusebio Rubio-Aurioles MD, PhD**  
Asociación Mexicana para la Salud Sexual, A.C. AMSSAC  
Tezoquipa 26  
Colonia La Joya  
Delegación Tlalpan, México DF 14000  
Mexico City  
Mexico

**Allen D. Seftel MD**  
Professor, Department of Urology  
Case Western Reserve University  
University Hospitals of Cleveland  
11100 Euclid Ave  
Cleveland, Ohio 44106-5046  
USA

**Ridwan Shabsigh MD**  
Associate Professor of Urology  
Columbia University  
Director, New York Center for Human Sexuality  
161 Fort Washington Avenue  
New York, NY 10032  
USA

**Ira D. Sharlip MD**  
President Elect, ISSM  
Clinical Professor of Urology  
University of California at San Francisco  
2100 Webster St Suite 222  
San Francisco CA 94115  
USA

**Michael Sohn MD**  
Professor of Urology  
Urologische Klinik Frankfurter Diakonie Kliniken/Markus KH  
Wilhelm-Epstein Str. 2  
60431 Frankfurt  
Germany

**Balasubramanian Srilatha MD, PhD**  
Department of Obstetrics and Gynaecology  
National University Hospital  
Yong Loo Lin School of Medicine  
National University of Singapore  
5 Lower Kent Ridge Road  
Singapore, 119074  
Singapore

**Luiz Otavio Torres MD**  
Past President, SLAMS  
President, Brazilian Society of Urology, Section Minas Gerais  
Director, Clinica de Urologia e Andrologia  
Av. Alfonso Pena 3111/204-205  
CEP 301 30-008 — Belo Horizonte  
Minas Gerais  
Brazil

**Marcel Waldinger MD, PhD**  
Neuropsychiatrist  
Department Psychiatry and Neurosexology  
Haga Hospital Leyenburg  
Leyweg 275  
2545 CH The Hague  
The Netherlands

**Beverly Whipple PhD, RN, FAAN**  
Professor Emerita  
Rutgers University  
87 Matlack Drive  
Voorhees, NJ 08043  
USA
The modern era in sexual medicine started in the 1970s when a few devoted pioneers and visionaries began to revolutionize our thinking and understanding in this field.

Prior to that time, sexual dysfunctions in men, particularly erectile disorders, were thought to be purely psychogenic or in rare cases caused by testosterone deficiency. Treatment of sexual disorders was considered to be predominantly the business of sex therapists or rarely of endocrinologists. And at that time, knowledge about female sexual disorders was practically non-existent; female sexuality was little more than a blank spot in sexual medicine.

The introduction of completely new surgical procedures, such as corpus cavernosum revascularization and penile implants, for the treatment of impotence, and the invention of new and creative diagnostic procedures, such as penile angiography, dynamic cavernosometry and penile Doppler ultrasonography, expanded our knowledge in this field and contributed to the better understanding of the causes and treatments of sexual dysfunctions. Several exceptional medical scientists deserve to be considered the true pioneers of this novel thinking in sexual medicine. First, Vaclav Michal, a Czechoslovakian vascular surgeon, introduced the concept of passive erection for the diagnosis of vasculogenic erectile dysfunction and the technique of penile arterial revascularization for the treatment of vasculogenic impotence. Jean-Francois Ginestie and A. Romieu, the inventors of the radiologic exploration of impotence, introduced selective pudendal arteriography and dynamic cavernosography as key procedures in the diagnosis of vasculogenic impotence. M.P. Small and H.M. Carrion invented the first internationally marketed rigid penile implant and B. Scott invented the first hydraulic penile implant. Gorm Wagner focused his scientific investigations on the physiologic and pathophysiologic processes involved in sexual responses and how they contribute to the manifestation of sexual dysfunctions in both sexes. Dr Wagner later became the first President of the International Society for Impotence Research, later renamed the International Society for Sexual Medicine. In the late 1970s, Adrian W. Zorgniotti, of New York University, gave the new scientific field of sexual medicine an organizational framework by convening the first and second conferences on "Corpus Cavernosum Revascularization" in 1978 in New York and in 1980 in Monte Carlo. After 1980, these conferences were continued at two year intervals, becoming first the World Congresses of Impotence Research in the 1980s and 1990s and then the Congresses of the International Society for Sexual Medicine in the first decade of the new century. Gathering biennially up to 2000 physicians and researchers from around the world, the first several of these Congresses made it clear that considering sexual dysfunctions as purely psychogenic was inaccurate and a new era in the history of sexual medicine was launched.

Having attended all these Congresses since 1980, we learned in person of the rapid progress being made in the field of sexual medicine. This book, the
work-product of the Standards Committee of the International Society for Sexual Medicine, classifies what has been accomplished so far and identifies where the main emphasis of future trends may be. This book updates current knowledge and present standards in the field of sexual medicine for both genders. It demonstrates as well the growing importance of female sexual medicine and psychology.

With this statement, we would like to express our thanks to all the members of the ISSM Standards Committee, especially to the Chairmen and Chairwomen of the respective sub-committees. Without their dedicated and untiring engagement, this work would never have happened in such a short time. Our deep gratitude extends also to the exceptional contribution of Astrid Brendt and the superb work of Helen Harvey and Blackwell Publishing without whose dedication and support this project could not have been completed.

By increasing knowledge in sexual medicine of many thousands of colleagues who deal with sexual dysfunctions across this globe, we hope that the work of the ISSM Standards Committee will provide even better health services in this medical discipline. It is our wish that this work will enhance sexual health and quality of life for the tens of million of couples world-wide who face the challenges of sexual dysfunction.

Hartmut Porst, MD
Chairman
Jacques Buvat, MD
Co-Chairman
ISSM Standards Committee
2006
Foreword

It is a mystifying paradox that among the most important functions of the human body, sexuality has drawn more public attention than any other, yet sexual function is one of the last areas to receive the careful attention of medical scientists.

Many studies have shown that sexual health is a very important element of overall health and quality of life. Yet in both the developed and the developing worlds, social taboos and religious restrictions surround human sexuality. In some places, ignorance about sexuality, illogical mores and/or irrational ritual practices impede medical research, interfere with medical education about sexual health, contribute to the propagation of sexually-transmitted diseases and/or prevent individuals from achieving a fully healthy and happy life.

Since its inception in 1982, the International Society for Sexual Medicine (ISSM) has strived to alter the paradox between the immense impact that sexuality has on human behavior and the limited state of scientific research and knowledge in human sexuality. The basic goal of the Society has been to introduce sound scientific knowledge to the experimental and clinical aspects of sexual medicine. In addition, ISSM aims to guide the field of sexual medicine into a position of prominence and prestige in the panoply of healthcare disciplines; to promote public education about sexual health; and to provide its members with a rich international environment for the exchange of scientific ideas and information.

In its global efforts to promote the highest standards of research, practice and treatment in sexual healthcare, ISSM conducts international scientific meetings in every continent, maintains an international registry of sexual health problems and promotes scientific publications in female and male sexual medicine. For example, the Society’s official journal, The Journal of Sexual Medicine, has become widely acknowledged as the leading journal, by all standards, in this field.

Standard Practice in Sexual Medicine is another milestone in the history of the ISSM. As the Society addresses a multiplicity of challenges in sexual medicine, we are heartened at the focused consonance in this book between clinical problems and contemporary scientific literature. As its name states, this comprehensive volume proposes standards for current practice of both male and female sexual medicine and provides direction for future investigation. At the crossroads of our quest to enhance the quality of life for man and womankind, this book will be an invaluable source for many years to come, not only for the deeply inquiring young scientific mind but for the more seasoned practitioner as well.

We must be certain to recognize the Herculean efforts of the far-sighted Editors, Dr Hartmut Porst and Dr Jacques Buvat, and all of the individual chapter authors in making this book a reality. We are especially indebted to Dr Buvat who, during his term as President of ISSM, had the vision to create the ISSM Standards Committee. This scholarly book is the first work of that committee. The prodigious scientific contribution of Drs Porst and Buvat in compiling this book is an extraordinary legacy to the future of sexual medicine. On behalf of the ISSM, we place on record our sincere gratitude for their uncompromising and timely efforts.

P. Ganesan Adaikan
President
Ira D. Sharlip
President-Elect
International Society for Sexual Medicine
September 2006
Introduction

Preclinical research typically involves the use of animal models of human sexual response, and is often conducted to investigate the effects of pharmacologic agents, instrumentation, new devices, or surgical procedures prior to clinical trials. This research may also examine certain side effects of such treatment; however, preclinical research may also include human tissue experiments or biochemical experiments with human products, e.g., native or recombinant enzymes. For the sake of simplicity, studies of toxicology, carcinogenicity, fertility, and safety will not be included in the definition.

The key issue for clinicians is the ability to extrapolate the preclinical results to human clinical populations, and in particular to determine the likelihood that a treatment will be successful or will warrant subsequent human tests. Besides studies conducted in anesthetized animals that have been extremely useful in the study of sexual physiology, behavioral experiments are crucial to providing a more integrative approach to understanding the physiologic and pathophysiologic aspects of sexual function and dysfunction.

In all species, sexual behavior is directed by a complex interplay between steroid hormone actions in the brain that give rise to sexual arousability, and experience with sexual reward or pleasure that gives rise to expectations of competent sexual activity, including sexual arousal, desire, and performance. Sexual experience allows animals to form instrumental and Pavlovian associations that predict sexual outcome and thereby direct the strength of sexual responding. Although the study of animal sexual behavior by neuroendocrinologists has traditionally been concerned with mechanisms of copulatory responding, more recent use of conditioning and preference paradigms, and a focus on environmental circumstances and experience, has revealed behaviors and processes that resemble human sexual responses.

Accordingly, we have summarized behavioral paradigms used with rodents and other species that are analogous or homologous to human sexual arousal, desire, reward, and inhibition. At a superficial level, human copulatory behavior does not resemble copulatory behavior in animals. For example, there is no human counterpart to female rat lordosis (at least not as an unambiguous, estrogen-dependent postural display of sexual receptivity in females), and human sexual behavior is so shaped by experience and learning that it seems to defy hormone actions that are critical to the display of animal sexual behavior. However, insights into the human experience can indeed be derived from animals, and in ways that are far less difficult scientifically and ethically to obtain than from human populations.

We have not referenced any experimental techniques because this was far beyond the scope of this chapter. Instead, we have proposed a list of review papers that will provide the reader with more in-depth insight into different experimental models.

What is required for a good animal model?

Predictive validity is the most important requisite of an appropriate animal model. In addition to this,
animal models should be simple and practical enough to have “high throughput”, meaning the ability to have experiments conducted relatively quickly. Issues of sample size and ease of testing and analysis are key factors. The validity of any homologous or analogous animal model can only be determined in situations that test whether a treatment that modifies behavior in the animal does so in humans.

Any animal “system” in which the homology or analogy has predictive validity to human responses or physiologic processes (and can be replicated) is a good model. If the model is practical from an experimental standpoint, then it will likely be used more than models that are cumbersome. In addition, the more information that is gathered from a particular model, the more the model will be used because it has a large literature associated with it. Rats continue to be the most frequently used animals in the study of sexual behavior. There are many reasons for this, the most obvious being that they are practical (e.g. small, easy to handle, and quite social) and they have a large literature associated with them. Rats also resemble humans in many analogous and homologous ways. Certain tissues and neuroendocrine systems in rats are strikingly similar to our own (e.g. the physiologic control of erection, or uterine tissue growth following estrogen treatment).

**Rectification of terms**

In humans, sexual dysfunctions form around the categories of sexual arousal, desire, orgasm, and pain. Arousal may be separated into physiologic genital arousal (sometimes referred to as “potency”) and subjective or psychologic arousal that denotes a conscious awareness of the genital sensations. However, this psychologic arousal may be an important component of sexual desire (sometimes referred to as “libido” or “motivation”). Sexual arousal and desire sum into behavioral responses of copulation.

---

**Penile erection**
- Recording of intracavernous pressure increases in anesthetized or conscious animals
- Penile reflex tests
- *In copula* erections
- *In vitro* studies of cavernosal strips / penile artery reactivity (organ baths)
- Cavemosal smooth muscle cells culture
- Biochemical studies of erectile tissue

**Ejaculation**
- Mating test: latency to ejaculate
- Urethrogenital reflex (anesthetized)
- PCA-induced ejaculation (anesthetized or conscious)
- Pudendal motoneuron reflex discharge (anesthetized)
- Electrical stimulation of peripheral nerves (anesthetized)

**La Peyronie’s disease**
- TGF-β1-induced La Peyronie’s like condition

**Priapism**
- Rabbits exposed to corporal hypoxia, then penile erection elicited by neural stimulation and the base of the erect penis clamped
- eNOS−/− and nNOS−/−, eNOS−/− mice

**Female peripheral sexual arousal**
- Anesthetized dogs, rabbits and rats: vaginal vasculo-muscular response along with clitoral tumescence induced by peripheral electrical neural stimulation.

**Table 1.1** Experimental paradigms that can be used as rodent models of human sexual functions. eNOS, endothelial nitric oxide synthase; nNOS, neural nitric oxide synthase; PCA, p-chloroamphetamine; TGF-β1, transforming growth factor beta 1.
Table 1.2  Paradigms that can be used as rodent models of human sexual behavior (from Pfaus et al., 2003).

<table>
<thead>
<tr>
<th>Sexual arousal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
</tr>
<tr>
<td>Penile reflex tests (physiologic erectile function; responses to somatosensory stimulation)</td>
<td></td>
</tr>
<tr>
<td>Noncontact erections (“psychogenic” erectile function; responses to primary or secondary conditioned sexual cues)</td>
<td></td>
</tr>
<tr>
<td>Copulatory measures: latency to mount, intromit or ejaculate (shorter latency = greater arousal)</td>
<td></td>
</tr>
<tr>
<td>Enforced interval effect (model of premature ejaculation)</td>
<td></td>
</tr>
<tr>
<td>Coolidge effect (increased arousal by changing sexual stimuli)</td>
<td></td>
</tr>
<tr>
<td><strong>Sexual desire</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Females and males</strong></td>
<td></td>
</tr>
<tr>
<td>Excitement (motor responses in anticipation of sexual activity or in response to hormonal stimulation)</td>
<td></td>
</tr>
<tr>
<td>Instrumental responding (desire to obtain a sex partner)</td>
<td></td>
</tr>
<tr>
<td>Sexual preference paradigms (desire to obtain unconditioned or conditioned sexual incentive characteristics)</td>
<td></td>
</tr>
<tr>
<td>Copulatory measures</td>
<td></td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
</tr>
<tr>
<td>Pursuit (desire to obtain sex partner)</td>
<td></td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
</tr>
<tr>
<td>Solicitation, hops and darts (desire to initiate sexual activity)</td>
<td></td>
</tr>
<tr>
<td>Pacing (desire to regulate copulatory contact; increased pacing = decreased desire for copulatory contact)</td>
<td></td>
</tr>
<tr>
<td>Lordosis (receptivity to vaginal penetration)</td>
<td></td>
</tr>
<tr>
<td>Lateral tail displacement in hamsters (receptivity to vaginal penetration)</td>
<td></td>
</tr>
<tr>
<td><strong>Sexual reward</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Females and males</strong> (to examine what aspect of sexual responding is rewarding, e.g. copulatory stimulation vs. ejaculation in males, or the ability to control sexual interaction in females):</td>
<td></td>
</tr>
<tr>
<td>Operant responding for primary or secondary sexual reinforcers</td>
<td></td>
</tr>
<tr>
<td>Conditioned place preference</td>
<td></td>
</tr>
<tr>
<td>Unconditioned or conditioned partner preference</td>
<td></td>
</tr>
<tr>
<td>Conditioned copulatory behavior (e.g. copulatory responses in places paired with sexual or other rewards, or in the presence or absence of conditioned incentive cues)</td>
<td></td>
</tr>
<tr>
<td><strong>Sexual inhibition</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
</tr>
<tr>
<td>Copulatory behavior after several ejaculatory series</td>
<td></td>
</tr>
<tr>
<td>Estrus termination</td>
<td></td>
</tr>
<tr>
<td>Tests using ovariectomized females primed with estrogen alone</td>
<td></td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
</tr>
<tr>
<td>Primary sexual inhibition (using access to nonreceptive females)</td>
<td></td>
</tr>
<tr>
<td>Second order sexual inhibition (using odors or other stimuli paired with access to nonreceptive females)</td>
<td></td>
</tr>
<tr>
<td>Recovery from sexual exhaustion</td>
<td></td>
</tr>
</tbody>
</table>

(sometimes referred to as “performance”). The terms used in the animal literature often do not resemble those in the human literature, and a rectification of terms is necessary to translate between animal and human sexual functions. We propose the Incentive Sequence Model (Fig. 1.1) as a place to begin such a rethinking of nomenclature and to bridge the gap between animal research and the clinical practice.

**Male Sexual Function**

Peripheral sexual reflexes (erection and ejaculation), copulatory behaviour (mounts, intromissions,
Fig. 1.1 Incentive sequences for human and rat sexual behaviors. This model provides a conceptual way to denote classes of homologous or analogous behaviors between the species (and sexes). The behavioral stream moves from left to right, through appetitive, precopulatory, and consummatory phases of behavior. This conforms to the movement of animals from distal to proximal to interactive with respect to the sexual incentive. Three types of appetitive responding reflect relative degrees of learning and necessity. “Preparatory” behaviors are learned responses that animals must make in order to acquire the incentive (e.g. operant behaviors, pursuit, etc.). “Anticipatory” behaviors are learned responses that occur in anticipation of an incentive, but are not necessary to obtain it (e.g. conditioned psychomotor stimulation that characterizes behavioral excitement). Unlearned appetitive responses also exist that are instinctual (e.g. unconditioned anogenital investigation). These aspects of behavior also occur once copulatory contact has been made, especially if copulation occurs in bouts (as it does in rats). From Pfaus, 1999.
and ejaculation), and appetitive conditioned sexual responses (e.g. conditioned arousal), have been examined in a variety of species. In most cases, sexual physiologic and behavioral responses are extremely similar between the species, making the generation of analogies and homologies, and their application to human male function and dysfunction, straightforward.

**Penile Erection**

Experimental research on penile erection dates from at least the 19th century, with the work of pioneer physiologists such as Eckhardt, Langley, and Anderson. Subsequently, during the 20th century significant advances were achieved thanks to the work of Semans and Langworthy in the 1930s, veterinary researchers performing experiments in conscious bulls and stallions in the 1970s, Sjöstrand using plethysmography to quantify penile erection in the rabbit, and then work by Lue’s and Goldstein’s groups in the 1980s, providing the scientific and medical community with experiments conducted in dogs, monkeys and rabbits that show the vascular component of penile erection and the crucial role of cavernosal smooth muscle fibers. Quinlan then introduced the first rat model to measure penile erection. More recently, investigations of penile erection have been performed in mice, opening the door to studies conducted with genetically modified animals.

From a physiologic perspective, it appears that there is a close similarity between local mechanisms of penile erection between non-human mammals and human males except for the role of striated muscles, which are less important in humans compared to various animal species.

**Evaluation of erectile response in anesthetized animals**

The gold standard for quantitative measurement of penile erection during experiments conducted in anesthetized and conscious animals is the recording of intracavernous pressure (ICP), also measurable in conscious animals by telemetry. It is noteworthy that ICP is closely dependant from arterial blood pressure. Penile erection can be elicited in anesthetized animals by electrical stimulation of peripheral nerves, i.e. pelvic or cavernous nerves (Fig. 1.2). It can also be elicited by electrical or chemical stimulation applied to brain structures. Drug delivery everywhere in the periphery (from intracavernosal injections to oral gavage) or within the central nervous system, including brain and spinal cord, is feasible in anesthetized animals to study their effect on penile erection.

Animal models have been widely used to establish the effects of phosphodiesterase-5 (PDE-5) inhibitors, and they have been predictive for the human situation for this class of compounds. There are crucial questions to be answered before extrapolating experimental data to humans, including: is the...
receptor targeted by the compound under investigation the same in animals as compared to the human male and does it play the same role; e.g. intracavernosal prostaglandin E\(_1\) (PGE\(_1\)) injections do not elicit penile erection in many animal species. When investigating the proerectile effect of pharmacologic compounds in animals, the following aspects must always be taken into account: dose used, route of administration, pharmacokinetics, half-life, metabolism of the studied compounds, etc.

**In vitro reactivity studies of erectile tissue**

These experiments are conducted in the investigation of the local cellular mechanisms of penile erection. Cavernosal strips from various animal species and humans have been studied in organ baths. These tissues are either pharmacologically precontracted, e.g. with phenylephrine, or electrically stimulated (electrical field stimulation) to elicit the release of neurotransmitters contained within the nerve terminals present in the tissue. Numerous compounds (e.g. prostanoids, \(\alpha\)-adrenoceptor blockers, endothelin antagonists, PDE-5 inhibitors) have been found to be able to relax cavernosal strips by targeting various intracellular systems. Primary cell cultures derived from animal or human corpus cavernosum have also been used as *in vitro* models to define cellular mechanisms involved in erectile function.

**Pathophysiologic models of erectile dysfunction**

A wide variety of pathophysiologic models of erectile dysfunction (ED) have been proposed, aiming to mimic the numerous pathologic conditions responsible for ED in clinical practice. A non-exhaustive list of these models comprises: hypertensive rats, atherosclerotic rabbits, diabetic rats and rabbits, aged rats, castrated rats, cavernous nerve-injured rats, alcohol-treated, or nicotine-treated rats. The question of extrapolation to humans using these various experimental conditions must always be asked before drawing conclusions regarding applicability. It is noteworthy that there is no established standard in this domain, therefore we propose that the endpoints must be analogous or homologous (e.g. the restoration of erectile capability sufficient for copulation).

A special caution must be paid to castrated animals: many conclusions regarding the role of testosterone on penile erection have been drawn from experiments conducted in castrated rats; unfortunately this experimental paradigm is very different from the human situation, which is highly prevalent—i.e. the ageing male with partial androgen deficiency syndrome due to age in males (PADAM). So far no reliable model of PADAM has been proposed.

Due to advances in molecular biology, genetically engineered mice have now become available. Although the ultimate goal of these models is to develop gene therapy to rectify gene activity, transgenic or knockout mice have recently contributed to our understanding of the physiologic mechanisms of erectile function, as well as to various pathophysiologic processes occurring during ED.

**Study of erection in conscious animals**

In conscious rats, penile erections can be studied in isolation to obtain measures of physiologic arousal, or in response to different types of sexually arousing stimuli (e.g. noncontact erections in response to estrous odors) to obtain measures of psychogenic arousal.

*Ex copula* reflex erection is a commonly used unanesthetized rat model of erection. The rat is lightly restrained in a supine position and the penis is retracted from the sheath. Relatively predictable “spontaneous” penile erections are thus elicited. *Ex copula* reflex erections are generated by spinal reflex mechanisms and modulated by supraspinal control. The effects of drugs and various central neural lesions can be examined in this model. It has the advantage in that it does not involve social interaction with the female and it examines penile reactions directly.

Several pharmacologic agents acting at different central brain regions have been shown to elicit penile erection in conscious rats during *ex copula* penile erection tests, i.e. in isolation. Penile erection during these tests has been inferred from a series of motor acts like standing on the hind limbs, the head of the animal oriented towards the genital area, licking of the genital area, contractions of the hip muscles, and sometimes by direct observation of protrusion of the glans. It remains unknown whether or not the putative neural structures representing targets for these “proerectile drugs” are all activated during the
penile erection that occurs in several natural contexts (sleep, copulation, psychogenic, reflex).

Male rats (but only pigmented strains) also show an analogy of “psychogenic erection” in response to the presence of estrous females, even when physical contact is prevented. A model of noncontact erections (NCEs) in rats was developed by Sachs and colleagues, and is studied in the presence of an inaccessible receptive female behind a mesh screen, or behind a series of walls with an air circulation system that brings the estrous odors to the male’s compartment. Erections in response to these salient sexual cues are viewed as a model of psychogenic erection because they do not require direct somatosensory stimulation to be induced. The neurochemical and hormonal mechanisms that control their expression have been studied in detail. Analysis of NCEs following discrete brain lesions has demonstrated important distinctions in the neural control of copulatory performance and erectile capability. Drugs that enhance noncontact erections also induce a “penile erection and yawning syndrome” in rats in the absence of sexual stimulation. NCEs offer at least one advantage over the study of erection during copulation: they do not require complex motor responses or direct social interaction. This makes their study relatively less ambiguous as a measure of subjective sexual arousal. One concern is that the dependence of these responses on olfactory stimuli is unlike human sexual responses, which are more dependent on visual and auditory cues. However, olfaction is analogous to vision in this case, as the former is the dominant sense in rodents, whereas the latter is the dominant sense in humans.

Conclusions
Experimental research has been very productive regarding the physiology, pathophysiology and pharmacology of penile erection. There exist several rodent models of penile erection, from higher neural control down to molecular events within the erectile tissue. Although care must always be taken before extrapolating quickly from experimental data to the clinical situation, there is a high degree of predictability from rat models to men. Nature appears to have conserved mechanisms of erection in mammalian males.

**Ejaculation and male orgasm**
Most of the experimental work done so far for the investigation of ejaculation is based on behavioral experiments. Ejaculations in rats can be studied much the same way they are studied in humans, with the latency from first mount or intromission to ejaculation being the key variables (Fig. 1.3). Male rats typically ejaculate following several penile intromissions, and can ejaculate several times before becoming sexually exhausted, in which the male no longer responds to estrous odors or female solicitations. During successive ejaculatory series, the refractory period or post ejaculatory interval between each ejaculation and the subsequent resumption of copulation increases progressively. Penile intromission requires erection, and ejaculation typically requires sensory feedback from the penis that accumulates with multiple intromissions. The number of intromissions before ejaculation, the number of ejaculations achieved in a timed test, and the length of the post ejaculatory interval, are all dependent on autonomic arousal and can be enhanced or disrupted by drugs that have similar effects on copulatory performance in men. For example, drugs that delay or abolish orgasm in men (e.g. selective serotonin reuptake inhibitors such as fluoxetine, paroxetine), increase the ejaculation latencies and reduce the total number of ejaculations in rats. As in men, the reduced ability to ejaculate is more pronounced in rats following long-term daily administration. Acute alcohol intoxication also delays ejaculation in men and male rats.

![Fig. 1.3](attachment:image.png) Typical copulatory pattern in the male rat over a 10-min period.
Experimental investigation of ejaculation in anesthetized rats

Compared to penile erection much less research has been conducted in anesthetized animals in order to elucidate the physiology and the pharmacology of ejaculation. However, four interesting paradigms have been developed:

1 **Urethrogenital reflex:** the urethrogenital (UG) reflex is elicited by mechanical stimulation of the urethra in anesthetized and spinalized rat. Such a stimulation causes a spinal reflex to occur that consists of rhythmic contraction of the bulbospongious (BS) and the ischiocavernosus (IC) striated muscles associated with penile erection. It may be considered as mimicking the expulsion phase of ejaculation.

2 **PCA-induced ejaculation:** A model of pharmacologic induced ejaculation; p-chloroamphetamine (PCA) is an amphetamine derivative that liberates catecholamines and serotonin (5-hydroxytryptamine, 5-HT) from monoaminergic nerve terminals. Systemic administration of PCA has been reported to induce ejaculation in both conscious and anesthetized rats. Pharmacologic data indicate that the primary role in mediating the effect of PCA on ejaculation involves 5-HT, whereas noradrenaline (NA) appears to be of secondary importance.

3 **Electrical stimulation of peripheral nerves and ejaculation:** in anesthetized rats, electrical stimulation of the hypogastric nerve can partially reproduce the ejaculatory process, i.e. eliciting a rise in seminal vesicle and bladder neck pressures that correspond respectively to seminal vesicles contractions and closure of the bladder neck, but it fails to induce the expulsion reflex.

4 **Pudendal motoneuron reflex discharge:** the recording of electrical activity in the efferent branch of the ejaculatory reflex, i.e. the pudendal motor response discharge (PMRD) elicited by the electrical stimulation of the afferent branch of the expulsion reflex—the dorsal nerve of the penis, is thought to be an experimental model representing events that occur in humans during sexual intercourse and that culminate with the expulsion of sperm.

**Orgasm and the consequences of ejaculation**

Although it is not known whether male rats experience orgasm during ejaculation, the peripheral reflexes appear very similar. Moreover, ejaculation is absolutely necessary for male rats to show subsequent evidence that sex was rewarding or “pleasurable”. For example, ejaculation is required for the induction of conditioned place and partner preference in male rats. These preferences are not displayed if males are administered the opioid antagonist naloxone during conditioning, suggesting that ejaculation induces the activation of endogenous opioids in the brain that mediate the critical rewarding properties of sex.

**Conclusions**

This research is still in its infancy. Apart from behavioral studies, there is a need for standardization and more research is definitely mandatory in this area. There is no model available, for example, to investigate delayed or absent ejaculation or painful ejaculation, and the experimental equivalent of the male orgasm is lacking.

**Sexual motivation and “desire”**

Desire has always been difficult to define objectively. In the DSM-IV-TR, the diagnosis of hypoactive sexual desire disorder is given when “desire for and fantasy about sexual activity are chronically or recurrently deficient or absent.” By converse logic, then sexual desire is the presence of desire for, and fantasy about, sexual activity. This definition appears coherent but is circular. How does desire manifest itself?

Like people, animals manifest sexual excitement behaviorally. They increase their motor output in anticipation of copulation and work for the opportunity to copulate or to obtain primary or secondary (conditioned) sexual rewards associated with copulation. Animals will also choose between two or more sexual incentives based on the strength of the incentive cues and the animal’s own internal drive state. What characterizes these behaviors is that they occur before copulation: Courtship, operant responses, conditioned locomotion in anticipation of sex, time spent near a particular sexual incentive, or choices made between two or more incentives, can all be considered analogies of anticipatory sexual desire. The strength of the behavior can be observed as increases or decreases, or can be tested by increasing the crite-
rion level of responding that animals must attain before they are given access to rewards. Simply put, animals with more “desire” will display more robust behavior than animals with less desire. Desire can also be inferred from certain appetitive responses that occur during copulation, such as solicitation in females or chasing behavior in males. A growing body of evidence indicates that these aspects of sexual behavior are altered in a relatively selective fashion by certain drugs that are known to alter desire in humans (e.g. by drugs that affect dopamine or melanocortin receptors).

**Models of male sexual dysfunctions**

**Erectile dysfunction**

Male rats that do not perform sexually are typically taken out of behavioral studies, so there is very little known about their actual erectile responsiveness. This proportion is generally low, especially if the males are pre-exposed to the test chambers prior to their initial sexual experiences. Some of these males do not display any interest in the female, and do not initiate any kind of sexual activity. However, other males display sexual interest and mount repeatedly, but do not achieve vaginal intromission. The lack of intromission may stem from an inability to achieve erection. Indeed, erectile responses in isolation and intromissions during copulation are both very sensitive to disruption by several classes of drug, including psychomotor stimulants, dopamine and noradrenergic antagonists, and opioid agonists. Acute or chronic treatment with selective serotonin reuptake inhibitors (SSRIs) does not appear to alter erectile responses or the number of intromissions prior to ejaculation. This profile of pharmacologic sensitivity is strikingly similar to clinical observations and anecdotes in men, thus male rats may be a useful model of drug-induced, if not also stress or vascular disease–related erectile dysfunction.

**Premature ejaculation**

In 1956, Knut Larsson published a series of studies that described many ways in which sexual reflexes and behaviors could be conditioned by experience. In one of these paradigms, called the “enforced interval effect”, male rats were given repeated access to females that were removed physically from the testing chamber by the experimenter after every intromission. In this way, Larsson was able to vary the time between intromissions and found that male intromission intervals that lasted longer than normal resulted in males that learned to ejaculate with far fewer intromissions. One of the interpretations of this data was that the imposition of longer intromission intervals made males more sympathetically aroused, and led to either a faster ejaculation or one that required less tactile penile stimulation. This model of hyperstimulation of sympathetic outflow by either highly stimulating, unpredictable, or stressful sex, formed part of the basis of Masters and Johnson’s model of premature ejaculation a decade later. Despite this, the model has not been developed further, nor has it been used widely to examine drug effects.

More recently it was reported that natural differences are found in the ejaculation latencies of male rats, which may indicate a more biological explanation of premature ejaculation that shares some of the characteristics of human premature ejaculation. In pooled populations of male albino Wistar rats during a 30 min standardized mating test, three categories of males were identified: (1) males that displayed a low number of ejaculations (0 to 1) and were considered as sexually “sluggish” or “hypo-sexual”; (2) a second category of rats that showed a range of two or three ejaculations and were considered as “normal” ejaculators; and (3) males who displayed four or five ejaculations and were considered as “rapid” ejaculators or “hyper-sexual” rats. The number of ejaculations across the various studies was distributed according to a Gaussian curve: on one side approximately 10% of rats displayed “hypo-sexual” behavior and on the other side 10% display “hyper-sexual” behavior after at least four successive weekly sexual tests of 30 min. Interesting differences were found between the “sluggish” and “rapid” groups of rats with regard to a variety of other parameters of sexual behavior, resembling clinical symptoms of men suffering from retarded and premature ejaculation, respectively.

The “hyper-sexual” animals have been further investigated in order to know whether they could be used as a model for human premature ejaculation. Compared to “normal” ejaculators, ejaculation
latency was shorter in “rapid” ejaculators and longer in “sluggish” ejaculators. Intromission and mount frequencies, the latter being considered as a putative index of sexual motivation, did not differ between the three categories of ejaculators, suggesting no differences in appetitive components of sexual behavior. When investigating the effects of 8-hydroxy-2-di-n-propylamino-tetralin (8-OH-DPAT) in these three categories of males, this compound was shown to induce a statistically significant increase in the number of ejaculations displayed by “sluggish” and “normal” rats, and to decrease in a statistically significant way the ejaculation latency in the “sluggish”, “normal” and “rapid” rats.

This experimental paradigm, despite the fact it has been recently reported and not yet confirmed by others, appears as extremely attractive. Indeed “hyper-sexual rats” likely represent a pathophysiological model of premature ejaculation. It remains to be seen whether drugs that can counteract premature ejaculation in men can increase the latency of male rats to ejaculate in this condition. It also remains to be studied whether such males are uniquely susceptible to an “enforced interval effect”.

Delayed ejaculation
Conversely, some male rats ejaculate infrequently, or take a long time to achieve ejaculation. As mentioned above, this can be induced pharmacologically with alcohol or chronic treatment with SSRIs, such as fluoxetine or paroxetine. It remains to be determined whether the subset of sexually “sluggish” male rats found in normal populations can be utilized as models of delayed ejaculation.

Hypoactive sexual desire
Some male rats do not copulate despite extreme attempts on the part of sexually receptive females to get them to do so (including repeated mounting of the male by the female). Some of these males can be stimulated to copulate with low levels of electric shock, tail pinch, or treatment with low doses of psychomotor stimulants, like amphetamine, suggesting that a more general hypoarousability mediates their lack of responsiveness. Stress may also induce hypo-sexual responsivity in male rats, especially if it is presented during their early sexual experience. For example, a sizable proportion (often nearly 50%) of male rats will not copulate during their first trial with sexually receptive females unless they are pre-exposed to the testing chamber. Indeed, a large proportion of these noncopulators will never copulate, despite repeated exposure to receptive females. Novel environments are stressful to male rats, and induce the activation of endogenous opioids. Treatment with the opioid antagonist naloxone can reverse this novelty-induced stress effect.

Another way to study hypoactive desire in male rats is to examine their sexual responsiveness following multiple ejaculations, a phenomenon known as “sexual exhaustion”. Male rats are able to ejaculate several times before becoming unresponsive. During this period of sexual activity, there is a progressive increase in the post-ejaculatory refractory period consonant, with a decrease in the number of intromissions before each ejaculation and a lengthening of the interintromission interval (a state that suggests a progressive loss of erectile function as the number of ejaculations increases). After males become sexually exhausted, they remain unresponsive to female solicitations for up to 72 hrs. Rodriguez-Manzo and colleagues have examined the ability of several classes of drug to increase the responsiveness of these males, including the opioid antagonist naloxone, 8-OH-DPAT, and the \( \alpha_2 \) presynaptic autoreceptor antagonist yohimbine. Only yohimbine increased the proportion of males that mounted, intromitted, and displayed an ejaculatory-like behavioral pattern (but without seminal emission), suggesting that a decline in adrenergic activity is an important component of inhibited sexual desire in males.

La Peyronie’s disease
An experimental model of transforming growth factor beta 1 (TGF-\( \beta_1 \))-induced La Peyronie’s like condition in the rat has been proposed by Tom Lue’s group. The fibrosis is induced by a single injection of TGF-\( \beta_1 \) in the tunica albuginea of Sprague Dawley rats. Following TGF-\( \beta_1 \) injection, a dramatic influx of inflammatory cells is observed in the tunica albuginea, whereas the normal architecture of the tissue remains preserved. At two weeks, the inflammation
decreases and the tunica albuginea structure is disturbed, which leads to fibrosis development both in the tunica albuginea and the adjacent corpus cavernosum of the penis at six weeks. This fibrosis is considered as a La Peyronie’s-like condition because it exhibits biochemical and structural features that are similar to the human La Peyronie’s disease plaque. Therefore, this animal model appears as a relevant tool to test innovative La Peyronie’s disease pharmacologic strategies.

**Hypogonadism/agonadism**

In male rats, castration or the administration of androgen synthesis inhibitors, like cyproterone acetate, disrupt and ultimately eliminate copulatory behaviors and penile reflexes progressively over time. They also shrink androgen sensitive peripheral tissues (e.g. penis and prostate). Although the degree of disruption depends on the amount of androgen synthesis inhibition that is induced (e.g. moderate following low doses of cyproterone acetate to total disruption following castration), the amount of time it takes to reach an asymptotic level of behavioral or reflexive performance depends on the level of sexual experience male rats have prior to treatment. In each case, subsequent exogenous administration of androgens or estrogens can restore sexual interest and copulatory behavior, with nonaromatizable androgens (such as dihydrotestosterone) restoring peripheral tissues, and aromatizable androgens (e.g. testosterone) restoring behavioural measures. As with hypogonadal men, restoration of copulatory responses in castrated rats requires a threshold dose of aromatizable androgen that can restore plasma levels lower than those found in gonadally intact, functional animals (higher circulating levels are required for additional anabolic effects on muscle). It is striking, however, that appetitive sexual responses are the least affected by castration and can be maintained for months following. This finding echoes observations that treatment of sex offenders with androgen synthesis inhibitors does not reduce certain appetitive patterns of abuse (e.g. fondling), despite the fact that these men do not achieve erection. There are currently no models of age–related hypogonadism, although a decline in the sexual responsiveness of older male rats (>one year) has been reported in a few studies. However, castrated males can be maintained on subthreshold doses of testosterone prior to behavioral tests, or on a threshold dose followed by a progressive lowering of the dose regimen to mimic a more progressive decline, such as might be seen clinically.

**Female Sexual Function**

Gonadally-intact female rats of reproductive age go into sexual “heat” every four to five days immediately after ovulation. This process is initiated by the sequential actions of estrogen and progesterone (and possibly also androgens) in the brain and periphery, so that sexual behaviour shows an “estrous cycle”. Although women (and certain other primate females) can engage in sexual activity throughout their menstrual cycle, there is a peak rise in female-initiated sexual activity around the time of ovulation, suggesting that estrogen–induced neurochemical systems have been conserved throughout mammalian evolution.

Peripheral sexual reflexes (e.g. vaginal blood flow), copulatory behaviour (solicitations, pacing, lordosis), and appetitive conditioned sexual responses (e.g. conditioned arousal) have been examined in female rats (Fig. 1.4), rabbits, and primates such as macaques. The physiologic mechanisms that regulate vaginal blood flow are extremely similar between species, and more is known about the hormonal and neural regulation of the reflexive posture lordosis (the dorsiflexion of the back that denotes sexual “receptivity” in many species) than any other sexual reflex. Recent work has also begun to elucidate the hormonal and neural control of complex behaviors used by females to regulate the initiation and rate of copulation, offering a real potential to utilize female rats as models for human sexual function.

It is important to emphasize that compared to human males, in whom ability to achieve and maintain erections sufficient for sexual activity is also good for self-esteem related to competent sexual performance, in women there is no clear relationship between physiologic performance and sexual desire. The subjective feeling of sexual arousal
results more from cognitive processing of stimulus, meaning and content than from peripheral vasocongestive feedback. Indeed, there are well-identified discrepancies between physiologic and subjective measures of sexual arousal in women, and often no correlation between them (e.g. following treatment with PDE-5 inhibitors). It is not yet known how vaginal responses are integrated with behavioral responses. It remains questionable that increased vaginal blood flow could be perceived by females and participates in the stimulation of behavioral measures of sexual arousal. Accordingly, a more integrative approach is necessary to investigate female sexuality experimentally.

**Genital sexual arousal**

Upon sexual arousal, the blood supply to the vagina is rapidly increased and at the same time the venous drainage is reduced, thus creating vasocongestion and engorgement with blood. Such an increase in blood flow combined with an enhanced permeability of the capillary tufts induces a neurogenic transudate, which results in vaginal lubrication. From arousal to orgasm, there is also an increase of vaginal luminal pressure.

Reliable and standardized models to study the physiology/pharmacology of female vaginal sexual arousal have been described in dogs, rabbits and rats. In these models, vaginal sexual arousal along with clitoral tumescence is induced by peripheral electrical neural stimulation, while direct measurements of various vaginal physiologic variables are performed. These models have been useful to initiate the exploration of the peripheral physiology of female genital sexual response as well as the consequences of various experimental pathophysologic conditions (e.g. atherosclerosis or hormonal deprivation).

**Female orgasm, the urethra–genital reflex, and the consequences of paced copulation**

It is not known whether female rats experience anything like orgasm during sex. However, like males, they display a genital reflex, called the “urethro-genital reflex” that is reminiscent of the

---

**Fig. 1.4** Sexual behaviors displayed by male and female rats. (a) Line drawing of proceptive behaviors (presenting, ear wiggling and approach) and receptive behavior (lordosis) displayed by the female that evokes interest, investigation, chasing, and copulatory responses (mounts, intromissions, and ejaculation) in the male. (b) Female and male sexual behavior in a bilevel testing chamber. Top left: Female (right) makes a headwise orientation toward the male (left) characteristic of a solicitation. Top right: Female hops over the male to reveal her anogenital region, allowing the male to sniff and become aroused. Bottom left: Female runs away, forcing the male to chase her. Bottom right: Female holds a lordosis posture that allows the male to mount and gain vaginal penetration.
orgasmic response in women. This reflex can be induced and studied in isolation by applying a mechanical stimulation to the urethra of anesthetized, spinalized female rats. The urethro-genital reflex includes rhythmic contractions of the vagina, uterus, and the anal sphincter, as well as the striated pelvic musculature. Stimulation of the urethra may mimic stimulation of the anterior wall of the vagina, which is the area with the highest “erotic” sensitivity. Indeed, the anterior wall of the vagina has a denser innervation than the posterior wall, and the distal area has more nerve fibers than the proximal.

During copulation, female rats typically control the initiation and rate of contact with males. In the same way that ejaculation is critical for conditioned sexual responses in males, the ability of female rats to pace their copulatory contact is critical for the induction of conditioned place or partner preferences. As in males, these consequences of sexual stimulation are blocked by administration of the opioid antagonist naloxone, suggesting that opioid activation is a critical feature of the sexual reward experienced during paced copulation. In addition, pacing imposes a delay between successive vaginal intromissions by the male. This delay distributes the vaginocervical stimulation that females receive over time, an effect that enhances reproductive capability and fertility in the female. Vaginocervical stimulation during orgasm in women may have a similar enhancing effect on reproductive capability.

**Copulatory behavior and measures of female sexual motivation or “desire”**

As in males, female sexual behavior can be divided into sequential appetitive and consummatory components (Fig. 1.1). In the female rat, these aspects of sexual behavior are also referred to as proceptive and receptive components, two different aspects of sexual behavior displayed by estrous females in the presence of sexually-active males. To solicit attention and approach of the male, the female displays a variety of active proceptive behavioral patterns, including solicitations, hops and darts, and earwiggles. As mentioned above, receptivity has been used to describe the behavioral postures assumed by females to allow mounting by a male, with the lordosis reflex being the best known and most studied response. Unfortunately, there is no counterpart for lordosis in women. In contrast, psychologic arousal or desire in women is likely to be very close to proceptivity. For this reason, the study of proceptive behaviors is also relevant to any preclinical investigation of potential of compounds for the treatment of female sexual disorders or dysfunctions (FSD). Indeed, recently it has been reported that the melanocortin agonist, PT-141, increased rates of sexual solicitation and hops and darts in female rats selectively. This same drug increased female-initiated sexual activity in early Phase IIa clinical trials. These two observations were critically important to begin to establish solicitation as a valid model of female sexual desire.

**Models of female sexual dysfunctions**

**Hypogonadism/agonadism and hypoactive sexual desire**

Although there are currently no established models of female sexual dysfunction in rats, there are several reasons to believe that such models could exist. The most obvious would be the consequences of hypogonadism induced by ovariectomy followed by maintenance with different doses of estrogen alone, or estrogen and progesterone. Ovariectomized rats treated with estrogen and progesterone display a complete pattern of proceptive and receptive behaviors, whereas those treated with estrogen alone display no proceptive behaviors, low levels of lordosis, and high rates of rejection responses. Certain pharmacologic treatments (e.g. apomorphine, oxytocin, PT-141), are able to increase proceptive behaviors and reduce rejection responses in ovariectomized females treated or maintained on estrogen alone. This pattern of data suggests that such drugs may be useful in the treatment of hypoactive sexual desire disorder, with or without accompanying hypogonadism.

A similar loss of interest in sexual activity occurs during the phenomenon of “estrous termination”. Estrous termination occurs progressively after the female receives a requisite number of intromissions and ejaculations during sex. It can also be induced by
manual vaginocervical stimulation using a lubricated glass rod that approximates the size of a male rat penis, and that is inserted to mimic the stimulation received during intromission. The first behavioral set to disappear is solicitation, and this precedes a rise in rejection responses. Females given vaginocervical stimulation also show a faster loss of lordosis over the next 12 hrs, compared to females given sham stimulation. It would appear, then, that sexual stimulation in females, as in males, activates inhibitory systems that bring about refractoriness. It is not yet known how different pharmacologic treatments might delay the onset of estrous termination, and whether such effects might prove useful in treatment of low desire.

It will be important to consider how androgen administration may alter sexual behavior in ovariectomized females, with or without estrogen treatment. Currently, combined androgen—estrogen treatment is used in postmenopausal women to restore sexual desire and arousal. It should be straightforward to examine this combined hormone therapy in ovariectomized rats and categorize the effects, along with studying potential mechanisms (e.g. steroid receptor activation and interaction, role of peripheral sex hormone binding globulins).

It will also be critical to study the sexual behavior of older female rats. Female rats have a homologue of “menopause” in which ovarian function is disrupted then declines to a continuous state of vaginal diestrus (accompanied by a progressive atrophy of the vagina and clitoris). It is not known how these females would respond to sexual advances by a male, or to manually applied vaginocervical stimulation.

**Hypoactive sexual arousal**

Treatment of rats with the peripheral nitric oxide inhibitor nitro-L-arginine-methyl ester (L-NAME) reduces vaginal blood flow. It is not yet known if this treatment alters female sexual behavior.

**Hypoactive sexual desire/conditioned inhibition**

Female rats treated with the opioid antagonist naloxone during paced copulatory trials do not form conditioned place or partner preferences. Such preferences are typically examined on a final test, when the drug is not administered (thus revealing the necessity of opioid reward during paced copulation). However, during this final test without the drug, females previously treated with naloxone display a conditioned disruption of solicitation and lordosis relative to saline-treated females, despite being primed fully with estrogen and progesterone. As a result, males engage in fewer intromissions and achieve fewer ejaculations with those females. A pattern of diminished sexual solicitation and receptivity, which leads to more restricted sexual contact with males, is analogous in many ways to the pattern of sexual behavior displayed by women with hypoactive sexual desire disorder. It is not yet known if this pattern of disrupted appetitive sexual behavior can be restored by pharmacologic or experiential treatments that increase desire in women.

**General Conclusion**

Real progress has been made in understanding the neuroanatomical and neurochemical mechanisms of erection, ejaculation, solicitation, and other sexual responses, and in the design of rational pharmacologic treatments for certain sexual dysfunctions. We have begun to examine the mechanisms that underlie desire, and how sexual stimulation and reward impact on endpoints like sexual arousal, desire, attractiveness, and even mate choice. Progress in these areas could not have been made without the help of animal models. The evolution of sexual physiology and behaviour have been highly conserved, therefore animal models of human sexual response can be used successfully as preclinical tools so long as the functional endpoints are homologous or analogous, and carry predictive validity. When setting up testing paradigms to study preclinical models of human sexual function in laboratory animals, it is essential to ask the animals human questions that they can answer in their own species-specific manner. Although standardization of models (and of paradigms between laboratories) is critical, this should never limit the inspired intuition of researchers or clinicians to envision new models or paradigms.