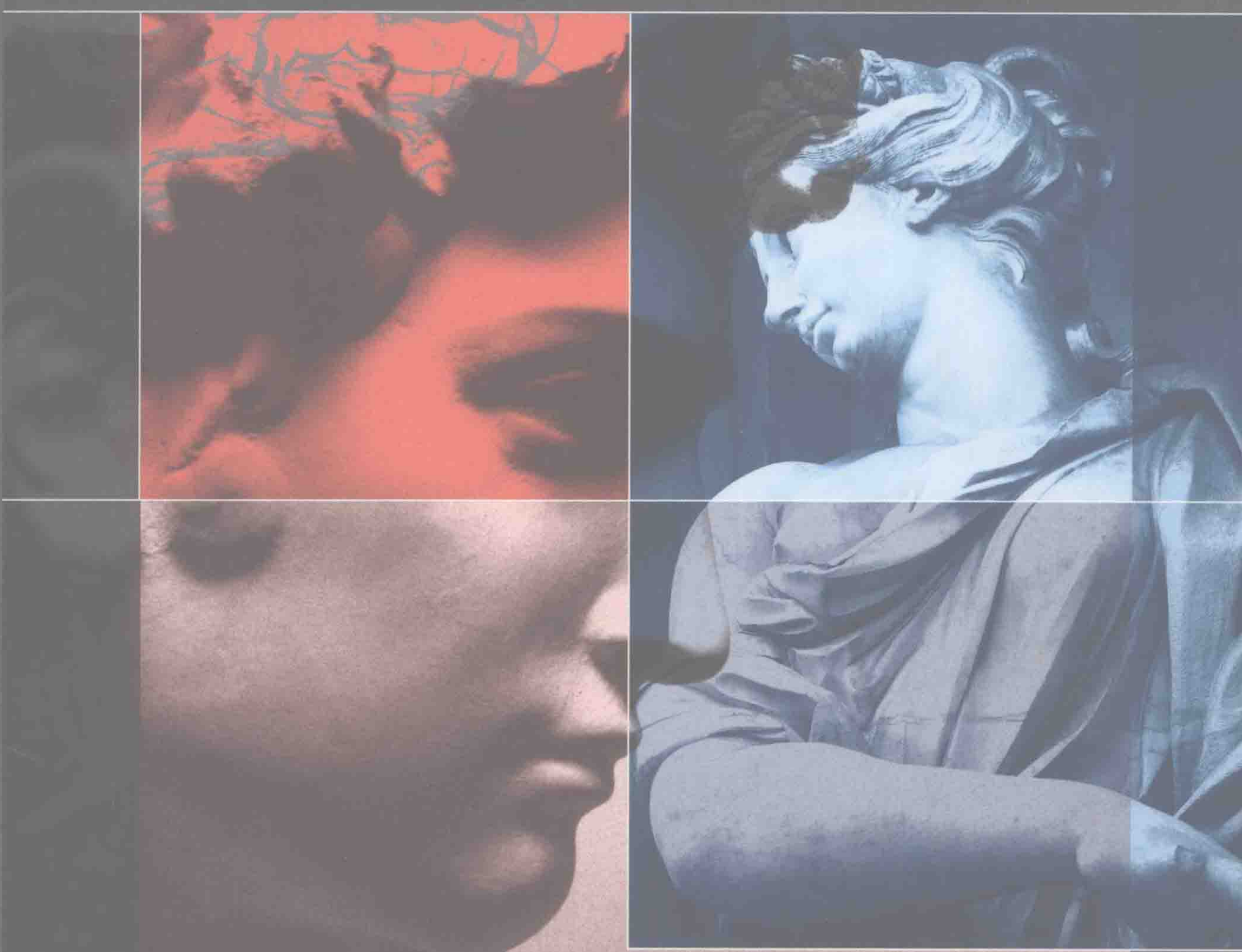
edited by

Gillian Einstein

Sex and the Brain



Sex and the Brain

edited by Gillian Einstein

The MIT Press
Cambridge, Massachusetts
London, England

MIT Press books may be purchased at special quantity discounts for business or sales promotional use. For information, please e-mail special_sales@mitpress.mit.edu or write to Special Sales Department, The MIT Press, 55 Hayward Street, Cambridge, MA 02142.

For information about special quantity discounts, please email special_sales@mitpress.mit.edu

This book was set in Times New Roman and Syntax on 3B2 by Asco Typesetters, Hong Kong.
Printed and bound in the United States of America.

Library of Congress Cataloging-in-Publication Data

Sex and the brain : a reader / edited by Gillian Einstein.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-262-05087-6 (hardcover : alk. paper) 1. Sex differences. 2. Sex (Biology) 3. Sexual dimorphism (Animals)
I. Einstein, Gillian.
[DNLM: 1. Brain—physiology—Collected Works. 2. Sex Characteristics—Collected Works. 3. Behavior, Animal—physiology—Collected Works. 4. Brain—anatomy & histology—Collected Works. 5. Gonadal Steroid Hormones—Collected Works. 6. Sexual Behavior—physiology—Collected Works. WL 300 S518 2007]
QP81.5.S45 2007
612.6—dc22 2007000653

10 9 8 7 6 5 4 3 2 1

Sex and the Brain

Sex and the Brain is dedicated to three generations:

To my grandmother, Juliet Lowell, who loved to make people laugh about lust;

To my mother, Margot Lowell Einstein, who embodies the passion that undergirds deeds worth doing; and

To my son, Alexander Einstein Gopen, whose existence has provided me with some of life's most satisfying pleasures.

Acknowledgments

This project has been aided by a few key people whose contributions, whether they are aware of it or not, for me stand out as crystalline against the haze of everyday encounters.

The list starts with Jean O'Barr (then, director of women's studies at Duke University) who provided the moment of inspiration for this intellectual journey by appointing me to the Women's Studies Advisory Committee. She was aided and abetted by Fred Nijhout (then, chair of zoology) who made it possible to develop and teach a course called, "Sex and the Brain". Kathy Rudy (also of women's studies) made the foreground/background shimmer of sex/gender an intellectual space I wanted to visit. Barbara Herrnstein Smith planted the seed for the organization of this reader by being the first person to tell me about Frank Beach's work. As well, her Center for Interdisciplinary Studies in Science and Cultural Theory helped sponsor Simon LeVay's visit to Duke in the first year of the course.

A generation of students have traveled with me on the journey to learn this material, adding enormously to the adventure—from the first class at Duke in 1995, which reported, "Dr. Einstein was such a good teacher that she made us feel that she was learning the material right along with us!"—to the most recent, at the University of Toronto, who are so much more savvy about the range of human sexual behavior—it has been fabulous to explore this literature with all of you.

Three undergraduates, in particular, deserve special thanks for their labors: Robyn Feder put together the very first coursepack at Duke, Magdelena Godowska put together what I pray will be the last coursepack at the University of Toronto, and Mihir Patel has been stalwart in his help to see the book project to its completion.

Thanks especially to Barbara Murphy, neuroscience editor at the MIT Press, whose enthusiasm for the project has made this reader possible, and her assistant Meagan Stacey, also indefatigable through all the hard work.

My valued colleagues Dominique Toran-Allerand, Anne Fausto-Sterling, Bruce McEwen, and Simon LeVay inspired me with their work and then inspired my students by coming to talk with them as young colleagues. Gratitude again to Anne Fausto-Sterling, Simon LeVay, and Nancy Forger, who read and critiqued my early efforts to synthesize this field in a chapter called, "Sex, Sexuality, and the Brain," that I wrote for the first three editions of the textbook *Neuroscience* (Purves D, Augustine GJ, Fitzpatrick D, Hall WC, LaMantia A-S, McNamara JO, and Williams SM, Andrew Sinauer and Associates, Sunderland, MA, pp. 711–732). Thanks, also, to the anonymous reviewers of the reader's prospectus, who made much valued suggestions that improved the list of papers included.

From among many colleagues and friends, Anthony-Samuel LaMantia stands out as supporting me personally and nourishing me intellectually while this course was being conceived and during difficult times—as does Lucy Suchman, another friend and colleague, who has generously given her time and insight to reading the section introductions in the guise of an "uninitiated" reader.

Finally, my list ends and starts again with Brian Cantwell Smith, whose ineffable sensibility, pluralities, and love enrich my life and dreams, convictions, and actions.

Preface

Development of the Reader

This compilation of papers was developed in the belief that students should read original science. It was organized in such a way as to give voice to the multiplicity of understandings within the field of hormones and behavior and the study of sex differences of the central nervous system. The small seed planted in the early days of Beach and Young has grown into a giant tree that links body and brain through studies in the fields of behavior, endocrinology, biochemistry and molecular biology of steroid hormones, neurophysiology, neuroanatomy, and neuroendocrinology. It is a wide-branching tree that stands as an example of how science grows and diversifies but all the time is firmly rooted in the soil of human curiosity. If one starts at the roots, travels the trunk, and follows each branch to its full extent, eventually a story that links body and brain, female and male, is revealed.

The chapters in this reader were originally collected for a course that I first taught in 1995, offered jointly through the Departments of Zoology and of Neurobiology at Duke University, "Sex and the Brain: The Science of Gender." It was not a standard hormones and behavior course because, at that time, I did not know about the field of hormones and behavior. I trained in neuroanatomy, not psychology; my expertise is in systems and cellular neuroscience in the areas of vision, aging, memory, and Alzheimer's disease. Embarrassing as it is to admit—I only learned that there was a whole field called hormones and behavior after I put the papers together. So the perspective of the course was from the brain out into behavior.

So, why did I develop the course?

To be honest, putting the course together was a political move. My appointment at Duke was in the Faculty of Medicine but I was also on the advisory board of the Women's Studies Program—their token scientist—and I got it into my head that it would be doing something important for women in the sciences to put together a course whose content was appropriate for cross-listing with zoology and women's studies and that would teach substantive biology. Courses covering the feminist critique of science or the history of women in science were already plentiful. I wanted to devise a course in which, through learning some aspect of the brain, the material itself would naturally lead to questions about sex, gender, and the cultural assumptions underlying the design of the experiments.

Thus, although these readings certainly teach students about estrogens, behavioral paradigms, sexual differentiation, the hypothalamic-pituitary axis and the regions of the brain that mediate aspects of sex, they also stretch students to judge experimental design, assumptions underlying experiments, the data, and the interpretation of the data. That is what I have tried to convey in the introductions to parts I through V.

In the more than ten years of teaching these papers it has been my experience that right from the beginning students are engaged by the material. While at first curious as to why they are being assigned papers more than five years old in a science course, they shortly understand how the papers build on each other conceptually and how, by reading the foundational papers, they are seeing core assumptions of a field being worked out. This is exciting to them. They are being let in on what has always been hidden from them: the human working out of what eventually gets presented in textbooks as fact. By reading these papers, they learn that science, like every other discipline, is knowledge in the making. Would students appreciate reading original and old papers in other fields of biology? Would they get as big a charge out of reading Linus Pauling's papers working out the structure of DNA or Watson and Crick's paper trumping Pauling's model? Possibly. But for teaching an awareness of how science progresses the papers on hormones and behavior have two major advantages over the papers in other fields:

1. The field is beautifully coherent (saying a lot about the collegiality within the field); and
2. The subject matter is sex, a topic that speaks directly to the students' own struggles and engagements on the topic.

Choice of Inclusion

In turning the course into a reader choices had to be made as to how the story should be developed and by which papers. Choosing which papers to include was, indeed, difficult. Being more knowledgeable now than in 1995 it is now apparent to me that there are some splendid classic papers that are not in this compilation. Likewise, this reader contains some very odd papers. As well, there are some papers with data that were ultimately not replicable, while missing are the papers that later did replicate some initially controversial findings. And, of course, the field is growing, so every day papers appear that should be included. Thus, out of all the beautiful work that is in the field, how did I choose these papers?

In putting this reader together, foremost in my mind was telling a story. The story is the tale we tell when we interpret a paper on sex differences in the brains of gay and straight males or differences in language areas of females and males or books on men being from one planet and women being from another. The story I wanted to tell was that of the science purported to back all that up. If a paper contributed to the flow of that story, it made its way in. Didactically it was important to give representation to how different methods can be used to answer the same question. Physiological or behavioral experiments studying the functional significance of an anatomical finding are included. Papers that allow the comparison of the primate case with nonprimate models are also included. Some papers are included to give a nod to a team that was first to publish a report on a topic. Some review articles are included to keep the story moving. On the basis of these criteria, the reader includes papers by Harris, Beach, Goy, Phoenix, Gorski, Toran-Allerand, McEwen, Kimura, Arnold, Swaab, Pfaff, O'Malley, and Meany, along with many of their students. Some surprising works by researchers from other fields also appear: Raisman, Goldman-Rakic, LeVay, and Merzenich. All of this makes a very rich blend of perspectives, approaches, methods, and findings.

In the end, the only reason papers were excluded was because the students do not have time to read any more!

Organization of the Reader

The overarching organization of the papers is not chronological. It starts with the question of what is a dimorphism, what are the behavioral observations, and how is it that the brain is an endocrine organ. It then moves to theories on how dimorphisms are established and how and where estrogens act. After that come the experiments to understand the relation between behavior and the brain, ultimately moving to papers on sexualities and gender identification—aspects of our selves. This compilation of papers poses those questions by having five major sections that build from background concepts to the early experiments establishing the organizational/activational hypothesis, from experimental models to humans, and from molecules to mind. Papers that address traits constitutive of personhood—cognition, gay/straight, and transsexual differences—do not appear until the last section because most would agree these papers are the most speculative and sensational.[1]

Each of the five sections has a number of subsections comprising papers relating to each other within the subtheme. Often papers in the subsections will juxtapose rodent models, primates, and, where possible, human experiments to highlight differences between rodents and humans. The five thematic sections are background; central nervous system dimorphisms; mechanisms for creating dimorphisms; dimorphisms and cognition; and dimorphisms and identity. Included in this collection is also an epilogue, which is by Beach, himself, describing the history of the field.

Each section has an introduction discussing key concepts covered in that section, explaining the reasons for the particular grouping of papers, how the papers relate to each other, what each paper explores, and some questions students might ask while they are reading.

Use of the Reader

My own use of this collection was as follows. Each week students would read a set of papers addressing one overarching topic within the development of the field or the underlying biology. These readings were juxtaposed with readings in popular press books on sex differences. They were chosen to create a point/counterpoint in the reductionist/pluralist debate. *Myths of Gender* or *Sexing the Body* (Fausto-Sterling) were assigned with the *Sexual Brain* (LeVay). Each week, students wrote two- to three-page commentaries on the readings to each other and responded to those commentaries also, to each other. After the first few weeks, which were spent making sure everyone had the same background, the students took over presenting the papers. Some years I gave a midterm quiz and other years, not. The final project was always a paper of no more than twenty pages in length dealing with a critique of the literature on sex differences in mental states, neuropsychiatric disorders, steroid biochemistry, or the molecular actions of estrogens.

Throughout the course, students were encouraged to think about (i) how the field developed; (ii) what the first observations were; (iii) what the diversity of opinions on sex differences is—whether these differences are dimorphic; (iv) what the evidence for and against the organizational and activational hypothesis is; (v) what the functional relevance of anatomical differences is; (vi) why the situation is more complicated in humans than in rodents; (vii) what the nature of the field is such that so many disciplines are represented? Reading the original papers allows questions such as these to flow. Always interesting, by opening up these questions students learn quite a lot of biology; by the end they know about the biochemistry of steroid hormones, molecular and cellular actions of estrogens, physiology of single cells, anatomy of the sexual brain, and how the endocrine system mediates many behaviors.

If a class is mixed with biology, philosophy and/or women's studies students there will certainly be the need to fill in gaps in students' understanding and provide current understandings of the science covered in the papers. This can be accomplished in the first three weeks of class, after which students begin to see the same principles repeated because of conceptual overlap between papers. The reader can be used as a primary text, augmented by popular press books like Simon LeVay's *The Sexual Brain* and/or Anne Fausto-Sterling's *Sexing the Body*. Alternatively, additional texts could be neuroscience texts or one of the major texts in hormones and behavior. First-person accounts on being transgendered, the David Reimer case, or searching for the "gay gene" open the door to wide-ranging discussion. For a women's studies course, assigning these papers with any book on gender (e.g., Judith Butler's *Gender Trouble* or Anne Fausto-Sterling's *Myths of Gender*) or books questioning the science of difference (e.g., *The Mismeasure of Man; The Mismeasure of Woman; The Mismeasure of Desire*) could also be useful didactically.

Whether or not this collection is matched with supplemental texts, it can be used to teach students that a scientific paper can be analyzed from a number of often independent perspectives: the design of the experiment, the data, and the interpretation of the data. With adequate discussion, exposure to these papers will give students an appreciation of this beautiful field and enable them to judge science independently—especially the current science in this area that is appearing on the front pages of the newspapers everyday either because public figures use it to support their prejudices or because, as humans, we are just plain interested. It is important to know about the development of the field to understand just how far the notion of a dimorphism can be taken. Whether or not individual students go on to a career in science, fostering critical thinking and confidence in intellectual judgment is the essence of our job as educators. These papers and this field support that goal.

Note

1. Since these are the papers students take the course to read, another possibility for organization is that the course could start there and then ask, "How did we get to this intellectual point?"

Contents

I BACKGROUND/INTRODUCTION

There are many assumptions embedded in any established scientific field that make a paper picked up and read at one point in time difficult to scrutinize and read critically. Without knowing what ideas have come before and how deeply they are lodged in the formulation of an experiment, one can be judging the depth of a work based on the tip of the iceberg. The purpose of this section is to take you to the early days of the field in which investigators were trying to put a quantifiable spin on the intuition that females and males are different; but how?—and give you the understanding necessary to unpack the assumptions from which papers in subsequent sections build. Papers in Part I take you to the earliest or the most elegant experiments that contributed to these understandings.

A paper purporting to show different activation patterns in the brains of females and males with a similar activation in the pattern of gay males and females is secure in this paradigm based on the following assumptions:

1. Anatomical differences represent functional differences;
2. Hormones effect behavior;
3. The brain and other endocrine organs are connected via the hypothalamus—an organ that is part nervous tissue and part gland;
4. Steroid hormones shape the development of the brain in a period shortly before and just after birth, called the "critical period";
5. Chromosomal sex, phenotypic sex and gender identification operate via separate mechanisms;
6. Hormones act on behavior via gene transcription;
7. Males have two times of life during which there are high circulating levels of androgens—the critical period and adolescence;
8. In order to make a "male" brain, circuits need to be both organized and "defeminized."

The selections in this section will provide a familiarity with these concepts and are grouped together in order to

1. Introduce the concept of sexual dimorphism and how it was wrestled with and formulated over a number of years, starting with Beach;
2. Establish an understanding of the intimate relationship between the hypothalamus and the pituitary through the elegant experiments of Geoffrey Harris;
3. Explain key mechanisms underlying sexual differentiation;
4. Demonstrate how chromosomal sex, phenotype, and gender identification do not have to align; and
5. Formulate an understanding of a key hypothesis in sexual differentiation: that there are organizational and activational events triggered by hormone action.

The Concept of Sexual Dimorphisms

Before embarking on the journey of reading papers purporting to show sex differences, let's lay out what is meant when we use the expression. "Dimorphism" means "of two forms," an interesting formulation of sexual display in all its variations. It means that there are two forms of behavior, two forms of what things look like, two mechanisms underlying those forms: female and male. XX and XY. Lordosis and mounting. Estrogens and Androgens. This is a key concept in this field and underlies the interpretation of the science—that there are, indeed, two distinct forms. It is kind of a digital notion of all the components of sex. As is apparent in the Goy and McEwen reviews and in the original papers from the father of the field, Frank Beach, even when the early experiments were written up, things were not so on/off as the term would suggest.

Goy and McEwen's book is important not only because it reviews the early literature in an extremely lucid and thorough manner but also serves as a pivot on which the field began to turn—a kind of "let's look backward before we go forward" or sum up before changing paths. Experiments related in their book are about behavioral differences, how the brain might mediate those differences, and how steroid hormones shape the brain during early development as well as at other key times of life, such as puberty. After the publication of their review, the field began turning more toward considering complex behavioral differences such as choice of sexual partner, the molecular biology of steroid hormone signaling, and differences in whole brain patterns of activation as revealed by in vivo imaging. In these later studies, however, what seemed rather plastic and malleable in earlier studies becomes hardened into two forms.

In their very complete review of experiments, behaviors, and species differences, Goy and McEwen demonstrate clearly that there are many ways to go about making sex. What seems a female behavior in some species is a male behavior in others. What is seen to depend on chromosomal components can be regulated by steroid hormones—and regulated in a fashion that places some animals in between what are commonly believed to be two distinct sexes. In their very complete review of the early literature across species, Goy and McEwen are steadfast in comparing rats to primates as well as rats to other rodents. By engaging in the comparisons across species, they make the very strong point that rats are not monkeys; monkeys are not humans.

Beach's papers take us back to the original findings of differences in behaviors and speculation that these behavioral differences might have a basis in the brain. This seems like a concept that needs no explaining to the contemporary reader but in Beach's day, this was a leap: there had been sparse, if any, direct correlation between sexual behaviors and brain structures until, in 1937, when Beach published "The Neural Basis of Innate Behavior. I. Effects of Cortical Lesions upon the Maternal Behavior Pattern in the Rat." In 1948, he solidified his invention of the field of behavioral endocrinology by the publication of his now classic book *Hormones and Behavior*, the title by which the field is now known. Just as Goy and McEwen's review leans on the idea that there is more variation and malleability in primates as opposed to the more stereotypical behavior or rodents, Beach's work is surprising in the individuality he observes in rodents. He makes abundantly clear a perception that has been lost in the literature—that just like primate behavior, rodent behavior depends on environment and circumstances. Beach observes and reports female rats entering into the stereotypical male sexual behavior, mounting. He also describes males enacting the stereotypical female behavior, lordosis. He sees these variations not as deviant but as behaviors on a continuum for both sexes. Beach's work astonishes in its openness to behavioral variations and reminds us that the best scientists are observers who are ready to see things they do not predict.

Read these chapters for their description of the definition of "sexual dimorphism," the explanation of the organizational and activational hypotheses, the necessity for both masculinization and defeminization, and their centrality to the idea of sexual dimorphisms, the "sex-typical" behaviors that are used as assays for brain differences, and the design of experiments to test the stability of the notion of two forms.

The Hypothalamic-Pituitary Axis

At the same time that Beach was working, Geoffrey Harris discovered that the pituitary is under the control of the hypothalamus. In a series of elegant and groundbreaking experiments, he documented the intimate connection via the blood supply of the anterior pituitary and the hypothalamus. He showed that nerve fibers from the hypothalamus released humoral substances into the capillaries of the primary plexus of the median eminence which connected to the portal vessels ultimately to release these substances in the anterior pituitary.

This work established the field of neuroendocrinology and cemented the connection between the brain and the reproductive system. From here it was a small conceptual leap to look for clusters of neurons in the brain that were sensitive to the influences of hormones and, which in turn, would influence the release of more hormones to regulate other endocrine organs via the pituitary. This work identified the brain as a member of the endocrine system as well as the nervous system.

The first selection in this section is a synopsis of Harris's establishment of and contributions to the field of neuroendocrinology by an anatomist who went on to do elegant experiments himself, using some of Harris' model, Geoffrey Raisman (see part II for Raisman's contribution). The other selections in this section are by Harris, himself, presenting a number of experiments that detail the connection of the hypothalamus and the anterior pituitary.

Read these chapters for the elegance of an experimental design that makes use of physiology, anatomy, and developmental biology to tell an unfolding story. Harris is a physiologist in the broadest sense of the discipline, taking into account whole body systems, using their function as the assay or test of his hypothesis. Think about the fact that if there is no circulating testosterone, males can develop a pattern of cyclic hormonal release. Note that there is no ovulation if the brain and pituitary are disconnected. This finding sets the stage for the understanding that there is a reverberating circuit encompassing the brain, pituitary, and reproductive system.

Sexual Differentiation

The next step in the history of this story was to ask: if female and male sexual behaviors differ, and behavior is mediated by the brain via the endocrine system, "how does it get that way?" How does the brain differentiate into one of two sexes? One hypothesis is that just as the body has a phenotype, so does the brain and as internal tubing, gonads, and endocrine organs move in a male or a female direction, so does the brain. Perhaps hormones, circulating early in embryonic development, move the fetal nervous system toward a female or a male phenotype. The selections in this section outline and build on that hypothesis.

The review article by MacLusky and Naftolin provides the insight of two longtime researchers in neuroendocrinology. The paper not only outlines what was known about sexual differentiation of the nervous system circa 1981 but presents key concepts such as "organizational and activational hypotheses," time frames for different aspects of sexual differentiation, steroid hormone structure and action, and the "estrogen protection" hypothesis. It's an elegant story and one that's worth reading about in its entirety. This is the story that underlies all future studies of sex differences.

The article by Sinclair and colleagues lays out the molecular biology of the testosterone switch and the discovery of SRY as the region on the short arm of the Y chromosome that turns on the differentiation of the testes and hence, the synthesis of testosterone. When there is no SRY, there are no testes and this most often leads to a phenotypic female. Haqq and colleagues take this discovery one step further to demonstrate that the expression of SRY leads to the activation of Mullerian inhibiting substance, or MIS, whose secretion is necessary for the regression of the Mullerian ducts and the development of the Wolffian ducts, or the male internal tubing.

Read these selections for their development of the steps involved in sexual differentiation. Note that the focus is on what happens to make a male phenotype with the female phenotype depicted as a passive outcome. It is interesting to note that, at the time this reader goes to press, there is still no active story for the development of the female phenotype. The female phenotype is conceptualized as a default pathway—what happens in the absence of testosterone. There is also an emphasis on two forms only emerging from the presence or absence of SRY, which is described as a developmental switch. Note that SRY not only switches on the development of the testes but the regression of the Mullerian ducts; it not only makes the male but also destroys the female. Finally, it is interesting to compare an approach that is anatomical and biochemical to the later, molecular biological, approach. Is one more informative that the other? Does one leave room for variation while the other is conceptualized as either on or off? These are two very different approaches and the genetic switch gains primacy.

The Alignment of Chromosomes, Phenotype and Gender

The notion of sexual dimorphisms requires that one believe that mammals develop into only two recognizable phenotypes: female or male. To do this, however, genetics, hormone action, and rearing all must align. If any of the switches on the pathway are inoperative or turn on at an earlier or later stage, or to a greater or lesser extent, the body will not represent the types in the ways in which we expect. Because much of making two sexes is a biological process, things do not always go according to plan. In fact, the words of Hamlet to Horatio are most appropriate here:

> There are more things in heaven and earth, Horatio, Than are dreamt of in your philosophy. (*Hamlet*, I, v, 166–167)

Some of the complications in the pathways for female and male begin by having an unusual compliment of chromosomes—if, for instance, the SRY portion of the Y chromosome ends up on an X chromosome, nature will have created an XX male. Others may result from defective or unexpressed genes: if after switching on SRY in an XY individual, the gene coding for the androgen receptor is absent or defective, nature will yield up an XY individual with a strikingly female phenotype (androgen-insensitivity syndrome). If all of these go according to plan but the gene for the enzyme that converts testosterone into dihydrotestosterone, 5-alpha-reductase, fails to be expressed, an XY individual will resemble an XX person until puberty, at which time, high circulating levels of androgens change the phenotype (Guevodoches). In addition, XX individuals can be born with a phenotype of their reproductive organs that is partially between female and male due to a condition of the adrenals that leads to very high production of androgens (congenital adrenal hyperplasia).

The selections in this section bother the categories of female and male by providing biological evidence that there are more than two hard and fast categories. They present cases in which the complicated path of making sex—from SRY to autosomes coding for hormone receptors to relation of hormones expressed to how people are treated—is illuminated. After reading these articles, you may question your own need to believe that humans come in only two types.

Page and colleagues report on the existence of XX males due to the exchange of terminal portions of X- and Y-chromosomal short arms. Saavedra-Castillo and colleagues suggest that phenotypic sex may be due to the involvement of sex-determining genes beyond SRY. Ahmed and colleagues describe cases of XY phenotypic females due to the absence of androgen