HORMONES, SEX, and SOCIETY

The Science of Physicology

HELMUTH NYBORG

Foreword by Bruce S. McEwen

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Foreword

The many attempts to explain human behavior have resulted in systems that rely on the concepts we use to describe our experiences and thought processes, and so these attempts fail to make any connection to the organ in which these processes are occurring, namely, the brain. A classic example is the work of Sigmund Freud, a neurologist who turned away in frustration from the limited prospects of nineteenth-century neuroanatomy as an explanatory tool for human behavior and psychopathology. Instead, Freud created a system of psychoanalysis that paved the way for systematic and humane treatment of mental disorders. At the same time, his system failed to provide a basis for eventually reconnecting itself to the living brain.

Neuroscience and biological and biomedical science have advanced enormously beyond the limited prospects of nineteenth-century neuroanatomy. As a result, we now know that chemical neurotransmitters and circulating hormones act to alter electrical brain activity and structure. Genes of the hereditary material are continually being called upon to change their expression by the actions of these chemical messengers, with the result that our heredity is continually contributing to our behavior. At the same time, heredity is no longer recognized as the omnipotent force it was in the nature–nurture debate of the last century. Hereditary diseases like familial diabetes and Alzheimer's disease have only a 50 percent concordance in identical twins, indicating the powerful role environmental factors play in their expression.

Environmental factors such as light and dark, heat and cold, the season of the year, and the experiences we have are all able to regulate the secretion of hormones of the gonads, adrenals, and thyroid gland, which have direct impact on gene expression throughout the developing and adult brain. The brain responds to these hormones by altering its circuitry and chemistry, and the brain is shaped and maintained by the interactions with circulating

hormones and its own neurotransmitters and neuropeptides. The developmental history of the brain includes its exposure to sex, thyroid, and adrenal hormones, and the developmental actions of these hormones determine how the adult brain responds to the environment, including how rapidly and in what way it ages. Even the processes of learning and memory now appear to be analyzable in terms of chemical and structural changes within the brain brought about by electrical activity and chemical messengers.

Thus, there is much to be said for renewed attempts at this time to bring biology into the analysis of complex behavior. Professor Nyborg's book is a first step in this direction by an experienced psychologist who has devoted his career to understanding how individual differences in complex behaviors may be shaped, at least in part, by circulating hormones. Professor Nyborg spent twelve months in the Laboratory of Neuroendocrinology at Rockefeller University in New York to learn about the biochemical and molecular basis of hormone actions on the central nervous system. His interaction in New York with neuroscientists keenly interested in these most difficult of questions of how our intelligence, personality, and behavior in general are shaped by the interactions between our environment and our genes, combined with the rapid advances in neuroscience during the past twenty years, demonstrate the new possibilities for analyzing brain mechanisms and show that the interdisciplinary nature of neuroscience research is creating a new breed of scientists able to work in multiple subdisciplines. This book is intended to inform psychologists as to some of the new possibilities for understanding molecular brain mechanisms subserving behavior.

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Preface

This book is about a search for simplicity and unity in a world that is often said to be too complex and fragmented ever to be fully understood. Common knowledge will have it that minerals, plants, animals, and humans are completely different in most respects and that humans stand above everything by their ability to think and their self-consciousness. Gradually, I recognized that there may be something fundamentally wrong with this rigid separation; that there may be more unity between minerals, plants, animals, humans, and the rest of the universe than a rigid Linnaean taxonomy would permit. Perhaps, behind most or all manifestations of form and function in nature there is a kind of basic simplicity.

To deal rationally with this idea, I began to study classical languages. It was my hope that by being able to read the old Greek and Roman philosophers in their own language, I could examine the basis of these central problems. Alas! The more I studied, the more obvious it became that the disputes among monists, materialists, and dualists about body–mind, nature–nurture, and human nature problems did not arise out of differences in the interpretation of data, but out of differences in opinion. There simply were too few controlled observations to quarrel about, and these otherwise eminent Greek scholars did not fully recognize the need to gather more. My hope to attack the problems successfully by traditional rational means waned. It was apparent that in those days everybody's interpretation was as good as anybody else's and that the person who came up with the best metaphor won the game of the day.

Discouraged by the meager outcome of the classical philosophical approaches and with a keen eye on the failure of more contemporary methods, I switched to the field of psychology. Psychology rests firmly on controlled experimentation, I thought. However, as the years went by, it became clear to me that mainstream psychology was no more likely than philosophy to

solve the classical problems. Like other rational approaches, most psychological theories are dualistic, vague, nonexperimental, or in the final analysis draw on notions of nonphysical factors. Hypothetical constructs, intervening variables, and mental agents are fabricated with ease and are often not accompanied by an obligation to test their causal status. Examples are motivation, cognitive structures, social norms, cultural stereotypes, memory, and ideas. The list of inferred variables is much longer than the list of attempts to prove their factual existence.

Once again discouraged by the speculative approaches, I devoted the next ten years to the exact study of relations between sex chromosome abnormalities, intelligence, and personality development. These studies generated much data and a few clinical recommendations. They provided very little in terms of a deeper understanding of the nature–nurture problem, however. Somewhat to my surprise I found that even the exact quantitative gene–environment interaction models I used were built on a dualistic ground. External nonphysical social and cultural factors are assumed somehow to mingle mysteriously with internal biological factors. Models for gene–environment interaction often lack a specification of mediating mechanisms and tell little about exactly where in the organism social and cultural impacts meet with the effects of genes. It appeared to me that the ontogenetic nature of sociocultural interaction is essentially unmapped territory. My own research left me with a surplus of correlation coefficients and nice statistical interactions, but did not tell much about the real-life child–environment interaction I was interested in. In addition, most genetic models are built on the assumption that genes work in splendid isolation from environmental factors. In fact, this assumption is at the heart of the notion that discrete genetic and environmental influences add up to 100 percent in the phenotype. But it simply makes no sense any longer. Environmentally caused changes in hormone secretion (during perception of, say, light, or under stress) have been found to influence the organism in such a way that a large number of genes can be permanently or transiently turned on or off during development, with truly profound effects on development or in adulthood.

These observations eventually convinced me that more than anything else we need to seriously consider alternative approaches if we really want to tackle body–mind problems efficiently. In particular, we need to develop more flexible models of nature–nurture interactions. The past five decades of research in brain and molecular sciences seem to provide some of the tools needed for this task. During the late 1960s I became fascinated with the possibility of formulating principles for the ways in which inorganic and organic elements relate to behavior. Having seen the largely untestable outcome of speculative and rational approaches, I further wanted to examine the practical value of this project. I looked for a testing ground that naturally encompasses the classical body–mind and nature–nurture prob-

lem in order to find a workbench suitable for testing the hypothesis that even society and culture are spinoff products of the way basic elements combine and in order to see whether their development follows preformulated principles.

This book documents what came out of this rather grandiose project. It presents what I see as a worthwhile alternative to the rational philosophical approach. As a testing ground, I chose the area of sexual differentiation of body, brain, behavior, society, and culture. In the process I arrived at the conclusion that Darwinistic selection is a special case of general selection of stable, economical systems, whether of organic or nonorganic origin. I also concluded that unity and simplicity can ultimately be found behind even the most complex manifestations, such as the individual and society. In a sense I walked in a circle all the time because I arrived at the point I started from many years before. However, I gained useful experiences on my way. I have made an attempt to systematize these experiences and would like to present them to other researchers so that they don't have to walk in circles as well. The experiences are formulated in the form of a research program I call *physicology*. Physicology substitutes moves of molecules for the psychic, social, cultural, and rational elements in psychological and philosophical explanations and examines the physico-chemical reactions they precipitate. The primary goal of the physicology program is not to study behavior as such. Rather, a physicological analysis concentrates on molecular processes that give rise to behavior, whether of individual, interpersonal, organic, or nonorganic nature.

The book takes as its point of departure a critique of mentalism and the anthropocentrism that it epitomizes. I take some time to show that mentalism lacks empirical documentation and threatens to reduce the psychological and philosophical accounts of behavior, human nature, and society to trivial, inconsequential, untestable speculations. The mentalistic program still has many adherents, who may feel offended by this book and by the goals of the physicological program. During discussion they sometimes present me with what they consider *the* key question: "Do you really believe that the mind is just the brain and that thoughts and desires are only moves of molecules?" What can a physicologist possibly answer to questions about his or her thoughts and beliefs? Molecules have never been observed to think, desire, or believe. All they do is move, combine, and give rise to systemic metabolic processes that sometimes become manifested in overt behavior. A physicologist notes nobody has ever documented moves of mind stuff in the brain, whereas oxygen molecules move in ways that are systematically linked to the type of activities mentalists call thinking. A physicologist acknowledges that the size of ion channels, the shape of the dendritic spines, and the postsynaptic membrane vary with experience, that is, as a function of presynaptic neurotransmitter activity. A physicologist would ask for good hard evidence before accepting the notion that

larger ion channels and more elongated dendritic spines are better able to pass over efficient verbal strategies, symbols, signs, representations, or just nice ideas than are smaller ion channels and less bulbous spines.

Let me admit that I am constantly surprised to find that I rarely impress mind stuff adherents by such demands. Most mentalists simply say that moves of molecules in the brain are of little significance for explaining individual differences in thinking, intelligence, and personality. We humans are much more than our molecules, they say. They react strongly against what they see as an inexcusable reductionism. However, time may have outlived this kind of self-glorifying anthropocentrism. It may have made the day on the Angoras in Athens eons ago, but now it clearly suffers from 2,400 years of lack of empirical support. Obviously, moves of molecules in the brain in no way prove that mind stuff does not exist, but this is not my point. My point is, rather, that thousands of years of search in vain for mind stuff should by now have lowered the expectation of ever finding it and that it is high time to draw the necessary conclusions. I present mine in this book. Those natural scientists who have seen early versions of this book seem to experience little difficulties seeing what I mean. This book is not written for them. Neither is it intended as a textbook in behavioral endocrinology or neuroendocrinology, because the choice of topics from these areas is quite selective. The book is written with the purpose of challenging the paralyzing impact that mentalism, dualism, and cultural anthropological thinking has had on the behavioral sciences and of reevaluating what it takes to explain human nature and society.

Most books depend on the assistance of other people, and this book is no exception. I am grateful to Henrik Albeck, Charlotte Nyborg, Hans Eysench, John Gerlach, Patty Gould, Kermit Hoyenga, Jens Kvorning, Bruce McEwen, Henrik Poulsen, June Reinisch, Gene Sackett, Donald Smith, Bob Spencer, and James Tanner, for discussions or comments on various parts of the manuscript. The considerable foresight of the board members of the Faculty of Psychology made possible the establishment in 1986 of the first International Research Center for PsychoNeuroEndocrinology within the Institute of Psychology, University of Aarhus, Denmark. This center, by providing me with favorable research conditions, helped make this book possible.

The project was facilitated by funding from several agencies. A grant from the Alexander von Humboldt Stiftung in Bonn, Germany, allowed me to work for almost two years (1976–77) at the Max Planck Institute for Behavioral Physicology, Seewisen, together with Hermann Schöne and Horst Mittelstaedt. Grant 515-15022 from the Research Council for the Humanities, Copenhagen, Denmark, enabled me to spend a year in 1979–80 doing research at the Department of Experimental Psychology, Oxford University, in the good company of Jeffrey Gray and numerous other excellent researchers, working hard on the formulation of some of the

principles presented in this book. Grant 23-03 43/84 from a NATO Exchange Program and a Fullbright stipend made it possible for me to work as a visiting professor during 1984–85 at the Institute for Behavior Genetics, Colorado University, Boulder, and at the Kinsey Institute for Research in Sex, Gender, and Reproduction, Indiana University, Bloomington, and to interact with Jim Wilson, June Reinisch, and many other experts. A senior research fellowship in 1987 from the Foundation for Research at the University of Aarhus, Denmark, in combination with grant 12-7466 from the Danish Medical Research Council, Copenhagen, made possible a half-year stay at the Institute for Child Health and Development, University of London, England. Here I had the good luck of sharing a huge office with *the* James Tanner, who was always willing to take time for discussion of developmental matters. Finally, a combined grant M12-8300 and M15-6870 from the Medical Research Council and the Research Council for the Humanities, Copenhagen, Denmark, allowed me to spend a year in 1988–89 as a visiting professor at the Laboratory of Neuroendocrinology, Rockefeller University, New York, and at the Regional Primate Research Center, University of Washington, Seattle. I benefited in particular from the company of Bruce McEwen and Bob Spencer at Rockefeller and Gene Sackett at the Primate Research Center in Seattle. Professor Edward Miller at the University of New Orleans, USA, had an active role in publication of this book. Thanks to all of you!

This book is dedicated to my wife Charlotte, who never fails to demonstrate the fantastic potentialities of molecular diversity.

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Introduction

The study of the sexual differentiation (SD) of body, brain, behavior, and society presents science with a number of interesting problems. On the *intrapersonal* side there is the classical body–mind problem. On the *interpersonal* side we encounter problems with entangling the nature of person–person and person–environment interactions. With respect to the *extrapersonal* dimension, we have many theories but little evidence about the origin of social and cultural norms or how they affect the mind. It is far from obvious what is meant by covariant evolution of body, mind, and society. We have no definite ideas about how to integrate data on body, mind, and society, collected by vastly different methods and interpreted at qualitatively different levels. Many students still try hard to combine soft qualitative psychological, sociological, and cultural anthropological evidence for the mind and society with hard quantitative data on body and brain.

This book has three purposes. The first is to argue that classical mentalistic and superorganismic ideas about human nature and society are counterproductive. Recent empirical research better explains the phenomena in question, and mentalistic ideas are now sustained only because they are based more on reasoning than on experimental evidence. Not restrained by data and control, mentalistic and superorganismic approaches encourage the fabrication of hypothetical variables. With time, these variables are gradually ascribed the status of being causal agents that are then used to explain behavior. Moreover, it is impossible to verify or falsify mentalistic and superorganismic theories. Probably they cannot even be reduced to anything else. It is mainly for these reasons that mentalistic and superorganismic thinking constitute an obstacle to further development of the behavioral sciences.

The second purpose of the book is to show that recent research in the molecular and brain sciences makes it possible to develop alternative

research programs that apply empirical, quantitative, and natural science principles and methods in order to unravel intricate problems like human nature and society.

The third purpose is to present a scientifically satisfying alternative to mentalism called physicology. Physicology refers to the study of physico-chemical processes behind body, brain, behavior, and society. It sees individuals as relatively open physico-chemical systems to be studied at an intrasystemic level. Social interaction is seen as complex but, nevertheless, strictly rule-bound exchanges of physical stimuli between largely similar physico-chemical systems, the manifestations of which can be studied at an intersystemic level. Impacts on intra- and intersystemic processes by the surrounding physical environment can be analyzed at the extrasystemic level. Level here simply means the actual selection of a particular series of molecular processes to be studied and does not refer to qualitative differences or to a higher-lower level differentiation. Physicology differs from physics mainly in its focus on processes in very complex systems. Physicology addresses the same phenomena as traditional behavioral sciences, but it substitutes all psychic, social, cultural, and superorganismic explanations with analyses of the underlying physico-chemical processes. Physicology is not primarily a behavioral science. It is a program for studying processes underlying behavior. Although physicology aligns with behaviorism in opposing mentalism, it differs fundamentally from it by its explicit focus on intrasystemic characteristics.

The book consists of four parts. In Part I, I show where I find that contemporary mentalistic theories of human nature and society fail. The physicological program is presented in Part II as an attempt to provide a coherent and testable alternative to mentalism. Part III presents a physicological analysis of the SD of body, brain, behavior, and society, with a focus on their physico-chemical basis. New experiments to further test predictions of the established principles are provided throughout the presentation. The Epilogue puts aspects of the physicological program into perspective.

Part I

MENTALISTIC APPROACHES

"But he hasn't got anything on!" said a little child. "Goodness gracious, do you hear what the little innocent says?" cried the father; and the child's remark was whispered from one to the other.

"He hasn't got anything on! There's a little child saying he hasn't got anything on!"

"Well, but he hasn't got anything on!" the people all shouted at last. And the Emperor felt most uncomfortable, for it seemed to him that the people were right. But somehow he thought to himself: "I must go through with it now, procession and all." And he drew himself up still more proudly, while his chamberlains walked after him carrying the train that wasn't there.

Hans Christian Andersen: *The Emperor's New Clothes*

Chapter 1

Mentalistic Approaches to Human Nature and Society

1.1. INTRODUCTION

Man has probably always reflected on the questions of existence and human nature, his relations to other people, and ways to interpret changes in the environment. One of the first answers to such questions was to assume the existence of supernatural powers. With increasing sophistication, the questions came down to one: how to make sense of one's self and relationships, within the organismic system, between body, self, and mind. Is mind basically an *intrapersonal* manifestation of a material brain, or does it reflect the workings of some immaterial dimension? The way we look at consciousness and personal identity depends on how we answer this question. Moreover, is mind best defined with reference to characteristics of the brain or to cognition, consciousness, self, identity, or constellations of personality traits?

At the *interpersonal* and *extrapersonal* level there are the problems of person–person and person–environment relationships. Is the person a product of genes, or a summation of the impacts of environment, or the product of additive genes and environment interacting? In the last-named case, what is the balance? How much is due to genes and how much to environment? Just how rigid are gene effects? How flexible is development? How much for stasis and how much for flow? Fundamental questions about the covariant development of body, mind, and society cannot be answered before such issues are addressed properly.

Social scientists, cultural anthropologists, and even a few neurophysiologists operate with a wide range of hypothetical *extrapersonal* factors, such as social norms, cultural stereotypes, or abstract "worlds" believed to have an impact on individual minds and behaviors. This raises questions about where norms, stereotypes, and abstract worlds come from? What is their

causal status? Which mechanisms mediate their impact on mind and behavior?

With respect to *phylogeny,* what is the exact timetable for the evolution of body, brain, mind, and society? Does selection take place at the level of genes, organisms, individual behavior, social norms, populations, or cultural stereotypes? Which selective pressures acted on exactly which functions or structures to bring about the evolution of mind, society, and culture?

Methodologically, how do we integrate observations made by different disciplines, using various levels of description, analysis, and explanation? With this problem unsolved, it is virtually impossible to establish consensus based on evidence from various areas like genetics, embryology, anatomy, physiology, endocrinology, auxology, psychology, sociology, and anthropology, to mention but a few. Should we, for example, look for ontogenetic developmental mechanisms at the level of the gene (e.g., DNA transcription), at the social learning level (e.g., internalization of social norms), or at the level of statistical gene–environment interaction? Will we ever be able to combine evidence from molecular biology and physiology with concepts of mind, society, and culture? Last, but not least, there is the question of whether to apply natural science or humanistic methods in the study of brain, mind, and society. The choice is between (1) the quantitative approach preferred by most natural scientists, (2) the less stringent qualitative approach of much psychology, sociology, and cultural anthropology, or (3) the rational/speculative/formalistic approaches of philosophy. If mind *is* the brain, a natural science approach probably would suffice. If mind, on the other hand, is a nonphysical phenomenon, application of the methods of physics would be inappropriate.

The nature–nurture dichotomy poses similar methodological problems. Are mind and behavior a function of biological circumstances, or rather the product of nonphysical social and cultural factors? Provided that mind and performance are biological phenomena, a natural science approach to nature–nurture problems may fit. If not, a natural science approach would be misplaced. Interactionists try to have it both ways but encounter problems with how to interpret the end products of physical and nonphysical factors.

1.2. POSITIONS

In this section I sketch the major contemporary intrapersonal, interpersonal, and extrapersonal explanations advanced to answer the above-mentioned questions. I will not go into any details in the presentation of positions; instead, I expose only the skeleton of the ideas. Some may find that I come close to making a travesty of the positions and they will demand more details. However, as I strive to show later, the positions are fundamen-

tally wrong in detail as well as in principle, and not all the details in the whole world are very likely to provide credence to make them scientifically acceptable.

1.2.1. Intrapersonal Positions

Plato proposed that humans possess a nonphysical rational mind that contemplates and construes reality in a nonphysical world of intelligibilia. Knowledge, according to Plato, is the object of the mind. Democritus, his contemporary, took the opposite view. He assumed that the reality of appearances, including what Plato referred to as the mind, is nothing but atoms and the void. This early dispute is known as the body–soul, body–mind, or dualist problem. The following presentation of more recent mentalistic nonphysicalistic positions attests that body–mind problems are still very much alive and come in many different shapes. The presentation and critique of these positions were much influenced by the incisive analyses by Patricia Churchland (1986), Paul Churchland (1981, 1984), and Richard Rorty (1970).

1.2.1.1. The immediate experience is given, is self-evidently and observationally true, and provides a basis against which psychological theories must be judged. The immediate experience is correct and irreducible.

1.2.1.2. Behavior can be explained only in terms of what we expect, think, believe, perceive, desire, and so on. One mental state is connected to another mental state, to perceptions, and to actions through these "facts." The content of expectations, desires, or beliefs is what makes our behavior rational or irrational, respectively. Rationality and irrationality are based on reasons and not on causes.

1.2.1.3. Mind refers to logical relations between, and computations on, representations, and all this has little affiliation to its neuronal basis. One elaboration of this theme is that representations (e.g., thoughts or sentences) can be about past, future, and even impossible things beyond the capacity of the brain and physical machine. Another variation will have it that thinking is rational, coherent, and intentional in that it can be about something external to and reaching beyond the brain itself.

1.2.1.4. Cognitive information theory assumes that processes at the semantic level are governed by logical rules and control principles at the syntactic level, and further that all this has little to do with the anatomical structure of the brain. Cognition is likened to manipulation of symbolic, sentencelike, or pictorial representations, in accordance with the logical relations between them. As in the computer, the causal relationships among the physical states in the brain are largely irrelevant for understanding the true nature of the cognitive processes.

1.2.1.5. Psychological states play a causal role in the internal system of states by arbitrating between sensory input and motor output. However, these nonphysical psychological states relate to the brain much as the functional states of a computer relate to the electronic components it is made of. Identical "programs"

can be run on very different computer hardware and in very different brains. Mental states refer to a functional description of physical states at a designated high level.

1.2.1.6. The meaning of a given mental state depends on its role in the total internal system of representations, and not on a particular brain organization.

1.2.1.7. The mind is more than the sum of the single parts of the brain.

1.2.1.8. "Boggled Skeptics" assume that the mind and the brain are far too complicated ever to be understood in physical terms. Boggled Skeptics think, to use Churchland's (1986) words, that "The brain is more complicated than it is smart."

1.2.1.9. All "Principled Skeptics" (Churchland, 1986, p. 315 ff.) hold that a distinctive mental dimension exists, and they maintain that it cannot be reduced to anything physical. They disagree about whether the mental dimension reflects a separate mental substance (substance dualism) or should be limited to nonphysical properties of the physical brain (property dualism). They concede, however, that meaningfulness and logical relatedness entirely elude physicalistic explanations. Although property dualists admit that the state of the brain causally affects subjective experience and vice versa, they maintain that the unique experience itself cannot be identified with neuronal activity.

1.2.2. Critique of Intrapersonal Positions

To say that an experience is *given* (Position 1.2.1.1) annuls questions about its truth-value and relocates the burden of proof from facts to beliefs. This is a dubious approach because the history of science clearly testifies that, however convincing immediate experience (whether based on external or internal sources) appears to be, it nevertheless may be dead wrong. Neither by definition nor in practice can self-evidence be an authoritative basis for scientific judgment. Inner processes may have no more immediate status than knowledge of outer processes and may require identical levels of justification. Defenders of Position 1.2.1.1 have not presented the evidence needed to discredit this methodological precaution.

Position 1.2.1.2 assumes that we behave according to what we think, desire, or believe. The major difficulty with this position is that we often err in what we think, desire, or believe, and sometimes we behave without knowing why. Accordingly, there is no safe way of deciding whether an intuitive explanation based on mental qualities may be correct in any given case. As previously argued, introspections are not outside the range of justification. Moreover, thoughts, desires, and beliefs are hypothetical, context-relative, linguistic categories. The total absence of an operationalization of the categories and their context, makes determination and the causal status of such categories vulnerable beyond reasonable doubt. Moreover, to claim that human rationality is essentially based on imprecisely defined, context-relative categories comes close to making a travesty of rationality itself.

Position 1.2.1.3 seems to imply that we must accept the existence of representations on face value. No empirical studies have, as far as I know, demonstrated their (f)actual existence in the brain in the form described. Obviously, this in no way implies that they do not exist, but it promptly raises questions about why a physical explanation of mind should automatically be inferior to untested ideas of nonphysical representations. Moreover, representations are typically defined in common-sense terms shunning operational definitions. The situation would be different, if representations are defined in terms of brain states, but Position 1.2.1.3 either denies this possibility or considers brain states to be less informative for understanding the working of the mind than are representations.

Position 1.2.1.4 asserts that the brain deals with symbols, sentences, and pictures that can act upon each other in accordance with certain rules. By doing so, cognitive information theory exemplifies a tendency to give what we do not yet understand a name and then to ascribe to it (f)actual existence without further proof, and finally to treat it as a causal agent. This criticism of reification applies equally well to explanations based on symbols, signs, sentences, pictures, desires, or for that sake souls, said to reside in the brain. Another shortcoming of cognitive information theory is that, should cognition really depend so heavily on manipulation of sentences or pictures, how it is that blind–deaf–dumb people and animals denied linguistic and symbolic capacities can nevertheless solve quite complex problems? It seems to me that many psychologists and philosophers overemphasize the role of verbal and symbolic factors in cognitive functioning, at the expense of nonverbal and metabolic aspects. Persistence in calling the "verbal" left hemisphere the *dominant* hemisphere and the "nonverbal" right hemisphere the *minor* hemisphere aptly illustrates this bias. The recent "surprise–surprise" that many lowly animals and also newborns actually possess quite sophisticated problem-solving capabilities are other signs of a very prevalent but regrettable neglect of nonsymbolic brain processing aspects.

Position 1.2.1.5 alludes to the existence in the brain of computerlike, programmatic, nonphysical brain states that determine relationships between perceptions and behavior relatively independent of the material basis of the brain in question. As far as I can see, there is no scientific evidence whatsoever to support the position that brains work by nonphysical programs. To the contrary, there is ample evidence that hundreds of chemicals have the capacity to modify brain states permanently or temporarily with selective, and to some extent now even predictible, effects on perception, intelligence, and personality. In other words, increasingly, the available empirical evidence actively testifies against the fundamental idea of Position 1.2.1.6, that "meaning" is independent of brain organization and functioning and represents a chemically inaccessible nonphysical internal system of representations.

Position 1.2.1.7 refers to the idea that the totality of mind is more than the sum of the single parts of the brain. This (w)holistic idea has the unfortunate consequence that lack of insight is covered by an empty proclamation of systemic potentialities beyond empirical scrutiny. To be taken seriously, the (w)holistic idea and all part–whole declarations must be operationalized to determine their scientific status.

The fear of the Boggled Skeptics (Position 1.2.1.8) that the brain is too complex a phenomenon to be operationalized can be dismissed for two reasons. First, the position represents nothing but a pessimistic prediction that may or may not come true. Second, recent research in neuroscience suggests that Boggled Skeptics were too pessimistic. The ontogeny and the functioning of the brain appear to conform to conventional physical principles (Weiss, 1970), and this seems to apply whether we talk about neuroembryogenesis, the adult anatomical distribution of a few hundred cell types, or neurotransmitter processes. Throughout Section 3, I present evidence showing that certain brain functions can be studied in terms of principles of actions of gonadal hormones and that variations in plasma hormones result in predicted changes in brain structures and functions, with related changes in intellectual functioning and personality.

There are major problems with the idea of substance dualism (Position 1.2.1.9). How on earth can mental substance interact with brain substance? According to the principle, it must nevertheless be the case as mind influences, and it can be influenced by mechanical, electrical, and chemical impacts. Moreover, if mind stuff arose during evolution, what then is its evolutionary history? If, on the other hand, mind stuff is not the outcome of selective pressures on the organism, what other sources are the likely candidates as the spring of mind stuff? When, during evolution, did the subjective qualities of the mind emerge? Substance dualists have not yet provided good answers to these questions. To say that mind is an emergent quality simply begs the original questions of where it came from, when, and how.

Property dualism raises questions about whether other primates have subjective experiences or whether they are instead to be seen as sets of instinctual chain-reflexes or just dumb machines. What is the scientific basis for the property dualists' assumption that what is called self-conscious qualities are uniquely and irreducibly mental and humane? Popper and Eccles (1977) seem willing to grant consciousness to creatures phylogenetically above honeybees, but only humans and perhaps chimpanzees show self-consciousness. The basis for this inference is, in part, studies of primates and humans reacting to distorted mirror image. Such studies may not provide an appropriate basis for critical demarcations between subjective experiences, consciousness, and self-consciousness. Perhaps the observation that some spot-painted chimpanzees become distressed when seeing themselves in a mirror, whereas spot-painted rats do not seem to care as

much, reflects a difference in the physical complexity of their brains rather than in degree of self-consciousness. Such studies indicate that species differ in their reaction to stimuli but seem less adequate to provide final proof of the existence or nonexistence of self-consciousness.

A main argument against the intrapersonal positions is that they have not yet substantiated their major claim that the brain works in accordance with nonphysical properties so that we need a concept of mind to explain behavior. Nothing in the arguments speaks against the possibility that one functional brain state succeeds another in a strictly physical rule-bound way and that this could explain behavior. What is considered the effects of logical deductions could equally well qualify as the effects of sequential brain events. According to the latter point of view, obviously the next task would be to explain how the brain works, but the intrapersonal mentalistic framework would be much too elusive to be of any scientific use in this large project.

1.2.3. Interpersonal Positions

Plato suggested that, though born noble, humans can easily be corrupted by training. His pupil, Aristotle, on the other hand, believed that nature allows for less plasticity and favors some over others and that this natural inequality can and should be exploited in the service of society. This discourse is known today as the nature–nurture problem. Psychologists, behavioral geneticists, classical behaviorists, and social learning theorists represent various interpersonal positions and typically subscribe to one of the following statements:

1.2.3.1. Mind is a multidetermined product.

1.2.3.2. Mind (or intelligence, personality, etc.) is the total phenotypic variance emanating from various genetic and environmental variance components, as well as interaction and correlation between the two.

1.2.3.3. There is no mind, but particular associations are formed between input and output relations as a function of positive and negative reinforcements.

1.2.4. Critique of Interpersonal Positions

Adherents of Position 1.2.3.1 presuppose that all sorts of factors, internal as well as external, may mingle and have an impact on the mind, but they are pessimistic about whether we will ever come to know which are the more important, for this may differ from person to person and from time to time. Some researchers even concede that it is not terribly important where traits come from. It is as well that they are here to be analyzed.

Behavioral geneticists represent Position 1.2.3.2. They are much more precise than are pure mentalists. They ask pertinent questions about pat-

terned familial transmission of genes and traits, about how different genotypes unfold in similar environments, and about how different environments affect similar genotypes. They apply sophisticated quantitative procedures for determining the relative contribution of genetic and environmental factors in the form of heritability estimates and test complex path-models. Behavioral geneticists have developed a quantitative tool for singling out and estimating the impact of variables in the environment (e.g., Plomin & Daniels, 1987), where social scientists often rely on intuition. Despite this enhanced precision, it has proven difficult to operationalize social variables. The closest they come is to interpret social variables in terms of shared and nonshared variance components operating within or between families.

Behavioral genetics is further stuck with the problem of substituting a close-to-the-matter, real-life account of how an organism meets, adapts, or transforms its environment with statistical models of the interaction (Nyborg, 1977, 1986a, 1987a, c, 1990a, b; Wahlsten, 1990). For example, we know very little about where in the organism or in the cell the effects of ontogenetic DNA transcription (gene unfolding) meet with effects emanating from environmental variation. What is the precise causal nature and locus of biosocial interaction? Provided suitable modulators of gene expression (see Section 3), genes produce proteins that may affect, say, the cell, but the effect of a single gene is almost never directly observable at the behavioral level. Behavioral genetics analyses often concentrate on elucidating familial transmission patterns of "genes for behavior" and provide population estimates of inheritance for a given trait. These analyses were usable in the past because they pointed to a generally ignored important contribution of genes to explain behavior. The problem now is that they hardly substitute for an examination of causal mechanisms of importance for a particular person's development. This task includes modern neuroscience. Behavioral genetics has in general been slow to make full use of the recent impressive progress in neuroendocrinological and behavioral brain sciences, although there are notable signs of change (see Plomin, DeFries, & McClearn, 1990).

Behaviorists (Position 1.2.3.3) tried hard to steer clear of mentalism. The Watsonian version of behaviorism exposed itself to another danger, however. Instead of the mind, John Watson adopted Ivan Pavlov's concepts of associative bonds between input and output. The American version of behaviorism came close to substituting the mind with an equally elusive idea of associations, taking place in a black box zone. B. F. Skinner was careful to avoid this trap, but then he had remarkably little to say about what goes on in between the stimulus and the response. This is, in Skinner's opinion, a secondary problem to be delegated to the brain sciences (Skinner, 1989). This position circumvents the observations of species-specific and individual organismic constraints on learning. I will demonstrate in Chapter 3 that gonadal hormones incur significant constraints on learning,

intelligence, and personality; that such constraints may remain stable, despite considerable efforts to change them by reinforcement; but that they can be changed by hormone treatment.

A methodological problem with behavioral genetics and social learning theory is that the data consist almost exclusively of correlation coefficients and variances. They neither give information about the direction of causality nor provide information about causal mechanisms.

1.2.5. Extrapersonal Positions

Thus far, I have discussed intrapersonal body–mind positions and interpersonal positions, and I have touched on problems mentalists run into when analyzing intrapersonal, person-to-person, and person–environment interaction. What about positions assuming that mind to some extent or fully reflects actions of extrapersonal factors?

Many such positions explicitly exclude the importance of brain characteristics, and some of the positions even claim that extrapersonal factors suffice to explain all of behavior (e.g., cultural relativism). These nonphysical, predominantly extrasystemic, superorganismic positions may take one of the following forms:

1.2.5.1. Mind (or the individual) is a social construct. Behavior is shaped by social norms and internalized through imitation, passive model learning, role selection, acceptance, participation, or by rejection. Mind reflects the distribution of economic factors.

1.2.5.2. Mind is a projection of culture, and behavior reflects cultural stereotypes or values.

1.2.5.3. Mind can be informed by abstract "worlds," and contact with such a "world" provides a person with certain skills, for example, the ability for abstract thinking and mathematics.

1.2.6. Critique of Extrapersonal Positions

Position 1.2.5.1 represents the essence of social learning theory or aspects of dialectic materialism. Many cultural anthropologists and cultural relativists subscribe to Position 1.2.5.2. Advocates of these positions rarely, if ever, attempt to clarify where norms and cultural stereotypes come from in the first instance. They rarely dissect their evolutionary history or raise questions about why norms or stereotypes did not turn out differently. Popper and Eccles (1977) refer to Position 1.2.5.3. They are property dualists and certainly refer to brain characteristics, but they also mention a superorganismic World 3 of abstract nonphysical objects. We communicate with this world through reasoning, they say, in order to perform mathematics at a high level. World 3 is attributed an existence independent of minds.

However, Popper and Eccles do not present the slightest empirical evidence to indicate where in the universe World 3 is to be found, how it landed there, or who put it in its place. There are further problems with the idea of a superorganismic World 3. Do computers also have to communicate (through reason?) with the nonphysical World 3 in order to solve sophisticated mathematical algorithms in accordance with logical rules?

The major problem with superorganismic variables is that concepts such as social norms, the burden of culture, the rich font of collective knowledge, World 3, and archetypes are hypothetical constructs and purely descriptive categories. Fabrication of abstract constructs, categories, and analogies has a long history. Plato suggested that there are close analogies between an animal and the world around it, and between an organism and the republic. This is abstraction by pure reasoning. At the beginning of the century, Alfred Kroeber (1917) made a strong case that culture is a superorganic entity. The idea that there is a purpose behind all natural phenomena is very old. Marx went as far as to suggest in his sixth thesis, Feuerbach, that from the beginning consciousness was the essense of social relations (*gesellschaftliche Verhältnisse*) and that it would be so as long as humans existed. Marx also talked about national consciousness and suggested that the social collective is the only reality, even though at other times he subscribed to more tangible matters and admired aspects of Darwinism. However, science is unable to deal with the former claims, partly because the operational status of the variables is far from clarified. In addition, science has no way to prove that something does not exist. The question of the existence and causal status of superorganismic strata, therefore, lies outside the empirically testable domain. This is probably the major reason why for the past two thousand years we have been asked to remain satisfied with firm assurances and remarkably little evidence. The notion of superorganismic powers appears to follow from the fallacy of negative proof. If nothing else can explain the phenomena I am interested in, my particular explanation does. And you better believe it!

1.3. EVOLUTIONARY QUESTIONS

Acceptance, refusal, or the particular formulation of the idea of mind determines what kind of questions can be posed about evolutionary history. If mind is seen as a purely nonphysical phenomenon, it makes no sense at all to ask about its evolutionary history. This leaves us with divine intervention as the only explanation. If mind is an emergent quality of the brain, it becomes of interest to query about its species-specific evolutionary developmental timetable in relation to the evolution of the physical brain. To the best of my knowledge, no satisfactory empirical evidence has ever been presented to clarify this matter, although the resolution of this important problem requires hard empirical data rather than visions and proclama-

tions. On the other hand, given that mind is the brain, it makes perfect sense to ask questions about which particular selective pressures may have worked on which brain processes to produce what is seen as manifestations of mind.

1.4. SUMMARY OF THE CRITIQUE OF MENTALIST POSITIONS

According to this analysis, *intrapersonal* body–mind positions rest on rational explanations (or involve ideas of the action of unconsciousness) rather than on experimental evidence, and are often based on face value, self-evidence, common sense, or metaphors. The application of natural science methods is shunned in the study of mind, brain differences are eluded, and evolutionary aspects are typically neglected.

This critique applies, even though we are still very far from providing a scientifically satisfying explanation of the functioning of the brain based on the methodology of the natural sciences. Fortunately, the recent rapid progress in the brain sciences has made it possible to study the intact brain in more detail than hitherto. Blood flow, nuclear magnetic resonance, and several other nonintrusive techniques are now routinely in use. None of these studies has yet come up with results violating any law of natural science, and none of the results benefits to the slightest extent from mentalist interpretations. Moreover, the critique does not presuppose a denial of the existence of mental phenomena (Paul Churchland, 1984; Patricia Churchland, 1986). It does suggest, however, that mentalist explanations of intrapersonal phenomena are misconceived and that the repeated insistence on their accuracy and causal status is misplaced, if for no other reason than for the total lack of hard evidence since their inception long ago.

The *interpersonal* positions on the nature–nurture question also raise what seems to me insurmountable problems. Most of the inter- and extrasystemic variables lack precision in definition but are nevertheless assumed to play a vital role for development and function. What mechanisms procure the integration of social experiences with organismic variables? The idea of mind (or cognition or personality, for that matter) as the sum of genes and sociocultural factors through interaction is intuitively appealing. However, genetic and environmental contributions refer to variance components and deviations from population means rather than to causal relations between identified agents that have a known impact through localized mechanism on particular processes in a particular individual. Such an approach fosters statistical anonymity with respect to which particular exogenous factors interact with which particular endogenous factors in a particular individual. External variables at a nonphysical level (e.g., a social norm) are more or less indiscriminately mingled with external physical variables (e.g., corporal punishment). On the internal side, nonphysical

(e.g., psychic) variables are then confused with physical brain characteristics. Watson's idea that external reinforcers work through associative bonds rather than on the mind is likely to promote understanding only if the precise empirical nature of the associations is elucidated. To present a correlation is to call attention to the possibility of whatever name is given to the statistical relationship, but not to prove an actual causal relationship. Skinner in the end no longer negated the existence of inner constraints, but then he assigned them secondary importance in explaining behavior. Chapter 3 presents empirical evidence to indicate that these interpersonal positions run into serious troubles.

Extrapersonal positions are based on the assumption that there are powerful social, cultural, or abstract other worlds out there—somewhere. The empirical documentation for their existence is nonexistent, and their evolutionary history is unclear.

If we take an overall perspective and compare the ancient literature on mentalism with more recent philosophical positions, it is difficult to free ourselves from the impression that most of the modern mentalistic and superorganismic explanations reflect more or less directly the ancient intuitive understanding. The more recent understanding is further systematized by logic and reasoning, but it is still largely undisciplined by data and evades the censorship of the physical world. It seems to me that the classical body–mind controversy is basically a linguistic pseudo-problem that stands little chance of ever being solved by further rational analyses of words, concepts, and meaning. Mind, psyche, and self-consciousness may defy reduction not so much because they are self-evident, but because they reflect the spiritual phlogiston of a time characterized by unbecoming and self-flattering anthropocentrism. I am even prepared to go as far as to suggest that the body–mind problem has survived for thousands of years because it has been considered a philosophical rather than an empirical/experimental problem and because even the greatest philosophers have readily reified concepts and twisted them around in clever word games without ever being called to order by hard evidence.

1.5. RESULTING STAGNATION IN THE BEHAVIORAL SCIENCES

The inescapable conclusion, at least as I draw it, is that mentalism, ever since its inception, has corrupted the basic understanding of human nature and the way we have studied it. It has continued to constitute a serious impediment to progress because explanations based essentially on reasoning about body–mind and nature–nurture questions are still widely and rather uncritically accepted today. We took a giant step forward when the idea of a God-given soul was relegated from science because of its religious rather than empirical connotations. Apparently, the vacuum was filled by

equally intangible, purely descriptive ideas of mind, consciousness, awareness, self, ego, subconsciousness, personality, cognitive structures, information processing capacities, logical rules, internalized social norms, and cultural stereotypes. This may actually be no more than old sour wine in new bottles because the new terms also lack proper attributive reference. Distressingly, many contemporary textbooks on behavior use these new fancy words and concepts, which have an unmistaken resemblance to Plato's nonphysical concepts. Dualism, trialism, and the most recent cognitive sciences have effectively relegated monist, materialist, reductionist, and physicist positions to a secondary platform in the behavioral sciences. Scientists, opting for a compromise in the form of an interactionist view on the nature–nurture problem, are either forced into conceptual and methodological permissiveness beyond stringency or, in the case of quantitatively oriented behavioral geneticists, are propelled to work with abstract high-level statistical models miles away from the analysis of actual causal relationships. The intolerable result is that large areas of the behavioral sciences are paralyzed, and psychology remains as much as ever a hope for a science.

The only way out of this dilemma is to focus the future research on human nature on the formulation of much more prohibitive models for body and brain development and function. The models must operate exclusively with variables that can be operationalized. The hypotheses must be formulated in such a way that they can be subjected to rigorous testing using the less compromising criteria from the natural sciences. Instead of operating simultaneously with biological and mysterious nonphysical variables, all variables must refer back to a common basis. Variables and hypotheses that cannot be defined operationally should be put into the large green box of potentially interesting ideas and should never be let out in the fresh air (or into the humid climate of the laboratory) before their causal status can be determined with a reasonable degree of certainty.

John Stuart Mill saw the problem long ago: "The tendency has always been strong to believe that whatever receives a name must be an entity or being, having an independent existence of its own. And if no real entity answering to the name could be found, men did not for that reason suppose that none existed, but imagined that it was something peculiarly abstruse and mysterious." Thomas Hobbes was also aware of the problem: "Words are wise men's counter, but they are the money of fools." Joseph Hart (1924) had the practical solution to the problem: "We shall have to give over the fun of arguing words and begin to face facts. Our intellectual joust is over; it is time to plant some beans." (All cited in Spearman, 1932, p. 14–15.)

Chapter 2 sketches a program for such a horticultural move. Chapter 3 illustrates how sexual differentiation of body, brain, and molecular processes behind behavior and society can be subjected to an analysis in accord-

ance with the program. The main purpose of the rest of the book is to illustrate that even today there are ways to deal effectively with important aspects of the physico-chemical nature of body–mind, nature–nurture, and cultural phenomena without ever having to invoke nonphysical notions of mind, desires, love, hate, norms, or stereotypes. In other words: *Secundum non datur.*

Part II

PHYSICOLOGICAL RESEARCH

So you are one of those wise guys from Rockefellers looking into the mystery of life.

I tell you something. People are born. People move things around. Then they die. That's all there is to it!

Now, where will I move you today?

Anonymous New York Yellow Cab driver

Chapter 2

The Physicological Research Program

2.1. INTRODUCTION

Alternatives to mentalism should be based on the following minimum guidelines. The attempt to explain behavior must be strictly pragmatic and should be guided by empirical rules. The programs must be characterized by a minimum of pure reasoning and fabrication of hypothetical variables, and should generate a maximum of experimentally testable hypotheses. These guidelines are obvious goals for any scientific enterprise but need to be reiterated time and again in the behavioral sciences. The new programs must further reflect an explicit preference for the simplest of alternative hypotheses (Occam's razor). For example, the hypothesis proposed in Chapter 3 states that all sexually differentiated aspects of society and culture are primarily a reflection of physico-chemical actions of gonadal hormones on individual bodies and brains. This straightforward hypothesis reflects a heuristic strategy that allows the possibility of falsifying the notion that a relatively few chemicals are responsible for the actions. In the positive case, the hypothesis focuses in the study of their locus of action and mechanism, and encourages testing in a dose–response manner to see whether the hypothesis survives.

Such a program may be implemented today. The medical sciences, the molecular sciences, and the neurosciences seem to have arrived at a point where it makes perfect sense to ask questions about mind, society, and culture in terms of their physico-chemical basis. The situation is reminiscent of the times when Watson and Crick began asking simple questions about the basis of life in terms of its then rather obscure physico-chemical DNA basis. Their approach paid off well. Watson and Crick actually found that nature works in much simpler ways than it was first assumed. Now it is time to try and ask equally simple empirical questions about the basics of

brain and behavioral development, too. It may be well to apply nothing but natural science methods in this analysis of brain and behavior. Preference should be given to questions that also make sense in an evolutionary perspective, for selective pressures probably work only on physical entities. For the lack of a better name, I call the particular research program to be presented here *physicology*.

2.2. THE PHYSICOLOGICAL PROGRAM

Physicology is concerned primarily with the study of the physico-chemical basis of development and behavior. The program capitalizes on the wealth of behavioral observations established by disciplines like psychology, sociology, anthropology, ethology, and biology, the medical sciences, chemistry, and physics. However, physicology makes no causal reference to mentalistic or superorganismic factors. Physicology is *not* a behavioral science in the traditional sense. It concentrates on the analysis of the processes behind behavior rather than on behavior itself (even though behavior is also in a sense a process). The reason for not seeing physicology primarily as a behavioral science program is simple: In complex systems, the effects of internally generated changes or of internal changes owing to variation in the physical surroundings often never show up in behavior, or they do so only after a long delay.

Physicology is a minimalist theoretical position with two basic assumptions. The first assumption is that molecules show differential stereotaxic affinity. The second assumption is that behavior reflects changes in the distribution of energy (depending on the time, place, number, and stereotaxic characteristics of available molecules. According to physicology, it makes no sense to assume that molecules have desires or wishes. Molecules simply bind or split according to their stereospecificity and time–space coordinates. With these two assumptions, physicology dispenses totally with mentalistic and superorganismic accounts of behavior. To give an account of the relevant molecular actions and reactions is, according to physicology, to explain phenotypic behavior. It follows that the primary level of description and analysis (and explanation if you insist) of development and function is the actions, reactions, and catalytic effects of molecules.

No other theoretical strings are attached to the physicological program. Questions about whether variation in the affinity of molecules is preordained by higher powers, whether the universe is final, whether the world runs along a completely determined path, or whether everything is eventually explainable in terms of some subatomic principles is of little concern to the physicologist. Phrased differently, the scope of physicology is deliberately kept narrow, pragmatic, specific, and as liberated from pure reasoning and speculation as possible. If, for example, an increase in androgen

makes many individuals react more aggressively (see Section 3.5.4), physicology raises questions about the reliability of the measurements, about the role of the molecular agents and their mechanisms of action, about exceptions, about the implications for intersystemic interactions (so-called social behavior), about the clinical implications, and about whether the observations fit an evolutionary perspective. It should be noted that I use the term *evolution* here in a much broader sense than do traditional Darwinists (see Sections 2.6 and 3.2.4).

2.3. THE INTRASYSTEMIC LEVEL OF PHYSICOLOGICAL ANALYSIS

Application of physicology means better integration of available information on the intrasystemic aspects of humans. The recent explosive development in the neurosciences, pharmacology, endocrinology, embryology, immunology, and neurology has shown beyond reasonable doubt that what Plato reasoned must be the manifestations of a nonphysical mind has turned out to be our speculative projections on a brain that works in strict accordance with general and well-known physico-chemical principles. Thinking and problem solving appear to be explainable in terms of effects of cascades of physico-chemical brain processes. Physical and chemical intervention influence these processes in numerous and increasingly predictable ways. Strict adherence to physicological principles facilitates the integration of various recent research. It becomes possible to seamlessly relate the effects of brain lesions to the effects of tissue transplantation and so-called thinking, because physicology operates at only one level, namely, that of molecules. Only in that case can observations on thinking be connected with observations made by, for example, magnetic resonance imaging, regional blood-flow measures, and positron emission tomography scanning techniques. It becomes possible to integrate evidence from neuroendocrinology with observations from neuropharmacology because of the common molecular framework.

If thinking and feeling reflect physico-chemical brain processes, then it becomes legitimate to ask questions such as, "What is the evolutionary and ontogenetic history of specific brain structures and processes responsible for what we now refer to as instincts, motives, unconscious wishes, or, for that matter men's and women's more or less different desires, beliefs, perceptions, and behavior?" Questions about to what extent medication can influence so-called desires or unconscious motives begin to make sense in an experimental framework. Physicology even makes it legitimate to ask questions about *inborn ideas* and how they relate to species-specific brain structures and processes, and about to what extent they are shared across species. Long ago William James and Carl Lange, concerned with the question of whether "I cry because I am sad," concluded that "I cry and,

therefore, I am sad." Physicology makes it possible to ask precise questions about whether "feelings" come before or after the physicological process of crying. It examines the physico-chemical agents that affect the intrasystemic processes behind crying and behind the physiological condition we call sadness, and it inspects the mechanisms responsible for a temporal delay in the molecular cascade of events. Similarly, James's idea of a stream of consciousness raises physicological questions about serial and/or parallel cascades of molecular events in the brain and elsewhere.

Perhaps an early warning is in place. Obviously, I have already applied many traditional mentalist terms in the introduction to physicology. I will continue to use mentalist terms throughout the book. This must be seen exclusively as a "Facon de Parler," a convenient way of referring to complex phenomena. The terms are never used as a "Facon de Penser," and my use of the terms is always completely devoid of explanatory value. Section 4.7 provides more details on this point and a regret for still having to use mentalist terms.

2.4. THE INTERSYSTEMIC LEVEL OF ANALYSIS

The physicological program enables us to empirically approach phenomena such as social learning and internalization of social norms and cultural stereotypes in terms of physico-chemistry at the *intersystemic* level. Thus, instead of asking how people communicate and impress each other by exchanging abstracts (signs, symbols, ideas, instructions, attitudes, or prescriptions), the physicological program asks questions about the physics and chemistry of interpersonal interaction. Social interaction is rephrased in terms of asking how complex physical systems succeed in communicating effectively by more or less systematic manipulation of light, sound, smell, and other physical parameters. Exactly how do we, for example, control the reflection of light so as to promote predictable physical changes in the visual system and other parts of the brain of a perceptive attendant? All aspects (internal and external) under which physical stimuli are produced, transmitted, sensed, and converted into modulation of neurotransmitter patterns (i.e., perceived), and stored transiently or permanently (i.e., remembered) can be subjected to physico-chemical analyses.

For example, physicology defines learning as the cumulative effects of more or less systematic changes in extrasystemic physical stimulus parameters, which lead to more or less permanent intrasystemic physico-chemical changes in the perceiver. The external changes may be caused by the wind blowing through the trees, by a tiger approaching, or by systematic manipulation by another person (e.g., a parent, a teacher). The only basic requirement for learning to take place is that the extrasystemic changes result in the observer's new and relatively permanent intrasystemic physico-chemical states. This puts the establishment of more or less automated motor

patterns (e.g., learning to ride a bicycle) on a par with learning from other people. The physicological definition of learning applies equally well to single-celled animals and to multicell physical systems. Evidently, single-cell systems are less flexible and complex than are people, but this is the only reason why they learn certain tasks less well than we do. Some of them, for example, are surprisingly good at learning to avoid noxious chemicals by sensing gradual changes in concentrations when moving in a fluid. According to physicology, even a steam engine "learns" to run at a slower speed when its steam pressure is down-regulated.

This kind of learning has little degree of freedom, however. A servo-regulator permits more varied responses and allows the steam engine to "learn" to keep the "right" speed while taking the workload "into account." This example of learning in a simple mechanical system is not meant as a metaphor; it is an analogy. This is so because, according to physicology, learning has nothing to do with instruction. It is not possible to instruct an engine. Neither is it possible to instruct molecules to go to certain places in a child's brain and to cause permanent changes there. All that a "teacher" can do while teaching is to systematically manipulate the physical circumstances, so that the steam engine is given the possibility to change speed within its mechanical limits, or the child to learn new tricks within its physico-chemical limits. However, in both the steam engine and in the child learning consists basically of changes in systemic parameters, determined by internal physico-chemical flexibility, stability, complexity, and effectiveness, and the salience of the external physical processes.

The physicological program implies that the effects of psychotherapy do not depend primarily on suggestions, attitude changes, reassurances, advice, or revelations. Rather, the successful psychotherapist should be seen as a skillful manipulator of the patient's internal and external conditions. The therapist accomplishes more or less well-planned changes in functioning by modulating light, sounds, and the like, in accordance with what worked well with other patients with similar complaints. Psychotherapy is the art of physico-chemical manipulation without medicine.

According to physicology, even love is a completely physico-chemical, mutually guided process that takes place among people. One implication is that changes in the physico-chemical conditions by, for example, depleting humans of gonadal hormones would mean that the processes we call love, affection, or sociability would no longer exist. Nobody, therefore, would go to movies, theater plays, the ballet, or read novels based on sexual plots (and most are), because they would no longer result in pleasant physico-chemical changes. Depletion of the physico-chemical basis of love would result in depletion of all those social institutions believed to regulate sexual behavior between people. According to physicology, such institutions merely reflect the actions of gonadal hormones and other chemicals.

Love is not a thing or a power, and it has no causal impetus of its own, although romantics would make us believe it has.

2.5. THE EXTRASYSTEMIC LEVEL OF ANALYSIS

This section outlines aspects of the physicological analysis at the extrasystemic level. The major reason for discriminating between the intersystemic level of analysis and the extrasystemic level of analysis has a practical rather than principal basis. Interactions among people are numerous and have considerable impact. It is, therefore, convenient to reserve a special category of extrasystemic impacts for so-called social relations. However, according to physicology, both inter- and extrasystemic factors are external relative to the individual, and both are basically physical in nature.

The physicological program redefines the study of culture/race/ethnicity. Thus, if groups of geographically longterm separated people show stable differences in behavior, the hypothesis to be tested is that this can be explained in terms of geographically conditioned differences in their physico-chemical construction and functioning. Physicology substitutes, in other words, the simplistic idea that culture causes cross-cultural differences in behavior with three testable hypotheses. First, behavioral differences reflect differences in proximate physico-chemical processes; second, prolonged differences in selective pressures produce differences in physico-chemical processes; and third, people who are physico-chemically similar tend to behave along similar lines, that is, to establish similar cultures. From personal experience I know that this is a potentially controversial implication of the physicological program. I will therefore be quite explicit about certain points of these hypotheses. In particular, the third hypothesis disarms the hotly debated racist controversy by boiling the matter down to a question of geo-climatically dictated differences in physico-chemistry and individual differences within borders. Moreover, physico-chemical differences across races and within races follow the same rules with respect to analysis and behavioral correlates.

A related point is that the physicological position solves a problem generated by the traditional nature–nurture approach. As mentioned several times before, physicology focuses primarily on processes in individuals and is less concerned with population averages. Physicology thereby circumvents the danger of generalized racism sometimes associated with population statistics. On the other side, individuals separated for extended periods of time by thousands of kilometers or by mountains or rivers often look, think, and behave differently. According to physicology, this is not at all because they have accepted or refused collective cultural prescriptions for behavior issued for their particular area, sex, or race. To the contrary, their behavior and culture show that they differ with respect to genotypic

modes and to other intrasystemic physico-chemical processes that modulate available genes.

The distributions of alleles and differences in individual internal physico-chemical parameters reflect the particular selective pressures exerted by the particular physical circumstances (e.g., tropical versus Arctic) to which their forefathers were exposed over extended periods of time. Individuals whose DNA material was badly tuned to a particular ecological niche found it difficult to adapt. They either left, died, or succumbed to severe stress, with resultant reduced fertility and eventual extinction. This does not boil down to racism because, as just mentioned, it can easily be demonstated that there is some variation within all known populations with respect to physico-chemistry and behavior. It seems that some variability within a group is permissible and, indeed, provides an advantage with respect to survival when circumstances change. However, people who behave too *oddly* are ousted from their group, regardless of sex or race. In other words, physicology deals with racial variation in terms of different individual rather than population means.

The physicological view of culture implies that cultural relativism has turned the question of causal relationships between culture and individuals completely upside down. Cultural relativists declare without any further proof that culture makes individuals similar. In contrast, physicology tests the hypothesis that physico-chemically similar people make similar cultures. The physicological program further implies that it would be a serious mistake to assume that genetic and environmental factors are separate entities and that their relative contributions to behavior add linearly up to 100 percent. Details of this radical reorientation in the traditional nature–nurture controversy are discussed later in this chapter.

2.6. EVOLUTION AND PHYSICOLOGY

The physicological program redefines certain aspects of the classical theory of evolution in part along the lines proposed by Dawkins (1983). Dawkins suggested that phenomena associated with life are best seen as being a result of Universal Darwinism. However, according to physicology, life is a superorganismic concept. There are live organisms, but there is no "life" as such; life is a process, and the borders between life and death matters is blurred. In this view evolution refers to gradual selection over eons for economical combinations of physico-chemical agents and related molecular processes and mechanisms. Evolution takes place at any and all levels from subatomic particles, to molecules, cells, organs, and organisms, to interacting systems, and again to the survival and death of stars, solar systems, and even the universe. Physicology sees traditional Darwinistic selection as a special case of selection among live organisms. Examples close to the human part of the scale are competition between agile spermatozoa

racing toward the ovum. However, spermatozoa do not rush because they are instructed to do so or wish to win the race. Their behavior reflects their particular physico-chemical makeup and their environment, the vagina. Their machinery was selected for among many other possibilities, and those less well equipped to deal with this particular situation faded away. Quite as is true of people, spermatozoa have no choices and no opinions; it only looks so. Those spermatozoa that cope best with the vaginal environment have a competitive advantage. They will never "know" of it, and, indeed, there is no need to know. All that is needed is molecular compatibility.

The interdependence of various chemical events for successful reproduction is obvious. For example, although the environment in the female reproductive apparatus can be hostile, it also supports the performance of some spermatozoa; their effective movements are actually facilitated by vaginal capacitation as well as by activation. Concomitantly, a physico-chemical selection for the best equipped eggs is also going on. Eggs full of nourishment or other advantageous characteristics win in the competition over less well-equipped eggs. There is even selection at the level of immunochemistry. Some combination of egg and Y chromosome material is capable of growing on the wall of the uterus and will survive, whereas those rejected owing to maternal immuno-incompatibility crumble. During embryogenesis and later in development, physico-chemical selection takes place among body and brain cells, resulting in the selective survival or death of cells (e.g., Neuronal Darwinism as discussed in Edelman, 1987). Postnatal exposure to factors in the extrasystemic physical environment also profoundly influences neuronal survival (e.g., Juraska, 1984, 1986; Juraska, Fitch, and Henderson, 1985). Even organ tissues compete for survival, growth, and functioning. Some "anlagen" blooms early in development, while others fade away. If one kidney is lost, the other kidney grows more than usual (see Section 3.11). According to physicology, selection takes place at any of these levels, and complete failure at any time during the early developmental stage prevents later development. All existing systems are tested for fitness at all levels (Freedman, 1967) and at all times.

By now it should be obvious that a physicologist would strongly maintain that there is no proof whatsoever for selection for thoughts, ideas, hopes, fears, or desperation. They are inferred hypothetical constructs, not attributive objects, and it is entirely impossible to justify their evolutionary history by known scientific means. On the other side, recent observations amply suggest that selection takes place among neuronal arrangements, neurotransmitters, and other structural and functional variables pertaining to the body and to brain processes. Organic systems in humans presuppose the availability of materials for their construction and maintenance. The fact that people can respond properly to and actively deal with the particular selective pressures in their part of the world demonstrates that their con-

stituents were combined adequately. In this way physicology brings geology within the ambit of behavioral determinants. Geography, geology, and variations in the climate, in water and mineral resources, and in the availability of food all affect physico-chemical processes. According to physicology, geographical differences translate to differences in body, in brain processing, thinking, and emotions, and in behavior. It is known, for example, that severe protein deficiency (Kwashiorkor syndrome) seen in parts of Africa can damage the liver, so that it becomes less efficient in breaking down plasma estradiol (E_2), one of the more potent estrogens. In men this syndrome results in feminization not only of the body but also of the brain and intellectual pattern (see 3.11.4). The example stresses the intimate interdependence of geography, climate, nutrition, gonadal hormones, brain chemistry, brain functioning, and behavior. The complex interplay of these variables in turn influences the effectiveness of the exploitation of available resources in a given habitat. All these factors and the selection for their optimal interaction ultimately boil down to individual physico-chemistry, survival, and reproduction.

According to the physicological program, however, selection does not stop here; it affects all other areas of physics and chemistry. This view implies that areas traditionally considered to be far outside the range of evolutionary theory now have to be included. Refraction of light in a prism exemplifies selection at the level of physical optics. Incoming light is bent in all possible directions as it enters a prism. However, from the other side of the prism escape only those beams of light that by incidence traveled in a direction that allows beams of that particular wavelength to pass through the prism in that particular direction. All other beams of that particular wavelength did not reach ("survive" to) the other side of the prism. They were trapped within the prism and converted to heat. From a physicological point of view, selection of behavioral types of light in a refracting medium is analogous to selection of certain types of gene expression, membrane permeability, and neurotransmitter modulation by gonadal hormones. In the latter case, certain cells survive, become functional, and are strengthened by use, whereas other cells die. The examples are meant to suggest that selection takes place at all levels of physics and chemistry. As organismic behavior depends on which somatic and brain cells become functional, it follows that types of behavior also conform to selection during phylogeny and ontogeny. In that respect, nature seems to follow the most economical or energy-efficient path (see Section 3.11).

Part III

PHYSICOLOGICAL ANALYSIS

Chapter 3

Intrasystemic Hormone Effects

3.1. INTRODUCTION

The following twelve chapters in Part III demonstrate how sexual differentiation (SD) of the body, brain, behavior, and society can be analyzed in terms of the underlying physico-chemical processes, selected for during evolution. The phenomenon of SD has been selected for demonstration because it is a prerogative for the evolution of higher life-forms. SD refers to extensive aspects of ontogenetic differentiation of the body, brain, intelligence, and personality, all of which lend themselves to an analysis at the intrasystemic level. In addition, SD plays a significant role in many aspects of social behavior, which can be analyzed at the intersystemic level. SD shows up in all cultures though to a varying degree, and can be subjected to a physicological analysis in terms of geographically and climatically conditioned differences (the extrasystemic level). SD is necessary for sexual reproduction. As such, SD is of the utmost importance to our understanding of phylogeny. Sexual reproduction ensures variation in the gene-pool, and the size of populations is a function of it. Successful reproduction marks the beginning of individual existence, whereas failing reproduction means the end of the species. It is little wonder, then, that Darwin and many others with him devoted so much of their talent and energy to unraveling its many facets. The average person also shows a disproportionately large interest in SD. One can hardly talk to another person without taking into account that other person's sex. Many sweet hours and not a few ravingly mad periods relate to SD.

In other words, SD has been chosen for physicological analysis here because it embodies somatic differentiation, which everyone acknowledges is a purely physical phenomenon, and also comprises covariant development of the brain, intelligence, personality, sexual inclination, and impor-

tant aspects of interpersonal behavior, including social and cultural stratification (e.g., in education, occupation, or political power structures). Most contemporary social scientists believes that these latter phenomena arise more or less exclusively on the basis of the actions of nonphysical, mental, psychological, social, or cultural factors. The field of SD reflects quite well the old and insurmountable dualism between physical and mental explanations that has made it so impossible to establish a parsimonious and coherent framework for understanding human nature.

Researchers of SD have historically tried to minimize the damaging effects of the schism by theoretically and methodologically keeping their areas more or less separate. One group of scientists concentrated on the molecular side of SD, whereas others focused on somatic or brain development. Some studied sexual behavior, whereas others studied the nonreproductive aspects of SD. Not a few worked out elaborate psychological or psychoanalytic explanations, whereas others concentrated on cultural relativist interpretations. The result has been kaleidoscopic. Endocrinologists, auxologists, biologists, ethologists, psychiatrists, psychologists, sociologists, and cultural and physical anthropologists came to employ more or less incompatible methods, worked at different levels of complexity, and ended up with different and often incompatible theories. The net gain of such a separation was supreme autonomy for each of the various scientific disciplines involved. The costs were many and grave: fragmentation of behavioral science, loss of overall perspective, and, in some cases, the development of relativist theories that make no sense whatsoever in an evolutionary perspective. Of course, many scientists are aware of the dichotomy and have tried to overcome it, but have not yet been able to establish a generally acknowledged coherent framework. Many scientists are therefore natural scientists early in the morning, questioners at lunch, and cynical or naive mentalists in the evening. In such a situation, insoluble philosophical body–mind and nature–nurture disputes are bound to erupt time and again.

The following sections illustrate how the physicological program offers its integrative service. As previously mentioned, physicology operates at only one level of analysis, and this paves the way for a unification within a common physico-chemical framework. The goal of the following sections is to show how previously difficult-to-relate types of data on SD can be placed on a common footing even if they are collected within widely different areas like biology, the psycho-sociocultural disciplines, and modern brain sciences.

3.1.1. Intrasystemic Sex Hormone Effects

According to Phoenix et al. (1959), sex hormones exert two kinds of effects: (1) organizational, irreversible, anatomical effects that take place

primarily in the early fetal or perinatal period, and (2) activational, reversible effects on functioning observed in the mature organism. However, recent observations suggest that this dichotomy may be too rigid (Arai & Matsumoto, 1978; Arnold & Breedlove, 1985; McEwen, 1988a). Thus, organizational brain processes take place in the adult members of some species. For example, the adult brain of some bird species undergoes quite dramatic organizational, that is, neuroanatomic, seasonal variations (e.g., Nottebohm, Nottebohm, & Crane, 1986; Nottebohm et al., 1987; see Section 3.4.3). For the time being, it seems that the human brain may be less subject to adult organizational variation, but it is known that stress and prolonged or high-dose administration of sex hormones may have deleterious permanent effects (see Section 3.4). On the other hand, mechanically caused lesions may elicit growth effects in the vicinity of the damage.

For simplicity, the following sections are organized in accordance with predominantly organizational or activational effects, respectively. Thus, sections 3.4 (principle 3), 3.9 (principle 8), and 3.10 (principle 9) deal mainly with *organizational* effects. Sections 3.5 (principle 4) and 3.7 (principle 6) provide details primarily on *activational* effects. However, whenever relevant, I will point to exceptions to the too rigid organizational-activational dichotomy in these sections. In addition, sections 3.2 (principle 1) and 3.3 (principle 2) deal with *evolutionary and proximate aspects* of SD, respectively. Section 3.6 (principle 5) discusses the common phenomenon of *conversion* of one sex hormone to another. Section 3.8 (principle 7) treats the ontogenetically very important phenomenon of *sex hormonal co-ordination of trait development*. This principle is, in fact, the backbone of the general model for formalizing the sex hormone coordination of sex-related traits during development (Section 3.8). Section 3.11 (principle 10) calls attention to the principle of *universal economy*.

3.1.2. Overview of Mechanisms of Sex Hormone Actions

Our advancing technology has made it obvious beyond doubt that sex hormones exert pervasive and profound organizational and activational effects in most organisms. Recent research has provided additional important clues as to their mechanisms of action, even though there still are many gaps in our knowledge. A multitude of factors influence the way sex hormones work, and even extremely low concentrations of certain sex hormones can still be biologically very potent. A further complicating factor is that sex hormones pervade most parts of the organism through the blood stream and not only exert profound effects in classical target tissues, but also affect the working conditions of various proteins, neuropeptides, and enzymes by changing cell membrane characteristics in both body and brain tissues, acting much like neurotransmitters. Sex hormones are often made temporarily inactive (see Section 3.9.2); they are later released and become

biologically active in other parts of the body and brain. Most actions of sex hormones further depend on the presence of specific receptors. Such receptors are discretely localized in target tissues, but may come and go during development. Adding to the complexity of this picture, there are individual and sex-related differences in the pattern of uptake of sex hormones. The maturity of the target tissue is another important factor for understanding the actions of sex hormones, regardless of sex. However, there also are sex-related differences in the rate of maturation of various tissues, and these, too, must be taken into account. Sex hormones often act as pro-hormones. This means that when they are metabolized, they will have effects that differ markedly from those to be expected before metabolization (see 3.6).

All these pieces of evidence lead to the inescapable conclusion that it is not enough to determine the plasma concentration of a given hormone in order to predict its effects on the organism. We also need to know the effects of the many modifiers of hormone actions. Moreover, many effects of sex hormones depend on the dose: high, intermediate, and low doses may have completely different effects. Different doses of one hormone sometimes produce what appears to be a paradoxical effect (see 3.7). All these factors make any simple assumption about the actions of sex hormones unwarranted. Nonetheless, they also hold the key to explaining how sex hormones have so many subtle, and some not so subtle, effects.

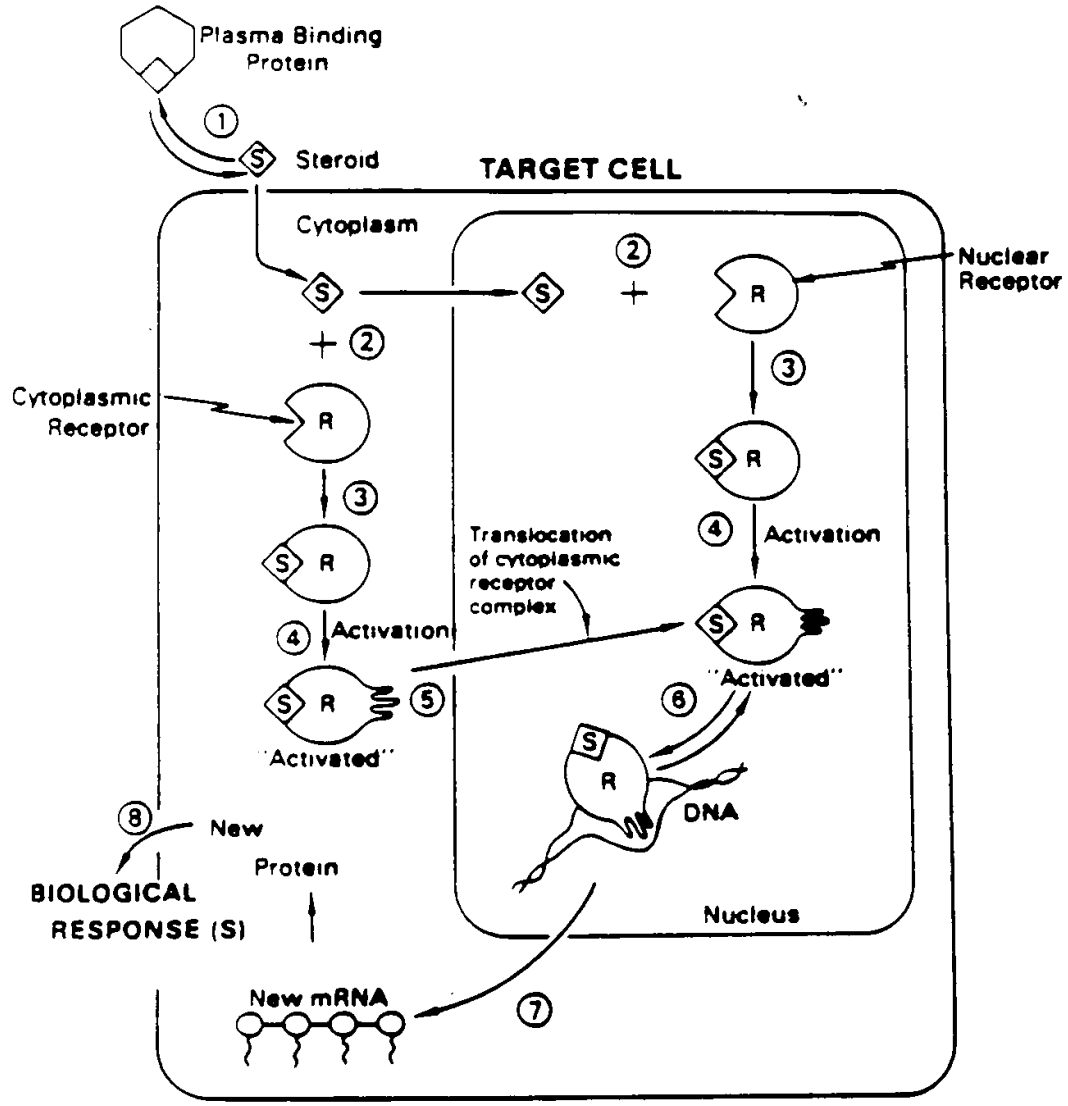
A terminological problem deserves a note here. The term *sex hormone* is used in this book despite its somewhat unclear status. Thus, various adrenal hormones also influence sex-related development, and so-called female sex hormones (estrogens) may masculinize in high doses. One solution to the problem is to use the term *gonadal hormones* instead of *sex hormones*, but this term also has its problems. The proper solution, of course, is to refer to the actual chemical constituents and to the reactions they give rise to, but this would not serve the purpose of this book, which is not primarily directed to chemists. However, I will stick to the use of *sex hormones*.

With these reservations in mind, in the following I will discuss three generally accepted major roads of sex hormonal actions: (1) actions on the genome, (2) actions on cell membranes, and (3) interactions with neurotransmitters.

3.1.2.1. Actions on the Genome

An avenue of action of sex hormone on the genome is through the cell nucleus (Fig. 3.1 after Norman & Litwack, 1987). The hormone is bound to a receptor after entering the target cell, and the cytoplasmic hormone–receptor complex enters the cell nucleus after activation, binding to a part of the gene with high affinity. Actually, there is some confusion as to whether the receptors are situated in the cytoplasm or in the cell nucleus with no sex hormone molecules available. Nonetheless, intracellular sex hormones in-

Figure 3.1
How plasma sex hormones regulate the expression of genes



Most of the sex hormone is chemically bound by protein in plasma (1), but the free fraction can enter the target cell (2) and is bound to a receptor, which is either in the cytoplasm or in the nucleus (3). After activation (4) the *cytoplasmic* hormone–receptor complex enters the nucleus (5) and then binds (6) to a part of the gene with high affinity. Alternatively, the *nuclear* hormone–receptor complex is activated (4) and then binds directly (6) to the gene. There is some discussion as to where the intracellular hormone receptor is situated, and accordingly which way the receptor–hormone complex goes. In either case, the result is gene transcription, new messenger RNA, and a new protein that can be utilized in body and brain tissues for structural or functional ends.

Source: Reproduced with permission from Norman & Litwack, 1987, p. 23.

itiate a process that eventually activates (or suppresses) gene transcription, brings about new messenger RNA, and furthers the production of what that gene is coded for: a particular enzyme, a neurotransmitter, a structural protein, or the induction of receptors important for the actions of neurotransmitters. A brief exposure to estradiol (E_2) can, for example, differen-

tially induce synthesis of some proteins, while at the same time the synthesis of other proteins will be suppressed (McEwen, 1988a, b). The products of gene activation and RNA synthesis are typically seen twenty minutes or more after hormone exposure, but the effects on the organism often outlast the systemic presence of the activating hormone. A definite temporal change in the pattern of synthesis is observed over the next few hours after infusion. This suggests that E_2 triggers a whole cascade of genomic activational events, which eventually either exert transient effects on the working conditions of neurotransmitters or may result in more lasting changes in the number and projection of synapses.

Because hormonally induced gene effects are delayed in onset and prolonged in duration, the level of hormone in plasma and target tissues does not always correlate directly with the effect. McEwen, Luine, Fischette (1987) have discussed whether there is a sex difference in genomic responses to E_2, and speculated whether sex-specific chromosomal proteins in the cell nucleus could mask or modify acceptor and effector sites on the gene on which the hormone–receptor complex acts to regulate transcription. This could explain why E_2 in some cases activates different biochemical responses in males and females, despite the similarity in the pattern of uptake in a given tissue (McEwen, 1987).

Ample evidence thus confirms that sex hormones enhance or suppress gene expression. The products are biologically active after a delay (minutes to days) at nearby pre- and postsynaptic sites, but they may also be transported to distant parts of the system before having an effect. It is food for thought to realize that the generalized effects of sex hormones on gene transcription are observable in all sexually differentiated species hitherto studied (McEwen, Krey, & Luine, 1978) and that the specific final effects, of course, depend on which genes are available for expression in a particular species. It appears that evolutionary processes are economical and use quite similar well-tested systems in many different species. Apparently, relative simplicity is a prerogative in evolution. As Jacob states, evolution "does not produce innovations from scratch. It works on what already exists, either transforming a system to give it a new function or combining several systems to produce a more complex one. . . . evolution proceeds like a tinkerer. . . . It is probably at the molecular level that the tinkering aspect of evolution is the most apparent" (1982a, p. 34ff., 1982b).

3.1.2.2. Actions on Cell Membranes

It is debatable whether hormones exert direct effects on cell membranes or whether the putative membrane effects may show up in the final analysis to reflect the genomic actions of the same or different hormones (McEwen, 1988a). But one thing is clear: Hormones can elicit very rapid systemic responses. Catechol estrogen, provided in supraphysiological concentrations, elicits a response within milliseconds, and intravenous infusion of E_2

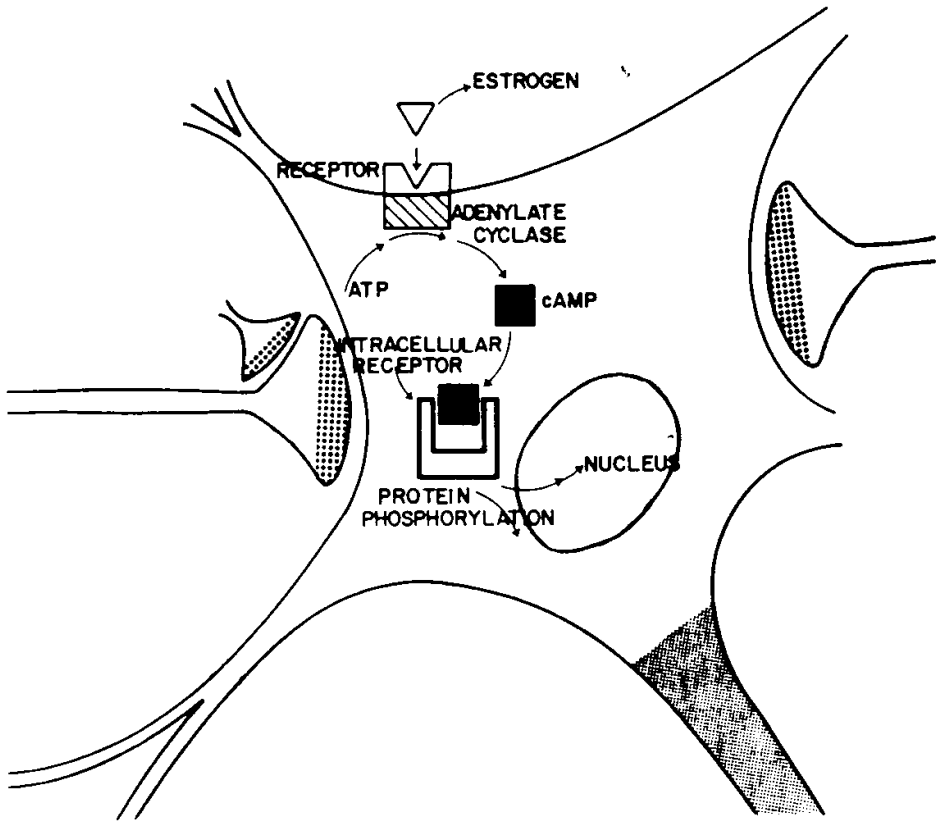
inhibits pulsatile LH release within minutes (Blake, 1974; Blake, Norman, & Sawyer, 1974). Nabekura et al. (1986) investigated the excitability of neurons by intracellular recording from brain slices of neurons in the rat medial amygdala. They found that E_2 produces rapid hyperpolarization and increases potassium conductance, so that the ionic conductance of the postsynaptic membrane of the medial amygdala neurons is rapidly affected. Dufy et al. (1979) injected E_2 directly onto the membrane of excitable cells in a prolactin-secreting pituitary cell line, and observed via intracellular microelectrode recordings that action potentials were induced within a minute. Such reactions seem much too fast to be accounted for as a result of a genomic cascade of events. Figure 3.2 illustrates membrane-mediated effects.

Estrogen is capable of stimulating intracellular production of cAMP by interacting with receptors in the cell membrane, but without actually entering the cell itself. cAMP next binds to an intracellular receptor and stimulates protein production which affects various intracellular processes. Yagi (1973) administered estrogen intravenously to the preoptic and hypothalamic areas of castrated female rats and noted a transitory increase in firing rates in some units, with a mean latency of response of between 15 and 16 minutes. Kelly, Moss, & Dudley (1977) applied 17-beta-estradiol hemisuccinate microelectrophoretically to the medial preoptic-septal unit throughout the estrous cycle of female rats, and found that this form of estrogen produces direct and rapid changes in the firing frequency of neurons. Orsini (1981) observed that testosterone (*t*) can also elicit rapid responses in rat lateral hypothalamic areas; some cells increased, while the firing rate of other cells decreased, with a latency of about five minutes. Yamada (1979) applied *t* iontophoretically to the preoptic area and lateral septum of male rats and noted responses within a few seconds. In such cases, either direct membrane effects of the hormone can be suspected, or a third mechanism must be made responsible.

Another observation dovetails nicely with the idea of a membrane effect, but is difficult to explain in terms of a genomic effect. Some hormone effects last only as long as the steroid is present. Drouva et al. (1984) investigated the effects of E_2 on LH-RH release from rat mediobasal hypothalamic slices. They concluded that E_2 selectively and specifically modulates process coupling, nerve ending depolarization, and LH-RH release by receptor-mediated effects without nuclear translocation of the steroid or transcription processes because the effects can be obtained even upon addition of the hormone to nerve endings disconnected from their cell bodies.

Hormonal effects on pre- or postsynaptic membranes in one area of the brain may result in rapid chemical changes in other brain areas, provided they share neuronal projections, but regardless of whether these connected brain areas themselves contain hormones (McEwen, Krey, & Luine, 1978).

Figure 3.2
How plasma estrogen affects nerve cell membranes



Plasma Estrogen affects nerve cells through a membrane-mediated action much like that suggested for some neurotransmitters. Estrogen interacts with receptors on the cellular membrane, and this interaction stimulates intracellular production of cAMP, which then binds to an intracellular receptor. This stimulates protein production and affects intracellular processes. Estrogen stays outside the cell during the process. The cellular response to estrogen can sometimes be seen within milliseconds as the membrane-mediated action circumvents the more time-consuming genomic activation processes.

Source: Reproduced with permission from Moss & Dudley, 1984, p. 11.

3.1.2.3. Interactions with Neurotransmitters

The traditional view that neurotransmitters are either excitatory or inhibitory can no longer be sustained. Presynaptic membranes have receptors that respond to transmitters just released from that membrane and that adjust subsequent releases correspondingly. Presynaptic membranes also have receptors that respond to transmitters produced by neurons in the vicinity. Postsynaptic dendrites are sensitive to their own neurotransmitters and can influence presynaptic neurotransmitter release as well.

Sex hormones interact with neurotransmitters (Dörner, 1981). For example, priming the female rat brain with estrogen for several days results in a decrease in monoamine oxidase (MAO) levels (Luine & Rhodes, 1983). If the animal is previously exposed to E_2, the administration of progesterone

results in a rapid increase in MAO activity. These observations are interesting from a behavioral point of view because variation in MAO may be related to intelligence and to abnormal personality functioning in humans (e.g., af Klinteberg et al., 1987), as well as to brain development (Lauder, 1983). Alteration of MAO activity changes the turnover rate of monoamine serotonin, and this transmitter degradation seems to facilitate the defeminizing actions of *t*. MAO activity also degrades catecholamine. E_2 treatment leads to an increase in the enzyme for acetylcholine formation in the basal forebrain, which innervate cortical and subcortical structures that seem to play an important role in intellectual functioning. E_2 further reduces the formation of the rate-limiting enzyme for the generation of dopamine in the basal hypothalamus (Blum, McEwen, & Roberts, 1987). Blocking MAO activity by drugs results in antidepressant effects on mood. Depression of mood is a relatively common phenomenon when estrogen secretion decreases in premenstrual and perimenopausal women. Progesterone can rapidly reverse the effects of E_2 and elevate MAO activity.

Dose and duration are critical parameters for sex-related effects of steroids (Section 3.7). Thus, low-dose E_2 decreases MAO in males but increases, or has no effect on, MAO activity in females. High-dose estradiol decreases MAO in both sexes (Luine & Rhodes, 1983). Variation in the dose of early estrogen priming has sex-related consequences for later actions of progesterone on MAO. Thus, with low-dose E_2, later administration of progesterone increases MAO activity in females but not in males (V. N. Luine, unpublished, in McEwen, 1987). A combination of early organizational and later activational effects of sex hormones seems to be related to neurochemical sex-related differences in cholinergic and monoaminergic systems in hypothalamic and preoptic areas, in the aromatization of t, and in the actions of the neuropeptide angiotensin II on thirst (McEwen, Luine, & Fischette, 1987).

These examples represent only a few of the many systemic interactions between sex hormones and neurotransmitters. Neurotransmitters are, in turn, known to be capable of influencing the organizational as well as activational actions of sex hormones. Thus, we talk about tightly integrated systems in which sex hormones can act very much like neurotransmitters and neurotransmitters may have profound effects on SD.

3.1.2.4. Conditions Modifying the Actions of Sex Hormones

A number of factors modify the actions of sex hormones. For example, α-fetoprotein (AFP) and sex hormone binding globulin (SHBG) bind and temporarily inactivate gonadal hormones to release them later (3.9.2). Hormones are biologically active only in their free form. As mentioned earlier, gonadal steroids exert many of their effects through receptors. A receptor is a protein with a binding domain for a particular hormone as well as for DNA. Hormones catalyze a conformational change in the

receptor in such a way that its DNA-binding domain is exposed. This makes it possible for it to interact with an enhancer-like part of the gene (Danielsen, Northrop, Ringold, 1986; Yamamoto, 1985).

The brain has receptors for all six kinds of steroid hormones: androgens, estrogens, progestins, glucocorticoids, mineralocorticoids, and vitamin D. However, the present work focuses mainly on the role of estrogens and androgens or their receptors. Estrogen and androgen receptors are present in all vertebrate classes of fish, amphibians, reptiles, birds, and mammals studied to date (Pfaff & McEwen, 1983), but, as previously hinted at, there is some confusion as to where in the cells the receptors are localized in the absence of a hormone. King & Greene (1984) found estrogen receptors in the nuclei of target cells, whereas Fuxe et al. (1985) localized receptors in the cytoplasm of cells with no available hormone. The spatial and temporal distribution of receptors is important because it determines, in part, which effect a particular hormone may have on neural development and functioning. In an evolutionary perspective, it is interesting to observe that the distribution of receptors shows major similarity across species. Thus, Kelley & Pfaff (1978), Kim et al. (1978), McEwen (1981), Morrell et al. (1979), and Morrell & Pfaff (1978) have reviewed the evidence on hormone-sensitive cells in representative species of the major vertebrate classes and noted the following basic commonality in distribution. Estrophilic neurons are localized predominantly in the pituitary, hypothalamus, medial preoptic area, and amygdala, with smaller concentrations in the hippocampus and midbrain central gray (Pfaff & Keiner, 1973). Androphilic neurons show a similar, though not identical, pattern of distribution, and there seem to be fewer differences in the concentration between brain areas (Sar & Stumpf, 1977). A few species [e.g., the amphibian *Xenopus laevis* (see Kelley, Morrell, & Pfaff, 1975; Morrell, Kelley, & Pfaff, 1975), the reptile *Anolis carolinensis* (Morrell et al., 1979), and the song bird *Poephila guttata* (zebra finch: Zigmond, Nottebohm, & Pfaff, 1973)] diverge from the basic pattern.

Progestin receptors show two different distributions in the rat brain. Estrogen-inducible progestin receptors can be observed in the pituitary, hypothalamus, and preoptic area, while nonestrogen-inducible progestin receptors figure in all parts of the brain, including the cerebral cortex where there are few estrogen receptors (McEwen et al., 1983).

Superimposed over the basic distribution plan are species-specific and individual variations in receptor distribution. These variations contribute to mammal cross-species diversity and to intraspecies differences, with respect to which hormones activate sexual behavior or cause SD and the extent to which particular traits undergo SD (McEwen, 1981; see Section 3.9.2).

Receptors show species-specific temporal variation with respect to appearance and disappearance. For example, estrogen receptors are hardly discernible in the rat in the early part of the fetal period. However, over the

last few days before birth there is a ten- to twenty-fold increase in the number of receptor molecules. This is followed by a more gradual increase during days 1–5 after birth (Friedman et al., 1983). The dramatic increase in the number of receptors is positively correlated with the onset of the so-called defeminization process, with an increased aromatization of *t* to E_2, with the presence of AFP, and with the appearance of new neurons (Gerlach et al., 1983). A surge in androgen receptors becomes evident about a week later than the increase in estrogen receptors (Lieberburg, MacLusky, & McEwen, 1980). The adult cortex contains relatively few sex hormone receptors, but cortical cells may have induced receptors early in development, which disappear during later development for reasons unknown. Presently, we know very little about their possible function in cortical development. In contrast to brain sex-typing in the rat, sex-typing of the human brain seems to take place much earlier during fetal development.

Adult sex differences in the overall distribution of estrogen and androgen receptors appear to be rather small, despite the fact that large subcortical sex differences in distribution have been observed during early development in rats (3.3.2, 3.3.3.1, and 3.5.3). Rainbow, Darsons, & McEwen (1982) noted that the medial preoptic area in the female rat has a higher estrogen receptor concentration than has the corresponding male area (3.10.2).

Sex hormones can induce neurotransmitter receptors, and this development may profoundly affect brain functioning. For example, E_2 elevates the level of receptors for acetylcholine, serotonin, and noradrenaline in discrete areas of the brain, and increases the neurotransmitter sensitivity of neurons. In addition, E_2 is antidopaminergic. There are sex-related differences in the impacts of sex hormones on neurotransmitter receptor regulation. McEwen (1988a, b) demonstrated that estrogen administration may lead to a 30 percent increase in the binding of alpha-2–receptors, which respond to catecholamine such as norepinephrine in some brain areas, while other estrogen-sensitive brain areas showed no change. The rat serotonin-1–receptor system is differentially sensitive to E_2 priming in males and females: Gonadectomized male and female rats show differences in binding to serotonin-1–receptors when exposed to identical estrogenic stimulation (Fischette, Biegon, & McEwen, 1983).

The importance of studying the powerful effects of sex hormones on the working conditions of neurotransmitters can hardly be overemphasized. Such studies may contribute to our understanding of temporary or permanent variations in the sensitivity of the central nervous system to incoming stimuli during puberty (3.3.3.2, 3.7.5), menstruation (3.5.3), adulthood (3.5.5), and during depressive illness (Charney, Menkes, & Heninger, 1981).

Certain enzymes can radically modify the effect of sex hormones by transforming them into an alternate form with different biological effects. For example, *t* can be reduced to dihydrotestosterone with

masculinizing effects, or aromatized to E_2 with either feminizing or masculinizing effects (3.6.2).

One sex hormone may inhibit or facilitate the action of other hormones in several different ways. For example, estrogen administration suppresses gonadotropin secretion, which, in the case of sufficiently high doses or prolongation of treatment, may result in a regression of testicular size and in a downregulation of androgen secretion (e.g., Meyer et al., 1981). Estrogen further increases the concentration of globulins capable of binding androgens in humans (Murray et al., 1975). High plasma androgen concentrations may also suppress gonadotropin secretion, resulting in a downregulation of estrogen secretion. Androgen may compete with estrogen at the estrogen and progestin receptor binding sites through the aromatase enzyme system. A number of "pseudo-hormones," among them certain drugs and synthetic steroids, may also play a significant role in such competitions (McEwen, 1988a; 3.3.3.3).

The endocrine system is sensitive to a multitude of inter- and extrasystemic environmental circumstances. Factors like stress, nutrition, drugs, and smoking by pregnant women are all part of the fetal environment. Perception of people and assessment of potential mates or dominant others significantly affects the adolescent and adult hormone system, which, in turn, feeds back on perception. It is vital for an organism to pick up and react correctly to subtle proceptive cues in order to successfully mate. This entails an intricate harmonization of the complex machinery of hormones that in no way seems to presuppose the intervention by desires. Perception is basically systematic modulation of neurotransmitters (2.3), and this may accomplish an induction of receptors for sex hormones (McEwen, 1988a). Conversely, sex hormones affect the induction of receptors for neurotransmitters. The exploration of the full implications of these dynamic processes is worthwhile because it provides us with important clues for an adequate physicological description of organism–environment relationships that supersedes our traditional body–mind, gene–environment, nature–nurture, and social learning paradigms. It also allows a search for the missing molecular links among perception, intelligence, personality, and emotions. The unification of these often separated topics is a major goal of the General Trait Covariance–Androgen/Estrogen (GTC) model (see sections 3.5, 3.7, and 3.8). The establishment of a coherent framework for understanding their ontogenetic and phylogenetic place in an entirely physico-chemical world is an important goal for the physicology program.

To summarize, sex hormones profoundly affect somatic and brain tissues by exerting organizational, activational, or combinatory effects. The effects take place via actions on the genome, on neurotransmitters, and on cell membranes. A number of factors influence the actions of sex hormones, and sex hormones can, for example, be inactivated by other chemicals. Sex hormone effects further depend on the presence of receptor molecules.

Although each sex hormone has its own type of receptor, several sex hormones or drugs may compete for identical binding sites. There are similarities but also some differences in the number and distribution of receptors (see Section 3.4.4) with respect to species, sex, and time in ontogenetic development. Sex hormones may be transformed to another hormone before action. For example, *t* can be reduced to dihydrotestosterone or aromatized to E_2 with quite different effects. Sex hormones interact with each other and with neurotransmitters. Numerous environmental factors drive neurotransmitter, sex hormone, and transmitter-hormone interactions. Each of these factors must be entered into a comprehensive and dynamic formula for sex differences in development and behavior, and this is worth keeping in mind when reading the following pages.

The remaining sections of Part III purport to illustrate ways in which the physicological perspective on these physico-chemical interactions enlarges our understanding of human nature and society. It is rather obvious that we still have a long way to go before we have the necessary data and that the process of collecting it will tax the technical skills and ingenuity of neuroendocrinologists, neuroanatomists, medico-technicians, and behavioral scientists for years to come.

3.1.3. Prelude to Extraction of Principles for Actions of Sex Hormones

The next section lists eleven general principles for steroid processes. It also illustrates how the physicological program attempts to bridge interdisciplinary gaps between the organism and its environment, and to connect the body with phenomena that are said to reflect the mind. Examples are provided to illustrate how combinations of gene–hormone–experience principles explain the environment–hormone–body–brain–behavior–society relationships in a scientifically more satisfying way than do the traditional mind–biology hybrids. Experiments designed to test implications of the principles are outlined, and reference is made to how the principles fit the notion of universal physico-chemical evolution.

The extraction of principles is based on human as well as on animal data. However, this raises the question about to which extent cross-species generalizations of hormone effects are valid. Animal data are used primarily because they can be collected in strong experimental designs which, for obvious ethical reasons, do not invite human participation. Such data make it possible to see whether similar *principles* are at work by comparing the consequences of well-controlled sex hormonal manipulations in animals to those from less well-controlled data on normal, medicated, or abnormal human groups. From a research-strategic point of view, it is indeed encouraging to know that the chemical structure of all the major sex steroids and of the receptor molecules show a high degree of cross-species similarity

(3.2.1). Moreover, the biochemical agents responsible for male and female development exhibit considerable evolutionary stability. This partly justifies making cross-species comparisons. However, the many factors involved in hormone actions and the genetic diversity remind us to be very cautious at all times. Even though basic principles of steroid actions show similarities across species, they may come in many shades. Important details vary with the kind of animal in question, but this variation may conversely mean that similarity in human–animal principles of steroid actions may easily be missed because sex hormones can actualize during ontogeny only those genes that selection allowed to remain in the DNA memory during phylogeny.

It is true that all living organisms share genes, but their genomes also differ in important respects. Thus, similarity in principle of hormone action may easily be masked because hormones activate different genes, although they do so through similar mechanisms. Obviously, rearing and selective pressures differ among species, and there is also a certain biochemical variation in response to sex hormones. Balancing the overall equation, it nevertheless seems feasible to generalize from principles for animal to principles for human sex hormone actions, as long as the limitations are kept in mind. The payoff is high: We gain experimentally well-controlled insight into what sex hormones mean to organismic growth and functions, and we may catch a glimpse of what this implies for individual and intersystemic (collective) interaction. The price we have to pay is running the risk of making false analogies.

The principles of sex hormonal actions presented in the following sections are based on a substantial body of evidence provided by innumerable researchers in recent years. In order to maintain clarity in the presentation, I have remained highly selective throughout the choice of data. I concentrate on a few representative studies and present evidence mainly from rat, mouse, bird, monkey, and human studies. In the case of human studies, I focus primarily on studies of spatial and verbal abilities, on selected personality traits, on aspects of social interaction, and on the influence of a few environmental factors. Even within this narrow framework, I make no attempt to provide the reader with a scholarly review. My more modest aim is to bring together sufficient information to support the notion that sex hormonal actions explain these few but essential aspects of the SD of body, brain, and behavior, as well as to illustrate that basic sex-related aspects of the evolution of intelligence, personality, society, and culture can be satisfactorily described entirely in terms of physico-chemical processes and principles. For the sake of coherence in presentation, I will at times formulate the principles in a way that deviates slightly from previous use. In such cases, or where others have already formulated workable principles, I will refer to the previous terms and to the authors thereof.

3.1.4. Preview of the Principles of Sex Hormonal Actions

Principle 1: Selective pressures in the past provide the ultimate evolutionary explanation for today's sexual differentiation.
This is *the ultimate cause principle.*

Principle 2: Sex hormones are the primary ontogenetic agents for sexual differentiation.
This is *the proximal cause principle.*

Principle 3: Sex hormones promote growth and induce permanent morphological and chemical changes—the so-called organizational effects—in target tissues.
This is *the organizational principle.*

Principle 4: Sex hormones may cause transient changes in the phenotypic expression of a sex-dimorphic trait.
This is *the enhance–suppress principle.*

Principle 5: Testosterone can exert indirect organizational and activational effects in the brain if the enzymes necessary for aromatizing or reducing testosterone are present.
This is *the conversion principle.*

Principle 6: Optimum development, organization, or functioning of estrophilic brain tissues depend on a range of intermediate cerebral estradiol concentrations.
This is *the optimum range principle.*

Principle 7: Sex hormones coordinate the timetables for the concerted appearance or disappearance of sex-related body–brain–behavior traits.
This is *the covariance principle.*

Principle 8: The fetus possesses the potential for graded sexual differentiation (SD).
This is *the multipotentiality principle.*

Principle 9: Low fetal E_2 feminizes the brain, whereas higher concentrations masculinize it.
This is *the estrogen alone–brain sex principle.*

Principle 10: Growth and functional capacity is subject to physico-chemical constraints, so that strong development or activity in one area is traded off by less development or activity in other areas.
This is *the economy principle.*

Principle 11: Sex hormones enhance individual phenotypic variability within and across male and female genotypic modal ontogenetic development.
This is *the individuality principle.*

Chapter 4

Physicological Analysis of Sexual Differentiation (SD)

3.2. EVOLUTION AND ULTIMATE CAUSES OF SEXUAL DIFFERENTIATION

3.2.1. Introduction

Principle 1: Selective pressures in the past provide the ultimate evolutionary explanation for today's sexual differentiation.

This is *the ultimate cause principle.*

To avoid misunderstanding, the term *ultimate* is used here to point to past circumstances in the physical environment thought to have exerted a selective pressure on organismic physico-chemical processes and mechanisms. In this book, the notion of ultimate causes always takes the form of hypotheses formulated in as pragmatic terms as possible. It should never be taken to refer to shrewd ideas about final causes or to connect to a particular philosophical position (see Section 4.2). On the contrary, the principle is actually used in such a way that it leads to simulation of circumstances that come pretty close to those believed to have existed during primitive times, and then to facilitate a scrupulous test of the explanatory power of evolutionary hypotheses (see Section 3.2.4).

The ultimate cause principle states, in effect, that remote intra-, inter-, and extrasystemic factors prompted the evolution of SD. The hypothesis implies that, in order to fully understand the manifestations of contemporary sex-related human differences, we must dig into our evolutionary past. The ultimate cause principle is based on the traditional point of view that SD is the result of selective pressures favoring particular phenotypic variations. Sexually reproducing organisms stand a better chance of surviving

and reproducing than do asexually reproducing organisms when living under unstable physical conditions. The basic reason is that, even after extreme changes in conditions, a few sexually reproducing individuals might survive, thanks to the particular arsenal of abilities conferred on them by parents bringing swiftly together beneficial mutations and by combining processes responsible for expressing beneficial traits. Even small advantages in survival value and reproductive success may be favored in the long run. For reasons given in Section 3.2.3 it seems that positive selection for each beneficial trait will not go on unlimited. Rather, the rule seems to be that there will eventually be a balanced selection among various physico-chemical body and brain processes, thereby optimizing coordination of the varying needs arising from sexual reproduction, increased variability, and protection of the offspring.

3.2.2. Operationalization of Evolutionary Variables

A physicological post-hoc analysis of the evolution of SD would remain incomplete without a discussion of ways to specify the relevant variables, their mechanisms, and their most important interactions. First, hypotheses about the physical nature of the early extrasystemic selective pressures must be developed. They must be followed by a qualified specification of which chemicals became available for selective pressures to act upon, which physico-chemical processes they led to, their intrasystemic locus of action, and the intrasystemic mechanisms through which they enabled intrasystemic harmonization of SD of body and brain tissues. This is the way to illustrate how intersystemic (interpersonal) behavior became optimally regulated, and how it best fitted other prevailing extrasystemic circumstances (adaptation, selection).

The major problem involved in reconstructing our most remote molecular past is that we can only make more or less qualified guesses about the early and later phases in the physico-chemical series of events that led up to the appearance of living systems. Delbruck (1978) saw this as "perhaps *the* fundamental question of biology," and several brilliant brains have tried to provide an answer. For example, Fox (1988) has discussed the fascinating story of the origin of life on earth, and he refers in some cases to experimental evidence in support of the hypothesis. Fox sees the suggestion that living processes must have originated somewhere other than on earth, where conditions were different (Crick, 1981), as "defeatist and unimaginative" (p. 66). Fox acknowledges his debt to Fritz Lipmann at Rockefeller University for emphasizing the importance of appreciating biochemistry as chemistry and for stressing the notion that energy flow is a physical rather than a chemical phenomenon with a strongly thermodynamic flavor. A true physicologist would certainly applaud Fox's view on the continuation of life processes as purely physico-chemical phenomena but until better data

become available would reserve judgment with respect to whether life processes came from outer space or arose here. The physicologist would definitely be surprised to find a clear reminiscence of mentalist and superorganismic reasoning as when Fox presumes that nonoperationalized culture can determine battles among different groups (p. 165), that mechanisms for evolution beyond the nervous system have made thoughts provide bonding much like energy couplings, and that with the brain, a new kind of life has emerged: multiindividual organisms (p. 166).

Fox's account of the very physical nature of the early selective pressures and of the chemicals and interactions involved is rather dispassionate, however, and can briefly be summarized as follows. The gravitational collapse of stars converts energy into heat and light, and drives the fusion of protons into α particles and then into carbon nuclei, under the release of tremendous nuclear energy when mass is converted to energy. More matter formed as temperature and pressure fell. Stellar nucleosynthesis resulted in the formation of elementary chemical elements, combining first into small molecules under the influence of natural energy sources. These basic building blocks of living systems form spontaneously from the primordial elements and, can now be reconstructed in the laboratory. They are also seen in interstellar space, in meteorites, and on the surface of the moon. Of the initial twenty-six elements, there is a primordial dozen elements of particular interest for understanding the genesis of early living systems, namely, the monomers—amino acids, sugars, and purine and pyrimidine bases, and a few others. They have the capability to link together into large oligomers and into still larger polymers or proteins, depending on the release of energy harvested from the breakup of phosphate bonds.

A highly interesting, almost alive-system intermediate step can be seen: the proteinoid microspheres. When particular combinations of amino acids are dry heated, they automatically turn into thermal proteins or proteinoids. If they are then dissolved in water, they spontaneously assemble into microspheres about 1 micrometer in diameter, wrapping a thin, sometimes double-layered, membrane around them. The membrane provides some protection from harsh geophysical processes and tends to keep the acids chains inside while allowing some chemicals and protons to cross. One species of such proteinoids can, in fact, act as a melanocyte-stimulating hormone, causing black spots to appear on frog skin. It actually has a particular sequence of amino acids comprising the active part of the hormone. The whole series of processes led eventually to the formation of the huge double-stranded polynucleotide known as DNA or chromosome, under the initial influx of geophysical and later of phosphate-derived energy. Chromosomes hold genes. A gene is actually an activated or deactivated portion of the DNA material, containing the coded instructions for specifying the amino acid sequences for building proteins needed for initiating and sustaining the general characteristics of living systems, in-

cluding the variations in excitable muscle and nervous tissues that make the differences between a bacterium, a human being, and an elephant. The differences among them are due to differences in the organization of matter rather than to differences in molecular constituents and mechanisms.

In order to understand living systems, it is important to realize that their behavior springs from the fact that they require transfer of higher order energy from the outside for buildup and maintenance of the system. Typically, this transfer requires that the systems must move—that is, behave. Movement often requires much fuel. The search for fuel can be either passive or active behavior. Passive behavior, such as flowing with the stream or for the wind, is relatively cheap but haphazard. The collection of energy can be improved by chemical warfare, such as when enzymes emitted by the passive mover breaks down suitable protein material in competitors that had the bad fortune of going the same way. Active movement is more advantageous, but it also costs more in terms of energy spending and can be very dangerous owing to increased exposure to predators or the risk of exhaustion. Active movement requires the evolution of a multitude of specialized instruments such as fins, wings, or legs. A central nervous system enhances the coordination of movements, and proper functioning of various sense organs for orientation, attack, or retreat. Tough competition necessitates a selection among various versions of instruments and nerve systems for optimum performance.

Aside from the general need for movement for fueling living organisms, most sexually differentiated systems have to move to find suitable mates for reproduction purposes. This can be tough and specialized work that often involves considerable expenditure of time and energy; thus, the evolution of SD is a story of its own. We know that sexual reproduction took place long before humans appeared on the earth (see Ghiselin, 1974; Symond, 1979). Molecularly speaking, cholesterol has played an important role in the evolution of SD. Being an essential element in the structure of cell walls, cholesterol is abundantly present in all living organisms. More to the point, cholesterol is *the* chemical from which all sex steroids are to be derived. It is found in the few survivors from about 300 million years ago that still are around today. Interestingly, however, these worms, snails, and fish are hermaphrodites, and they use gonadotropins to mobilize their primordial germ cells (Witzmann, 1981). The later, more complex differentiation required further specialization in the form of (1) physical separation of male and female traits, but also (2) restrictions on this process of differentiation, so that females and males could still meet for mating, and quite importantly (3) harmonization of male and female behavior for optimal rearing of the offspring (at least in some species). Individual survival is fine, but evolution is basically driven by the differential survival of offspring.

The double task of sexual specialization and mate synchronization was made possible through the evolution of enzymes, and some of these en-

zymes metabolized cholesterol to androgens. Other enzymes allow androgens either to be aromatized to estrogens (often with feminizing effects) or to be reduced to dihydrotestosterone (DHT, typically with masculinizing effects). Sometime during evolution, a primitive Y chromosome appeared. Despite probably having few functional genes on board, this little Y chromosome greatly enhances male SD because it is capable of stimulating the development of specialized testicular tissue and thus amplifying the intrasystemic secretion of androgen.

The evolution of enzymes, the differentiation of secretional tissues, and the powerful chemical compounds that followed gave rise to many new traits for selection to work among. Sex hormones facilitate and direct the growth and functioning not only of the reproductive organs, but also of the body in general, of the brain, and behavior. Aside from penile growth, androgens promote strong bones, narrow hips, broad shoulders, the accumulation of muscular tissues, a deep voice, aggression, and dominance. Estrogens have in certain, but not all, respects the opposite effect. At the peripheral level, estrogens promote a delicate body build, broad hips, narrow shoulders, early closure of the growth zones of bones, fat accumulation around hips, and breasts. Estrogen seems to relate to behavioral submissiveness. However, these opposite effects of androgens and estrogens must be seen in proper perspective. It is true that physico-chemical evolution seems in general to work against concomitant excessive estrogen-induced accumulation of fat *and* androgen-induced heavy musculature in one and the same person. It is also true that the agonistic effects of sex hormones may explain the molecular nature of the phenotypic antagonism, but Section 3.11 discusses important compromise solutions in one and the same individual.

Intrasystemically, selection also took place among steroids for receptor binding sites. All this made it possible for extrasystemic selection to work on chance variations in intrasystemic steroid chemistry through individual variations in body and brain function, with the resultant differentiation into two, and only two, intraspecies types of organisms: a lean, tall, strong, fast, mean male with a predominant androgen/estrogen balance, and a smaller, softer, more delicate, copious, and sociable female with generous nutritional reserves and a predominant estrogen/androgen balance. Some species do deviate from this general pattern, but they are outside the scope of this book and so are not discussed here.

The main point here is that androgens and estrogens are for two good reasons well suited for coordinating the timetables for male and female body, brain, and behavioral development and for making the necessary reproductive adjustment to the opposite sex possible (3.8). First, androgens and estrogens exert intrasystemic effects that spread out to all parts of the organism and, second, androgens and estrogens exert, in many respects, antagonistic influences on body and brain development and functioning.

In mediating their effects, the secretion of gonadal steroids is adjusted and curbed by dynamic, fine-gauged, intrasystemic positive and negative feed-forward and feedback control mechanisms. Moreover, the endocrine system is constantly linked via neurotransmitter-mediated variations to changes in the extrasystemic environment. In this ingenious handshaking among various intra-, inter-, and extrasystemic molecular systems lies the explanation of how it becomes possible to harmonize the right appearance and functioning of the right organs and to initiate the right behavior at the right time for successful reproduction (3.8), in the presence of the right mate partner at the right time of the day or year. Steroid processes *are* the modus vivendi of sexually reproducing species, and with even minor disturbances of the steroid system, extinction is guaranteed.

3.2.3 The Price of Specialization

SD of the body and the brain, and its concomitant behavior, the sexual reproductive mode, has a price: a specialization of functions within a species. Details of the nature of this tradeoff are considered in Section 3.11 (the economy principle). Suffice it here to state that the two slowly evolving sexes became increasingly subjected to a series of different selective pressures. Organisms that evolved as females became positively selected on a strongly competitive basis for producing relatively large eggs rich in nutrition, for attracting and mating with capable males, for effectively carrying one or more fetuses in the womb, for perfecting breast-feeding, and for expert rearing of the offspring after birth. This selection eventually led to specialization of behavior through the optimization of several intrasystemic processes. These processes differed in complexity from those of the presexual period but were nevertheless based on the same old well-tested physico-chemical principles that also applied before the differentiation process.

Organisms gradually evolving into males also had to compete and were harshly selected among. Males, capable of using specialized techniques for common hunting of big game, of fighting individually for breeding ground and of attracting females, of supporting the mate, and, in some species, of helping protect the offspring, began to dominate the evolutionary scene. Males were often exposed to life-threatening situations during hunting and fighting, so the selective pressures on physico-chemical processes and mechanisms beneficial for performing these activities were probably very harsh. Unfit individuals faced sudden death, and the less adequate physico-chemical organization they represented disappeared from the evolutionary scene. The male-female difference was further enhanced because it became increasingly difficult for females to smoothly combine newly evolved specialized and sedentary reproductive functions (e.g., being pregnant) with the daring and strenuous task of hunting big game. The result was that

they became subjected to sets of self-reinforcing selective pressures during their relatively brief life span. Most of them probably spent their adult life being pregnant, breast-feeding, and short-distance foraging. Despite this self-reinforcing tendency, it is important to note that the sex-related physico-chemical and behavioral differences thus accomplished increased only up to a certain point. Then, a stabilization or tradeoff between traits seems to have taken place. Too aggressive men and too sedentary women were probably too expensive in terms of evolutionary economy (3.11).

3.2.4 Problems with Evolutionary Theory

Evolutionary theory presents a serious problem in that we can only guess about the precise physico-chemical nature of the selective pressure of the past. This is the main reason why a theory of human evolution must be developed in retrospect. It also explains why there are unpleasantly few constraints on the development of evolutionary theory and why evolutionary theory sometimes reflects an unhealthy air of speculation and abounds with "just so" solutions and fabrication of hypothetical variables. In Section 2.6, I ventured the daring notion that the classical Darwinian model of evolution is a special case of a more general principle of survival of the economically most efficient and stable physico-chemical system. A reference was made to Edelman's (1987) discussion of the Darwinian-like selection of brain cells during development, and this provides a good beginning for further developing the idea. Many more cells are manufactured during development than is found in the adult brain. Apparently, there is a selection for certain cells that survive. Some of the losses of cells seem explainable in terms of selective cell death (Ebbesson, 1984; Hinchliffe, 1981; Hinsull and Bellamy, 1981; Wyllie, 1981). A growing body of evidence suggests that steroids are heavily involved in programmed cell death actions (Bowen, 1981; Brawer & Naftolin, 1979; Brueckner, Mares, & Biesold, 1978; Gorski, 1984; Greenwald & Martinez-Arias, 1984; Keyser, 1983; Toran-Allerand, 1984a, b; Truman & Schwartz, 1984).

It may be possible to use these mechanisms to test several hypotheses about the evolution of SD in a compressed time perspective, employing available quantitative methods. Consider the following possibility. A series of experiments are undertaken with a number of rather large populations of genetically different, say, inbred, but all sexually multipotent castrated individuals of a given species. These groups are then administered various sex hormones in accordance with different treatment schedules, and each single individual's social and reproductive success is monitored across a variety of environmental circumstances. By simulating selective pressures of the past (or present), it might be possible to experimentally test a number of implications of the hormone principles presented in various parts of this book. We could, for example, examine whether a given gene–sex hormone

combination leads to predicted covariant change in somatic development, in brain functioning, in intellectual specialization, and in a particular kind of behavior. It could then be determined how this experimentally manipulated intrasystemic specialization influences the individual's intersystemic relationships to mates and offspring, and to which extent it facilitates or hinders adaptation to particular extrasystemic conditions—in short, how it affects that particular population's probability of survival. Some such data are already available from a number of studies, but they often focus on quite limited aspects of the problems and rarely consider testing evolutionary hypotheses in a large perspective.

It should be possible to perform more comprehensive studies in which intra-, inter-, and extrasystemic variables are varied quantitatively and in such a way that broad hypotheses about the evolution of SD can be mimicked. Breeders of domestic animals have more or less systematically followed similar models for thousands of years. Now we are able to measure sex hormone concentrations quite accurately, have begun to elucidate sex hormonal mechanisms of action, and can monitor their impact on the body and brain with several nonintrusive techniques, it seems possible to begin large-scale testing of basic aspects of the evolution of SD in a convenient time-slice perspective. Indeed, the near future holds great promise. In addition to declaring that the 1990s is the decade of the brain, we might perhaps also humbly suggest that this is the decade when we finally became prepared to experimentally recall our molecular past, general and sexual.

Chapter 5

The Proximate Cause of Sexual Differentiation

3.3. RESEARCH ON THE PROXIMATE CAUSE

3.3.1. Introduction

> Principle 2: Sex hormones are the primary ontogenetic agents for sexual differentiation.
>
> This is *the proximate cause principle.*

The notion of proximate cause, as defined here, is a rather comprehensive principle. At the intrasystemic level, the principle stipulates that sex hormones govern SD by modulating the expression of available genes for body and brain development and by altering the working conditions of neurotransmitters over the entire life span. The proximate cause principle also implies that many social events at the intersystemic level are caused or colored by the proximate actions of sex hormones. Thus, phenomena referred to as sex role behavior, love, submission to dominance, sexual attraction, mate preferences, and sex-related differences in social play, education, occupation, and the power structure of society are hypothesized to reflect the proximate physico-chemical effects of sex hormones on the body and the brain.

The proximate cause principle is fully compatible with sex-related mentalistic concepts such as social norms and cultural stereotypes, which are convenient short-hand names for categorizing the effects of sex hormones. As mentioned previously and again later, the descriptive categories themselves are not here ascribed any causal status whatsoever. Unfortunately, often this is surprisingly taken to mean that the proximate cause principle automatically downplays the impact of the environment. Such an interpre-

tation is a complete misinterpretion of the position. The proximate cause principle *in no way* neglects the powerful effects of environmental factors. Literally hundreds of reports have clearly documented that intersystemic (social external) and extrasystemic (nonsocial external) factors have profound effects on the body, the brain, and sex hormone secretion via neurotransmitter modulation and otherwise. The misunderstanding seems essentially due to the unpreparedness to realize that inter- and extrasystemic effects may be less based on easily fabricated descriptive categories than on very concrete changes in the physical circumstances in the environment (Section 2.4), which affect the organism within limits laid down by a combination of its genetic equipment and previous exposure to its physical environment (learning, nutrition, etc.).

The following sections in this chapter provide an overview of some areas to which the proximate cause principle applies. References are given in the overview to later chapters where particular aspects of the proximate cause principle are discussed in more depth.

3.3.2. Animal Research

Bouin & Ancel (1903) were among the first to reinstate the ancient idea that sex hormones are heavily involved in SD. Since then, several lines of positive evidence have been established. One early line concentrated on showing that sex hormones exert profound effects on the genitals and on sexual behavior, defined, however, in a narrow reproductive sense. A more recent line has demonstrated that variations in the balance of various sex hormones correlate not only with brain development but also with variations in broad areas of nonreproductive behavior.

Pfeiffer performed a number of experiments in 1935 and 1936. He concluded that rats start life with a sexually neutral pituitary and that steroid hormones are capable of overruling genes in determining their SD. Two years later, Dantchakoff (1938) demonstrated that treating pregnant guinea pigs with androgens will masculinize the adult reproductive behavior *of the offspring*. Later studies indicated that early castration, combined with adequate sex hormone manipulation, or precise hormone manipulation alone (Phoenix et al., 1959), or receptor failure (3.4), may reverse whatever sexual development could be expected on the basis of genetic sex. Phoenix and colleagues suggested that the effects of sex hormones naturally come in two different types: "organizational" (3.4) and "activational" (3.5; also see 3.1.1).

Singing in canaries—among several species of birds (the passeriformes)—is predominantly an adult male behavioral specialty. Female canaries sing little or not at all. In addition, castrated male canaries keep silent. Nottebohm (1980a, b, 1981), Nottebohm & Arnold (1976), and Zigmond, Nottebohm, & Pfaff, (1973) became interested in this phenomenon and in a

series of studies demonstrated that the intrasystemic presence of testosterone is needed for singing in canaries to take place. They also demonstrated that silent female and castrated male birds begin to sing if treated properly with testosterone (3.4.3).

Maze learning in rats involves several spatial as well as memory components and shows a sex-related difference in adulthood. Male rats typically begin to outperform female rats at puberty. Quite interestingly, this is not so much because the males become better, but rather because many females begin to make more errors at that time than they did before. Then, Dawson (1972; Dawson, Cheung, & Lau, 1975) in an early series of experiments, demonstrated that castration of females prevents the appearance of the sex-related difference in spatial ability and that estradiol treatment made males begin to make more errors than they did before the treatment. These results suggest that the rat's sex-related difference in expression of spatial ability depends on timing, availability, and kind of sex hormones. On the other hand, the studies needed replication in better controlled experiments. Since then, a number of studies have confirmed many of the earlier observations. For example, Williams, Barnett, & Meck (1990) looked systematically at various aspects of the spatial performance of rats in a modified radial arm maze. They were able to confirm that controlled early sex hormone exposure indeed has selective effects on performance (3.4.3).

It is not entirely clear which mechanisms enable sex hormones to procure a sex difference in spatial performance in rats. One possibility is that sex hormones affect motivation, emotion, or explorative tendencies differentially in the two sexes and that this explains the differences in maze performance. However, as long as terms like *motivation, emotion,* and *exploration* are left undetermined, we have no operationalizable hypotheses to test. A second, more precise set of hypotheses is that sex hormones affect morphological brain lateralization through permanent organizational effects and that asymmetrical brain organization results in high spatial performance (3.3.3.1, 3.4.4). A third hypothesis is that sex hormones exert activational effects on the brain, with concomitant but transient changes in spatial ability (3.5.3).

3.3.3. Human Research

In view of its potential importance for understanding basic aspects of sex-related human behavior today, it is interesting to find that ideas closely associated with the proximate cause principle were already quite familiar to members of the Hippocratic school in classical Greece more than two thousand years ago (Hippocrates, 1968, 1972, 1979, 1981). These early scholars regarded healthy human development and functioning as a matter of a proper balance between bodily fluids or "humors." Of course, without

the aid of modern molecular technology they erred in many empirical matters and were forced largely to remain satisfied with intuition and common sense—fragile tools indeed. The ancient characterization of humors must, among other things, be taken lightly. Nevertheless, the classical scholars got many aspects of modern endocrinology right. Organ (read: target receptor) satiation, for example, was a well-known principle to them. Centuries later, another famous Greek scholar, Galenos from Pergamon, refined the then already old humoral theory and made it a leading concept in medicine for ages to come (Daremberg, 1885; Galen, 1979; Irwin, 1947; Siegel, 1973). After the brilliant contribution of Galenos, no major development was made in humoral theory until fairly recent years.

Human male fetuses are more active than female fetuses, and newborn males move around more and make more noises than do newborn females. Men behave significantly more aggressively than do women, especially around puberty and early adulthood. Adult men commit far more violent crimes than do women. However, after the age of 35 to 40, the male crime rate drops gradually, so that in late adulthood and in old age the sex differences in activity, aggression, and crime are minimized (Danmarks Statistik, 1985; Moyer, 1974; Reid & Wormald, 1982). According to the proximate cause principle, such sex differences and their timetables reflect the proximate prenatal and postnatal effects of testosterone or other androgen metabolites. The first step in testing the hypothesis of a testosterone–aggression relationship is to document a temporal covariance between the two. After puberty, this requirement is not difficult to meet. The pubertal increase in male physical activity, aggression, and crime and the decrease in old age corresponds fairly well to increases and decreases in testosterone production over the life span. The next requirement is to demonstrate that the relationship is of a causal rather than of a correlational nature. This requirement is more difficult to meet, even though a growing number of studies support the hypothesis of a causal relationship (3.5.5).

The proximate hypothesis of a hormone–aggression connection makes sense in light of the ultimate cause principle. Males, according to this principle, have been selected throughout evolution for testosterone-related strength, activity, and aggression. Obviously, a male with an abnormally high testosterone level and overly aggressive behavior would run the risk of being severely wounded in repeated fights or of being rejected by potential mates. His probability of having numerous surviving offspring would be reduced accordingly. The economy principle (3.11) addresses the possibility of a stabilizing effect of selection for intermediate hormone levels (3.7) and predicts enhanced but still tempered aggressiveness in males as compared to females. Random variations in testosterone around the male mode might explain behavioral plus and minus deviations. The principle obviously predicts more aggression in high-*t* females than in low-*t* females. Evidence for this is now accumulating (3.5.4).

3.3.3.1. Brain Lateralization

Brain lateralization studies do not always present an uneqiuvocal picture of sex differences. It is not entirely clear for example, how large the sex differences are in degree of brain lateralization. We are not quite sure whether the putative differences have an anatomical or a functional basis. We do not even know exactly what brain lateralization means to behavior. Numerous early studies and some more recent ones found that the male brain is more unilaterally organized than the female brain, perhaps even before birth or at least from age 13 onward. Other studies find no or just marginal differences (3.4.4).

The proximate cause principle implies that all sex-related differences, both anatomical and functional, in brain specialization are a function of differential exposure to sex hormones. The study of people with prenatal hormone abnormalities is a good testing ground for the principle, because early hormonal aberrations can be expected to lead to variations in brain lateralization. Preliminary evidence indicates that prenatal hormone deficits or medication of pregnant women by hormones or pseudo-hormones may, in fact, have an effect on brain lateralization (3.4.4).

3.3.3.2. Ability and Personality

Human spatial abilities are to some extent influenced by sex hormones and seem to be sex-limited. However, these abilities seems to be neither sex-linked nor fundamentally masculine (McGee, 1979; Nyborg, 1979, 1981, 1983, 1986a, b; Vandenberg & Kuse, 1979). The proximate cause principle accounts for sex differences in spatial ability development as well as for the large male-female overlap in distribution in terms of effects of sex hormones mediated via differential activation of genes and modulation of membrane characteristics and neurotransmitters.

To be sure, the expression of spatial ability is, according to the proximate cause principle, exclusively a function of physico-chemical processes. Thus all intermediate steps in these processes can and should be examined in as intimate detail as available techniques permit (3.5, 3.7). The proximate cause principle further implies that variations in sex hormones have an impact on all those other abilities that show sex-related differences. Accordingly, sex-related differences in verbal ability, motor skills (Nyborg, 1981; 3.5.3, 3.11.4), in play patterns and rough-and-tumble play (3.5.2, 3.5.4), in general intellectual development (3.7.5, 3.7.6), in pre- and postpubertal educational and vocational interests (Nyborg, 1983; 3.5.3), and in personality, including gender identity (Nyborg, 1984), can be explained in terms of the effects of sex hormones. In the remaining chapters of Part III, I will describe details of some of the hormonal mechanisms that most likely will be found to lie behind the manifestation sex differences in various trait combinations.

3.3.3.3. Clinical Aspects of Sex Hormonal Actions

The impact of normal variations in plasma sex hormones has not yet received the attention it deserves. In contrast, we know a great deal about the effects of abnormal sex hormone variations. The impacts of some of the abnormal sex hormone variations on body, brain, and behavioral traits are illustrated in Section 3.4.6. Medically caused androgen-induced aggression is discussed in Section 3.5.4.

The physicological program focuses on molecular processes. The following chapters therefore detail ways of operationalizing the relevant processes and point to behavioral consequences whenever possible.

Chapter 6

Permanent Organizational Effects of Sex Hormones

3.4. RESEARCH ON PERMANENT EFFECTS

3.4.1. Introduction

> Principle 3: Sex hormones promote growth and induce permanent morphological and chemical changes—the so-called organizational effects—in target tissues.
>
> This is *the organizational principle.*

Sex hormones significantly affect body and brain tissues and permanently shape the body and brain in male or female directions. By doing so sex hormones give later behavior definite form and direction. This much is now clear beyond doubt. Unfortunately, however, many gaps remain in our knowledge of the exact nature of these processes. What is more, relevant research is often performed in highly sophisticated research environments, and key reports occasionally appear in a form that makes it difficult for a nontechnical reader to judge their behavioral implications. Adding to the complexity of the problem is the fact that the organizational effects of sex hormones come in many shapes. For example, estradiol affects not only neuronal number and size, but also dendritic size, branching and spines, numbers, types and organization of synapses and synaptic organelles, axonal density, and nuclear and neuronal volume (Toran-Allerand, 1984a, b, 1986; Toran-Allerand, Gerlach, & McEwen, 1980). The maturational stage of estrophilic tissue is of decisive importance in ascertaining the potential effects of estradiol. This hormone is particularly effective in stimulating dendritic branching during early "sensitive" periods. A comparable estrogen exposure outside this sensitive period will either be less effective, be

without effect, exert a completely different permanent effect, or even have temporary activational effects. The brain of many species responds with few, if any, neuro-architectural changes to estradiol exposure in adulthood. A further complexity is that sex hormones themselves may in part determine the time when neural tissues become less plastic and open for organizational effects of steroids (3.7.5, 3.11.3) and open to learning (3.11.3).

In addition to morphological changes, sex hormone exposure may also result in permanent neurochemical reorganization. Studies by McEwen and others (see De Vries et al., 1984; McEwen, 1980, 1981, 1983) confirm that gonadal hormones exert permanent organizational changes at the molecular level. Such early organizational effects interfere with later activational effects of sex hormones, so that priming of the prenatal brain by sex hormones may preset adult brain sensitivity to circulating hormones by, for example, permanently modifying the regulation of the number of adult receptor molecules. This dependency of the late on early hormone effects makes it quite difficult to predict the size of adult activational responses to circulating plasma concentrations, unless the organism's previous hormonal and experiential history is also known (3.12).

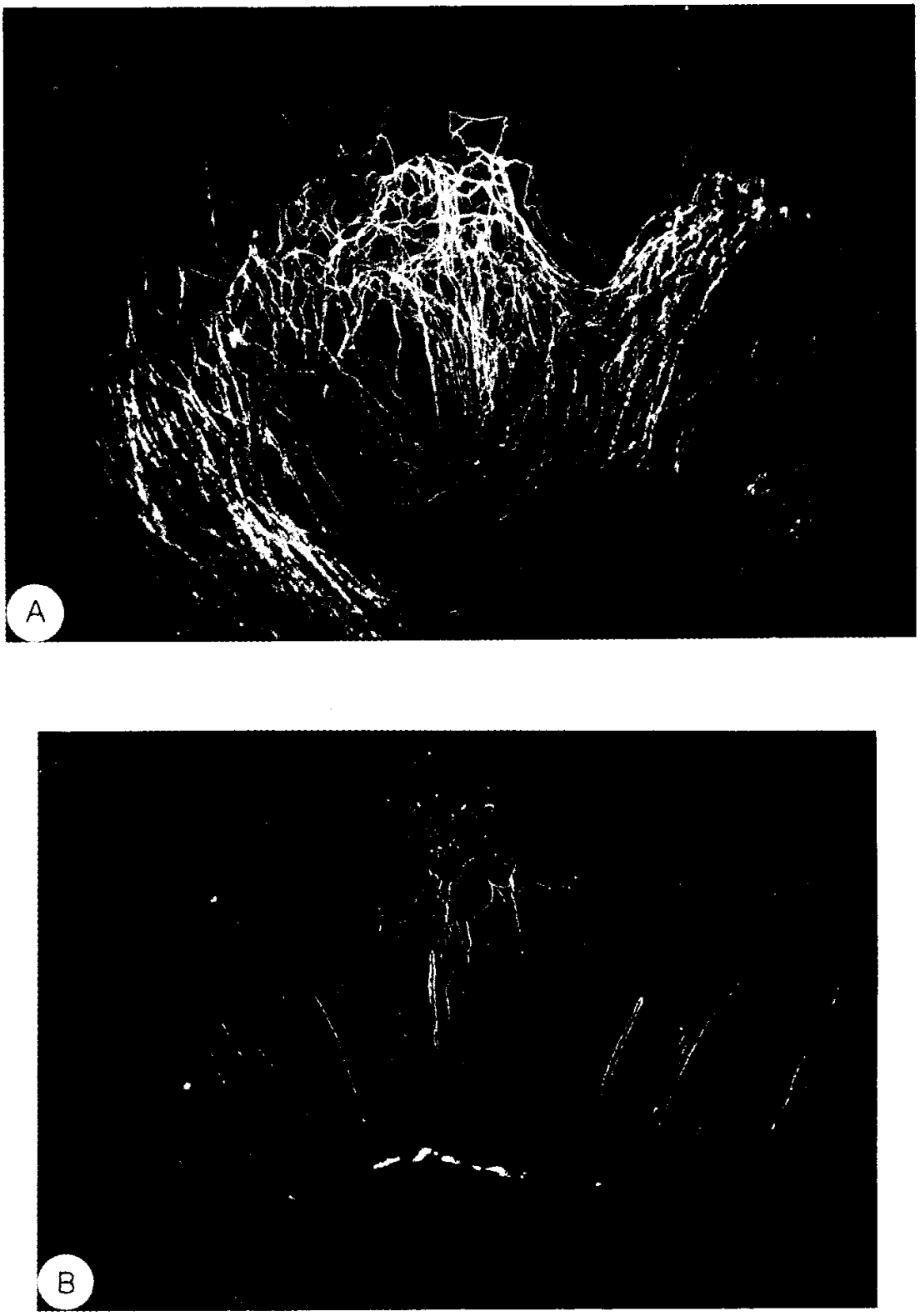
3.4.2. In vitro Studies

Studies by Toran-Allerand have been seminal in answering questions about the induction of neuronal growth by estradiol. In a series of in vitro studies (1980a, b), Toran-Allerand first cut neighboring pairs of slices out of the preoptic area of male and female newborn mouse brains. She then cultivated one of the two homologous explants in serum that contained antibodies to bovine serum albumin (A in Figure 6.1). The other piece of homologous explant was kept in serum containing antibodies that inactivated the estradiol present in the serum (B in Fig. 6.1). The experiment showed that inactivation of estradiol is related to a radical reduction of neuritic outgrowth in male as well as in female mouse brain tissues. In another experiment, Toran-Allerand exposed homologous mouse brain explants to serum containing estradiol in either a small amount (200 pg/ml) or in a somewhat higher concentration (50 ng/ml).

The effects of exposure to the lower concentration of estradiol can be seen in A, and the effect of the stronger concentration is illustrated in B in Figure 6.2. Clearly, exposure to the higher estradiol concentration is accompanied by impressive neuritic branching in estrophilic brain tissues. Testosterone was not nearly as effective in promoting neuritic branching in the tissues studied.

Tobias & Kelley (1986) isolated the vocal organ and afferent nerves in the African clawed frog (*Xenopus laevis*) and demonstrated that such a *vox in vitro* preparation is able to produce the male mate call when stimulated

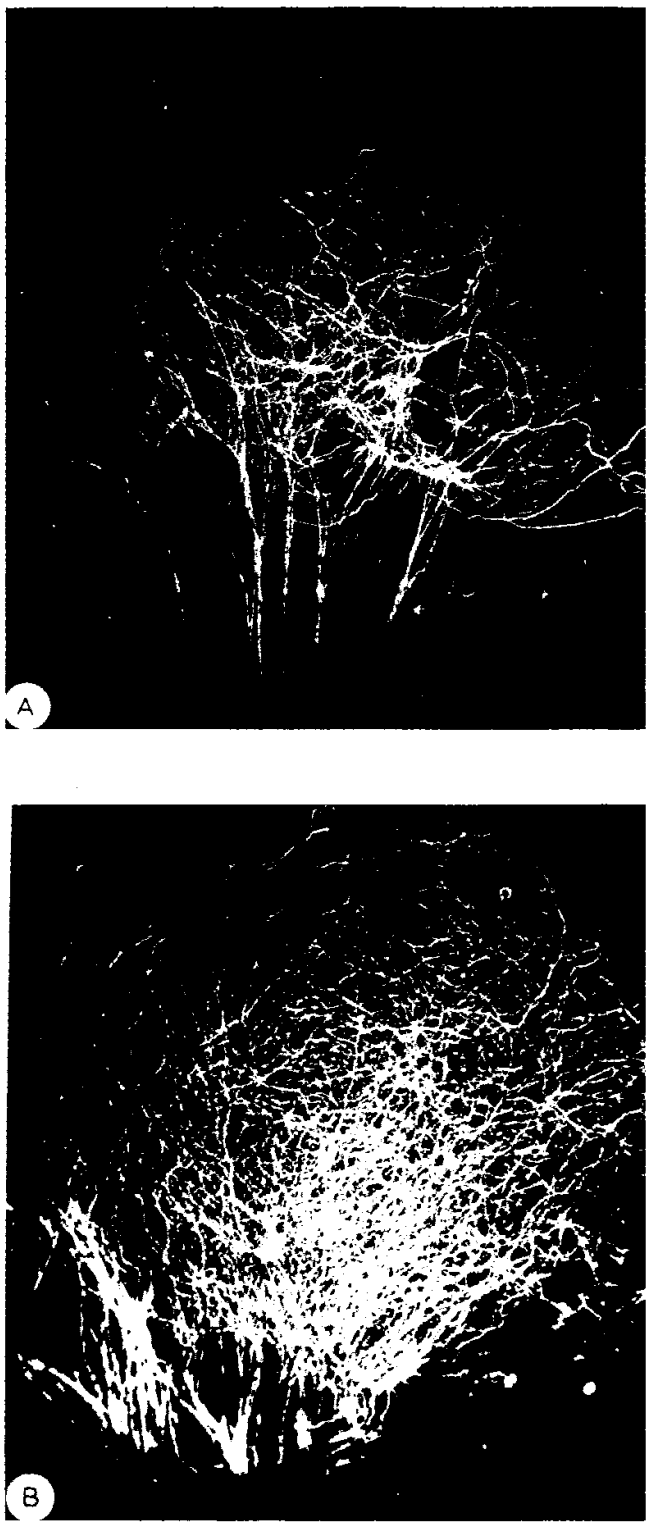
Figure 6.1
Importance of estradiol for neuritic development



Homologous pair of explants from the mouse preoptic brain area was exposed in vitro to serum containing either (A) antibodies to bovine serum albumin or (B) antibodies to estradiol. The physiological inactivation of estradiol in (B) resulted in a striking reduction of neuritic outgrow.

Source: Toran-Allerand, 1980b.

Figure 6.2
Steroid induction of neuritic branching in homologous pair of 17-day fetal or newborn mouse brain slices.



The explants are from the mouse preoptic area, 13 days in vitro. (A) Control (horse serum, endogenous estradiol 200 pg/mL); (B) 50 ng/mL in horse serum. The high unit density in (B) is striking and suggests that estradiol induce neuritic branching.

Source: Toran-Allerand, Gerlach, & McEwen, 1980.

electrically. They also found that *vox in vitro* systems are not equal: only preparations that were androgenized prior to isolation were capable of uttering the fast trills required for effective mate calling (Kelley, Morrell, & Pfaff, 1975; Kelley et al., 1989; Kelley & Pfaff, 1978; Kelley & Tobias, in press). This experiment shows that the frog's capability to behave adequately in social encounters, leading to successful reproduction, depends on precise steroid priming of the brain as well as of the peripheral laryngeal apparatus. The GTC model suggests that human socio-sexual interaction also depends on precise hormonal priming (3.8.4).

3.4.3. Animal Studies

Male and female canaries begin life with a sexually neutral brain. The neural song centers of the female canary contain the same type of androphilic neurons and the same number of primary dendritic branches as do the male song centers (Gurney, 1983). However, grown-up male canaries sing in nature, while female birds and castrated males mostly keep quiet, unless they are treated with testosterone. It is assumed that testosterone exerts early organizational effects in the canary by promoting neuronal growth and differentiation of specific brain areas. In particular, testosterone (or its metabolites) augments the number of dendritic segments per unit in the song centers of the canary brain and generates new synaptic connections in the bird brain. The buildup presumably increases the transmission capacity of the neural song system (DeVoogd, 1984) and enables the bird to sing. With regard to hormonally conditioned social interaction, male singing elicits in the hormonally prepared female canary a cascade of endocrine reactions, so that the behavioral and hormonal synchronization of mating behavior becomes possible (Section 3.8). The scenario of Romeo, singing under the balcony of the beloved one, may bear more than a superficial resemblance.

The medial preoptic area of the rat brain shows no sex-related differences before birth. However, shortly after birth *s*exually *d*imorphic *n*uclei become visible in the *preo*ptic *a*rea (*SDN-POA*; see Gorski, 1984). From then on, there is a greater number of neurons in that area in the male than in the female rat brain. The sex difference in volume is so conspicuous that it can be seen with the naked eye in preparations of brain tissue sliced on a glass plate. The Gorski group followed up on this study and demonstrated that castration results in a reduction, whereas testosterone *or* estrogen supplementary medication restores the neuronal volume. They concluded that the size of the sex-related difference in SDN-POA volume can be monitored completely by exogenous steroid manipulation and that ordinary sex-typing of this area of the rat brain depends on systemic sex hormones. The full behavioral implication of the androgenized SDN-POA is not completely understood, however. A small lesion dorsally to the SDN-POA disrupts

male copulatory behavior, and a transplant of brain tissues, taken from a newborn androgenized SDN-POA rat brain, enhances male *as well as* female copulatory behavior (Arendash & Gorski, 1982).

Swanson (1988) called attention to a possible relationship between stress, testosterone, SDN-POA, and brain lateralization. Prenatal stress, for example, has been shown to depress fetal testosterone, resulting in inhibition of male SDN-POA development (Anderson, Rhees, & Flemming, 1985) and cerebral lateralization (Fleming et al., 1986). The adult rat corpus callosum is made sex-dimorphic through the early organizational effects of sex hormones. Berrebi et al. (1988) found that the adult male corpus callosum is larger than the female callosum, even after controlling for differences in brain size. This seems to be an effect of prenatal testosterone because Fitch, Berrebi, & Denenberg (1987) found that testosterone treatment enlarges the female callosum, whereas male castration on day 1 had little effect in reducing male callosal size.

Williams, Barnett & Meck (1990) studied the spatial performance of rats in a radial arm maze. They compared the performance of (1) neonatally castrated and later sham-operated males, (2) neonatally sham-operated control males castrated at about 45 days of age, (3) females treated with 10 micrograms of estradiol benzoate on postnatal days 1, 3, 5, 7, and 9, and gonadectomized at about 45 days of age, and (4) oil-treated control females, gonadectomized at about 45 days of age. Gonadectomy at puberty was performed to avoid possible confounding activational effects owing to adult hormone secretion. Williams and her co-workers found that the performance of neonatally castrated males was uniformly substandard during acquisition, whereas the performance of oil-treated, gonadectomized females was highly variable. Neonatally, both the estradiol-treated females and the late-castrated control males showed a significantly faster acquisition performance than the two other groups. Eventually, the learning curves reached a similar asymptote for all four groups; this finding, according to the authors, could not be explained by a test-specific ceiling-off effect. Williams and co-workers concluded that early sex hormone manipulation has an effect on the acquisition rate in maze learning and that estradiol is the active agent. The study is interesting for two reasons. First, it shows that the organizational effects of early hormone manipulation promote differences in adult acquisition rate in a spatial task. Second, the effect seems to level off with training.

The Denenberg group has found that sex hormones significantly influence rat maze learning in a swimming version of the Lashley III maze. It was concluded that female rats rely primarily on extra-maze information. Male rats seemed to utilize both intra- and extra-maze information, and therefore show better performance (Denenberg, Berrebi, & Roslyn, 1988; Freter et al., 1987).

The precise nature of the relationship between sex hormones, brain organization, and spatial ability is not known in detail, and there are several possible accounts. As mentioned previously, one possibility is that early sex hormone exposure has a permanent anatomical effect explaining brain lateralization and spatial performance. The Williams study mentioned above and the following observations are relevant for discussing this option. First, the left cortex in the adult female rat is thicker than the right. Second, gonadectomy completely reverses this sex difference. Third, the right cortex of the adult male is thicker than the left. And fourth, gonadectomy partly reverses this pattern (Diamond, Dowling, & Johnson, 1981; Diamond et al., 1983; Pappas, Diamond, & Johnson, 1978). Sandhu, Cook, & Diamond (1986) confirmed the previous finding of Friedman et al. (1983) that the number of estrogen receptors reaches a zenith on days 2 and 3 in both left and right cortex, regardless of the sex of the rat. Sandhu and his colleagues further noted that the female right cortex contains significantly more estrogen receptors during this high estrogen concentration period than does the left cortex, whereas the male cortex exhibits the exact opposite pattern. In addition to the observed morphological difference, a sex difference in lateralization of cerebral blood-flow pattern has also been observed (Ross, Glick, & Meibach, 1981).

Sandhu and his co-workers interpret their observations in terms of the growth-inhibiting effects of estrogen: The female right cortex is growth-inhibited because of the high estrogen uptake, whereas the left cortex is spared owing to the decreased responsiveness to estrogen. In males, the left hemisphere is growth-inhibited by the high estrogen uptake.

The Sandhu group's notion that estrogen inhibits left hemispheric growth in males clashes with Geschwind & Behan's (1982) notion that androgen inhibits male left hemispheric growth. Each of these two accounts could explain the prominence of right hemispheric growth in males (3.3.4.1), but the two notions raise questions about which hormone, or what hormone ratio, is actually responsible for the sex differences in cerebral brain growth. Still, a solution to this problem would not tell us whether the adult difference in spatial performance is best explained in terms of early organizational or later activational effects. The Geschwind and Behan suggestion is problematic for other reasons as well. First, the idea of a neuronal growth inhibition effect of androgens is not based on much empirical evidence. Second, there are few, if any, sex differences in lateral cortical androgen receptors induction, so that a hemisphere-specific testosterone–brain growth connection is not secured. Sandhu and co-workers' notion that estrogen may be involved is more plausible because estrogens are known for their impressive effects on neuronal growth (e.g., Toran-Allerand, 1984a, b). However, the Sandhu interpretation may need an addendum to correct for the nonlinear dose-response effects of estradiol. This suggestion, and the question of whether the early organizational effects of

sex hormones on cerebral lateralization fully explain the expression of spatial ability in adulthood, are addressed more fully in sections 3.4.4 and 3.7.2. These sections suggest that early hormones may have an organizational effect on anatomical brain lateralization and that they may play a role in presetting later sensitivity to sex hormones via regulation of the numbers of receptor molecules. As the sections show, however, the early effects explain neither the advent of the adult sex differences nor the dynamic changes in spatial performance in adult females.

3.4.4. Organizational Effects on the Human Brain

The male human brain appears to be more unilaterally organized than the female brain, and this already seems to be the case before birth (Bryden, 1979; Gur et al., 1982; Lansdell, 1964; Levy, 1974, 1981; McGlone, 1978, 1980; McGuinness, 1976; McGuinness & Pribram, 1979; Wada, Clarke, & Hamm, 1975; Walker, 1980; Witelson, 1976).

One way to explain the apparent female brain bilaterality is to assume that the corpus callosum, which connects the two cerebral hemispheres, is larger in women than in men early on, and therefore allows for more direct interhemispheric communication. In fact, de Lacoste-Utamsing & Holloway (1982) and Holloway & de Lacoste-Utamsing (1986) noted such a difference and concluded that the difference was already established by week 26 of gestation (de Lacoste, Holloway, & Woodward, 1986). Byne, Bleier, & Houston (1988), confirmed the existence of a difference by use of magnetic resonance imaging technique. They found that the minimum width of the callosal body is significantly larger ($p = .04$) in women. However, Byne and collaborators made the point that this morphological sex difference is marginal in size, that the corpus callosum is of unknown importance for cognitive functioning, and that a number of other studies were unable to confirm any callosal sex difference (Demeter, Ringo, & Doty, 1985; Kertesz et al., 1987; Oppenheim et al., 1987; Weber & Weis, 1986; see also Hahn, 1987). Witelson (1985) found complex sex–hand preference interactions. She observed that left-handed and ambidextrous people have an 11 percent larger corpus callosum than have right-handers. In a later study, Witelson further noted that the isthmus region of the corpus callosum is 56 percent larger in mixed-handed than in right-handed males but that there is no such difference in females. However, the absolute isthmus region is larger in consistently right-handed females than in consistently right-handed males (Witelson, 1988).

These complex findings indicate that we still have some way to go before we can establish the precise nature, ontogeny, extent, and functional relevance of possible sex-related human morphological brain lateralization. A simple "left-right, large-small" terminology apparently does not apply. The relative absence of positive findings of sex differences using magnetic

resonance imaging techniques is puzzling when compared to the findings based on anatomical techniques, and may in part be a function of the lack of very high resolution of the pictures. Then again, anatomy might tell less about functional brain sex differences than does molecular reorganization. In later sections, I will discuss this matter further and point to evidence suggesting that examination of dynamic molecular reorganization of the brain by sex hormones holds some promise for advancing the study of sex differences in intelligence and personality. The picture is not a simple one, however. Some composite traits (e.g., temperament) may be shaped mainly by early organizational effects, whereas other traits (e.g., intelligence) may depend on both early organizational and later activational effects.

It is by now generally accepted that learning affects morphological brain development after birth. However, learning is probably of much less importance during prenatal growth. This leaves us with either a genetic, a hormonal, or a still not accounted for reason for the observed sex differences in prenatal lateralization of the brain. Fortunately, there are ways to address these questions. If early sex hormones affect brain lateralization in humans as we previously saw they do in rats, we can expect hormonally abnormal groups to vary with respect to brain lateralization. The little evidence there is favors a hormonal explanation. For example, patients with Turner's syndrome suffer from drastically reduced secretion of sex hormones due to atrophy of the gonads. Their parents are in the majority of cases genetically normal in every respect, and Turner syndrome appears with equal frequency in all social groups and societies. The condition seems due to random nondisjunction of chromosomes. Compared to normal females, Turner women show a more than usual bilateral brain organization (Gordon & Galatzer, 1980; Netley & Rovet, 1982). They perform poorly on most spatial tasks and encounter problems with mathematics, but score in the lower half of the normal range in many verbal tasks (Money, 1968; Money & Alexander, 1966; Nielsen, Nyborg, & Dahl, 1977a, b; see also Sections 3.4.7 and 3.7.3). However, Pennington et al. (1985) were able to confirm that spatial abilities are lower than verbal abilities in Turner's syndrome patients, but they were unable to confirm that the minimal overall neuropsychological impairment was lateralized. They concluded that the verbal-spatial discrepancy does not relate to lateralized cerebral dysfunction.

Pennington et al. (1985) also found deficiencies in long-term memory in Turner women, suggestive of anomalies in the medial temporal and hippocampal brain structures. These are the very brain structures that are densely occupied with hormone receptors and thus highly sensitive to sex hormones. The timing of puberty may be normal in patients with Turner's syndrome, but the abnormally low plasma concentrations of steroids have profound effects on the extent of somatic and central nervous development. It has been suggested (Nyborg, 1990b) that the abnormally low prepubertal

steroid output leaves the body and brain of Turner patients open to organizational effects long after the chronological age at which somatic and neuronal plasticity disappears in normals. That being the case, the proximate and the organizational principles provide the basis for the prediction that hormone substitution therapy at puberty or later may exert organizational effects on the body and brains of Turner women. The findings reported in Section 3.7.3 on the effects of pubertal estrogen or adult estrogen–gestagen substitution therapy in Turner women are affirmative (see also 3.8.4.3 and Nyborg, Nielsen, Naeraa, & Kastrup, 1994). There is a great need for histologic studies of Turner patients. To the best of my knowledge, there is only one postmortem neuroanatomic study of (two) brains of Turner women (Reske-Nielsen, Christensen, & Nielson, 1982).

Considering the clinical and theoretical importance of studying the responses of an inherently sex hormone, low brain to treatment in women with Turner syndrome, it is unfortunate that the first analysis of the effects of cyclic estrogen–gestagen substitution therapy on abilities was made in retrospect. When the study began in the late 1960s, an effect of sex hormones on brain development and abilities was not at all expected. The unfortunate result is that we still do not know whether the observed estradiol effects on abilities are of a permanent or a transient nature. Future studies, preferably coordinated on an international basis, should examine the morphological consequences of estrogen therapy of women with Turner's syndrome by neuro-imaging, blood-flow, and other nonintrusive techniques for measuring the brain. Such studies may take as their point of departure the observation that lack of X chromosome material in Turner patients cannot in itself explain their low spatial ability (Nyborg, 1990b; Nyborg & Nielsen, 1981a). A recently concluded Danish study examined covariant trait development and abilities in 9- to 16-year-old Turner girls before and after various combinations of one-year minimal-dose or maximal-dose estradiol, growth hormone, or androgen therapy. The hypothesis was that estradiol treatment would accelerate the development of abilities in a normal female level and that androgen treatment would raise the ability level to normal male levels (Nyborg, Nielsen, Naeraa, & Kastrup, submitted).

Women who are treated with a synthetic estrogen (diethylstilbestrol, DES) during pregnancy, tend to give birth to daughters with a pronounced verbal response lateralization pattern (Hines, 1982). DES-exposed daughters, of course, have a perfectly normal female sex chromosome complement, for hormones probably do not alter basic cytogenetic aspects of the karyotype but rather the expression of available genes. Since learning and genetic factors can probably be excluded as an explanation of a putative early atypical brain lateralization in the case of Turner and DES-exposed women, we are left with a sex hormone explanation. This hypothesis should be tested very carefully, however, because the human evidence for laterali-

zation is not nearly as strong as are the observations of sex hormone involvement in rat brain lateralization.

Evidence for sex-related differences in other areas of the human brain continues to accumulate. In recent years, a nucleus in the human preoptic area has been found to be sexually dimorphic. After having examined more than one hundred human brains, Swaab & Hofman (1984) and again Swaab, Hofman, & Fisser (1988) concluded that the human SDN-POA becomes sexually differentiated much like the rat SDN-POA, but at about the age of 2 to 3 years. The differentiation seems to be due to a *decrease* in the number of cells in the female SDN-POA, whereas the male cell number remains unaltered until about age 50, at which time the number of cells declines sharply.

Long ago, it was observed that the presence in the womb of a male fetus can masculinize the body, brain, and behavioral features of his female co-twin. This interesting phenomenon has been observed in several mammalian species. The hypothesis is that the high male fetal testosterone secretion somehow transfers to the female partner. This phenomenon has been referred to as the inter-sex freemartin syndrome (e.g., Marcum, 1974) and is routinely noted in multiple births in cows. Rat studies suggest that male fetal androgen induction affects later spatial performance in female co-twins. Thus, Williams, Barnett, & Meck (1990) discuss evidence that female rats from litters with a high percentage of male fetuses show more accurate maze performance during acquisition of the task than do females from litters with a low percentage of males. Seen in a cross-species perspective, it is indeed thought provoking to note that Cole-Harding, Morstad, & Wilson (1988) found that female dizygotic twins who had a male co-twin (*o*pposite sex - *di*zygotic: OS-DZ) obtained significantly higher spatial ability scores on the Vandenberg modification of the mental rotation test than did female dizygotic twins whose co-twin was female (SS-DZ). However, it was not before the third test trial that the performance of the OS-DZ females actually equaled that of their twin brothers. In other words, the OS-DZ females showed a slower acquisition rate than males, but they were capable of reaching the significantly higher male than female level of proficiency after some training. As far as I know, the Cole-Harding group considered this potentially very important finding of only minor significance. Today it is still published only in passing as an abstract of a meeting, despite my urging that the information become more widespread. We clearly need more detailed human studies of this phenomenon, preferably involving radioimmunoassay and brain imaging techniques.

Waber discussed whether pubertal changes in sex hormones influence normal human cerebral lateralization processes and whether such an influence could explain her observations of maturation–brain lateralization–spatial ability relationships in humans (e.g., Waber, 1976, 1977, 1979; see also

3.4.4, 3.5.3). Again we need more goal-directed studies and precise measures.

3.4.5. Organizational Changes of the Human Body at Puberty

Sex hormones coordinate the appearance of the secondary sexual body characteristics upon which adequate mating behavior depends. The tremendous surge in sex hormones at puberty at first accelerates and differentiates the development of traits that come to characterize the adult male and female body. For example, early in development, the human female's delicate upper arm contains as many muscle fibers as does that of a heavy male body builder. However, an unknown number of body builders have demonstrated beyond reasonable doubt that testosterone causes male muscle fibers to swell and perhaps also to increase in number. Androgens bear the primary responsibility for the 50 percent male advantage in adult raw strength in the upper part of the body appearing at puberty. Differences in steroid balances, particularly in the hormone secretion timetable, account for the fact that females are one or more years advanced in body and brain development as compared to males.

Boys show a larger growth spurt at puberty than do girls. They also continue to grow for quite a number of years after puberty, under the influence of anabolic steroids, although at a much slower rate. Having had their terrific growth-promoting effects, the steroids eventually cause a closure of the epiphysal growth zones in the bones, and this permanently arrests body growth. The relationship between plasma hormone concentration and bone growth is curvilinear: Intermediate concentrations promote bone growth, whereas large doses inhibit it (see Section 3.7).

3.4.6. Organizational Effects on Personality Traits

3.4.6.1. Effect of Prenatal Progestins and Androgen

Over a period of nearly forty years, millions of pregnant women and their unborn children participated, more or less unknowingly, in a large-scale experiment on the effects of fetal hormones on childhood and adult personality. The women were treated with progestins (some of which are known to have androgenic effects). The treatment was typically justified on the basis that it might prevent miscarriage. Many of the thus treated women gave birth to daughters whose behavior, ability pattern, and personality were more similar to those of their brothers than their sisters (Ehrhardt et al., 1985; also see review by Hoyenga & Hoyenga, 1979). The prenatal progestin treatment also left a mark on adult sexual inclination: A higher than expected proportion of the progestin-treated daughters manifested a bisexual or lesbian orientation.

Many similarities to progestin-provoked development can be observed in girls who, because of a genetic error, secrete higher than usual amounts of androgen prenatally and later (Money, Schwartz, & Lewis, 1984; for general discussion, consult Meyer-Bahlburg, 1984). To be sure, girls exposed to androgen prenatally may develop a perfectly ordinary female gender identity. On the other side, the observations made so far strongly suggest that prenatal sex hormones may *organize* human brain structures and function and influence postnatal behavior in quite a systematic and circumscribed way. In addition, women, exposed to DES during the prenatal period are at increased risk of developing bisexual or homosexual behavior (Ehrhardt et al., 1985; Meyer-Bahlburg et al., 1984, 1985, 1987). In the case of DES, this synthetic estrogen apparently circumvents the ordinary female protection against estrogen, and the additional exposure to the fetal brain of estrogen apparently increases the incidence of bisexuality or homosexuality. Unfortunately, very little is known about the mechanisms and precise locus of molecular action. DES apparently causes no changes in female gender role behavior (regrettably a terribly imprecise term). This is puzzling, because changes in female gender role behavior ordinarily seem to require the presence of androgens, and at least some DES-exposed women showed an abnormally enhanced testosterone production. In male fetuses, prenatal DES exposure reduces testosterone secretion and may lead to moderate reduction of typical adult male gender role behavior. However, increased bisexuality or homosexuality has not been observed in DES males (Ehrhardt et al., 1985). Again, it should never be forgotten that as far as one can tell from available evidence, about 75 percent of the prenatally DES-exposed women develop a quite ordinary female gender identity.

3.4.6.2. Testicular Feminization

The testicular feminization syndrome teaches us several important lessons. Individuals with testicular feminization syndrome are genetically males, have functional testes, and may secrete normal amounts of testosterone. Nevertheless, they develop a female phenotype. The explanation for this is that, because of a recessive genetic error, they fail to induce androgen receptors. As a result, the normally androphilic tissues are incapable of taking up the testosterone presented to them (Bardin et al., 1973; Spellacy, Bernstein, & Cohen, 1965). Invariably, then, the chromosomally "he" develops into a phenotypically "she."

The first lesson is that availability of sex hormone is a necessary, though not a sufficient, condition for ordinary SD; receptor proteins and other factors also play an essential role in the biological potency of a sex hormone. The testicular feminization syndrome further illustrates that sex-typing based on the karyotype can be very misleading. The presence of Y chromosome material provides no guarantee of male development, although this usually is the case. The Y chromosome is somehow involved in the early

formation of fetal testicular tissue that a few weeks later become a main source of testosterone, and this in turn influences the masculinization process. But the very complex developmental process of SD can be interfered with at any stage, and the effects of plasma testosterone can be blocked at the level of receptors. Moreover, genetic and hormonal mechanisms are intricately interwoven. The testicular feminization syndrome provides strong evidence that early, permanent, biochemical, organizational events can affect body and brain, and thus intelligence and personality development.

3.4.6.3. 5-α-Reductase Deficiency Related Pseudohermaphroditism

Imperato-McGinley and her colleagues (Imperato-McGinley et al., 1974, 1979, 1980) have studied a number of Dominican children with a very unusual development. These children first developed and were reared as ordinary girls. Then, at puberty they underwent an unexpected transformation: from being a girl to becoming a young man (Nowakowski & Lenz, 1961). We now know that this intriguing metamorphosis is due to the initial lack of an enzyme necessary for the reduction of some of the normally available androgen (Wilson, George, & Griffin, 1981) to dihydrotestosterone (DHT). DHT is required for normal male genital development. In its absence, the external (but not internal) genitalia will appear feminine.

The enzyme defect automatically leads parents to classify such children as girls at birth, and they are brought up like other girls. When DHT then begins to appear in quantities at puberty, the external genitals respond adequately because there is nothing wrong with them: The clitoris begins to grow and approach the adult male penile form, the labia close, the testes descend into the newly formed scrotum, and there is a production of fluids. Such men seem unable to conceive children, however.

The most interesting point from a physicological point of view is the observation that these "first girls–then men" encounter few, if any, difficulties in assuming a male gender identity, even though they were reared as girls from birth (Bancroft, 1978). They even seem comfortable with male role behavior (Wilson, 1982). The Imperato-McGinley group explains this "surprising" development by assuming that androgens had already exerted an early permanent organizational effect on their fetal brain, so that it was set and ready for the development of a traditional male gender identity. The syndrome, which has variously been called pseudohermaphroditism, 5-α-reductase deficiency, or Guevedoce (which means "penis at twelve"), has been studied by researchers elsewhere with essentially similar results (see Imperato-McGinley et al., 1980).

The findings have been taken to mean that female socialization processes have little impact on adult gender identity. Some social scientists remain unhappy with this interpretation (e.g., Feder, 1984), whereas others (e.g., Meyer-Bahlburg, 1984) have criticized the whole conceptualization and the

methodology of the Imperato-McGinley group. One argument launched against the Imperato-McGinley interpretation is that socialization may still explain the observations, because when the sex-change phenomenon first became generally known, control was lost over the effects of parental knowledge and expectations. However, this critique does not apply to the early cases where a sex reversal was not suspected, and nobody has documented a difference between early and late cases. A more decisive argument against the social learning idea is that, as argued in Chapter 1, a social learning argument can be tested only to the extent that variables such as parental knowledge, expectation, or suspicion can be defined in precise operational terms and shown to act independently under controlled circumstances as genuine causal agents in the process of forming gender identity. These quite ordinary requirements to a scientifically valid explanation are never met in social learning research, as far as I can see. The Imperato-McGinley interpretation is to be preferred on scientific grounds, not so much because it must be true or because it is based on already available independent evidence on the effect of prenatal sex hormones on adult gender identity, but rather because it has the potential of being empirically falsified by closely monitoring the effect of controlled or natural variations in a well-defined causal agent. It is important to remember, however, that an early hormone–gender identity relationship is far from being finally established (3.9). All that can presently be said with some confidence is that the available evidence suggests that what we somewhat imprecisely referred to in the past as gender identity seems less of a conceptual than of a physico-chemical problem (4.7).

3.4.7. Perspectives on Organizational Effects

Research at the intrasystemic level makes it abundantly clear that sex hormones exert a wide range of early organizational effects on ontogenetic development, and preliminary analyses of physico-chemical processes suggest to us new ways to study how fetal body and brain become permanently hard-wired, cytoarchitecturally speaking. The basic idea, in other words, is to examine in detail the nature of lasting molecular transfigurations of the developing brain. Before undertaking this task with full speed, it is wise to remember that there is obviously no hormone for a particular piece of behavior. Rather, the early, more or less permanent hormonal events seem to increase the probability that a particular bodily, perceptual, ability, or behavioral trait will be realized, also depending in part on inter- and extrasystemic conditions. Intrasystemic analyses of organizational events hold the key to unlocking the nature of structural constraints on such various phenomena as social communication in birds and frogs, sexual and spatial behavior in rats, development of secondary sexual characteristics, brain organization, spatial and verbal ability, and even what is called gender

role behavior, identity, and sexual inclination in humans. Most of these phenomena have hitherto been thought to be far outside the realm of operationalization and experimental control. The organizational principle holds the promise that a major part of tomorrow's way of working scientifically with sex-related phenomena will be to examine permanent early changes in an individual's anatomy, endocrinology, and neurochemistry. A mountain of evidence shows that experiences may also permanently influence brain development. Tomorrow's science will therefore include the analysis of the impact of experience as a natural part of any physicological analysis of organizational effects.

The physicological study of organizational effects faces a number of tough problems. Many of the decisive sex-related structural and molecular organizational changes seem to take place in phylogenetically "old" parts of the brain, where the sex hormone receptor concentration is high. This seems to be true for most species that have been studied thus far. However, we know almost nothing about whether the human neocortex responds with morphological changes to sex hormone exposure. Perhaps the neocortex contains fewer receptors than does the midbrain at all times. More likely, however, receptors are present in numbers or in an asymmetrical fashion early in development but then disappear. What does that mean to cortical development? Moreover, the fact that a few receptors exist at all in the phylogenetically youngest parts of the adult brain makes one wonder whether steroids could nevertheless have a subtle impact on the way sensory input is handled. How do we operationalize this hypothesis? To begin with, we have to develop better measuring techniques.

Dimensional descriptions of the brain such as unilateral-bilateral or left-right may be too simple to fully describe its sex-related morphological organization. Kimura & Harshman (1984) have suggested that sex differences in specialization may also take place within the single hemisphere. Sex-related specialization probably also involves the subcortical-cortical axis (Nyborg, 1983), and many aspects of the putative relationship between cerebral lateralization and abilities evade our present understanding. In sections 3.5 and 3.7 I argue that a one-to-one relation between structural bilateral brain organization and specialized spatial ability functions represents an oversimplification.

Refinement of magnetic resonance imaging and spectroscopy, regional cerebral blood-flow, and other techniques for studying ongoing processes in the intact brain holds the promise of harvesting more precise knowledge of the organizational effects of sex hormones on the brain. A combination of minimal speculation with uncontrolled fabrication of intervening variables and hypothetical constructs of unclear status, and of maximal operationalization and experimental control points the way to progress in this exciting and important area of research in the proclaimed decennium of the brain.

Chapter 7

Transient Effects of Sex Hormones

3.5. RESEARCH ON TRANSIENT EFFECTS

3.5.1. Introduction

> Principle 4: Sex hormones may cause transient changes in the phenotypic expression of a sex-dimorphic trait.
>
> This is *the enhance–suppress principle.*

Many human traits come and go during the life span. According to a traditional view, the early appearance of a trait means that it is genetic, whereas the late appearance of a trait is taken to reflect the effects of the environment. Moreover, stable traits are often taken to reflect the constant influence of genetic factors, whereas traits that come and go are assumed to reflect variations in the environment. According to physicology, these assumptions represent an unwarranted simplification. Genes are, for example, turned on and off during the life span by other genes, by sex hormones, and by changes in the value of a large number of extrasystemic parameters.

3.5.2. Sexual Motivation and Play

Sexual motivation and childhood play patterns are good examples of how various phenotypic manifestations may depend on variations in sex hormones. Androgen affects libido in men, whereas castration gradually lowers male libido over a period of time ranging from months to years, depending, in part, on the previous history of sexual activity. Androgen therapy restores libido after castration, and anti-androgen therapy lowers libido. Androgen therapy has been found to increase activity, initiative, and general well-being in men with Klinefelter's syndrome (Nielsen, Pelsen, &

Sørensen, 1988). On the other side, androgen is not particularly effective in alleviating impotence in men with normal *t* status (Bancroft, 1981; Bancroft & Skakkebæk, 1979; Skakkebæk et al., 1981), so we are not talking about simple relationships here.

Female libido is also affected by androgens. One way to explore this topic is to monitor the effects of androgen treatment in women with surgically induced menopause. Sherwin and Gelfand (1985) and Sherwin, Gelfand, & Brender (1985) used this approach to examine the sexual motivation of hysterectomized women with intact ovaries and of surgically menopausal women. They used a prospective crossover design, and the women received either combined estrogen-androgen, estrogen–alone, androgen-alone, or placebo treatment. Exogenous *t* was found to enhance the intensity of sexual desire and arousal. It also increased the frequency of sexual fantasies in both groups, without necessarily eliciting a physiological response or affecting interpersonal aspects of sexual behavior. Estrogen-alone treatment did not influence sexual motivation. In a later study, Sherwin & Gelfand (1987) demonstrated that ovariectomized women, receiving an estrogen–androgen compound, reported a higher rate of sexual desire, sexual arousal, number of fantasies, and actual number of coitus and orgasms, as compared to women who received estrogen alon, or to untreated women. Finally, Sherwin & Gelfand found that during the treatment month sexual desire, arousal, and number of fantasies co-varied with plasma *t* but not with plasma E_2. Sexual desire and autoeroticism have also been found to correlate positively with the *t* peak at about the middle of the menstrual cycle in intact women (Abplanalp et al., 1979; Bancroft, Sanders, & Warner, 1983; Persky, Smith, & Basu, 1971; Persky et al., 1978).

Taken together, these observations suggest that important aspects of female sexuality are of a rather transient nature. They also indicate that the changes make sense in terms of the proximate principle of an underlying physico-chemical agent and of brain mechanisms that work in accordance with the enhance–suppress principle. Recently, we demonstrated that sex-related differences in mating strategies, often explained in terms of choices and desires, are explained more consistently in terms of the enhance–suppress principle and the GTC model (Nyborg & Bøggild, 1994). Other examples of phenotypic dependency of variations in hormones are human and other animal play patterns, including rough-and-tumble play (3.5.2). Human childhood play patterns become more or less suppressed in most individuals around puberty, very much as in those subhuman species where play takes place mainly among the young and before the serious undertaking of becoming adult calls for other qualities. The putative hormone–brain mechanisms behind pubertal suppression of playfulness is discussed in Section 3.7.5.

3.5.3. Menstruation, Cognition, Education, and Occupation

Sex differences in cognitive abilities are generally found to be small or nonexistent before puberty. However, girls seem generally at a slight advantage in some verbal abilities and tend to keep this superiority throughout life. There are also reports testifying that preschool girls may score higher on some spatial ability tasks than do boys of comparable age (Lunn & Kimura, 1989). This intellectual advantage probably relates to a general physical advancement of the female body and, in particular, the brain, relative to boys. However, male and female spatial and verbal abilities begin to diverge significantly with the arrival of puberty, and the differences reach a maximum shortly after puberty. When evaluating observed sex-related differences in general ability, it is worth remembering that most IQ tests are deliberately constructed to minimize such differences and that for exactly this reason they are unable to provide meaningful estimates of the real differences in performance (Nyborg, 1994a).

The parallel development of a tremendous sex-related differentiation in plasma sex hormone concentration and the sex-related differences in specific ability development suggests a sex hormonal involvement. On the other side, correlations prove nothing about what caused what. At least theoretically, it is possible that sex differences in abilities influence hormone concentrations. Fortunately, we can already draw on results from experiments studying the enhancing and suppressing effects of sex hormones on spatial performance in animals. These experiments strongly suggest that spatial ability is, to some extent, an enhance–suppress type trait, amenable to systematic hormone manipulation (3.5.2). Then again perhaps spatial ability, as measured, for example, by rat maze learning, is differently influenced than human spatial ability. Let's examine the evidence.

Several studies show that the highs and lows of human spatial ability are inversely related to plasma E_2 concentration, suggesting that human spatial ability also complies with the enhance–suppress principle. When the principle is translated into a menstrual timetable, it predicts that spatial ability will rise to optimum expression in women during the premenstrual and menstrual period, whereas it will be curbed in the middle of the menstrual cycle.

We can now determine the power of a rigid morphologically or gene-based traditional brain lateralization-spatial ability model versus the power of the dynamic enhance–suppress principle, and see which best explains sex-related variations in human spatial ability. However, to fully understand the nature of the menstrual variations in specific abilities, we need a model such as, for example, the General Trait Covariance-Androgen/Estrogen (GTC-A/E) model with its associated covariance principle (3.8.4). The need of this integrative model will be obvious when it is realized that not only the spatial but also the verbal (Nyborg, 1979) and perceptuo-motor skills are concomitantly influenced by changes in sex hormones over the menstrual cycle (Hampson and Kimura, 1988). Hampson and Kimura later

formulated this general pattern in the following terms: heterotypic "male" traits (e.g., spatial ability) are suppressed in females by high concentrations of "female" E_2 and progestin, whereas homotypic "female" traits (like speeded motor and speech-articulatory performance) are enhanced by high concentrations of E_2 during the menstrual cycle (3.7.6). This pattern is understandable only given the basic assumption of the GTC-A/E model, that all sex-related differences are proximate reflections of variations in sex hormones. A more detailed discussion of studies on the effects of menstrual changes in sex hormones on cognitive performance is presented in Section 3.7.6.

Not much is known about which brain mechanisms mediate variations in plasma sex hormones to specific abilities during the menstrual cycle. It is known, however, that changes in plasma sex hormones are systematically associated with rapid fluctuations in the electrical activity of the brain, possibly via rapid membrane effects (3.1.2.2) as well as via slower effects through genes (3.1.2.1) and fast interaction with neurotransmitters (3.1.2.3). Several of the EEG wavelength patterns change in concert with menstrual changes, and birth control pills annul the ordinary monthly changes in the electrical potentials of the brain (Bisanti & Cavallotti, 1972; Buchsbaum, Henkin, & Christiansen, 1974; Deakin & Exley, 1979; Hendrickson & Hendrickson, 1980; Klaiber et al., 1971a, b, 1974a, b, 1982; Mackenberg et al., 1974; Matsumoto et al., 1966; Nansen et al., 1965; Pfaff & McEwen, 1983; Prange & Lipton, 1972; Vogel, Broverman, & Klaiber, 1971; Wuttke et al., 1975).

The combination via the GTC-A/E model of the proximate cause principle with the enhance–suppress principle allows for a number of testable predictions. From these principles it follows, for example, that the expression of spatial, verbal, and fine-motor abilities will stop cycling in women after menopause. It also follows that healthy postmenopausal women will obtain higher spatial ability scores than they did before menopause. These two predictions have not yet been subjected to testing. Another prediction is that female monozygotic twin pairs will show greater intrapair variability in spatial ability scores than male pairs. The reason for the greater intrapair variability in female twins is that they often cycle hormonally out of phase with each other at the time of testing, whereas the scores of male intrapair twins would be more stable. This prediction was borne out in a 1962 study by Vandenberg, McKusick, & McKusick. As predicted, they observed that female monozygotic twin pairs are more variable than male pairs with respect to spatial performance. Future studies should routinely include radioimmunoassays in order to be able to monitor plasma estrogen variations over the menstrual cycle. The enhance–suppress principle further predicts that postmenopausal women on a sex hormone replacement schedule will show low spatial ability in estrogen treatment periods and high spatial ability in no medication periods. This prediction was recently proven true (see Section 3.7.6).

The enhance–suppress principle accounts for trait variability in a number of areas that are not ordinarily thought to change over time. For example, the SD of some of the major parameters of the body is to some extent reversible. Many men become slightly feminized in old age, and many elderly women will show slight, and a few not so slight, signs of masculinization for reasons discussed in Section 3.5.5.

Only the most hardened feminists will not find considerable sex differences in most areas of human educational and vocational selection strategies and personality parameters (Dalton, 1968, 1976, 1979; Ehrhardt, 1975; Ehrhardt & Meyer-Bahlburg, 1979; Hoyenga & Hoyenga, 1979; Money & Schwartz, 1975; Reinisch, Gandelman, & Spiegel, 1979; Rose, 1972; Yalom, Green, & Fisk, 1973). To what extent do these differences depend on dynamic sex hormone effects as formulated by the enhance–suppress principle? The honest answer is that we simply don't know. There is no systematic and controlled longitudinal study of the effect of sizable ipsative changes in sex hormones on these parameters during, say, a twenty- to fifty-year age span. Accordingly, it is possible, though perhaps not likely, that the stable differential expression of particular sex-related vocational preferences depends on an enhancing effect from a stable secretion of a particular sex hormone, whereas changes in plasma concentrations would result in suppression of that preference. In that case, the preference appears to be permanently expressed only because over time there was little variation in sex hormone concentration. Only a few traits appear absolutely irreducible: female traits such as menstruation, lactation, and gestation and male traits such as erection and ejaculation. However, even with respect to those traits, rudiments can sometimes be traced in the opposite sex. When they are prominent, there is usually a history of extreme or otherwise atypical hormone exposure, whether of endogenous origin or due to medical intervention, to explain it. Some boys lactate around puberty when perturbations in sex hormone secretion are pronounced, and female genitals swell during sexual excitement. An evolutionary extreme is the female hyena who develops a malelike penis but menstruates through it. In general, with adequate dosage and timing, most sex-related traits can be enhanced, compromised, or reversed in total independence of the karyotype (the multipotentiality principle, see Section 3.9.2). Only further research can determine which traits are formed permanently early in development and which traits are subject to later activation or deactivation according to the enhance–suppress principle.

3.5.4. Testosterone and Enhanced Aggression

The following example provides a good physicological illustration of how physico-chemical manipulation at the intrasystemic level in the form of medical intervention can cause profound planned and beneficial effects

(the enhance–suppress principle), while at the same time causing quite unexpected and highly unwanted covariant changes in the expression of other intrasystemic traits. In this example, hormonal interdependency as formulated in the covariance principle of the GTC-A/E model was neglected, with dire consequences for behavior at the intersystemic level. Thus, a group of men were treated for infertility due to hypogonadotropin hypogonadism at the Middlesex Hospital in London, England. By implanting an automated pump, a pulsatile hypothalamic secretion of gonadotropic hormone releasing factors (GnHR) was simulated. This, in turn, stimulated pituitary-luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion. The LH and FSH production eventually initiated spermatogenesis with the much hoped for result: The men became fertile (Morris et al., 1984). The point of interest in this study is that this ingenious treatment had unexpected side-effects. Despite the fact that most couples succeeded in having a long-desired child, a high proportion of them (about 50 percent) soon asked for a divorce. This outcome makes little sense in terms of the fact that the couples finally got what they so desperately wanted for years. It becomes perfectly understandable, however, if we for a moment combine the proximal cause principle with the optimal range and the enhance–suppress principle in the GTC-A/E model (see Section 3.8.3). Further inquiry revealed that the wives became increasingly anxious and concerned about a profound change in their husband's personality as the treatment proceeded. Before treatment, many of the men were reportedly somewhat shy and withdrawn. The optimum range principle predicts that this personality pattern will be characteristic of low *t* males (see 3.8.4.1). The principle further predicts that during treatment they will gradually begin to behave in an increasingly aggressive manner. And indeed they did! Actually, some of them took over command in relation to their spouse, and one even began to abuse his wife physically. A few were also seen provoking a fight in pubs or in the streets. In extreme cases, the markedly changed behavior brought them in contact with the police.

The proximal cause principle explains this change in behavior by a relationship between brain centers for control of behavior and plasma *t* concentrations. The optimal range principle specifies the curvilinear relationship between dose and effect. The enhance–suppress principle would count aggression to be among the more or less transient traits. The GTC-A/E model accounts for the harmonization of effects on different traits—here, testicular development, fertility, and aggressive behavior in terms of sex hormonal coordination of traits. It is important to realize that the model also provides the key to obtaining better control over behavior by carefully monitoring the medication, with tight control over GnHR secretion and a sharp eye not only on plasma *t* but also on the interdependency of the many different effects of harmonization. It remains to be seen whether such an extended formalization of the therapeutic regime can lead to the desired

goal of making the men fertile while keeping them acceptable to their partners. Most certainly, an integration of the various hormone principles will enable us to better understand how to properly take a middle-aged man through the stormy phases of puberty within a narrow time frame. This matter requires close attention, careful instruction, and a deep appreciation of the subtleties of the powerful processes behind behavior. Only then will we perhaps avoid unwanted consequenses. This task is not made more easy by the fact that individuals have varying sensitivities to hormones and that different traits might show different sensitivities over time.

The few examples illustrate an important point about the effects of sex hormones. Sex-related traits tend to emerge in company. For example, aggression, libido, number of offspring, and dominance tend to covary even over the theme of tremendous individual variation. A number of studies suggest an androgen-easily elicited aggressive behavior relationship (Dabbs et al., 1987; Huesmann et al., 1984; Kreuz & Rose, 1972; Mattsson et al., 1980; Meyer-Bahlburg, 1981; Meyer-Bahlburg et al., 1974; Olweus et al., 1980; Rose, 1976; Rubin, Reinisch, & Haskett, 1981; Sciavi et al., 1984; Sussman et al., 1987). The studies also make it clear that we cannot expect simple relationships between *t* and aggression. Dosage, sensitivity, maturation, timing, inheritance, and circumstances are all critical parameters. Most probably, we are dealing with a very delicate balance between a slightly increased plasma *t* and "positive" effects on behavior, whereas a further increase may result in losing control, with consequent disorganized behavior (3.5.4). Even with these reservations in mind, we may put some confidence in the growing evidence that the general type of criminal act may relate to particular plasma *t* concentrations. Studies have suggested that slightly increased *t* levels (relative to the group mean) are related to disinhibited behavior in general, higher levels to destruction of objects, and the highest level to violent behavior against other people (Sciavi et al., 1984; Theilgaard, 1984, 1986). But again, even though such *t* aggression–crime relationships may be explainable in terms of the model presented here, none of the principles implies that there must be a simple relationship between *t* and aggression, nor that all forms of crimes must have a hormonal basis (see 3.5.4).

3.5.5. The Enhance–Suppress Principle in Life-Span Perspective

In terms of body (and perhaps also behavioral) phenotype, the two sexes become more and more alike with age. Many men (and perhaps also women) regret the gradual change over the years from an athletic to a pyknic body type and the changes to a more feminine fat/lean mass ratio. The process is self-reinforcing because fatty tissues are capable of aromatizing large amounts of *t* to E_2. The demasculinization and increasing

feminization of elderly men raises questions about the permanence of body characteristics that have traditionally been considered irreversible.

Not a few women become defeminized or masculinized; for example, with the advancement of age, they develop facial hair and a characteristic deepening of the voice. The enhance–suppress principle implies that phenotypic characteristics that depend on transient activational effects will disappear when their sex hormonal basis disappears, whereas differences caused by permanent organizational sex hormone effects will remain despite hormonal changes. Guttman (1975) noted that not only do some sex-related differences decrease with age, but also other traits actually reverse in old age. Unfortunately, there is no systematic, large-scale, longitudinal study of sex reversals of traits in old people. We need prospective life-span studies to decide which traits depend on virtually irreversible organizational effects and which only appear to be irreversible because there were only minor changes in sex hormonal status over prolonged periods of time. Such studies should take into account that the normal plasma sex hormone pattern changes from low childhood concentrations in both sexes to high concentrations and maximal difference between the two sexes at puberty, again becoming more similar in old age.

In men, on average, free and unbound *t* declines steadily with age after 50 (e. g., Stearns et al., 1974) but never ceases completely. Ellis & Nyborg (1992) observed a steady decline with age in *t* in over 3,000 males 31 to 49 years of age. They also found racial/ethnic differences in the *t* values in young males, but in the oldest age groups the differences reversed themselves, so that those who initially had the highest plasma *t* ended up with the lowest. Plasma E_2 in old men arises partly from E_2 produced by the testes, partly from E_2 of adrenal origin, and finally from E_2 aromatized from *t* (Marcus & Korenman, 1976). In women, the gonadal secretion of E_2 ceases completely at menopause. The only E_2 secretion left is of adrenal origin or arises from converted *t*. Thus, the plasma concentration of E_2 in old women is at a par with or may actually even be lower than that of men of comparable age. Couwenbergs, Knussmann, & Christiansen (1986) found that the serum hormone concentrations of both E_2 and androgen showed a tendency to drop with age, even in subjects who were in or near their third decade.

Such hormonal changes can be used to examine which sex-related traits depend on activational sex hormonal influence, as such traits will respond to the changes. It would be interesting, for example, to take a closer look at the so-called empty nest syndrome with this model in mind. Social and psychological theory explains why many women assume new challenges around the time of menopause. Changes in expectations or desires, or relief from major responsibility for small children are assumed to explain why many menopausal women decide to turn to activities outside the home. In contrast, a physicological analysis would inquire into whether physicochemical changes at menopause could explain the observed change in

behavior on a testable basis. The analysis would take as its point of departure the fact that women experience a combination of rapidly declining estrogen and a short-lived increase in *t* secretion (due to ovarian stromal hyperplasia caused by a high level of luteinizing hormones at menopause [Vermeulen, 1983]). Using a combined intra-intersubject design, the analysis would then examine whether these hormonal changes are related in any quantitative manner to the empty nest syndrome behavior. Such analyses would help clarify whether naturally occurring individual differences in sex hormone secretion patterns can explain individual differences in the intensity of the empty nest behavior.

A variation on this theme is to examine whether supplementary cyclic estrogen therapy given for menopausal difficulties more or less completely suppresses the empty nest behavior, or whether it does so only in the estrogen-high periods during treatment. Women who for endogenous or exogenous reasons show increased plasma androgen concentrations tend to be less interested in, or even hostile to, the idea of having children (for discussion, see Hoyenga & Hoyenga, 1979, p. 101ff.). In short, a number of predictions of the principle and of the GTC-A/E model have already been substantiated over different age periods. This reduces the need to invoke desires, social responsibility, and similar mentalistic or superorganismic factors to explain, say, empty nest syndrome behavior or the lack of "interest" in having children.

Chapter 8

Conversion of One Sex Hormone into Another

3.6. AROMATIZATION AND CONVERSION

3.6.1. Introduction

> Principle 5: Testosterone can exert indirect organizational and activational effects in the brain if the enzymes necessary for aromatizing or reducing testosterone are present.
>
> This is *the conversion principle.*

For a long time it was seen as something of a mystery that the so-called male sex hormone, testosterone (*t*), could, under certain circumstances, exert a strong estrogenic effect and that estrogens might sometimes mimic the effects of androgen. A solution to the first problem was found when it became evident that various cell tissues, including brain tissues, may contain enzymes that intracellularly convert—or aromatize—*t* to estradiol (E_2; Goto & Fishman, 1977; Longcope, Kato, & Horton, 1969; MacLusky & Naftolin, 1981; MacLusky, Naftolin, & Goldman-Rakic, 1986; MacLusky et al., 1985; Naftolin, Ryan, & Petro, 1971; Reddy, Naftolin, & Ryan, 1974; Shapiro, Levine, & Adler, 1980; Weisz, 1980). In other words, with the right enzyme present, *t* may act as a plasmatic prohormone, and the effect will be estrogenic. It may then have, say, an indirect organizational effect on the neuroarchitechture of the brain or a transient functional effect, as formulated in the conversion principle.

3.6.2. Aromatization and Reduction

Actually, the situation is a bit more complex. Testosterone can be converted via two pathways and have two quite different effects. One pathway

is 5-α-reduction, and the other is aromatization. The product of 5-α–reduction is 5-α-dihydrotestosterone (DHT), which binds to androgen receptors. The product of the aromatization process is E_2, which interacts with estrogen receptors. Male and female rats appear to have similar complements of enzymes for aromatizing testosterone to estradiol and for producing 5-α-reduced DHT. However, not all estrophilic neurons are capable of aromatizing testosterone to E_2, and this allows for a sex-related difference in the pattern of uptake. Thus, only a subset of male E_2 receptors is accessible when exposed to his own intrasystemic testosterone, while all female estrogen receptors would be labeled when they are exposed to her intrasystemic E_2 (McEwen et al., 1984). The cerebral cortex of young rhesus monkeys is capable of aromatizing testosterone and binding the ensuing product—E_2 (MacLusky, Naftolin, Goldman-Rakic, 1986). This observation has potential relevance for the study of human sex-related differences in cortical brain functioning (Section 3.3.3.1).

There are various pharmacological and genetic means for distinguishing the actions of aromatization from those of 5-α-reduction. For example, Meaney et al. (1983) found that DHT mimics the action of *t* on play-fighting behavior in rats, whereas flutamide (with anti-androgenic effects) blocks the enhancement of play-fighting. Rat pups with the Tfm mutation, rendering them insensitive to their own systemic androgen, display a female level of play-fighting. Meaney and McEwen (1986) used the technique of implanting *t* directly into the amygdala of female rat pups on day 1. They removed the canula again on day 8 and made sure there was only minimal diffusion of the hormone to neighboring tissues. Female rats with *t* implantation engaged significantly more in play-fighting than did control females (3.5.4). Moreover, female sexual behavior is defeminized in rats by *t* as well as by E_2, but defeminization does not follow DHT treatment. Aromatizing enzymes are present in high concentrations in the amygdala of the rat but not in the pituitary. Thus, estrogen receptor occupancy by aromatization of *t* differs from that of systemic E_2.

In one of her numerous interesting in vitro experiments, Toran-Allerand (1980a) found that *t* is not particularly active in promoting growth of brain tissues in rodents. One problem associated with determining the direct growth-promoting effects of *t* per se is the potential or actual presence of enzymes that convert *t* to E_2. It is therefore often hard to know with assurance whether *t* exerted its moderate growth effects directly or via conversion. For example, it is not entirely clear from the observed significant correlation of a surge in *t* during the mating season and the appearance of male song, whether *t* alone promotes the significant growth of the song centers in the canary brain or whether the growth effect is due to *t* aromatized to E_2. It is even quite likely that *t* and E_2 act synergistically. It is not too difficult to map the distribution over time of labeled *t* in the brain and to confirm by autoradiographic techniques that it accumulates in

certain brain nuclei shown to be important for song production. The problem, however, is that we cannot be sure by this technique that the accumulated *t* was aromatized intracellularly so that E_2 in the end was responsible for the obvious growth promotion of the song nuclei. Walters, McEwen, & Harding (1988) recently concluded that it is in fact E_2 that significantly influences the vocal control nuclei in the male zebra finch, and Nottebohm keeps open the possibility that E_2 acts synergistically with *t* (Nottebohm, 1980a, p. 112).

3.6.3. Implications of Conversion

One of the more important methodological implications of the possibility of conversion from one hormone to another is that isolated measures of plasma *t* concentration is a good predictor variable for neither androgenic nor estrogenic effects on the brain. We must also know the conversion factor(s) as well as the number and pattern of distribution of receptors, in addition to the receptor uptake factor in the particular tissues. On the positive side, the existence of conversion processes opens up an appreciation for one of the many vital roots of individuality in development. For example, it becomes perfectly understandable how a man with a strongly masculinized bodily appearance—by direct (?) androgenic effects on muscular tissues—can at the same time be cerebrally overflooded with E_2 due to a lively aromatization of plasma androgen in the brain. Such possibilities open the way for various testable hypotheses, as illustrated graphically in the GTC-A/E model (Nyborg, 1979, 1983, p. 125; see Section 3.8.4).

3.6.4. Measuring the Effects of Conversion in the Brain

No doubt, it will take some time before these complex issues of conversion and synergism are adequately addressed. However, through the further development of existing techniques, eventually it may be possible to come to terms with the problems and even to study details of the processes in the intact brain. Work is underway in several laboratories around the world to label and monitor the relevant enzymes, as well as to represent the cerebral uptake and metabolization patterns by positron emission tomography-like and high-resolution magnetic resonance imaging and spectroscopy techniques. Other possibilities are to supplement the observations with refined versions of radioimmunoassay techniques, ultrastructural analyses, chemical fractionation of dissected tissues, ultramicrodissection, and quantitative autoradiographic procedures (Pfaff & McEwen, 1983). These and other techniques will enable us to better understand the many implications of conversion. This is a very important goal because the conversion

principle may, for example, serve as a crucial heuristic tool for understanding one of the many ways in which brain sex may come to differ from body sex in some people and for illustrating that multiple individual forms and expressions spring from a common source (see Section 3.12).

Chapter 9

Intermediate Brain Estradiol Concentrations

3.7. THE OPTIMUM RANGE PRINCIPLE

3.7.1. Introduction

> Principle 6: Optimum development, organization, and functioning of estrophilic brain tissues depend on a range of intermediate cerebral estradiol concentrations.
>
> This is *the optimum range principle.*

To avoid misunderstanding, the term *optimum,* as used here refers either to what appears to be the full phenotypic expression of a particular genomic growth potential in the case of an organizational effect of sex hormones, or to a facilitation of neural functioning in the case of an activational effect of sex hormones. The term is in no way synonymous with "ideal" because the phenotypic organizational or neuronal facilitatory effect may or may not be ideal for, say, intrasystemic well-being, or for the survival of the organism in intersystemic competition, or when dealing with other extrasystemic circumstances.

3.7.2. Concentration Effects in Biological Systems

Sex hormones are often biologically most effective with respect to the expression of a given trait when keeping within a limited range of concentrations. It is as if plus and minus deviations from a given range of sex hormone concentrations either weaken or completely change their biological effect with respect to that trait. It is important to note, however, that this is not an exclusive characteristic of sex hormones. The optimum range principle reflects, in fact, a very common phenomenon with respect to the

biochemistry and physiology of organic systems. Schatz, Schalscha, & Schatz (1964) have dealt extensively with the occurrence and importance of various concentration effects in biological systems, and have mapped several important biochemical mechanisms or modes of action. They found that a change in the concentration of a particular chemical can provide it with quite different biochemical or physiological characteristics. Several enzymes in an integrated biochemical pathway may vary in susceptibility to an inhibitor or to the intermediate products that accumulate as a result of inhibition as a function of variation in concentration. In other cases, an addition to one of the chemical components may create a new molecule species with rather different properties. Schatz and co-workers regret that these biochemical intricacies are often seen as *paradoxical,* and that in many instances experimenters interpret their seemingly confusing findings as experimental errors or as a sure sign of contamination by uncontrolled factors. The unfortunate result is that they draw straight lines or smooth curves through scattered observations, thereby effectively preventing proper recognition of essential aspects of the workings of the compounds in question.

Acknowledgment of the fact that sex hormones are subject to concentration effects cannot easily be underestimated. In fact, this phenomemon dictated the curvilinear shape of the GTC-A/E model for hormone effects on body, brain, and behavior.

Toran-Allerand (1987a, b) was able to confirm by in vitro experiments that the growth-promoting effect of E_2 is dose-dependent. First, she showed that gradual increases in the E_2 content in the nutrient resulted in increased neuritic branching in cultured brain tissues. She then showed that increasing the E_2 concentration above certain limits resulted in neurotoxic reactions. The most likely effect of this increase in an intact organism is a regular deterioration of estrophilic brain tissue, with resulting impaired functioning (e.g., Döhler & Hancke, 1978; Döhler et al., 1984).

Another example of the nonlinear effects of steroids can be found in bird brains. Thus, ordinary development of the male canary's brain song centers depends on the amount of *t* excreted intrasystemically. However, the systematic extrasystemic administration of hormones to female birds gave interesting insights. A small *t* dose made the female bird capable of uttering a few harsh sounds and clicks. Increasing the dose greatly improved the quality of song. The apparent optimum *t* dose enabled female birds to sing with about one-third the syllables of a normal unmanipulated male bird. The fact that the female *t*-treated birds never actually reached the male level of song proficiency suggests that early steroid priming of the canary brain may play an important role for later development of full male song capacity. I have not been able to find reports in the literature on the organizational or activational effects of very high doses of *t* on singing. We apparently do not know whether there is a ceiling effect or even a reversal of growth effects

of *t* as a nonlinear function of further increase in the plasma steroid concentration. A complicating factor is that the 5-α-reduction enzyme may be scarce in the canary brain, so that further exposure to *t* might not lead to increased concentrations of E_2.

We need more research in this area. The observation of a steroid-brain dose-response relationship in birds may have potential relevance for a better understanding of mechanisms associated with retaining plasticity in bird neuronal systems and thus for new learning (Nottebohm, 1981, 1989). My reason for bringing up the matter in a human context is quite specific, however. Elsewhere, I have compiled evidence to suggest that human creativity may be partly a question of retaining childhood neural plasticity as a function of the surge in sex hormones at puberty (Nyborg, 1993b; see Section 3.11.3). Nottebohm noted, for example, that the time to acquire new song variations depends on the temporal variations in the bird's plasma *t* concentration. When plasma *t* is high, song is stable and of good quality. However, the bird seems unable to learn new song variations during this period. When the mating season comes to an end, the male birds stop singing and they remain silent for months to come. Then, during the months preceding the following mating season, plasma *t* concentrations begin to rise and the four song nuclei grow, with the result that new synaptic contacts become established. This period of neural plasticity with establishment of new synaptic connections is precisely the period when male birds are capable of incorporating new song variations into their song repertoire. With further increase in plasma *t*, the new repertoire stabilizes and no further learning of syllables takes place. It is as if high *t* concentration cements neuronal plasticity and a "rejuvenation" of the adult canary brain is needed for learning new song variations (Nottebohm, 1981, 1989). I will take this interesting bird model of learning new tricks a step further in Section 3.11.3 and propose human models for sex differences in creativity as well as for different kinds of scientific creativity, details of which are presented elsewhere (Nyborg, 1993b, c).

Manipulation of sex hormones in rats may also be of interest in this connection. Thus, Dawson (1972) administered estrogen to adult male rats and found that this treatment caused them to make more errors in a maze-learning situation than they did before the treatment (Section 3.3.2). The GTC-A/E model would predict this outcome on the basis of the optimum range principle with an "overshooting" of the optimum brain E_2 concentration. This interpretation is in line with the observation that one estrogen pellet had no measurable effect (i.e., none or a slight overshooting) but that a doubling of the dosage resulted in significantly reduced performance. Williams, Barnett, & Meck (1990) showed that neonatal estrogen treatment makes female adult gonadectomized rats perform as well as male rats. The optimum range principle explains this effect in the following way. The extrasystemically administered increase in estrogen exerted early or-

ganizational effects on the immature female rat brain and eventually resulted in the enhancement of the expression of spatial ability, very much like male rats aromatizing early *t* to E_2. The optimum range principle further predicts that the administration of super- or supraphysiological doses would result in suppression of spatial ability in adult gonadectomized rats. The optimum range principle of the GTC-A/E model obviously invites further considerations as to the dynamics of hormones–human sex differences in spatial ability relationships. I shall discuss this matter in later sections in connection with the effects of the pubertal surge in hormones as well as in relation to plasma variations over the menstrual cycle.

Section 3.4.3. reported on the observation by Sandhu and co-workers (1986) that the right cortex in the female rat contains more estrogen receptors than the left during the early high-estrogen concentration period, but ends up being smaller than the left. The exact opposite pattern was found in male rats. These observations were explained by the growth-inhibiting effects of estrogen, and this explanation makes perfect sense in view of the observation that estrogen can cause selective cell death. Moreover, the high concentration of estrogen receptors in the right female cortex coincided in time with high plasma estrogen concentrations. It further makes sense to assume, with the optimum range principle, that the lower concentration of estrogen receptors in the left female cortex allows for optimum growth-promoting effects by estrogen. This stresses an important point of the optimum range principle: It is primarily a principle established for promoting a better understanding of individual and sex-related development and functioning. Thus, by taking into account not only plasma concentrations but also, among other factors, receptor activity, it becomes perfectly understandable that a given plasma sex hormone concentration can, at a given time in ontogenetic development, result in simultaneous functional suppression, growth inhibition, or even cell death in tissues inducing many receptors. At the same time, the very same plasma sex hormone concentration may result in functional enhancement or growth-promoting effects in tissues inducing few receptors, while concomitantly leaving still other tissues untouched because they did not induce receptors at that point in development.

3.7.3. Estrogen Treatment of Women with Turner's Syndrome

Well-controlled, double-blind, prospective experiments conducted to determine the optimum ranges of steroid concentrations in the human brain are, for obvious ethical reasons, not feasible. We therefore have to resort to less exact, but still instructive, ways of examining whether the optimum range principle of steroid actions applies to humans as well as they do to other animals. The optimum range principle states that the full expression of spatial ability depends on intermediate brain concentrations of estrogen. According to the principle, we can expect to see very low

spatial ability in untreated women with Turner's syndrome. They have extremely low levels of plasma estradiol, which, according to the principle will show up in incomplete development of neural areas involved in spatial analysis. The optimum range principle also predicts that estrogen therapy will promote growth effects on those estrophilic brain tissues that subserve spatial analysis.

A re-analysis by Nyborg & Nielsen (1981a) of data from a previous study on spatial ability in forty-five Turner women (Nielsen, Nyborg, & Dahl, 1977a) indicated that women receiving cyclic estrogen/gestagen treatment for about one year perform as well as do their normal age-matched sisters on a variety of spatial tasks. The optimum range principle finally predicts that Turner women who receive estrogen for many years may run the risk of overshooting the optimum range which would result in suppression of the expression of spatial ability. The re-analysis also confirmed this expectation. The long-term treated group (with a history of, on average, eight years of cyclic estrogen/gestagen medication) scored as low as the untreated patients on the rod-and-frame test, on the embedded-figures test, and on Money's roadmap test of direction sense. Nyborg & Nielsen (1981a) also monitored the mathematical achievement of the Turner women because it has been argued that achievement in this area relates to spatial ability (Benbow, 1988; Connor & Serbin, 1985; Fennema, 1977; Fennema & Sherman, 1977; Guay & McDaniel, 1977; Sheckels & Eliot, 1983; Sherman, 1980; Sherman & Fennema, 1977; Smith, 1964). The re-analysis of the Turner data indicated that the untreated and the long-term treated Turner women encountered difficulties in mathematics, whereas the short-term treated women performed on a par with their age-matched sisters who acted as controls. (See Table 9.1 for a summary of observations on visuo-spatial abilities).

It is not known whether the positive impact of estrogen therapy on mathematics achievement also found in this study was mediated via forced brain development of areas subserving spatial ability or via other mechanisms. Regardless of the mechanisms of action, the observation raises the expectation that at least in the case of women with Turner's syndrome, suppression of spatial ability and mathematics achievement might be partially or fully remedied by hormone therapy. The optimum range principle warns us, however, that the dose must be monitored carefully. Perhaps the expression of spatial ability is a sensitive indicator of whether the hormone substitution therapy is on the right track.

Unfortunately, there were problems with the Nyborg & Nielsen (1981a) study of Turner women, and this made any final conclusions about the effects of E_2 on the brain and abilities of Turner women premature. For example, little was known about how duration of treatment related to concentration effects. In the 1970s little was known about the prenatal hormonal conditions of Turner fetuses, although the prenatal maternal

Table 9.1
Visuo-spatial abilities (means ±SDs) in Turner's syndrome girls, treated with estrogen/gestagen[a]

Test	Rod-and-Frame Unsigned deviation			Children's Embedded-Figures test			Money's Road-Map test for left-right discrim.		
Duration of Treatment	Untreated	Short-term	Long-term	Untreated	Short-term	Long-term	Untreated	Short-term	Long-term
Age (Yrs.)									
< 12	**20.3** ± 4.0			**180.0** ± 0.0			**13.3** ±4.9		
12.1-14	**15.2** ± 7.1			**119.2** ±30.0			**12.5** ±6.4		
14.1-14.9	**13.0** ± 6.2			**116.3** ±45.1			**7.8** ±7.3		
15+	**10.4** ± 8.2	**7.1** ±7.1	**11.1** ±8.3	**111.5** ±52.6[1]	**60.8** ±26.5	**123.6**±35.1[2]	**7.6** ±6.1[3]	**2.0** ±1.6	**5.4** ±4.9[4]

Untreated = No estrogen treatment
Short-term = Treatment between 3 months and 2 years (average 1.1 year)
Long-term = Treatment for more than two years (average 8 years)
Significantly higher error score than that of the short-term treated group:
[1]($t(15) = 2.34, p = .02$), [2]($t(22 = —4.24, p < .001$), [3]($t(10) = 2.77, p = .01$),[4] ($t(21) = 2.55, p = .01$)

[a]Visuo-spatial performance improves with time in untreated Turner girls, but short-term treated girls perform better than untreated and long-term treated Turner girls, and no different from their age-matched sisters. This suggests a beneficial effect of short-term and a noxious effect of prolonged high-dose estrogen treatment on visuo-spatial development.

Source: Nielsen, Nyborg, & Dahl, 1977a, b.

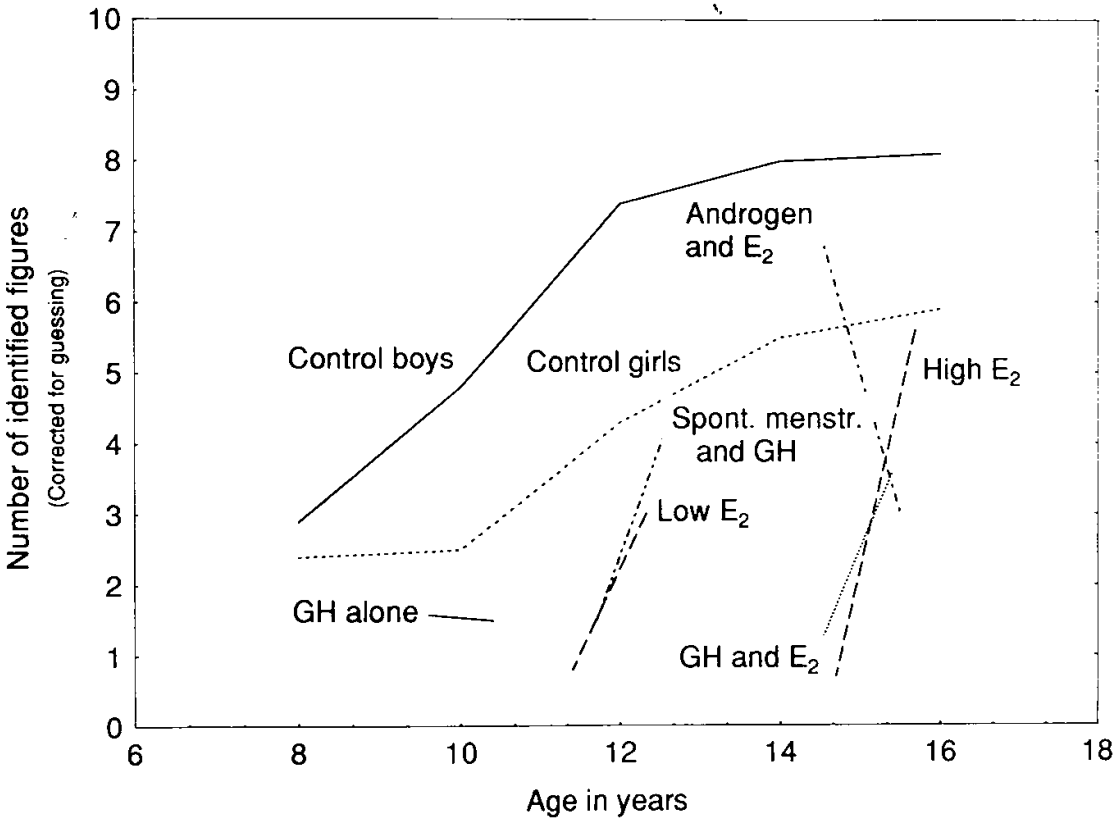
exposure seemed sufficient to ensure the development of a feminine gender identity. It also seemed that fetal secretion was normal during early development but later became compromised and perhaps increasingly so over time (Weiss, 1971). We now know that about 15 percent of all Turner girls have sufficient sex hormone production to begin menstruating spontaneously at puberty. The variability within the syndrome helps make detailed studies of the fetal and postnatal development of patients with Turner's syndrome a potentially valuable source for learning more about the effects of both early and late sex hormonal actions.

Because of the retrospective nature of the Nyborg & Nielsen (1981a) study with its obvious lack of control over the hormone substitution therapy, it was decided to undertake a new study. This time we applied a pseudo-experimental design and took advantage of the fact that hormone-deficient Turner girls need controlled substitution therapy to develop properly. Six different groups of 9- to 14-year-old Turner girls were treated with either growth hormone (GH) alone, low-dose E_2 alone, low E_2 and GH, high-dose E_2 and GH, oxandrolone (OX, anabolic steroid) and GH, or received GH in addition to their own gonadal hormone production leading to spontaneous menstruation. The effect of the various treatment regimes was measured on various tests for intelligence or specific abilities. Age-matched normal schoolboys and girls acted as controls. The study indicated that GH has little effect on abilities, whether when given alone or in combination with other treatments. E_2 appeared to accelerate the development of specific abilities in Turner girls, so that after one year of treatment they were on a par with control girls. Two years of treatment with OX brought Turner girls on a par with control boys, but the following one year of E_2 treatment seemed to inhibit the previous superior spatial ability performance of the androgen-treated group. Figure 9.1 illustrates this effect with respect to performance in the mental rotation test only. Results for several other tests are presented elsewhere (Nyborg et al., 1994).

The study confirmed our previous finding that it is possible to normalize the development of visuo-spatial abilities in Turner girls with one-year of E_2 substitution therapy (or with androgen). The results are perfectly in line with the prediction of the GTC-A/E model. Use of the optimum range principle can even explain the regression in spatial abilities observed when E_2 was administered after two years of OX treatment. Thus, provided that the OX treatment brought the Turner girls within the optimum range for full expression of spatial abilities, the principle predicts that further administration of E_2 would make them overshoot the optimum range, with resulting inhibition of the abilities. Before too much confidence is ascribed to these results, we must remember that the number of girls in each treatment group was small (between five and eleven girls in each group) and that we are not talking about a double-blind prospective study. The investigator was not, of course, aware of which particular treatment the girl examined

Figure 9.1

Effect of growth hormone (GH) and estradiol (E2) treatment on visuo-spatial ability in young girls with Turner's syndrome as compared to untreated control girls and boys



Visuo-spatial ability was measured by the Vanderberg & Kuse (1968) version of the mental rotation test. The GH alone group was treated only with growth hormone, and performance was measured before and after one year of treatment as for the other groups. The low E2 and high E2 groups received one year of estradiol treatment alone. The spontaneously menstruating group got GH alone. The GH and E2 group got low-dose estradiol combined with growth hormone, and the androgen and E2 group first received two years of oxandrolone (anabolic steroid) followed by one year with low E2. Growth hormone seems of little effect on visuo-spatial ability, but the one year of E2 treatment brought young Turner girls with the normal female range of abilities. Two years of androgen treatment appears to improve their spatial ability to a normal male level, but the subsequent E2 treatment may have made them "overshoot" the optimum level and led to suppression of visuo-spatial ability.

Source: Modified from Nyborg et al., 1994.

had received. Nevertheless, we need replication of these preliminary observations, with even better controlled designs and a larger number of girls.

3.7.4. Low Prepubertal Steroid Secretion in Childhood

In childhood boys and girls show no or only small differences on standardized psychological test performance of cognitive abilities (e.g., Maccoby & Jacklin, 1974). When a sex difference in, say, spatial ability or mathematics

is found before puberty, it is sometimes in the direction of male advantage and sometimes a female advantage. Throwing accuracy is a male specialty, whereas paper-and-pencil tests like the preschool embedded-figures test tend to favor girls (Lunn & Kimura, 1989). A sex difference in verbal abilities usually favors females throughout life, and more boys than girls stutter and are dyslexic. Contemporary techniques for measuring sex hormones are not sufficiently sensitive to safely establish sex-related differences in the patterns of secretion from about six months after birth and up to 7–8 years of age. From the little we know, this seems to be a period of little sex hormone activity. A morphological sex difference in brain lateralization in animals (3.4.3) and in humans (3.4.4) is fairly well established very early in development, but this does not seem to be reflected functionally in a significant sex difference in, say, spatial ability during childhood. At about 8 years of age, the adrenal glands begin to pour out measurable amounts of various sex steroids. Katz (1982) has suggested that adrenal secretions are important for understanding sex-related changes in cognitive development well before puberty. This interesting suggestion deserves a closer look.

3.7.5. Sex Hormone Perturbations at Puberty

Puberty is the prime time for SD of the body, abilities, and personality. According to the proximate principle, increasing SD in these areas is a function of changes in sex hormone balances. The optimum range principle formalizes this function by suggesting that sex hormones have effects that are best described as curvilinear and depending on the dose. The proximate and optimum range principles combine with the covariance principle (3.8) in explaining the relationship between sex hormones at puberty and development of body, brain, abilities, and personality. To illustrate how the principles can be considered together, let us, for example, examine details of the predictions of the optimum range principle with respect to the different expression of spatial ability in pubertal boys and girls. According to the optimum range principle, high and low E_2 concentrations are equally incompatible with the expression of high spatial ability. The equally low level of plasma sex hormone in both boys and girls explains the absence of a sex difference in spatial ability in childhood, and the correlation to the absence of marked prepubertal sex differences in body development is explained by the covariance principle. The tremendous sexually differentiated pubertal surge in E_2, androgens, and aromatization of androgen changes this picture radically. A number of factors, probably heavily involving E_2, promotes the development of brain areas subserving spatial ability.

Let us now assume that a moderate surge in E_2 brings the adolescent male into the range just below the brain concentration for the optimum expression of spatial ability. In that case, a slight further increase in E_2 (whether of endogenous or exogenous origin) would enhance the expres-

sion of spatial ability (see figures in 3.8.3). The E_2 surge would also counteract peripheral androgen and show up as a slight feminization of some body traits. This is the way the optimum range principle explains the observation that androgynous men (that is, men who, in addition to their masculine attributes, also show some more or less clearly feminine traits) tend to obtain higher spatial ability scores than do more definitely masculinized men (see Section 3.8.2.1).

The optimum range principle also explains the development of spatial ability in pubertal females. The explanation takes as its point of departure the tremendous two- to three-fold female pubertal increase in plasma E_2, relative to men. This surge in E_2 makes more girls than boys transcend the optimum range of cerebral values. The result is concomitant inhibition of spatial ability. Dawson's (1972; Dawson, Cheung, & Kau, 1975) experiments on rats seem to provide the animal analogue to this overshoot-suppress hypothesis of female spatial ability. It will be remembered that Dawson found that intact adult female rats began to make more errors in a maze test at puberty than they did before puberty. Dawson also found that if female rats are castrated at puberty their spatial ability remains close to the male level and shows no tendency to drop, whereas ample administration of E_2 pellets led to a reduction in performance.

The overshoot–suppress part of the optimum range principle allows for several testable hypotheses. For example, further increases in E_2 concentration at puberty can be expected to lead to further suppression of the expression of spatial ability as well as to further feminization of the body and behavior (3.8.2.2). There is a growing body of evidence to confirm this prediction. More females than males regress in overall IQ score and, in particular, in spatial ability shortly after puberty (Bradway & Thompson, 1962; Campbell, 1976; Conrad, Jones, & Hsiso, 1933; Hernstein, 1971; Hopkins, 1971; Maccoby, 1966; Nyborg, 1983; Terman, 1936; Tiger & Shepher, 1975). Witkin, Goodenough, & Karp (1967) found that females on average tend to score lower after puberty than before on the rod-and-frame task, which is a good measure of spatial orientation. They explained their finding by a bias in subject selection, but they could not indicate its nature. The repeated appearance in American psychological literature on sex-related differences of such tendentious and undocumented suggestions makes one wonder to what extent they are intended to keep feminists happy or facilitate publication in a society unconditionally dedicated to equality.

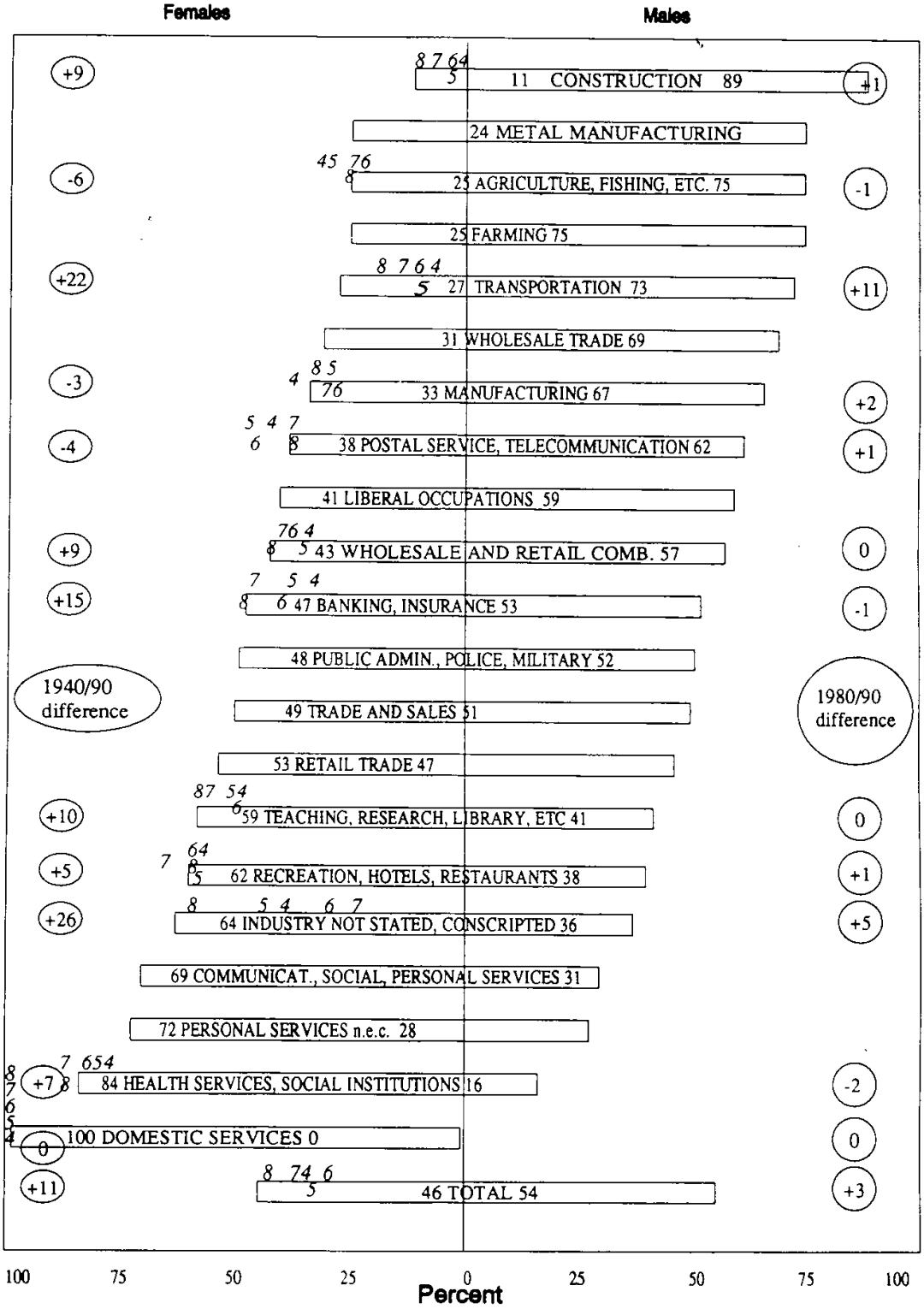
Play and creativity may also be under the influence of sex hormones, and the relationship seems to be curvilinear. It is interesting to note, for example, that the advent of sexual maturation marks the point in life when sexually differentiated youthful play comes more or less to a halt in most species in which the young play (Fagan, 1981; Symond, 1979). This is also the time when signs of childhood creativity diminish. Social learning theory explains the decrease in childhood play and creativity during the later school

years by referring to the possible negative effects of formal education, to the children being attuned to a more mechanical reproduction of learned material, to the acceptance of an adult role, and so on. According to the proximate principle, creativity and play are expected to belong to the group of essentially on-off traits, and in that case the optimum range principle leads to a prediction of arrest or even inhibition of playfulness and creativity during the pubertal plasma sex hormone surge (3.11.3). In other words, the overshoot–suppression hypothesis associated with the optimum range principle account for the common disappearance of childhood play and creativity. Fortunately, we no longer have to remain satisfied with vague hypotheses. It is actually possible to test the new hypotheses because the hormone principles tell us where to look for possible falsification. We can, for example, expect adult creativity and playfulness to be more suppressed in sexually well-differentiated adults than in less sexually differentiated androgynous adults. Another testable hypothesis is that adult playfulness and creativity will be less characteristic in the early-maturing than in the late-maturing individual. Late and less sexually differentiated adults are therefore expected to have a higher probability of remaining creative and of retaining a playful attitude during adulthood. Section 3.11.4 elaborates further on this theme.

The Scandinavian countries are sometimes cited as prime examples of sexual equality in education, occupation, and in general. Thus, primary and higher education is free to everyone with ability. There is no tuition, admission is explicitly independent of sex, race, or creed, and the state guarantees considerable economic support for the needy. The Danish population is highly homogeneous (perhaps one should rather say *was*, because the economic boom since the 1960s and the several later tragic events of war caused an influx of fugitives from various parts of the world). Several private and governmental agencies have supported specific, goal-directed, countrywide carefully planned schemes to level out sex-related differences in education and occupation. Pornographical matrials have been legalized many years ago in Denmark, the state's official policy on marriage and cohabitation of same or opposite sex with or without formal ties is positive, and the official church keeps a low profile in these matters. Nevertheless, profound sexual biases are clearly traceable in almost all aspects of the Danish society. Women still totally dominate in the helping professions, while men dominate in technical, theoretical-abstract, and executive fields. This bias is obvious in most areas of education (Kelly, 1978; see also Fig. 9.2) and occupation (Danmarks Statistik, 1985 see Fig. 9.3, from Nyborg, 1994b).

An almost identical pattern can be observed in Sweden (Scriven, 1984), England (Lockwood & Knowles, 1984; Reid & Wormald, 1982; Wormald & Reid, 1982), former East Germany (Job, 1979), Israel (Tiger & Shepher, 1975), the United States (Larwood & Gutek, 1984), and the former Soviet Union (Yanowitch & Dodge, 1969). Denmark's carefully planned official attempts

Figure 9.3
Half a century of changes in female-male proportions in the total workforce, broken down by major industries (ISIC 1968 classification)



Solid boxes = 1990. The position of italized figures indicates the sex ratio in: 4 = 1940; 5 = 1950; 6 = 1960; 7 = 1970; 8 = 1981.

Source: Statistical Yearbook 1992 and adapted by Nyborg, 1994b.

to recruit women to male-dominated areas (or vice versa) have utterly failed. There is no doubt that some women found the perfect place, but the campaign, apparently left many women in a rather difficult situation. Elsewhere I have discussed evidence for this state of affairs and concluded that future attempts to change societal sex biases be based on scientitic principles rather than on largely politically inspired feminist ideology, speculative cultural anthropology, and basically unfounded social psychology. I also called attention to the fact that the GTC-A/E model, with its physicological framework, actually points to all the causal agents and some of their mechanisms needed to level out or even totally reverse existing sex biases in society, should one wish to do so. Finally, I pointed to the danger that shortsighted, politically inspired, evolutionary ignorant people were allowed to guide such a program (Nyborg, 1994b).

As stated earlier, the proximate principle implies that sex-related differences in education and occupations reflect the effects of sex hormones. The optimum range principle allows for several specific, testable hypotheses about the hormonal basis for these sex differences in society in terms of the curvilinear model. The model predicts, for example, that men and women joining traditional areas will have relatively higher plasma sex hormone concentrations than people making an atypical field choice for their sex. Based on the optimum range principle and the overshoot–suppression hypothesis, individuals making sex-stereotypic choices will, everything else being equal, have low spatial ability and show pronounced sexual differentiation of body, brain, and behavior. For reasons given elsewhere (Nyborg, 1981, 1987b, 1994b), the GTC-A/E model implies that androgynous people with moderate sex hormone values tend to occupy leading positions in fields requiring so-called abstract thinking. The model also predicts that they would be loners (Hingley & Cooper, 1983; sections 3.8.4 and 3.11). From a practical point of view, it could be quite interesting to pursue these hypotheses to determine their predictive value.

3.7.6. Cyclicity and Abilities

Section 3.5.3 briefly observed that several cognitive traits show an enhance-suppress pattern that varies in phase with the menstrual cycle. The optimum range principle actually demands such dynamic changes in abilities over the menstrual cycle, and the early 1979 version of the GTC-A/E model predicted that verbal and spatial abilities would cycle in opposite phases. The good news is that it is now possible to test details of this physico-chemical dynamics and its consequences.

To test the hypothesis, it is necessary to keep two observations in mind. First, the sex-related adult difference in spatial ability arises not so much because male performance improves after puberty, but rather because many females begin to regress to a prepubertal level of spatial ability (3.7.5).

Second, male spatial ability remains fairly stable throughout adulthood, whereas female spatial ability varies. Keeping these two sets of observations in view, we can test details of the overshoot hypothesis (briefly, that female spatial performance drops as a function of secretion of estradiol in excess of the optimum range).

We can explore two possibilities here. Either females regress at puberty because they overshoot the optimum range (the overshoot–suppress hypothesis), or (2) they undershoot (not the overshoot–suppress hypothesis). In both cases, the GTC-A/E model predicts low spatial ability, but if case (2) is correct, the overshoot–suppress hypothesis must be wrong. To decide this matter, we can simply monitor the monthly variation in plasma E_2 and in spatial ability, and note whether spatial ability goes up or down when estradiol goes down. If spatial ability is enhanced with increasing plasma E_2 concentration, the females must have undershot. That is, when they passed through puberty with its surge in E_2, they did not surpass the optimum range but remained on the left side of the curve below the optimum range, so that a further increase would improve spatial ability. If, on the other hand, spatial ability is suppressed with an increase in plasma E_2, we can deduce that the females actually overshot—that is, that during puberty they passed through the optimum range and went down on the right side of the curve (see in 3.8.2.1). In that case, the model further predicts that female spatial ability improves peri-menstrually when E_2 is at its lowest.

Several studies provide support for the overshoot–suppress hypothesis. Klaiber et al. (1974) administered the rod-and-frame test (probably reflecting efficiency of cross-modal optic-vestibular-[somesthetic] sensory interaction, see Nyborg, 1971a, b, 1974, 1977 and, later; Nyborg et al., 1994) to normally cycling women over three consecutive menstrual cycles. The expression of spatial ability cycled with the menstrual cycle in such a way that spatial ability was enhanced in periods when E_2 was low and suppressed when E_2 was high. Similar results were obtained by Anderson (1972), Dor-Shav (1976), Hampson (1986, 1988), Hampson & Kimura (1987, 1988), and recently by Silverman & Phillips (1991) using the mental rotation test in four independent investigations. Using the embedded-figures test, Hampson & Kimura (1988), Hughes (1983), and Klaiber et al. (1971a, b) obtained essentially similar results.

Changes in mood could be a factor in explaining these observations. Thus, Hampson & Kimura (1988) controlled for effects of changes in mood during the menstrual cycle and found that such a control did not influence the observed hormone—abilities relationship. Another possibility is that progesterone could have interfered with the effects of E_2 on spatial ability in the early studies. To control for this possibility, Hampson (1989) repeated her own study, but this time testing the women during their pre-ovulatory period when progesterone is relatively low and E_2 is at its

highest. Again spatial ability was found to be significantly higher during the E_2 low phase than during the E_2 high phase. Hampson finally looked at the actual plasma E_2 concentration for each person to see whether the relationship between absolute E_2 and spatial ability was curvilinear. This was found to be the case for the space relations subtest of the differential aptitude test, but this finding generalized neither to the hidden figures nor to the rod-and-frame test.

To sum up the evidence: (1) there is a tendency for a significant number of females to show inhibition of spatial ability after puberty, (2) it appears that E_2 affects the expression of spatial ability, (3) and in a way suggesting that the inhibition can be explained by the overshoot–suppress hypothesis; and (4) the peri-menstrual decrease in plasma E_2 brings the concentration close to or within the optimum range, accounting for the female tendency to approach the male level of spatial ability by lifting the hormonal suppression.

3.7.7. Perspectives for Future Research

Other methods can be used to test predictions of the optimum range principle, but most of these are as yet unexplored. For example, changes in specific abilities can be expected to take place during pregnancy when the plasma concentration of many sex hormones changes markedly. The optimum range principle predicts, for instance, that periods of pregnancy with very high plasma E_2 will be associated with suppression of spatial abilities but enhancement of verbal and motoric abilities. The optimum range principle predicts an ipsative depression of spatial ability in old men and a relative facilitation of spatial ability in old women, after control for the general effects of ageing. These predictions are based on the observation that the ovarian production of estrogen ceases completely at menopause, whereas old men decline in *t* and may actually have higher plasma estrogen than have old females. When testing these predictions, it will be necessary to control for the previous life-span hormonal history of old people. The optimum range principle predicts that postmenopausal women on E_2 substitution therapy will obtain higher spatial ability scores in medication-free periods than during periods of estrogen medication. This prediction was confirmed by Rosenthal & Kimura (1987).

Chapter 10

Sex Hormones as Harmonizers of Body, Brain, and Behavioral Development

3.8. HORMOTYPES AND HARMONIZATION OF TRAITS DURING DEVELOPMENT

3.8.1. Introduction

> Principle 7: Sex hormones coordinate the timetables for the concerted appearance or disappearance of sex-related body–brain–behavior traits.
>
> This is *the covariance principle.*

The covariance principle constitutes the backbone of the GTC-A/E model and is the integrative principle behind it. The covariance principle refers to the fact that sex hormones have an important role in the coordinated development and expression of sex-related traits. The principle explains the smooth ontogenetic synthesis of traits by referring to the actions of the physico-chemical processes by which sex hormones manage to coordinate trait development. The principle is based on the fact that sex hormones act simultaneously and in an ordered, sequential cascade of processes on various tissues that can be widely separated in space and in such a way that the expression of sex-related body, brain, and behavioral characteristics is harmonized.

3.8.2. Range of Applications

The covariance principle has a wide range of applications across different species. It explains, for example, vital connections between body, brain, and behavioral development in the bird. If the development of the bird's particular traits get out of tune with each other or with adaptation to

changes in the environment, survival is threatened. The covariance principle refers to the mechanisms behind the timetable for the precise appearance of such diverse characteristics as singing, genital development, feather coloring, aggression, territory marking, mating, nest building, and all other sex-related characteristics essential for successful breeding. The covariance principle also highlights mechanisms through which the trait repertoire will be readjusted once the breeding season is over. As the length of the day changes, *t* secretion decreases dramatically, the genitals shrink as does the neural song system, feather coloring changes, the defense of the breeding area tapers off, and this marks the end of the breeding season. In the case of birds, the covariance principle refers to the physico-chemical processes by which males and females become almost alike, and then again become sexually differentiated during their particular life-history. As the daylight increases, sex hormone production increases once again, reactivating the various physico-chemical programs for SD, so that the reproductive cycle takes another turn. Basically, these processes are guided in birds by photoperiodic adjustment and endocrine reactions.

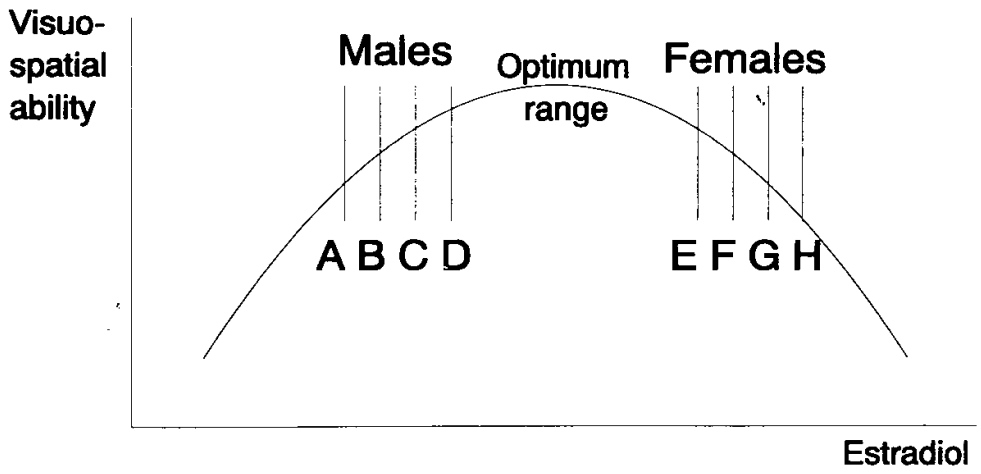
The canary example illustrates two important points. First, it shows that sex hormones can simultaneously influence a large number of intrasystemic processes in complex physico-chemical systems under the guidance of extrasystemic modulation of sensory input. Photoperiodic changes modulate neurotransmitters, which have an impact on neuroendocrine secretions via the pineal gland, in addition to inducing receptors for sex hormones. This allows sex hormones to act as buffers and coordinating agents in a dynamic interaction vital for survival and reproduction. Second, the example shows that all aspects of this dynamic interaction lend themselves to a coherent and integrative analysis at the basal level of physico-chemistry.

3.8.2.1. Coordination of Male Traits at Puberty

The covariance principle is incorporated in the GTC-A/E model and together with all the other hormone principles, explains how it becomes possible to harmonize the various sex-related traits by hormones at puberty in human males (Nyborg, 1983). To illustrate the point, we can start with the assumption (as we did in 3.7.5) that the average male E_2 concentration at puberty is slightly below the optimal range for the full expression of spatial ability. Figure 10.1 illustrates one of the many early attempts to formalize hormone-ability connections (from Nyborg, 1984, p. 503).

A further increase in plasma E_2 would feminize the body of subjects A-D, so that they would assume an androgynous appearance. In that case, the optimum range principle predicts an enhancement of spatial ability. It will be remembered that men are called androgynous if they, in addition to their masculine attributes, also score high on some feminine traits; for a definition and critique of such a classification, see Berzins, Welling, & Wetter, 1978; Lenney, 1979a, b; Lott, 1981; Myers & Gonda, 1982; Pleck, 1975; Schenk &

Figure 10.1
Early version of the General Trait Convariance-Androgen/Estrogen (GTC-A/E) model



Most males undershoot the optimum brain estradiol range for full expression of visuo-spatial abilities, whereas most females overshoot. The model predicts that males slightly feminized by surplus estradiol will show high visuo-spatial ability and that females slightly masculinized by androgen antagonizing estradiol will also show high visuo-spatial ability.

Source: Nyborg, 1983, 1984.

Heinisch, 1986; Spence & Helmreich, 1979. The covariance principle then combines with the proximate cause, the optimum range, the organizational, and the enhance–suppress principles, and explains the observation that men with a slightly feminized body show higher spatial ability than do masculinized men, as noted by Maccoby & Jacklin (1974).

In the case of the markedly masculinized man, the optimum range principle allows for one prediction and two different explanations (discussed in Nyborg, 1983, and alluded to in Section 3.7). Briefly, according to the first explanation, high concentrations of *t* heavily masculinize the body but also expose the brain to high levels of E_2 due to aromatization. This would explain low spatial ability in very masculinized men. However, according to the other explanation, the high plasma *t* concentration antagonizes E_2 in plasma, resulting in low cerebral E_2 concentrations and low spatial ability. Which of the two explanations (or perhaps a combination or even a third explanation) is to be preferred cannot be determined on the basis of available data. We have to await further methodological and technical progress to permit an informed decision in the matter.

3.8.2.2. Coordination of Female Traits at Puberty

Next, let us consider trait coordination in pubertal females. As discussed in Section 3.7.6, many pubertal females produce E_2 concentrations in excess of the cerebral concentrations for enhancement of spatial ability (subjects E-H in Figure 10.1). Additional E_2 further feminizes their bodies, increases the exposure of the brain to E_2, and increases suppression of spatial ability.

This series of simultaneous events would explain why distinctively feminized women tend to show low spatial ability. A rise in *t* antagonizes plasma E_2, keeps the cerebral exposure to E_2 modest, and enhances spatial ability in addition to masculinizing the body. In this way the GTC-A/E model explains the observed high spatial ability in androgynous women. The covariance principle further predicts that women with a heavily feminized body (and low spatial ability) will conform to feminine stereotypes to a greater extent than will females not overshooting the optimum range of brain E_2.

There is some support for this notion (Horney, 1967; MacFarland & Sontag, 1954). Socialization explains the observed female suppression of spatial ability by model learning, social expectations, or harmful effects of social or cultural stereotypes. The GTC-A/E model uses the E_2 surge to explain the suppression of spatial ability, and the coordinated actions of sex hormones on various tissues to explain the enhancement of feminine body traits and stereotypic behavior. The obligatory appearance of the sex difference in spatial ability around puberty, as well as the relationship between extent of SD of the body, brain, and abilities, are thus explained at one and only one level. This parsimonious explanation has the obvious advantage that any and all of the physico-chemical processes underlying these phenomena can be subjected to a scrupulous in-depth analysis by well-known scientific methods, so that we no longer have to resort to intangible processes or causal agents without any material locus of action.

These are but a few examples of how the covariance and the other principles combine in the GTC-A/E model to account for relations between steroids and SD of the body, the brain, and behavior. Elsewhere I have exemplified even broader covariant relationships between steroids, brain, intelligence, and personality (Nyborg, 1984, 1986a, 1987a, 1988). An important point of the GTC-A/E model is that the development and function of body, brain, intelligence, personality, and society refer to highly interdependent physico-chemical processes that must be considered jointly in any complete developmental analysis. Too often, these many processes and principles are studied separately.

3.8.3. Recent GTC-A/E models

3.8.3.1. Introduction

The GTC-A/E model was presented in various early forms in previous sections. This reflects the evolution of the model from its first, primitive appearance in the late 1970s to today. To be sure, the model is still under revision, but even preliminary versions might help focus the discussions. The most recent version was presented in the symposium on "Hormones, Intelligence, and Personality" at the biannual meeting of the International

Society for the Study of Individual Differences in Baltimore, Maryland (Nyborg, 1993a). To see how this model works, it is important to realize that individuals are first categorized in accordance to their particular hormotype.

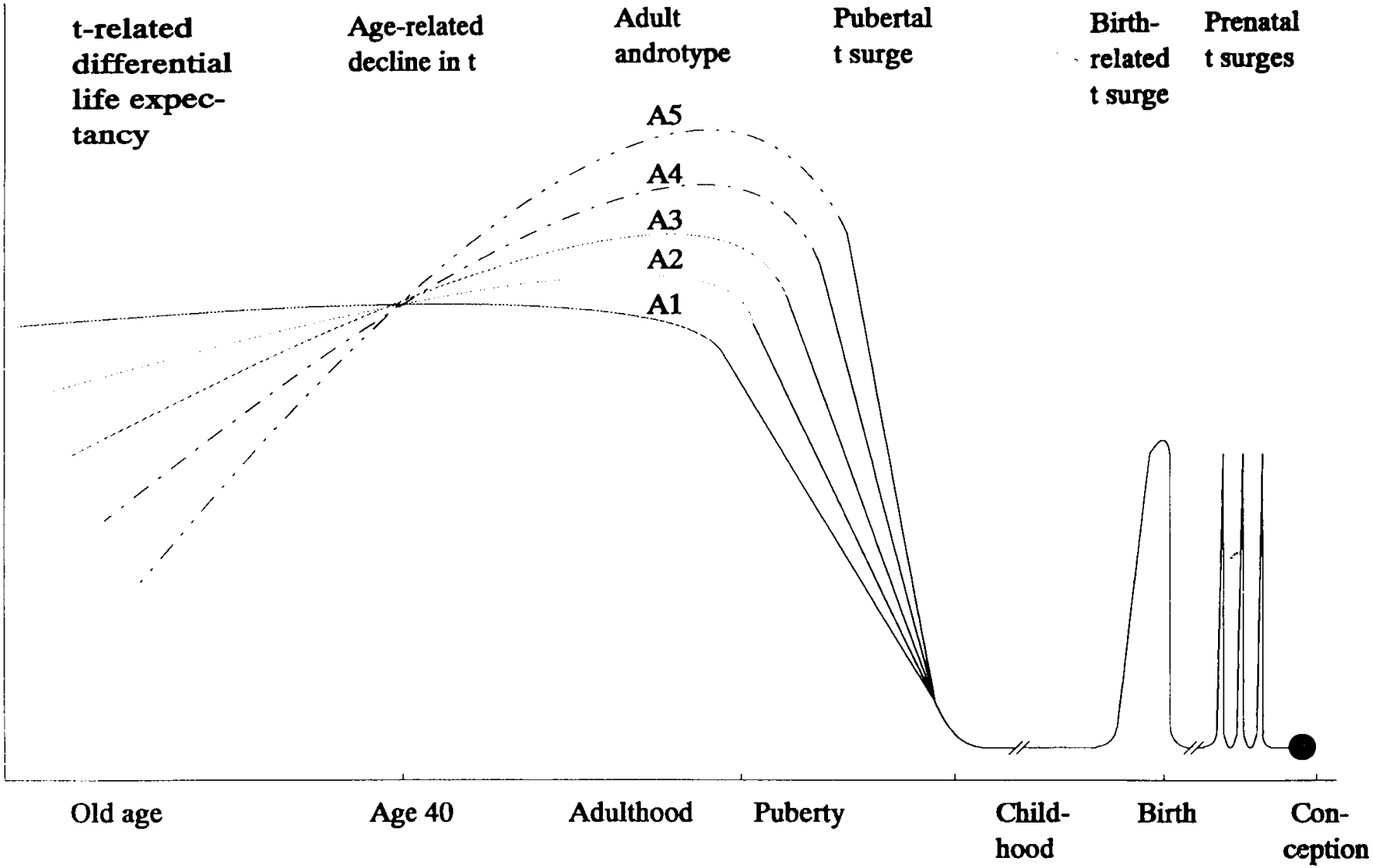
3.8.3.2. Hormotyping

Hormotyping takes advantage of the fact that males can be classified in accordance with their plasma androgen concentration and females in accordance with their plasma estrogen concentration. I have found it convenient to androtype males into one of five groups: A1 (very low androgen) through A5 (very high androgen), with A3 (moderate androgen) as the average individual. Females are similary estrotyped into one of five groups: E1 (very low estrogen) through E5 (very high), and with E3 (moderate) as the average individual. Let there be no misunderstanding here. This hormotyping uses completely arbitrary cutoff points in definitely continuous distributions of plasma hormone concentrations in males and females. It may be more convenient, though not necessarily so, to make many more hormotypes. With more experiences with hormotyping, I suspect that we will find more comprehensive and useful estimates of the androgen/estrogen balance than is the simple measure of only one parameter value, but this is a problem to be resolved by future research.

Finally, the term *type* may have unhealthy associations with previous rigid typology. Unfortunately, I could not come up with a term that relates better to the commonly used notions of genotype and phenotype, invented by the Danish geneticist Wilhelm Johanssen in 1903. The harm created by using terms such as type might not be great, however, when we consider that a person may even change hormotype as a function of permanent endogenously or exogenously caused changes in plasma hormone concentration.

Figure 10.2 illustrates general changes in plasma *t* concentrations in males in a lifespan perspective. About fourteen weeks after conception, the male fetus begins to pour out adult amounts of *t* in a burstlike manner. Around birth, *t* increases again, to drop about two to six months postnatally. It is believed that fetal and perinatal *t* and its metabolites masculinize the body and the brain of the fetus. Puberty is characterized by steeply rising *t*, and this is the time when adult hormotyping begins to make sense. However, the prepubertal exposure to sex hormones is of great importance as well, but this matter is further explored in Nyborg (1994d). Figure 10.2 shows that some males experience a relative small and late *t* surge at puberty. They are androtyped as A1 low *t* males. Other males show considerable and early rise in *t*. They are the androtype A5 high *t* males. Males with a close to average rise are the A3 moderate *t* males. There is indirect evidence to suggest that androtype A5s decline more in plasma concentration over the adult years than do A1s, so that in old age A5s may actually

Figure 10.2
Androtyping according to the GTC-A/E model



Source: Nyborg, 1993a.

end up with lower *t* than the A1s (Ellis & Nyborg, 1992). However, this preliminary observation was made in a cross-racial comparison (Nyborg & Bøeggild, 1994), and it remains to be seen whether the differential decline in *t* in different androtypes also appears in within-race comparisons. There is some evidence of an antagonistic effect of *t* on E_2, so that androtype A5 males tend to show a high degree of masculinization with few "feminine" traits and androtype A1 males tend to show more feminine traits in addition to their unquestionably masculine traits, as discussed elsewhere in the book. We are in great need of good data on the practical implications of this antagonism.

The picture is a little different for females (Fig. 10.3). The female fetus is flooded with E_2 during pregnancy and is further exposed to a host of other maternally conveyed and, perhaps, own hormones. In addition the steep rise in E_2 during puberty can be used for adult estrotyping of females. Thus, females with a very low and slowly increasing plasma E_2 content are classified as E1s, females with a very high and rapidly raising E_2 concentration are classified as E5s, and females close to average E_2 development are said to represent estrotype E3.

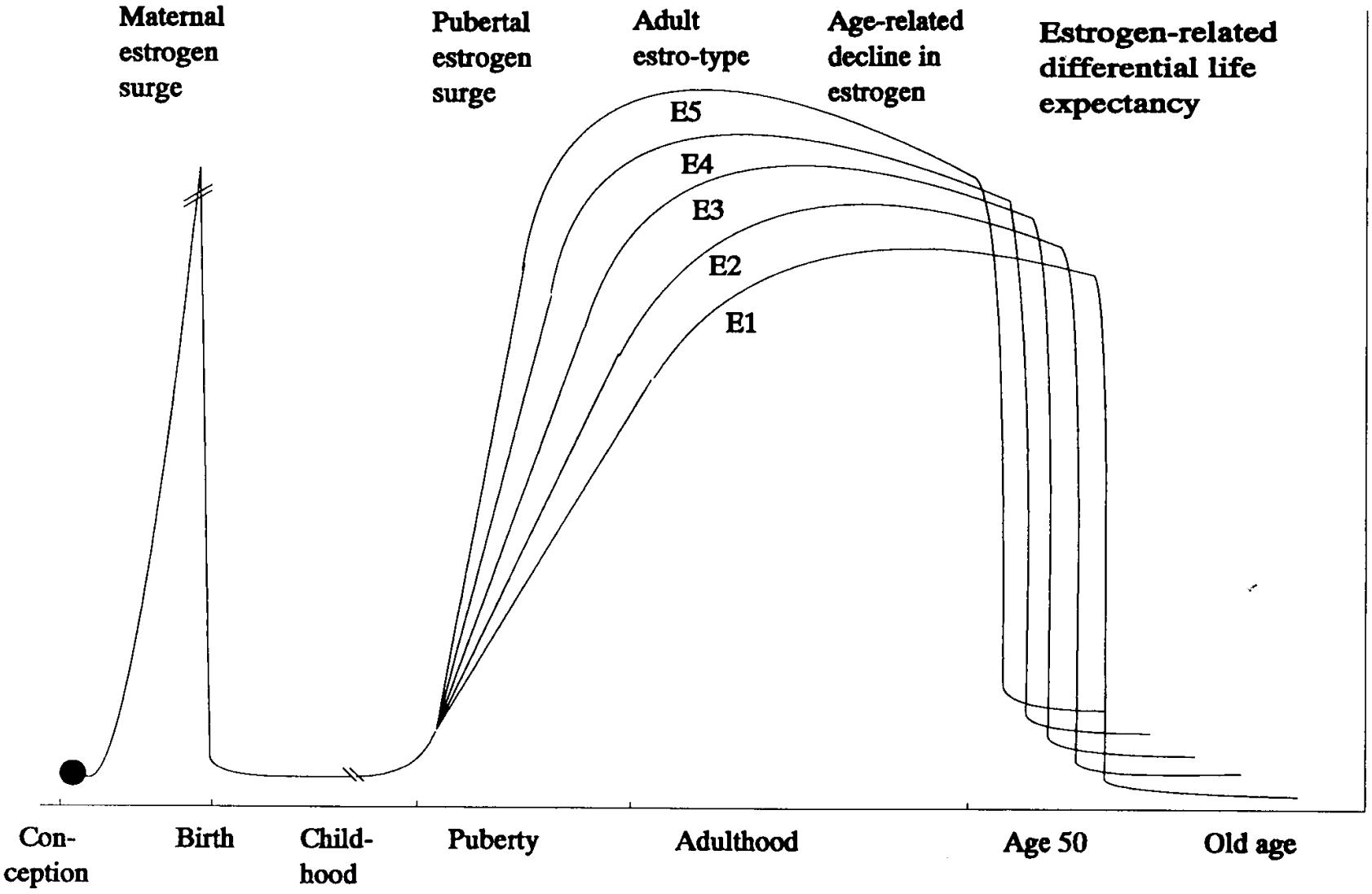
Estrotyping of females differs from androtyping in males in more than one important respect. For example, females vary considerably in plasma hormone concentration over the menstrual cycle, whereas males show large diurnal rhythmicity and smaller season-related yearly changes. The dramatic female cyclicity makes estrotyping somewhat more difficult than androtyping. Aside from controlling in both sexes the time of the day when the hormone sampling is done, we also have to keep track of the time in the menstrual cycle. Methodologically speaking, this female cyclicity has one great advantage. The naturally induced variations in E_2 can be exploited in the service of testing several predictions of the GTC-A/E model, as discussed in Section 3.8.4.3 and elsewhere.

With this brief presentation of the main aspects of hormotyping, we can now go on to consider a narrow selection of the wealth of testable predictions that the GTC-A/E model generates about the development, function, and trait coordination of various hormotypes.

3.8.4. The General Trait Covariance-Androgen/Estrogen Model

Several predictions of the GTC-A/E model have been presented in the preceding chapters. This section summarizes some of these predictions and a few new ones, first as they relate to a particular androtype and then as they relate to particular estrotypes.

Figure 10.3
Estrotyping according to the GTC-A/E model



Source: Nyborg, 1993a.

3.8.4.1. Predictions from Androtyping

As we can immediately see in Table 10.1 (from Nyborg, 1993a), androtype A5s and A1s are expected to differ in a number of important respects. A5s are thus expected to have low body stature, to be muscular, and to mature early, whereas A1s are expected to be tall, fat, and slow maturers. The basis for these predictions is that early high *t* makes for a fast maturing male, disposes for a high muscle/fat ratio, but curbs stature by early closure of the epiphysal growth zones at the end of the long bones. Masculinization effects on the brain of high *t* (and/or metabolites) is reflected in a somewhat stereotypic sexual identity with few female traits in A5s, whereas the lower *t* disposes for neural plasticity and androgynous development in A1s. High *t* A5s are expected to score high on extroversion, whereas low *t* A1s are predicted to appear introverted and to be somewhat shy and lonely individuals. High *t* predicts the increased probability of having many children, even though the predicted lower offspring rate of A1s does not imply lower fertility. Most likely, differences in libido explain the different expectations in number of offspring, but this is an empirical question.

It has been suggested that high *t* is a health risk factor, increasing, among other things, proneness to coronary failure, circulatory disturbances, and prostate cancer (Ellis & Nyborg, 1992), so A1s are predicted to live significantly longer (and more healthy lives) than A5s. A large body of evidence suggests that *t* enhances physical energy expenditure (e.g., Hoyenga & Hoyenga, 1979), so A5s are predicted to be physically more active than A1s. However, A1s are predicted to show a higher level of brain-based, so-called intellectual activity. Several arguments have previously been made in this book regarding the possibility that high plasma hormone concentration inhibits the expression of specific abilities. Because of high *t* androtype, A5s are expected to show inhibition of verbal and performance IQ, and accordingly low *g*, whereas A1s are expected to show as high level of abilities as possible within familial genetic and environmental constraints. Androtype A3 is expected to represent male modal development for all these traits.

It can easily be seen that these predictions incorporate many traits considered basic in anthropometry as well as in trait theory and that they have rather sweeping implications. Moreover, the selection of traits presented here represents only a narrow selection of many more traits assumed to be under hormonal influence and leading to SD. This makes it all the more urgent to examine the empirical value of the predictions thoroughly before leaving the surface of the earth. In the following sections, we will first examine the predictive power of androtyping with respect to some of the traits in a large male sample and then proceed to illuminate still fewer predictions based on particular estrotypes in much smaller samples.

Table 10.1
Predictions of the GTC-A/E model by androtype

Androtype	Body measures			Sexual identity	Sociability	No of children	Life expectancy	Energy level	Abilities		
	Body height	Fat/ Muscle ratio	Maturational tempo						Verbal	Performance	g
A5	- -	- -/++	++	++M(-F)	++	++	- -	++	- -	- -	- -
A4:	-	- /+	+	+M	+	+	-	+	-	-	-
A3:	Mean	Mean	Mean	M	Mean	Mean	Mean	Mean	Mean	Mean	Mean
A2:	+	+/-	- -	- M (F)	-	-	+	-	+	+	+
A1:	++	++/- -	- -	- -M (+F)	- -	- -	++	- -	++	++	++

[a]Androtype is defined by plasma testosterone concentration (ng/dL) in males.

Source: Nyborg, 1993a.

3.8.4.2. Test of Androtyping in a Large Male Sample

The following examples of test of the predictions based on androtyping are taken from a recent analysis of a sample of over 3,500 31- to 49-year-old white males. Extensive life-history, military, medical, and psychological data were collected from these men by the Centers for Disease Control (CDC) in Atlanta, Georgia (e.g., 1989) and kindly put at my disposal for further analysis. The primary purpose of the study was to see whether exposure to Agent Orange (dioxin) during active military service in Vietnam had had adverse effects on veterans as could be studied in the period of 15 to 20 years following duty. Examination of the first 774 veterans indicated that the measured blood levels of dioxin were "normal" and did not permit confident estimates as to possible noxious effect. The study was then turned into a rather more general examination of the potential deleterious effects of participation on medical and psychological well-being (e.g., post-traumatic stress disorder). About half of the sample served in Vietnam proper, whereas the other half served elsewhere and appeared as controls.

The use I made of the mountain of data differs in certain aspects from the way the CDC analyzed the evidence. Briefly, with respect to testosterone assays, I removed the upper and lower 1 percent of the plasma *t* values in order to eliminate outliers (defined as ±2 SD or more), including clinically clearly aberrant data suggestive of underlying medical disorders. This procedure reduced the material, with thirty-seven individuals at the high end of the distribution and thirty-six individuals at the low end, and left 3,581 males for androtyping. Post-hoc analyses indicated that this elimination procedure did not affect the following analyses to any significant degree. The males were divided into five groups, each containing approximately an equal number of subjects, that is, close to 710 members in each group. As expected, low *t* individuals tended to be slightly older than high *t* individuals; thus, the ensuing analyses were statistically corrected for age whenever possible. To save space in the following I will discuss data on the A5s and A1s only. However, for most analyses the scores of the androtypes represented an almost linearly graded scale of effects, and the general MANCOVA analyses concern a summary of fixed effects, including all five androtype groups. Most of the few nonsignificant general effects became highly significant if only A5s and A1s were compared in ensuing contrast analyses, and some of them became significant even when A5s were compared to the average androtype A3 or when A1s were compared to the A3s. Readers interested in details may consult the original paper on the hormotyping of the white sample of veterans (Nyborg, 1993a).

A cursory summary of the findings is as follows. A1s tended to be taller than A5s, but the difference is indeed small and not statistically significant (176.7 cm SD 6.7 vs. 176.0 cm SD 6.4; $F(4,3575) = 1.34$, $p = .25$). A1-A5 weight

differences were highly significant and in the predicted direction (90.6 kg SD 16.5 vs. 77.2 kg SD 12.6; $F(4,3574) = 86.66, p < .001$). Quetelet's body mass index accordingly showed a significant difference favoring A1s (29.0 SD 4.7 vs. 24.9 SD 3.8; $F(4,3574) = 97.61$, $p < .001$).

It is possible to reliably translate the clinical MMPI data collected in the veteran study into Eysenck's major personality dimensions (Nyborg, 1994c), and then to inspect differences in personality among androtypes. The GTC-A/E model predicts that A1s will be low on sociability and A5s high, and this prediction was borne out. A1s score 18.8 SD 4.8 on extroversion, and A5s score 19.7 SD 4.6. The overall androtype difference is significant $F(4,3575) = 2.72$, $p < .03$. Further to personality, A1s got a lower Neuroticism score, 26.2 SD 11.7, than A5s, 28.0 SD 11.5; but the overall difference just missed significance $F(4,3575) = 2.06$, $p < .08$. However, A1s were significantly lower than A5s in Psychoticism score (6.8 SD 2.8 vs. 7.5 SD 2.7; ($F(4,3575) = 4.12$, $p < .003$).

With respect to the use of various drugs and stimulants, A1s had fewer drinks per month ($F(4,3558) = 10.04$, $p < .001$), smoked fewer cigarettes per day ($F(4,3573) = 11.72$, $p < .001$), and used fewer drugs (any–past year: Pearson Chi-square (4) = 16.92, $p = .002$; Gamma = .25) than did A5s. On the other side, A1s were more often on a special diet (Pearson Chi-square (4) = 15.4, $p = .004$), scored higher on the current medication index (Pearson Chi-square (4) = 12.42, $p = .01$; Gamma = -.10), and tended to suffer more from allergies (Pearson Chi-square (4) = 8.38, $p = .08$; Gamma = -.07) than A5s.

The Vietnam study further contained various ability scores lending themselves to examination in terms of androtype. Regardless of type of test, A1s always scored higher than A5s. This was the case in the Army General Technical Aptitude Test (111.5 SD 19.0 vs. 106.0 SD 18.8; $F(4,3531) = 5.30$, $p < .001$), the WAIS-R Information subtest (10.7 SD 2.8 vs. 9.9 SD 2.7; $F(4,3576) = 8.48$, $p < .001$), and WAIS-R Block Design subtest (11.1 SD 2.5 vs. 10.6 SD 2.5; $F(4,3576) = 5.0$, $p < .001$). Therefore, it is not surprising to find that A1s get a higher formal education index (years) than do A5s (13.6 SD 2.4 vs. 12.9 SD 2.3; $F(4,3574) = 7.31$, $p < .001$) and have a higher pay grade at discharge index (4.3 SD .7 vs. 4.0 SD 1.0; $F(4,3575) = 9.23$, $p < .001$).

As can clearly be seen, almost all of these data are in line with predictions of the GTC-A/E model based on androtyping. The typical low *t* A1 is a trifle taller and considerably heavier than the high *t* A5 male. He scores low on Psychoticism, Extroversion, and Neuroticism. He tends to be allergic, use more medicine than the average, but smokes and drinks less than the average. He performs well on verbal and performance tasks and accordingly, gets a high *g* score. He spends much time in school and later gets paid accordingly. The A5 contrasts him in most respects (Nyborg, 1993a).

With these findings in view, the next question is: How large are the effects? The answer seems to be: Not very large or almost negligible from

a practical point of view! The reader probably observed that many of the differences were rather small. However, the particular age distribution of the Vietnam veteran sample may conceal larger real differences. Thus, the mean age (as well as the mode) for the population was 38.4 years with an SD of only 2.5. As can be seen from Figure 10.2, depicting life-span changes in plasma *t*, this age is close to the time in life when the sharply declining curve for *t* in A5s meets with the slightly declining curves for A1s and for the other androtypes. The implication is that androtyping has its lowest resolution power in this sample of predominantly middle-aged males. Any androtyping of males closer to late puberty would probably raise its discriminative power. It is worth noting that after age 40 individual with high and low positions in the *t* continuum may even reverse. We clearly need more data on this matter, but it is already obvious that regardless of age at time of examination, it is vitally important to take chronological, or better biological, age into account when androtyping.

3.8.4.3. Predictions from Estrotyping

Table 10.2 formalizes predictions based on estrotyping. As with A5s and A1s, E5s and E1s also represent in many respects opposite trait patterns. Compared to the average and the E1s, the E5 female will show stunted growth because her early high estrogen closes the epiphysal growth zones in the long bones. High estrogen also predisposes for massive fat deposits; thus, the E5 will show a much more pronounced feminine fat distribution than average than the tall, lean E1 type. E5s are predicted to mature at a rapid rate, whereas E1s are expected to be slow maturers. E5s will manifest a so-called stereotypic sexual identity with a distinctively feminine flavor, whereas the E1s would rank among androgynous females, typically directed toward a professional career and with less emphasis on domestic activities. The E5 is expected to be oriented primarily toward other people in an extroverted way, whereas E1s will be introverted and prefer solitary activities. An important factor in life for E5s is children, and they are expected to have them in high numbers. The E1s may have higher libido than E5s because they have relatively higher *t*, but they would nevertheless be expected to have fewer children. This apparent puzzle may be explained by considering trait patterns rather than single traits, as recommended by the GTC-A/E model.

The combination of introversion with low social and high career orientation may dampen moves to establish a large family, with all the social demands involved. High E_2 E5 females may, on the other hand, be more submissive to male dominance. This, combined perhaps with higher fertility owing to early maturation, stable ovulation, and other factors, might explain their higher number of offspring as compared to E1s, despite a lower *t*-driven libido. One implication is that we can expect more E1s than E5s to use all types of contraceptives. Obviously, these predictions of the

Table 10.2
Predictions of the GTC-A/E model by estrotype

E-stro-type	Body measures			Sexual identity	Socia-bility	No of children	Life exp-ectancy	Energy level	Abilities		
	Body height	Fat/ Muscle ratio	Matura-tional tempo						Verbal	Perfor-mance	g
E5	- -	+ +/- -	++	++F	++	++	- -	- -	- -	- -	- -
E4:	-	+ /-	+	+F	+	+	-	-	+	- -	-
E3:	Mean	Mean	Mean	F	Mean	Mean	Mean	Mean	Mean	Mean	Mean
E2:	+	-/+	-	- F (M)	-	-	+	+	(-)	+	(+)
E1:	++	- -/+ +	- -	- -F (+M)	- -	- -	++	+ +	++	++	++

[a]Estrotype is defined by plasma estradiol (E_2) concentration (ng/dL) in females.

Source: Nyborg 1993a.

GTC-A/E model are fully testable. Like high *t* in males, high estrogen in females, according to the model, is assumed to constitute a health risk in old age. The model therefore predicts shorter life span for E5s than for the average female E3, and increased life span for E1s. The relatively high *t* in an E1 provides a basis for the prediction that she will already be physically very active in childhood but also later in life, whereas the relatively high estrogen in E5s will predispose them for a more sedentary life-style. High estrogen in females is assumed by the model to hamper the expression of spatial abilities and to promote verbal abilities, but very high levels are predicted to hamper both verbal and performance abilities. Accordingly, E5s are predicted to show lower than average *g*, which is the averaged sum of verbal and performance scores. E1s are predicted to fully express their specific abilities and, accordingly, to score very high on *g*-loaded tests.

An interesting detail is how the model handles the effects of variations in E_2 over the menstrual cycle. It certainly is taxing the model too much to assume that menstruating females change all their estrotypic parameter values in accordance with the monthly variation in estrogen. Traits arising predominantly from organizational effects are not expected to change much under these circumstances, but traits pending in their expression on activational effect may actually show significant fluctuation. The ability pattern seems to depend in part on activational effects as discussed previously. In this respect, the abilities of an E3 female may actually look quite similar to those of an E4 during the middle of the menstrual cycle, when her plasma E_2 reaches a zenith: Her verbal abilities will be enhanced, and her spatial abilities would be depressed. When the E_2 level gets at its lowest, she might temporarily show abilities like an E2, with enhanced spatial abilities and slightly depressed verbal abilities.

3.8.4.4. Test of Predictions from Estrotyping

I am not aware of the existence of any study of females that lends itself to testing predictions of the GTC-A/E model with respect to estrotyping at the same grand scale as does the Vietnam veterans study. Thus, for the time being we have to remain satisfied with less, and the reader is referred to the bits and pieces of evidence presented elsewhere in this book (e.g., in 3.5.3, 3.7.3, 3.7.5, 3.7.6) and in the literature (e.g., Hoyenga & Hoyenga, 1979). Suffice it here to say that available evidence tends to provide encouraging support for most of the predictions of the GTC-A/E model based on estrotyping. Clearly, the strong propositions of the model require much better evidence before final acceptance. Most likely, such evidence will necessitate further revision of the model, but such a move is totally in line with the largely empirically driven program of physicology.

3.8.5. Androgynous A1s and E1s: When the Gulf Narrows

Earlier I made an attempt to exemplify how the GTC-A/E model predicts maximum differences in the appearance of sex-related differences in terms of hormotypes. To be sure, the model also predicts similarities. Both A5s and E5s are predicted to mature early, to become highly distinctive sexually, to be quite stereotyped with respect to sexual identity, and to meet in fecundity and in a less than optimum expression of abilities, and both A1s and E1s are expected to mature late, to become less distinctive sexually, to blend their homotypic sexual identity traits with those of the heterotypic sex, and to leave few children behind them, while at the same time turning to the full use of their superior abilities. Perhaps the most important task of the GTC-A/E model is to put these sex-related differences and similarities into proper context, to generate precise hypotheses, and to allow the acid tests of assumptions of what causes the comprehensive covariant trait pattern development. In other words, the model is meant as a tool to understand all the steps in what it takes to make originally multipotent individuals differ maximally in important traits, as do A5s and E5s, or minimally, as do A1s and E1s.

A second point of the model is that when females in their low-estrogen phase of the menstrual cycle approach the male hormone balance, they also do so with respect to the expression of verbal and spatial abilities. The GTC-A/E model thus accounts for dynamic as well as for static aspects of covariant trait patterns. This means that sex dimorphic notions of what it takes to be a "real" male or female lose the importance they once enjoyed. This would mark a considerable leap forward in the study of sexual differentiation. It is actually quite surprising to see that this insight, although it has been on its way for quite a while, has had so little effect on mainstream research. Finally, with its explicit focus on causes and mechanisms, the GTC-A/E model is primarily about different individuals and only secondarily about individual differences. The model explains how a given individual can be more or less masculinized or feminized with respect to many or few traits in a more or less stable fashion over the life span. In this perspective, it is nonsense to talk without further ado about an eternal war between *the* males and *the* females, to talk about *the* rights of men and women, to talk about equality without specifying for whom, and to defend the claims of a particular feminist research program. To make any sense out of such discussions, participants must in the future be well equipped with carefully qualifying statements about what kind of men or women they are talking about. They should realize that in many important respects A1s and E1s may have more in common than have A1s and A5s or E1s and E5s. The GTC-A/E model may be of some assistance in clarifying questions about how much and why.

Chapter 11

Origin of Sexual Differentiation of the Fetus

3.9. THE MULTIPOTENTIALITY PRINCIPLE

3.9.1. Introduction to the Notion of Basic Femaleness

Principle 8: The fetus possesses potentials for graded sexual differentiation.

This is *the multipotentiality principle.*

The original biblical account of the male Adam being the first human on Earth was later substituted by suggestions that the female sex is the primary and the basic one. In 1849 A. A. Berthold argued that pure speculation about whether the male or the female sex is the more fundamental sex should be replaced with scientific studies using suitable experimental control over physico-chemical processes. Unfortunately, the obvious is not always so obvious to everybody. It took almost one hundred years before Alfred Jost (1947) finally demonstrated experimentally that the castration of embryos results in feminization of development, regardless of whether they have the male or the female karyotype. This finding led Jost to believe that, in most species, the basic developmental pattern is female. In birds the reverse appears to be the case. According to Jost, for a male mammalian to develop properly, something has to be added on top of female development, and that something apparently includes a Y chromosome, H-Y antigen, testicular tissues, and androgens. Having examined the available evidence, Jost concluded that the testis is *the* active body sex differentiator, but that female development is passive and basic (Jost, 1970).

The physicological research program holds that all aspects of organismic development, functioning, and behavior reflect energy-consuming

physico-chemical processes. SD, being no exception, reflects, according to the proximate principle, particular actions of sex hormones. For a physicologist it is therefore difficult to accept the ideas that femaleness is more basic than maleness and that female development is passive, whereas male development is active. The primary aim of physicology is to address phenomena for which there is a causal basis or, at least, a good testable hypothesis for it, but where is the cause of passive development? The phenomenon must be operationalized and their relationships determined. Otherwise, we don't know what we are dealing with. According to this approach, one sex hormone or process is no more basic than the other. Moreover, female development depends on the presence of estrogen as well as on androgen during development, and from what we now know there is no evidence that female development is more passive than male development. It makes a difference, however, if the balance between various hormones is different or, say, if enzymatic processes differ. To genetically oriented researchers, the idea of passive female development may have persisted so long because it was impossible to isolate its genetic cause (whether of sex-chromosomal or autosomal origin), so there was no other way to account for development of the female pattern. However, Jost's conclusion was essentially based on the observation that the ovum does not contribute much to female SD, because it made little difference to female development whether or not the female was ovariectomized.

There are problems with the experimental control in studies of passive femaleness. For example, it cannot be excluded that placental or maternal sex hormones passed through the maternal-fetal barrier and contributed to female development. Even experiments in which transplantation tissues were removed early in development are vulnerable to this possibility. The idea of passive femaleness would be incorrect if extrafetal gonadal sex hormones reached the fetus and affected development in a feminine direction. Unsuccessful or partly unsuccessful sex reversals reported in the literature would have to be reinterpreted in terms of incomplete or too late castration to be fully effective, a placental or maternal hormone influence, or an inadequate medication regime. Moreover, little is known about the fetal gonadal and adrenal secretion of sex hormones. Finally, the possibility of male-female asymmetrical brain differences in the fetal induction of receptors for hormones must not be forgotten.

3.9.2. The Multipotentiality Principle

Döhler, Gorski, and co-workers had problems with the idea of basic, passive female development and referred to a number of findings that appear anomalous to the hypothesis (Döhler et al., 1982, 1984; Döhler & Gorski, 1981; Döhler & Hancke, 1978; Hancke & Döhler, 1981). As a viable alternative, the research group suggested that the fetus is originally "neu-

tral" or "undifferentiated," and that the notion of basic female passive development is better substituted with a concept of active and progressive sexual brain differentiation. This hypothesis has gained credibility for several reasons that the early researchers could not possibly have known in detail. For example, we now know that even microscopic doses of sex hormones, not previously measurable, may profoundly influence embryonic brain development. We also know that the placental barrier provides no guarantee of total effectiveness against the transfer of maternal sex hormones. The idea that α-fetoprotein (AFP) (e.g., Döhler et al., 1984; Toran-Allerand, 1984b) protects the human female brain against the effects of E_2 has recently been questioned (see below). Finally, recent research presents a number of experimentally attractive alternatives to the passive basic femaleness hypothesis. We need, for example, to explore the implications of the receptors, come-and-go-during-development phenomenon and of the asymmetrical distribution of steroid receptors early in development.

The multipotentiality principle is *a priori* completely dispassionate with respect to one or another explanation of female or male development. The principle is further independent of whether some genetic or other extragonadal sex-conditioning factors can be localized in the future. The principle is rather strictly pragmatic and is validated to the extent that absence or variations in prenatal sex hormones (whether of endogenous or exogenous origin) overturn genomic or other nonhormonal effects with respect to male or female development. To demonstrate the extent of this is a sufficient basis to ascertain whether the embryo has the potential for developing into either a male, a female, or a "something in-between" individual. In either case, it can be examined whether male and female development is an active process pending on hormones. Questions of whether one type of development is more basic than the other and of whether development of the body and the brain can rest on a "passive" process is of little importance to physicology. Such questions reflect *a priori* attitudes rather than testable hypotheses.

Ten years ago Toran-Allerand (1984b) reevaluated the role of AFP. Her discussion focused on AFP in rats, but the treatment may have relevance for understanding female development in at least some other species. It is widely believed that AFP binds plasma E_2, thereby preventing E_2 from reaching the fetal brain. AFP thus protects the female brain from the effects of plasma E_2, whereas the male brain is exposed to E_2 from the testes and through local aromatization of *t*. However, Toran-Allerand noted that neurons lack the mRNA needed for producing AFP. Nevertheless, AFP is found inside neurons. In other words, the only way AFP could have entered the neuron is by transcending the cell membrane. But this means that heavily E_2-loaded AFP must have invaded the neuronal cytoplasm from plasma. Next, Toran-Allerand noted that E_2 binds more readily to nuclear receptor molecules than to AFP because nuclear receptors have higher affinity to E_2 than has AFP. This difference in affinity results in intracellular

dissociation of the plasma protein-E_2 complex and liberation of E_2 for subsequent use in nuclear RNA transcription. What all this boils down to is that AFP, rather than protecting the brain from E_2, is an important contractor of the E_2 needed for specialized intraneuronal modulation of gene expression.

Toran-Allerand's observation may, at least in part, explain one important aspect of the puzzle of SD of the originally multipotent rodent brain. It remains to be seen whether her model applies to the SD of the human brain, however, because the guinea pig and human form of AFP lack the estrogen-binding domain. Nevertheless, AFP is found inside some brain cells in these species (Ali et al., 1981). It may be that human AFP lost its estrogen-binding characteristics during evolution because it was not under directional pressure during the postnatal period in species in which the actions of androgens, mediated by E_2, take place in utero (Plapinger & McEwen, 1978).

This is not the only puzzle AFP presents to the neuroendocrinologist. AFP is present in intercellular fluids as well as inside some neurons, but cells with intracellular AFP contain no intracellular estrogen receptors (Toran-Allerand, 1982). The implication seems to be that E_2 is introduced into cells that are unable to respond to this hormone. More complications arise because hormone–brain–behavior relationships differ among boys and girls. For example, neither the timetable for the secretional hormone pattern nor the binding pattern is alike in the two sexes. The conversion pattern also differs between the sexes (MacLusky et al., 1985).

The empirical evidence for accepting the notion of basic passive female development is weak, to say the least, but it is equally obvious that we most certainly have a number of problems to solve before we know details of the presumed active process. Section 3.4 refers briefly to studies suggesting that exposure to so-called male and female sex hormones are important for female as well as for male differentiation and that atypical exposure causes atypical development.

Chapter 12

Cerebral E_2 and SD of the Brain

3.10. THE ESTROGEN ALONE–BRAIN SEX PRINCIPLE

3.10.1. Introduction

> Principle 9: Low fetal E_2 feminizes the brain, whereas higher concentrations masculinize it.
>
> This is the *estrogen alone–brain sex principle.*

During the early examination of the effects of sex hormones on development, it became obvious that at least under certain circumstances, estrogen could have masculinizing effects and thus was capable of mimicking the effects of androgen. It was found, for example, that large doses of estrogen may masculinize female as well as castrated male animals and that the effects applied not only to somatic but also to behavioral characteristics. Since these observations ran counter to common sense about what female sex hormones do, for a while they were considered to be paradoxical results. Then Döhler & Hancke (1978) undertook a series of studies that led to the suggestion that low-dose E_2 exposure feminizes the brain, whereas high-dose exposure masculinizes it. The estrogen alone–brain sex principle reflects this idea.

3.10.2. Problems with the Estrogen Alone–Brain Sex Principle

Without doubt, estrogen has a very powerful influence on prenatal brain development. The question remains, however, whether the actions of estrogen explain all aspects of brain sex-typing and, by implication, the sex-re-

lated differences in behavior and gender identity observed in adulthood. An obvious problem with the estrogen alone–brain sex principle is that the exact steroid value for switching from feminizing to masculinizing effects has not yet been determined. It may be that the critical value differs between species, within a species, and from early to late in the critical period in a given animal. Another problem for the estrogen alone–brain sex principle has to do with an observation by Goy & Goldfoot (1975). They found that the balance between suppression and enhancement of masculine and feminine traits during development differs between species. For example, female rats undergo some masculinization and behave more bisexually than do male rats, whereas male rhesus monkeys are not fully *defeminized*, and behave more bisexually than do female rhesus monkeys. By analogy, the human male may be masculinized but not fully *defeminized* (see 3.9 and 3.11.3). The term *defeminized* is italicized here because it sometimes refers to the unproven notion of basic femaleness. More problems arise with the estrogen alone–brain sex principle because species seem to differ with respect to which sex hormones activate sexual responses. In some species E_2 acts synergistically with progesterone to elicit a sexual response, whereas in other species, such as the rhesus monkey, progesterone apparently decreases the attractiveness of the female to the male (Baum, 1979). Male copulatory behavior may depend on androgen receptor activity in the rhesus monkey, but on aromatized testosterone and estrogen receptors in the male rat (Goy et al., 1980). The kind of hormone responsible for defeminization and masculinization also seems to vary across species. McEwen (1981) suggests that this reflects species-specific differences in the genetic programming of neurons of various hormonal sensitivities, so that early in development they become organized within appropriate brain circuits and later are activated during adult life.

Brain sex-typing seems to be a permanent rather than a transient phenomenon. Analysis of mechanisms for brain sex-typing has therefore focused more on organizational than on activational phenomena. However, it is important to realize that it has not yet been possible for morphologists to clearly link anatomical brain structures to gender identity. Moreover, it is quite likely that SD of the brain involves not only morphological aspects, but also subtle permanent presetting of a number of biochemical parameters. Nordeen & Yahr (1982) found that female rats retain more estrogen in the medial parts of the basal hypothalamus and the preoptic area than do male rats after systemic administration. They also found that unilateral implantation of estrogen pellets in the left hypothalamus leads to defeminization, whereas implantation in the right hypothalamus results in masculinization.

The above discussion makes it highly likely that the hypothesis that E_2 is *the* sex hormone for prenatal SD of the brain represents an oversimplification. A more likely hypothesis involves the two major pathways to SD of

the brain: the androgenic and the estrogenic pathways. The androgenic pathway is characterized by the actions of *t* or its metabolite dihydrotestosterone, whereas the estrogenic pathway is dependent on the aromatization of *t* to E_2 (Martini, 1978, 1982; Motta et al., 1980; see Section 3.6.2). McEwen (1983) has suggested that defeminization processes involve aromatization and that masculinization involves androgenic as well as estrogenic pathways.

Considering the evidence, it is obvious that the estrogen alone–brain sex principle reflects a heuristic strategy rather than a satisfatory explanation of a set of well-documented observations. However, simple hypotheses sometimes facilitate the who's who game when it comes to determining the complex relationships in a system in which several chemicals interact in a dynamic fashion. A good example of this is the hypothesis about relationships between menstrual changes in sex hormones and specific abilities (3.7.6). It is also worth noticing that, for several reasons, the estradiol alone–brain sex principle is not to be confused with the optimum range principle. First, it makes little sense in an evolutionary perspective to say that one sexual phenotype is more optimal than the other, unless a number of contextual qualifications are provided, and they might be quite difficult to find. Second, the estrogen alone–brain sex principle refers primarily to prenatal or very early brain sex-typing via organizational effects (even though this notion is not presently built on sufficient neuroanatomic and neurochemical evidence), whereas the optimum range principle applies during the lifetime of an organism and incorporates transient activational effects.

Chapter 13

Universal Economy and Fixed Budgets

3.11. ECONOMY AND THE TRADE-OFF HYPOTHESIS

3.11.1. Introduction

> Principle 10: Growth and functional capacity is subjected to physico-chemical constraints, so that strong development or activity in one area is traded off by less development or activity in other areas.
>
> This is the *economy principle.*

In this chapter I will try to bring the principles and the evidence presented in the previous chapters into broader perspective, involving intrasystemic as well as intersystemic and extrasystemic factors in their fullest sense and, finally, into an evolutionary perspective. Phrased differently, I will now make a stalwart attempt to apply the GTC-A/E model and physicology in order to address several difficult questions, such as, for example, inquiring into the much disputed transition from Neanderthal to Cro Magnon man during recent evolution. I will attempt to relate hormotypes to the most likely nature of the selective forces of tomorrow's world by hypothesizing which types will prosper.

Everything in the universe is physical, and everything that changes involves a change of energy distribution. This is the bottom line of a physicological analysis and applies equally well to organic (i.e., carbon-based) as to inorganic processes. Moreover, most if not all processes in nature are economical. An electrical current runs the shortest—one is almost tempted to say the—easiest way (but better resist that temptation!), and a chemical reaction absorbs the smallest amount of energy possible. In this way everything in nature seems to follow a kind of law of least effort. Sex hormones are no exception to this rule. Thus, although nature takes a toll

for all chemical reactions, the processes involving estrogens and androgens are economic and make no detours. The energy price for their reactions is as low as circumstances allow.

In the following discussion, I take up the notion of economy in physico-chemical processes in terms of considering the universal evolutionary hypothesis that economical systems have a higher probability of surviving than less economical systems. In this connection, I assume the more specific hypothesis that sex hormone actions provide the most economical solution to the efficient evolution of SD, survival, and the reproduction of complex organisms.

It was the poet and scientist Goethe who, in 1795 suggested that the general total in nature's budget is fixed, but nature is free to allocate partial sums for any expense it wishes. If it spends in one way, it is obliged to economize in another. Goethe wrote that this is why nature can never fall into debt or become insolvent. Later, Goeffroy St.-Hilaire (1859) expressed similar ideas about what I would take as intrasystemic economy and referred to a *Loi de balancement*. Notions of least effort and of limited growth potential also go into the concepts of *recapitulation* and *neoteny* (see Gould, 1977, 1981; 3.11.5 and 3.11.6). Ghiselin (1974) has provided a critical discussion of the evolution and economical aspects of sex, and I have borrowed freely from his detailed treatment.

3.11.2. Examples of Intrasystemic Economy

It would be an extremely expensive solution first to let the complex physico-chemical blueprint for differential male and female development be invented from scratch time and again in each individual, and then to let selection work on the plethora of individual variations to settle for only those few specialized developmental programs that fit exactly into particular ecological niches and reproductive options. From both an engineer's and a physicologist's point of view, it would be much simpler and far less expensive to modify an already stable, well-tested basic physico-chemical system (e.g., 3.9.2), endowed with a variety of intrasystemic potentials or programs for the development of different general functions, and to change its developmental parameters in accordance with specific inter- and extrasystemic requirements. Costly complex and multifactorial modification processes could also be reduced to a matter of selection among a narrow range of chemicals having the capabilities to enhance or suppress the different developmental programs lying dormant in the system. According to the economy principle, selection would favor chemicals that economically and without detours guide processes facilitating the necessary intrasystemic adaptation to inter- and extrasystemic necessities. Further economy could be attained if some of these chemicals could work well in extremely small concentrations and be progressively more effective up to a

certain point of concentration, above which they would work in opposite ways until, in very high concentrations, they would accomplish completely new reactions. Several hormones seem to work that way.

When these rather general notions are combined with the quantitative hormone principles presented earlier and with the principle of multipotentiality, we see the outline of the ultimate hormonal economy. The principle of multipotentiality states, in effect, that selection has singled out a fairly simple "hormone dial" solution to accomplish the immensely intricate task of enhancing or suppressing one of two general types of developmental programs out of a multitude. A light turn of the sex hormone dial or balance profoundly affects a large number of intrasystemic developmental and functional parameters. This not only makes possible the harmonious intrasystemic coordination of literally hundreds of processes, but does it in such a way that various economical adaptations to intersystemic reproductive purposes and to the other extrasystemic environmental requirements of physico-chemical systems becomes possible. However, such an account would make little sense in terms of physicology unless the active components used for adjusting the system could be operationalized. This raises questions about (1) the chemical nature of these components, (2) where they came from, (3) what their locus of action is, and (4) how they relate to each other and to the development, and function of the total system.

Cholesterol was probably an important chemical species in the chain of chemicals that selection worked on in primitive times in the evolution of SD. As hinted previously, there were several good reasons why cholesterol was that important. First, then as now, cholesterol was present in every "live" cell. Second, there are several specific enzymes that metabolize cholesterol to progesterone, androgens, estrogens, and several other systemic metabolites, and can do so with a minimum of error and consumption of energy. Third, each of the metabolites of cholesterol may have powerful and pervasive systemic effects. They regulate the protein production of genes, and they affect membranes with effects on cell metabolism and the working conditions of neurotransmitters, either in the vicinity or far away in anatomically or functionally more or less separate tissues. The point is that these sex hormones are well suited to accomplish what seems to be an otherwise almost magical task of coordinating the multiple aspects of body, brain, and behavioral trait development and function in highly economical cascades of serial and parallel molecular operations.

The (probably too simple) E_2 alone–brain sex principle implies, for example, that a light turn on the hormone dial actualizes the transcription of dormant genes, the protein products of which are needed to procure female development. A well-tested multipotential genetic blueprint (read: sets of DNA coded instructions) is already there (read: coded by parental DNA) and does not first have to be invented de novo and then singled out in an energy-consuming selection process. However, there is a price for

running, say, the female program—total or partial sacrifice of the male program—because the budget is more or less fixed. Again, however, this bill is low because the costs are easily and economically covered by simply suppressing the transcription of gene products needed for male development. In other words, the energy price for these operations becomes so low because (1) the process requires switching or suppression of some and facilitation of other, already available genes, and (2) this enhance–suppress mechanism—at least in its simplest form—is accomplished by regulation of the balance between two major metabolites of cholesterol, namely, estrogens and androgens. I am convinced that a modern engineer would be hard pressed to come up with a more elegant and foolproof mechanism for reliably securing a pervasive intrasystemic tradeoff between cells and organs, so that the organism never falls into debt or becomes insolvent while adapting to extrasystemic circumstances.

The covariance and other principles of the GTC-A/E model strive to account for the details of how sex hormones manage to coordinate these cascades of probably strictly rule-bound actions. The problem to be solved is to routinely secure a sexually stabilized development into one of two (and only two sexes in the case of mammals) but nevertheless to procure sufficient intrasystemic variability for selection to work on and furthermore to allow for highly adaptive sex-related specialization, but also to limit the extent of sexual specialization so that smooth cooperation between the two sexes during reproduction and rearing of the offspring becomes possible. The covariance principle combines with the economy principle to account for how the intrasystemic tradeoff between cells, organs, and functions makes an intersystemic tradeoff between behavioral traits possible. In other words, careful harmonization of all intrasystemic somatic and brain processes has to be coordinated in the phenotypic equation with a host of intersystemic and extrasystemic necessities. Serious failure at any molecular step, in the proper implementation of any principle or in any of the many derived complex forms, would constitute a serious threat to intrasystemic survival or intersystemic reproduction of the exclusively physico-chemical systems we call people. Minor disturbances may raise the bill and would give competitors an advantage by then representing a slightly more energy-efficient survival or reproduction system. Large disturbances may either mean extinction if the bill becomes too high or favorable selection if the disturbance results in fewer expenses in accordance with a particular set of inter- and extrasystemic circumstances.

The initiation of male development may in principle be as inexpensive as that for female development, but more seems prone to go wrong. The body is probably masculinized by the rather direct chemical actions of androgens on peripheral tissues. With respect to masculinization of the brain, the E_2 alone–brain sex principle implies that the sex hormone dial is simply turned further around than in the case of feminization. However,

the different uptake in the male brain of E_2 produced by the gonads and of E_2 from aromatization of androgens may complicate matters. Androgens reduced to androstenedione may also be needed for the masculinization of the brain. Obviously, when more processes are involved, more can go wrong, and, indeed, male development seems to be more vulnerable than female development. But whatever the details of brain masculinization, some of the gene transcription of products needed for development of female brain characteristics will be suppressed, and gene products necessary for male ontogenetic brain development will appear in greater amounts. These peripheral and central processes result in a stronger, heavier, taller, noisier, and more energy-consuming organism than does the realization of the female program. An organism characterized by an androgen/estrogen balance consumes more energy per kg body weight even at rest and runs at a higher metabolic (and running) speed throughout the life span than does an organism with an estrogen/androgen balance.

The high-speed solution comes with a hefty price tag: a shortened life span. Women and eunuchs live longer than do intact males (e.g., Hamilton & Mestler, 1969; Hamilton, Hamilton, & Mestler, 1969)—and more calmly, too! There is a certain irony—if Darwin is right in his sexual selection principle—that it is the female preference for masculine, aggressive, dominant, victorious males that led to favorable evolutionary selection for further androgenization of such high-energy consuming physico-chemical systems, but at the same time resulted in a male metabolic burnout phenomenon with consequent reduction of the lifespan in thus androgenized systems. On the other hand, this might not matter much in an overall evolutionary perspective. Whereas each female with her relatively few eggs is precious in terms of rate of reproduction and thus evolution, each male produces so many sperms that the majority of men actually are expendable. Quantitatively speaking, a few males could easily fertilize many females around them using the old-fashioned method. Using modern (but perhaps less inviting) fertilization techniques, a few men could impregnate all females on earth. Qualitatively speaking, this would not be a good idea, fortunately!

This view on intrasystemic economy is based on principles established in classical economy and in evolutionary theory alike. The classical economists probably took a close look at the history of evolution as well as at the routines of the individual's daily life and became inspired to formulate their principles of economy to explain human transactions and possessions, assigning greed a role as an essential motive of behavior. Darwin was inspired by reading Malthus and formulated the principles for survival of the fittest in accordance with the principles of economy. In this book, the economy principle provides a general framework for understanding the hormonal nuts and bolts of solving the problem of never becoming insolvent during the process of sexually differentiating originally multipotential

beings. This framework would stand even if the E_2 alone–brain sex principle had to be abandoned.

Expressed more generally, it appears that selection favors elegantly simple and inexpensive evolutionary solutions to more complex and uneconomical ones. The simplicity of the solutions is often difficult to spot, however. This may have more to do with the manifestation of the many varieties and forms than with the actual number of basically simple principles behind the manifestations. Only a fool would deny that we still miss many vitally important details of steroid chemistry, but from what little we already know it seems that the actions of sex hormones nicely illustrate the general tendency for selection of simple, reliable, economical, and flexible agents and mechanisms to increase the frequency of systems that respond in economical ways to an ever-changing evolutionary scenery. It was the central role of sex hormones in SD and reproduction during evolution that made me choose them in this book in order to illustrate the major points and consequences of the physicological program. Obviously, I could just as well have adopted other points of departure because physicology is more than the story of SD.

3.11.3. Males, Females, and Intermediate Androgynous Economy

The E_2 alone–brain sex principle suggests an almost dichotomous male–female dimension based on a kind of halfway switch. This idea fits well with the finding in traditional studies of self-reported gender identity—namely, that most people are unequivocally able to define themselves as to whether they are male or female. On the other hand, most of the other sex hormone principles speak against such a crude dichotomy. In fact, the principles as well as the molecular evidence strongly suggest that biochemical actions take place along more or less continuous and interdependent scales. A notion of physico-chemical continuity would, for example, facilitate our understanding of the mechanisms behind androgynous (and neotenic) development, whereas straightforward application of the E_2 alone–brain sex principle would give problems. Then again, the optimum range principle suggests that sex hormones typically act in nonlinear ways.

Aside from the question of physico-chemical continuity–discontinuity, it appears that each somatic, brain, and behavioral trait has its own particular developmental timetable. This source of variability springs from several different factors. Thus, part of the tremendous within-sex variability in rate of maturation can be explained by individual differences in the patterning and timing of sex hormone secretion, guided by genes and environment. The differences between individuals in time of induction and distribution of sex hormone receptors probably also play an important role. The observation that androgynous people sometimes simultaneously develop very

feminine and very masculine traits in apparent independence is intriguing, particularly when it is considered that trait compromising and economical tradeoff seem to be the rule within the intrasystemic budget. However, the explanation for relative independence in trait development can be found in the fact that masculinization, feminization, demasculinization, and defeminization processes unfold in relative independence within the energy constraints of the overall system. Thus, several tissues may simultaneously reach their critical periods for optimum development, partly because they synchronously induce receptor molecules during a state of relative immaturity. All such tissues would be strongly and concomitantly affected by a temporary or permanent increase in the concentration or metabolization of one or more plasma sex hormones. The result could either be permanent morphological or transient activational changes (or both) in different hormophilic tissues.

Various kinds of behavior could be covariantly affected in this case. Other tissues, inducing only few receptors at that particular time or which were already fixed in development, would miss this opportunity to be stimulated by hormones. However, outside these critical periods there is always the possibility that the nonphysiological hormone stimulation of mature tissues may result in neurotoxic reactions and systematic selective degeneration of tissues. Considering the versatility of the hormonal mechanisms, it is not difficult to understand that even minor changes in any of the parameters gives nature much to trade with. This goes some way to explain the tremendous individual variability seen around the general modal male and female constraints on sexual development. It is worth repeating that nonlinear models of mechanisms are called for in order to visualize how minor changes in one molecular process may accomplish major changes in another or in a whole cascade of related intrasystemic events. In the following sections I will use these general notions to illustrate details of androgynous and neotenic development.

3.11.4. The Intrasystemic SD-IQ Tradeoff Hypothesis

The economy principle helps us understand in a general evolutionary perspective why in the long run selective pressures must impose certain limits on sexual variability. Economic development means harmonization of traits within boundaries. Uninhibited growth of any tissues within the total intrasystemic budget would be uneconomical, would lead to energy disturbances in other areas, and would thus threaten the survival of the organism. Cancer can illustrate the point. The result could be lack of reproductive success—the final measure of successful evolution. Androgynous development provides an example of how compensatory growth inhibition can be harmoniously regulated, and shows that there is a price tag for regulation of the system and that no trees grow into heaven. To be

sure, full and even extreme development of one or a few sex-typical traits can be observed in androgynous individuals. However, the rule seems to be that, in the case of simultaneous development of homotypic and heterotypic SD traits, most of the traits of both domains appear in a weaker form than found in the more distinctly sex-typed individuals. Although a few androgynous estrotype E1,E2 females will develop very heavy musculature, the rule is that the body build of androgynous females becomes less heavy than that of androgynous A1,A2 males. The rule applies even after intensive exercise. Similarly, although the androgynous male has a higher body fat/lean tissue ratio than the average A3 male, his fat/muscle ratio will typically be lower than that for the androgynous female. Androgynous children of both sexes tend to mature later than their sexually more well-differentiated peers, and after puberty some androgynous individuals begin to score higher on standard IQ tests than do the earlier and sexually more well-differentiated children.

The higher IQ may be due to the prolongation of time to complete brain development, but that does not seems to be the only possible explanation. As mentioned earlier, the abilities of many early-maturing, high SD children actually regress at puberty. This observation may be generalized using as a point of departure Goethe's notion of a fixed developmental budget and the hormone principles. The covariance principle implies that the fast sex hormonal promotion of full sexual differentiation of the body is accompanied by fast maturation of the brain. The economy principle implies that this requires intrasystemic energy resources that detract from complete brain development (larger body, thicker bones, and relatively smaller head/brain). The optimum range principle and the overshoot hypothesis both predict a reduction in neural plasticity and less than full and flexible expression of specific abilities. These limitations apply equally well to male and female body and brain development.

A much less sophisticated formulation of this SD-IQ tradeoff energy dilemma is reflected in the old saying: "Too much muscles, too little brains." The equally offensive: "She is too beautiful (i.e., distinctively feminized) to be smart," also makes sense in lieu of the covariance, the SD-IQ tradeoff hypothesis, and the economy principle. Well-intended equality-seeking people typically see such statements as unbecoming stereotypes, to be laughed at only in extremist sexist quarters. The more sober side of the matter is that quite a number of studies in fact support the notion of an inverse SD-ability economy (e.g., Crockett & Petersen, 1985; Petersen, 1976, 1979; Rushton, 1985a, b, 1987; Waber, 1976, 1977, 1979). Let me hasten to add that some of these authors may disagree with my interpretation of their observations.

Obviously, neither abstract ideas of an overall universal economy nor of an intrasystemic economy and neither unfounded sexist stereotypes nor uncritical use of principles should find a convenient home base in physi-

cology, even though in the early phases of research we must be able to use ideas or grand proposals, however loose, as a point of departure for more serious scientific inquiry. As stated many times before, physicological analysis requires a specification of causal agents, mechanisms, relationships among variables, and at least a testable hypothesis about the intrasystemic locus of their actions. Unfortunately, little is known about the precise hormonal basis for an SD-ability tradeoff in humans. However, the previously mentioned bird studies by Nottebohm et al. (1986, 1987) and Nottebohm (1989) may provide some important preliminary insights.

Nottebohm demonstrated that the canary song develops in stages: a period of subsong is prevalent up to about two months of age, followed by a period of plastic song, which ends at about eight months of age. At about this age, the canary plasma *t* peaks, and the bird reaches full sexual maturity in preparation for breeding season. His song is now characterized by the full number of sounds (syllables) that are mastered in a stable and highly stereotyped way. The point to be noted here is that the canary is unable to learn new song variations during the high *t*–high SD peak. Moreover, *t* goes down again, and this marks the end of the mating season, but this is also the time for the concomitant recession of masculine body tissues and a reduction of the neural song nuclei tissues. A zooming in on the time-window for the increase in sex hormone production teaches us an important lesson about the role of steroid molecules in an SD–new learning tradeoff. The time when song nuclei increase in size and extensive synaptic reorganization takes place is exactly the time for plastic song and the time when the canary is able to learn new syllables. This coincidence in the chain of events led Nottebohm to suggest (1981) that a kind of yearly rejuvenation of the canary brain is actually taking place. The loss of old synaptic connections explains why the bird "forgot" some of his old syllables, and the increase in learning capacity can be explained by the establishment of new synaptic connections during the neural growth period and the associated neural plasticity which enabled him to learn new syllables. Still higher plasma *t* stops growth and inhibits plasticity; this leads to stereotyped and stable song with no new learning.

Nottebohm's studies of canary song, the SD-IQ tradeoff hypothesis, and the various hormone principles may combine in a more general flexibility-of-learning or creativity model based on neuronal plasticity. Let us set out with two testable assumptions: (1) adult learning of new or nonstereotypic use of old elements depends to a large extent on retention of intrasystemic brain plasticity (modifiability), and (2) this restriction applies across species. Note that these assumptions are fully in line with the physicological notion of basic similarity among learning processes in very different systems (see Section 2.3). With these assumptions, the model for flexible human learning or creativity can be tested as follows. First, we have to control for the effect of the familial genetic transmission of ability and

creativity, for the level and kind of prenatal hormone exposure and priming, and for familial dispositions for high or low adult plasma hormone concentrations. We can then test whether higher neuronal plasticity and the related flexible learning capacity of androgynous people actually presume moderate pubertal and adult exposure to sex hormones. A moderate to low early hormone level would go some way to explain late somatic puberty and moderate SD of the body; a later moderate to low surge in hormones would go some way to explain delayed neuronal development at puberty; and a moderate to low adult concentration would explain residuals of neuronal plasticity in adulthood by no or little overshooting of the optimum range.

A testable implication of this set of predicted events is a prolongation of the learning period to well into adulthood and perhaps into a life-long condition without stiffening of synaptic plasticity. This would in a sense correspond to a permanent human condition analogous to the brief plastic song period in the canary. Obviously, early maturing members of both species would also be able to learn a few new tricks, but the prediction is that hormonal fixation of the synaptic pattern will put an end to this. The analogy should not be pressed too hard, however. The adult canary brain is probably anatomically more malleable than is the adult human brain, and prenatal hormone priming of brains probably plays an important role in later brain development and function.

In Chapter 2, I suggested that learning is lasting intrasystemic neuronal modification (probably more of a chemical than of a mechanical nature) caused by orderly variations in neurotransmitters as a function of intra- or extrasystemically caused changes in perceptual systems. In other words, this molecular definition of learning is combined here with the SD-ability tradeoff hypothesis in order to explain that, also in humans, high plasma hormone concentrations alleviate neuronal plasticity, stabilize what is already learned, and reduce capability for further learning.

Perhaps part of the explanation for why it was difficult to realize the potential importance of SD-ability tradeoff phenomena in early human studies was that individuals with high prepubertal plasma hormone concentrations initially enjoy a developmental advantage before the ensuing postpubertal recession. Benefiting from advanced maturation, they often outperform their more slowly developing peers in SD of the body, in mature adult interests, and in popularity and leadership. Because of advanced brain development, they can be expected to obtain prepubertal ability scores that are at least as high as those of their more slowly developing peers. Too close attention to the early phases of development may lead the focus away from the possibility that many early maturers later pay dearly for a compression of the early phases of development: early closure of the epiphyses, early arrest of dendritic sprouting, relatively sparse establishment of new synaptic connections. All this means pubertal restrictions on body and brain growth and reduced neuronal plasticity and new learn-

ing. As in the fully matured canary, performance is stabilized, behavior and sexual identity become stereotypically frozen at this high hormone level, and little new learning can take place. A number of fairly circumscribed functions are perfected, in particular those that are relevant for reproduction, but the price is a characteristic loss of creativity and flexibility in the sexually well-differentiated individual. The late maturer is like the rejuvenated plastic song period canary in this respect.

There is as yet no large-scale test of these rather sweeping SD-ability tradeoff hypotheses of the GTC-A/E model. However, a rather large cohort-sequential study of several hundred children was initiated in 1976, and this study is now nearing completion (Nyborg, 1994d). This study tests a couple of hypotheses. We expect, for example, to find that low plasma concentrations of sex hormones stimulate the growth of brain and body tissues, that moderate doses are associated with increasing rate of growth, and that high doses shorten the developmental span by bringing bone and brain growth to early completion (the optimal range principle). According to the economy principle, we expect that body height will be positively correlated with adult abilities. In fact, moderate correlations have been found in several other studies (e.g., Baker, 1983; Jensen & Sinha, 1993).

Recently, I analyzed data from a subsample of 1,824 white middle-aged veterans, who never did service in Vietnam during the war period, and found correlations between body height and WAIS-R Information, WAIS-R Block Design, and General Technical Test ranging from .12 to .13. All these correlations are significant at $p < .001$ (Nyborg, unpubl.). There is some evidence to support the notion that early-maturing children enjoy a brief period of covariantly accelerated body, brain, and intellectual growth relative to late-maturing children, but that after puberty they will be intellectually outperformed by late-maturing children (see Nyborg, 1983). Rats with accelerated body and brain development, due to neonatal thyroid hormone treatment, showed reduced postpubertal spatial learning. Moreover, the reduction in learning capacity correlated with long-term potentiation, a technique believed to reflect neural plasticity in models for learning (Pavlides et al., 1991). However, the sparse evidence and the fact that most human studies did not control for familial abilities stress the need for well-controlled combined cross-sectional longitudinal studies. Another problem is that there is less than a perfect relationship between measured IQ and measures of actual achievement in society. Moreover, flexibility in learning is sometimes defined in terms of creativity, but we have neither good definitions of creativity nor a standard measure for it. Finally, we still know disturbingly little about whether extensive new learning in adults presumes neuroanatomical or biochemical functional neuronal plasticity, or, most likely, both.

3.11.5. Maturation, Economy, Recapitulation, and Neoteny

Phenomena involving maturation and the tradeoff between traits have long been the subject of debates among evolutionary theorists. Some of the discussions have focused on ideas of recapitulation and neoteny, and they have generated much disagreement. First, I will briefly outline the notions of recapitulation and neoteny and then discuss some of the problems they raise. I will then reinterpret the phenomena in terms of the principles of the GTC-A/E model and focus on likely causes, mechanisms, and loci of action, as expected by the physicological research program. The ultimate purpose of the discussion is to demonstrate—with a little luck—that operationalization and the empirical approach may end the philosophical and ideological hype surrounding recapitulation and neoteny that prevent progress in our understanding of some of the lessons from our recent evolutionary past.

Briefly, the nineteenth-century German zoologist Ernst Haeckel defined the idea of recapitulation as "ontogeny recapitulates phylogeny." Gould (1977) has provided a detailed account of the history of this idea and the problems it entails, and I will use Gould's presentation as a point of departure. However, it will soon be obvious that my interpretation differs from Gould's. Inspired by creationist biology, it was postulated that the embryogenesis of "higher" species runs through the phases that represent adult ancestral forms and in the right order. If we map these very early stages of development, we can reconstruct evolutionary lineages and can rank species and individuals in terms of how far they have progressed. The gill slits apparent in the early phases of human embryonic development represent an ancestral fish, and the rudimentary tail points to a reptilian or mammalian ancestor.

The idea of recapitulation was carried forth with great vigor and had a considerable impact on several biological disciplines in the nineteenth century. One of the more controversial aspects of the idea was that recapitulation provides a rationale for ranking race, sex, or individuals in terms of "inferior" and "superior" varieties with respect to intelligence and personality. An individual arrested at an early embryonic stage during development would, according to recapitulation, appear primitive or childish as an adult. Another controversial notion was that adult females represent cases of early embryonic arrest, and this explains why they must be less mature, more primitive, and more emotional than males. Recapitulation also states that nonwhite primitive adults become arrested in early embryonic development, so they are like white children. Cope (1887) used the recapitulation theory to argue that southern Europeans will appear more primitive than the superior Nordic stock because their warm climate imposes early maturation and cessation of development. This is the reason why they become emotional, childlike, and feminine, Cope stated, whereas northerners—in particular the English—move to a higher stage before their development is curtailed.

According to Gould (1977), the theory of recapitulation collapsed around 1920, but it was subsequently substituted with an exactly opposite idea: the theory of neoteny (Bolk, 1929). Neoteny is derived from Greek and literally means "holding on to one's youth." Where recapitulation implies that "adult traits of ancestors develop more rapidly in descendants to become juvenile features" and that "adults of inferior races are like children of superior races," neoteny implies that "juvenile traits of ancestors develop so slowly in descendants that they become adult features" (Gould, 1981, pp. 119–120). In contrast to recapitulation, neoteny refers to retarded instead of forced development. A newborn ape looks remarkably like a human. "Unfortunately," it soon loses its humanlike juvenile appearance during its fast developmental course toward the adult stage. Happily, the human retains many of its juvenile traits in adulthood owing to a slowdown of maturation. According to neoteny, and contrary to recapitulation, it is now a major characteristic of superior groups or extraordinary individuals to retain their childlike features. Gould couldn't resist the temptation to draw the only logical implications of recapitulation and neoteny with respect to the ranking of races: "Under recapitulation, black adults should be like white children. But under neoteny, white adults should be like black children." With neoteny, upper-class males are inferior, Gould goes on, if they lose, while other groups retain, the superior traits of childhood"! Havelock Ellis (1894) drew further logical implications from neoteny: he posited that females must be superior to males because they retain childish anatomical features and he said, that men who develop a womanly anatomy must be superior to more masculine men. Ellis even went on to look for the evidence. In comparison to rural men, he found that urban men have larger heads and brains, more delicate faces and smaller bones, and a larger pelvis. Ellis took this as evidence in support of the idea that urban men follow a path first marked out by women.

Gould concludes that the whole enterprise of ranking groups by degree of neoteny is fundamentally unjustified. He states that he would be more than mildly surprised if the small differences in degree of neoteny among races bear any relationship to mental ability or moral worth (Gould, 1981, p. 121). Gould criticized the conclusions of a study on neoteny by Eysenck (1971). Eysenck pointed out that (1) very young blacks show more rapid sensorimotor development than whites (are less neotenic), (2) the average white IQ surpasses the average black IQ by age 3 and, finally (3) early-maturing children tend to end up with slightly lower IQ. Eysenck suggested, in other words, that the theory of neoteny can be used to explain group differences within a species. Gould did not question Eysenck's observations. Instead, he argued that Eysenck based his proof for the theory of neoteny on "what is almost surely a non-causal correlation." Gould further pointed to the possibility that lower IQ in blacks may be a result of a generally poorer environment. However, Gould did not properly address

the problem of how a poor environment could dispose at the same time for rapid black sensorimotor development and diminished IQ. Moreover, Gould's objection to a causal within-race relationships between maturation and IQ contrasts his belief that there are causal neotenic differences across species. This is puzzling because Gould so clearly favors the importance of the theory of neoteny in the evolution of species differences. Thus, he believes that humans evolved by neoteny and that we are permanent children in a more than metaphorical sense. We retain not only the anatomical stamps of childhood but its mental flexibility as well. The whole idea that intrasystemic selection worked for flexibility in human evolution, Gould states, is an implication of the fundamental process of neoteny.

I have a purpose in taking up Gould's well-publicized and often quite polemical analyses of the theories and implementation of recapitulation and neoteny. In my view, they expose some of the fundamental weaknesses that also characterize the mentalist argumentation criticized in the first part of this book. Discussions of recapitulation and neoteny often make multiple references to glittering forms and complex manifestations of phenomena, but the heated debates rarely reflect a genuine interest in identifying the cause(s), in operationalizing the mechanisms of the presumed agents, and in tracing the loci of intrasystemic action of the since long totally reified concepts (e.g., recapitulation or neoteny). We hear about the "fundamental process of neoteny," but we are provided with no details of exactly what it is, where it goes on, what drives it and what it drives, and when? What precisely is implied by the statement that "humans evolve by neoteny"? Is it a description or an explanation? What is the causal nature of the selective forces that drives the "fundamental process of neoteny"? What particular causal mechanisms link rapid maturation with low adult IQ? Although it is not likely, improper nutrition could be the answer, but simply to state this as a valid counterargument without any data is not sound. The analyses of recapitulation and neoteny thus appear to have much in common with philosophical and mentalist literature. The battlefield is the deep armchair at the faculty club. The scientific tools are clever philosophical or logical arguments, often spiced with anecdotal evidence and more or less blatant anthropocentrism and human self-glorification.

The closest such discourses ever come to a kind of physico-chemical reality is the ensuing obligatory three-course dinner with an equal number of good wines. (Let this be no critique of University College in Oxford, where I enjoyed dining at the excellent High Table for a full year in learned company.) Ideas of recapitulation and neoteny are often used in a perfectly circular way and sometimes to justify a priori racist views. What sense is there in ranking species by degree of neoteny but not in ranking intraspecies groups by the same token? It becomes problematic to state that females are superior to males because they remain childish and that childish males must follow a womanly path to become superior to masculine men, unless

we redefine our language. How literal should the statement "Ontogeny recapitulates phylogeny" be taken? Does it mean that a human embryo arrested in the phase with gill slits will later get a fishy adult appearance or a sharky personality? Will an embryo arrested in the tail phase later reveal an adult, sly reptilian identity or show the intelligence of a dinosaur?

Perhaps I am overdoing the critique, but the basic problem is real enough. Rarely do we hear anything concrete behind metaphors and sweeping generalizations, and theories are presented in such a form that almost any observation can be accommodated or deduced from them to fit one's particular fancy exactly, be that of a sexist, elitist, or racist flavor. I consider it no accident that two of the least exact, most prolific, and basically metaphor-producing figures in recent times, Sigmund Freud and C. G. Jung, were ardent recapitulationists. They were also ardent adherents of ancient Greek mythology, so they certainly did not start from scratch. Freud speculated without the obligatory empirical censorship as to whether the Oedipal urge to parricide reflects actual bloody events among ancestral adults, and Jung ventilated a strong but empirically equally unfounded opinion that archetypes and ancestral anima and animus were basic constituents of human nature.

Obviously, the history of science contains many examples of even very bold conjectures leading to significant progress, but the main problem with some of the ancient Greek scholars—and definitely with Freud, Jung, and the whole industry of dreams, unconsciousness, and archetypes, as well as with most other recapitulationists or neotenists—is that they are so eager to reify daring and flashy metaphors that they cannot find the time to assure the (f)actual existence of their concepts and metaphors, which uncensored become things and then causal agents that even interact with each other. I believe Gould (e.g., 1981) is correct in stating that reification is the basic problem and that sweeping generalizations are often based on reified concepts. When pressed for data, they pour out mythology, anecdotes, or uncontrolled nondirectional correlation coefficients. Like the Greek scholars, very few recapitulationalists and neotenists felt an obligation to leave the armchair to go to the lab or to do field studies. Few have a strong commitment to take the trouble and collect the necessary hard and controlled evidence through blood, sweat, and tears, or at least to make a full-hearted attempt to operationalize and present testable hypotheses in order to become able to harvest the evidence or to falsify the idea. This critique is a far cry from unjustly accusing scientists of yesterday for not using today's methodology. It is, however, an unmasked reminder from Galilee that scientists should feel the strong obligation to count, weigh, and measure, or else to keep their mouth shut (except, perhaps, for whispering bold, testable conjectures). The story of recapitulation and neoteny reminds us, once again, that the scientific study of (human) nature is too important to be left to armchair philosophers, mentalists, sexists, ageists, elitists,

racists, or feminists, all of whom are armed only with words, concepts, logic, correlation coefficients, and a microscopic database.

Can we subject the theories of recapitulation and neoteny to scrupulous testing today? Well, perhaps not the theory of recapitulation, for it actually died out by itself during the 1920s. In part it died because some of its implications ran in the face of readily available evidence, and in part because aspects of the theory were formulated in such a way that it was impossible to subject them to rigorous testing. I think it is fair to say that the idea of recapitulation created more confusion than clarity.

The theory of neoteny is a different story. The theory is actually in line with some recent evidence, and part of the theory is formulated in ways that allow for testing. Before further discussion however, I would like to point to an inherent danger here. Neoteny bears on sex and race differences, and I know from personal experience that it is very difficult to move with sufficient scientific vigor in these emotionally charged minefields of research. At least some important funding comities in the behavioral sciences are manned by administrators with a keen eye on political correctness, with uncompromising equality-seeking ideologues, with well-intended humanists (and they are sometimes the worst), and with social learning theorists. It happens that they operate with different standards when evaluating traditional "society-creates-people-and-we-use-questionnaires-to-study-this-fact" kind of research applications and when evaluating an application for an experiment to examine the potential material basis for the development of individual-, age- sex-, and race-related differences in development.

In general, I encountered few problems over the last quarter of a century in raising ample support for "neutral" research projects. As soon as my applications went in a hormonal direction, I routinely got the answer: "Your application has been deemed worthy of support. Unfortunately, in comparison with other qualified projects yours came second, so we regret we cannot provide the support you asked for." There is nothing really to point fingers at. The "possibility" of "unintended" racist interpretations of the potential results by others caused a recent rejection of a major project and a paper was rejected by a leading journal editor out of fear of potential racism from the backdoor. He now operates with higher scientific standands for reports on race differences than on other matters. Such common attitudes may explain why we proceed scientifically at a much slower rate then is needed in vitally important areas. This is perhaps an important part of the explanation of why we witness so many socioeconomic and other human catastrophes in different parts of the world and why we stand basically with empty hands when asked to remedy them. To properly address these problems, we need a precise diagnosis of the problem, identification of agents and mechanisms, and testable models. Instead, we often get empty rhetoric, obligatory repetition of social explanations that

sound nice but do not work, or have to face negative fund administrators and editors.

The GTC-A/E model and physicology are meant to be used as tools for examining the causes, effects, and processes behind behavior and for substituting untestable theoretically and ideologically based speculations with testable hypotheses. Moreover, the individuality principle (see Chapter 14) strongly advocates for a clear focus on the single person rather than on the group mean (except perhaps as a starting point for serious investigation of the reason for average male–female or race differences). Physicology implies that only if a sufficient number of individuals within or across sexual or racial groups show clear similarities that make them differ in a characteristic way from the others with respect to agents, processes, or effects should we be prepared to follow through with the necessary analyses of this apparently widespread group phenomenon. This applies whether we stumble on race- or sex-related differences. This would not fuel excessive sexist or racist generalizations because the main focus would always remain on the single individual and would be turned away from generalization from a group average (Nyborg, 1977).

Thus, let us try to identify the causes, effects, and processes behind the theory of neoteny in terms of testing predictions from the GTC-A/E model. Let us make an attempt to specify neotenic speculations in terms of the basic assumptions of physicology, which are that molecular affinity, space–time coordinates, and energy flow define development, function, and cessation.

There is good evidence from population genetics that prolonged geographical isolation results in genotypic differences and that differences in the frequency of DNA sequences arising by selection co-determine individual differences in the production of particular proteins. Expedient regional combination of such variations by sexual reproduction may go some way to explain the material basis for observed geographical differences as well as local similarities in the frequency of early and late maturers, in particular when combined with studies of local gene transmission of growth and sex hormone patterns. The available evidence suggests that maturational tempo reflects individual variations in sex hormones, whether we talk about humans or other animals, or whether we talk about different races, about males or females, or about individuals. The third set of causes conditioning individual variability in maturational tempo can be found in the extrasystemic environment, fetal as well as postnatal.

Given that neoteny refers to slow (probably a better term than the negatively loaded "retarded") instead of forced development and that there are significant (geographical and local) individual differences in maturation rate, the GTC-A/E model prompts us to ask empirical questions about hormotype right from the time of conception. Which kind of hormone exposure was the originally multipotent embryo exposed to? Which familiarly transmitted genes became modulated with what resultant expression

of particular protein patterns? Where did these proteins go intrasystemically, and how did they affect structure and function at their destination? Did the perinatal male surge in *t* affect the later maturation rate? How did temporal variations in the prepubertal and peripubertal surges in estrogens and androgens affect maturational tempo? Is there a genetically separate familial disposition in the DNA material for early-late maturation, and did the effects of stress, nutrition, or other environmentally induced variation affecting such dispositions? Many more empirical questions can and should be asked about neotenic development. Unfortunately, the present lack of a precise strategy for exploring all this means that, for the time being, we must remain satisfied with the questions.

A more humble approach would be to inquire into the question of whether the GTC-A/E model accurately posits androtypes A1s–A2s and estrotypes E1s–E2s as late-maturing neotenic individuals and androtypes A4s–A5s and estrotypes E4s–E5s as their opposites with respect to maturation and early unfolding of trait patterns. After inquiring into this matter, the rest of the work would be for the lab technicians to verify or falsify the material basis of the predictions, so that uncensored speculations could be brought to rest. Then perhaps statements like "Juvenile traits of ancestors . . . ," "White adults should be like black children," "Females must be superior to males because they retain childish anatomical features," "Humans evolved by neoteny, and . . . we are permanent children . . ." will fade away or serve as warning signs to future scientists trying to substitute data with metaphors. Neotenic racist statements such as: "Superior groups retain childlike features" and polemic statement such as: "I would be more than mildly surprised if the small differences in degree of neoteny among races bear any relationship to mental ability or moral worth" (Gould, 1981, p. 121) could be rephrased in empirical terms and without the "higher-lower," "better-worse," or "moral worth" hype. Questions such as, "To which extent do individuals differ in A/E balance?" How is hormotypic variation related to modulation of identical or different DNA segments, and through which molecular processes are quantitative differences in protein production associated with differences in body and brain development and, accordingly, with behavior?" could then be operationalized.

Dealing with individuals, separated for ages geographically, reproductively, or nutritionally, we must, of course, feel a strong obligation to address questions about which environmental factors are likely to enter the gene–hormone–body–brain–environment formula. The survivors in each group would testify that they had successfully adapted to their particular long-term ecological circumstances. The economy principle speaks against other possibilities. However, successful adaptation to certain ecological circumstances may spell misery or extinction if the ecological circumstances change (see Section 3.11.8). Although Darwin was never entirely consistent on the point, he at least warned that we had better abstain from using

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"higher-lower" value-loaded terms when dealing with species, races, and individuals during evolution.

Havelock Ellis's (1894) implication of neoteny—that men who develop a womanly anatomy must be superior to more masculine men—can be rephrased with the assistance of the GTC-A/E model to let us formulate less passionate and testable hypotheses. The model actually predicts that the modal trait development of slightly feminized, slowly maturing A1s and A2s will differ quantitatively, to a moderate extent, from the modal trait patterns of "neofugic," masculinized, fast maturing A4s or A5s. It then becomes an empirical question whether A1s and A2s have relatively bigger brains and more fragile skulls, broader hips and narrower shoulders, live in cities, and earn a higher performance score on ability tests, whereas A4s and A5s have relatively smaller brains and thicker skulls, narrower hips and broader shoulders, live in the country, do better on tasks requiring physical strength and gross motor skills but score lower on ability tests.

Should all this actually be the case, we would have identified the neotenic and the neofugic individuals and explained the material basis. Even then, it would be wise to remember that the actual ecological situation still determines which performance would lead to survival and reproduction. If your life depends on sheer brutal force, you had better be a neofugic A4 or A5. If survival depends on subtle tactics, you stand a better chance if you are a neotenic A1 or A2. Unfortunately, people usually do not have much of a real-life choice in these matters. They might find themselves trapped in a mismatch between their particular hormotype and a particular situation. The following sections take up various aspects of the balance between hormotypic trait patterns and environment.

3.11.6. Economy and Limited Intrasystemic Capacity

The economy principle may help explain the observation of sex-related differences in the balance between verbal and performance IQ (Maccoby & Jacklin, 1974). As noted before, female suppression of spatial ability is often accompanied by enhancement of at least some verbal abilities, whereas males typically are more proficient in spatial abilities than in at least some verbal abilities. This observation led Burt and Vernon to form an early British orthodox position, according to which spatial and verbal factors together constitute a bipolar factor, with the spatial and verbal components being inversely related, apart from *g* (Smith, 1964, p. 81). The data have been interpreted in terms of the notion that the brain is a functional system with limited capacity (e.g., Carter & Kinsbourne, 1979; Kinsbourne, 1970; Kinsbourne & Hiscock, 1981). This raises questions about which agents and which mechanisms are responsible for the inverse trait constellation, and about which agents support a female verbal/spatial and a male spatial/verbal balance, and not vice versa. Convergent evidence suggests that the

spatial-verbal relationships in men and women are not specifically related to a particular karyotype (Nyborg, 1983, 1984, 1986a; Nyborg & Nielsen, 1981a, b). According to the proximate cause principle, all sex differences have a hormonal basis. Therefore, many years ago, I suggested that *"There exists a range of estradiol values optimal for the expression of verbal ability,"* and further that *"the optimal central estradiol values for verbal ability are inversely related to those central estradiol values optimal for spatial ability"* (Nyborg, 1981, pp. 16–17). In terms of the GTC-A/E model, this means that a person with either high or low central E_2 concentrations would tend to show higher verbal than spatial ability and, conversely, that a person intermediate in central E_2 concentration would tend to show lower verbal than spatial ability.

A comparative analysis of intelligence and personality in hormonally different groups indicated that some, but not all, hormonally atypical groups conform to this prediction (Nyborg, 1983, 1984). Later, Hampson (1986, 1989) and Hampson & Kimura (1988) tested the predictions for variation in abilities over the menstrual cycle in normal women. The studies partly confirmed the prediction of the GTC-A/E model that spatial and verbal abilities cycle in opposite phase during the menstrual cycle. Apparently, it is more problematic to correctly predict the expression of abilities from the GTC-A/E model on the basis of aberrant hormone values. Furthermore, it is an open question to what extent the appearance of adult sex-related differences in the verbal-spatial balance depends on fetal and perinatal exposure to sex hormones, but there seems to be some connection. A related matter is whether an early selective growth promotion of hormophilic brain tissues relevant for the expression of spatial ability is accompanied by reduced growth in brain areas of importance for verbal abilities. Logically, if certain brain tissues expand in volume, then other tissues must recede, given that the volume of the adult skull is fixed. However, even if we tentatively assume that morphological sex differences are behind the hard-wiring of brain lateralization, we still have not explained all of the observed adult sex difference in the verbal-spatial balance. The putative morphologic sex-related differences in brain organization may arise before birth, but the sex-related verbal-spatial balance difference takes on importance only at puberty, at a time when sex-related differences in the hormone balance reach their zenith. The sex-specific spatial-verbal asymmetry may further be influenced by an early differential setting of the adult number of sex hormone receptors, but presently we simply do not know enough about the nature, extent, and adult consequences of such an adjustment.

It seems that a combination of the enhance–suppress, optimal range, and economy principles provides more possibilities for better and more dynamic explanations for the spatial/verbal tradeoff phenomenon than do the less flexible organizational principles. It will be remembered that Hampson (1986, 1989) and Hampson and Kimura (1988) monitored simul-

taneously the expression of verbal, motor, and spatial abilities in menstruating women, and found that low E_2 phases are associated with the suppression of verbal and speeded-motor performance and the enhancement of spatial ability, whereas high E_2 phases are associated with the reverse pattern. Although not incomprehensible, such a dynamic tradeoff between the expression of skills is probably better explained in terms of dynamic functional cyclic physico-chemical changes in the brain than by changes in brain morphology. However, recent studies, remind us not to exclude at least moderate cyclic morphological changes of the adult human brain as a function of hormone variation.

Provided that male expressions of verbal, motor, and spatial skills are all influenced by hormones, we can expect that the male SD-ability tradeoff takes on a static rather than a cyclic form. The obvious implication is that permanent male under- or overshooting of the optimum estrogen range results in a permanent suppression of spatial ability and enhancement of verbal ability. A few studies confirm that androgenized men tend to do better on verbal than on nonverbal tasks (Broverman et al., 1964, 1968; Broverman, Klaiber, & Vogel 1980; Klaiber, Broverman, & Kobayashi, 1967; Petersen, 1976). Christiansen & Knussman (1987) measured actual plasma androgen levels in a study of men with plasma *t* concentrations within the normal range. They found that plasma *t* concentration correlates positively with measures of spatial ability and field-independence, and negatively with measures of verbal production. Petersen (1976) further found that androgenized girls show the opposite pattern. However, Nyborg (1993a) observed low verbal as well as low spatial scores in high *t* A4s and A5s in a large sample of 3,654 white middle-aged male veterans.

The differences among these studies may be due to the lack of a standard for what counts as high or low plasma hormone concentration. This difficulty also shows up in cross-racial comparisons. Nyborg (1987a) used the GTC-A/E model to predict race differences in the verbal/spatial balance under the assumption that Oriental populations have a high frequency of A2s,E2s, white populations a high frequency of A3s,E3s, and black populations a high frequency of A4s,E4s. In that case, the model predicts that Orientals would show a high frequency of higher spatial than verbal balance individuals, that blacks would show a high frequency of higher verbal than spatial balance individuals, and that whites would show a high frequency of more balanced individuals. There is some evidence in the literature to support these predictions of race differences in frequencies in the tradeoff among abilities (e.g., Lynn, 1987, 1991; Vernon, 1982).

To summarize, not only are there large individual differences in the size of the total body–IQ budget, but also a tendency for differential spatial-verbal-motor ability tradeoff in males and females and across races. Sex hormone principles may explain the tradeoff in either morphological or functional terms. The tradeoff can take on a very dynamic form, as seen

during hormonal changes synchronized with monthly variations in spatial, motor, and verbal abilities. Ability differences are probably influenced by early organizational hormones, but even more strongly so by later activational hormones. This means that sex hormones act both as powerful static and as very dynamic enhancers or suppressors of specialized brain growth and function, thereby providing economical solutions to the problem of suitable SD of the body, brain, and behavior relative to particular ecological niches.

3.11.7. Economy and Survival

The economy principle and the notion of fixed budgets are in line with a general consideration of the survival value of optimum synchronization of body and brain development and of a tradeoff between traits. This point is illustrated most clearly in birds. It would indeed be costly for a male bird to fly around, singing through all seasons, weighed down by fully developed genitals, clad in brilliant feathers conspicuous to preying animals. Such assets are really needed only during the brief periods of breeding. Similarly, it would be disastrous if children were able to reproduce long before they could care for their offspring, or if old people reproduced at the same rate as young people at a time when they become feeble and increasingly dependent on others for support. Such disasters would be expensive in terms of loss of offspring; they are accordingly selected against during evolution. Systems with reliable and economical mechanisms for the concerted appearance or disappearance of reproductive and other capabilities would enjoy a competitive advantage. In seasonal breeders, most behavioral traits associated with reproductive functions come and go when it suits survival and mating best or would be selected against. Offspring typically arrive when food is in plentiful supply. Species, whose behavior is out of tune with geographical, climatic, and nutritional variations would soon run out of food and become extinct.

In nonseasonal human breeders, the picture is somewhat different. Males and females retain their reproductive capabilities year round, but as mentioned previously, this has a negative effect on males in particular. Males must be competitive all the time. The selection by females for male dominance, aggression, fertility, and other masculine traits translates to a female selection for a male with permanently high androgen/estrogen balance, but the extreme androgen balance is uneconomical. The androgenized, sexually differentiated male has a shorter life expectancy than his more androgynous cousin. Even among the longer living women, sexually more differentiated women tend to have a shorter lifespan.

There is no need to try to explain the evolution of the economical adaptive capabilities of the survivors by an evolution of emergent qualities. Selection, reinforced by exposure to harsh physical constraints, works on

all aspects of the intrasystemic physico-chemical organization and prunes the processes. Thanks to their particular intrasystemic constitution, some systems are built to meet the demands more efficiently, or to show sufficient adaptability to change in accordance with the requirements. This is a matter of stability as well as flexibility of physico-chemical processes, and there is no need to invent the emergence of abstract qualities to explain it.

At the heart of the differential survival rate is the question of an intricate balance between the give and take of intra- and extrasystemic characteristics. The study of SD illustrates this. Male and female systems evolved on the basis of different reproductive demands. Extrasystemic physical circumstances further refined this differentiation of intrasystemic physico-chemical functioning. The metabolization of a widely distributed protein, cholesterol, allowed for the evolution of a few steroid species. Random variations in the balance between these steroids and the enzymes that metabolize them, guided in part by the internal chemical environment and in part by outside forces via neurotransmitter modulation, allowed some systems to develop and respond more efficiently to future demands than other variants. Organisms that were slightly out of tune eventually lost the game, whereas those with a slight reproductive edge survived and lent copies with some similarity to themselves for further test for efficiency by their particular ecological niche.

This asymmetry in selection toward an optimum carbon-based physico-chemical economy probably differs in no important way from the selection for economy in inorganic processes. Human beings may not after all be as special as mentalists assume. Like the stars, we are perhaps made of cosmic dust and nothing but that. Stars have their economy, their budget, and their evolution, so have we. Our physico-chemical organization is much more flexible than that of the stars, but that adds only complexity. The basic agents, mechanisms, and principles seem to be much the same. There is no evidence to the contrary, only heroic anthropocentrics statements.

3.11.8. Brave New World?

Evolution is not likely to pause with a hormotypic stabilization around, say, androtype A3, as recently defined in a study of 3,654 middle-aged white males by a plasma *t* mean and median value close to 654 ng/dL (with control for age) and a range from 599 to 707 (Nyborg, 1993a), nor with a not yet determined plasma E_2 value for contemporary E3 females. In fact, the question of future evolution invites some quite interesting speculations about the nature of tomorrow's most likely selective powers, mechanisms, and effects. The GTC-A/E model was used above to postdict the past 100,000 years of hormotypic selection.

Based on the assumption that neotenic trend in human evolution will continue from the past and well into the future, I will now demonstrate how

the model can be used to project into the future. An aim of the Nyborg (1994b and 1994e) papers was actually to predict which hormotypes will be favored in the near future and which types most likely will pay a price. I fear that should these projections become tomorrow's reality we are facing major problems, the solution of which requires a number of difficult and important decisions.

Even a superficial view on the recent history of postindustrialized nations allows for the projection that many future extrasystemic conditions will differ radically from those of today. The difficult physical workload has already been alleviated in these parts of the world, and mechanical devices of all kinds have taken over the work. At the same time, many of the routine tasks along the assembly lines have been assigned to semiconductor technology and industrial robots. This development has forced many unskilled or semiskilled workers out of jobs. They now line up in increasing numbers among the unemployed, as they are being substituted by fewer highly skilled operators, computer wizards, and electronic service personnel. More recently, a number of postindustrialized nations have witnessed a clear trend toward large-scale export of workplaces from high-cost countries to less developed areas of the world where salaries and other major production costs are more limited. Most likely, this redistribution of high-tech workplaces requires some education that will attract the more skilled individuals in the developing areas. They will earn the money even if for a while they may be willing to work for lower salaries than the experts in the country of origin. The less skilled will be the losers in these newly developed areas as they were in the postindustrialized areas. This is so because high-tech societies will benefit highly skilled individuals that have the capability to pick up and use relevant information quickly and to operate complex communication and production devices. Populations or even continents that for various reasons are unable to take advantage of the many sophisticated tools of high-level technology risk becoming losers.

The GTC-A/E model can be used in two complementary ways to assist in analyzing the likelihood that future society will be sharply divided by favored and disfavored hormotypes just as in the past. The model is first used to predict from intrasystemic conditions which hormotypes are most likely to enter the types of education and occupation that will pay off in the future. The model is then used to predict from the extrasystemic point of view which hormotypes will be favored by the selective powers.

Let us first predict from hormotype to the most likely type of education and occupation. The model predicts that the trait combination of strong body build, stereotypic sexual identity, and low abilities would dispose androtypes A4s and A5s for little formal schooling and heavy-duty work. The delicate body build, the androgynous and flexible sexual identity, and high abilities would dispose A1s and A2s for years of formal schooling, a professional career, paperwork, books, and culture. Although Dabbs &

Morris (1991) and Dabbs, de la Rue, & Williams (1990) did not operate with hormotypes, they made some important observations that could be translated into a hormotypic context. They found that high *t* males tended toward blue-collar occupations, whereas males with low *t* tended toward white-collar occupations. Curiously (or perhaps not!), there was a definite trend for ministers to have very low plasma *t*. Nyborg (1993a) analyzed the same large database from the hormotypic point of view and found, that A1s obtain significantly more years of formal education than A5s, attain a higher military rank at time of dismissal, stay more years in their longest held job after military service, and end up earning more money.

The GTC-A/E model explains the hormotypic asymmetry in joining particular educations and occupations by the effects of *t* or its metabolites, modulating available genes and changing cell membrane characteristics, with consequent selective effects on body and brain development, ability, and personality and with resultant unfolding of trait patterns that increase the likelihood of fitting into particular educations and occupations. Translated into the selection for particular occupational fields, the GTC-A/E model accurately predicted that A4s and A5s (and E4s and E5s) would not have much advantage of formal schooling and would appear with a high frequency in unskilled and semiprofessional areas, whereas A1s and A2s (and the E1s and E2s) would appear with a high frequency in technical and other areas calling for extensive education and particular skills. The intrasystemic part of the equation states, in effect, that different individuals will be differently disposed for particular activities owing to their trait constellation and that sex hormones play an important part in this.

From an analysis of extrasystemic variables, the model can be used to predict the likelihood that a particular hormotype will survive in that particular environment. Phrased differently, various niches favor particular personality and ability tradeoff patterns, determine who are most likely to remain in the area and how far they might reach. This complementarity of the model does not necessarily make its predictions circular because hormones break the ring and provide the necessary independent evidence. Hormones dispose for particular appearances, and particular educations and occupations reward various hormotypes differently. The model predicts that the 4s and 5s will soon be pushed out of business should they ever happen to join a high-tech or leading position involving complex decisions, whereas the abilities and personality characteristics of the 1s and 2s will make them a dearly paid necessity for high-tech employers.

There is no doubt that the early phases of industrialization brought disaster to many A4 and A5 families. Many were dismissed and ended up at the bottom of society with no public network to support them. The machines took over precisely what they were good at. This trend has not completed its gruesome harvest. Today 4s and 5s live in increasing numbers on public support in the old industrialized world, their personal sorrows

and stress untold, or they fight hard for the fewer positions in hard-work low-pay areas. The 1s and 2s are the winners, and they take most or all in a free market economy system. They prosper in their role as innovators and experts in an export and high-level service- minded world. Past history and the free market economy suggest that individuals matching extrasystemic demands in an economical way are the champions of tomorrow and that the losers are those with an intrasystemic budget that is out of sync with present reality and incapable of quickly accommodating to the requirements of tomorrow's world.

This is admittedly a gloomy perspective of a society that will probably find itself increasingly divided by class in the near future. According to this analysis, Marx made a major mistake in giving socioeconomic factors the status of independent variables in his attempt to explain what he saw as an unavoidably growing worker–capitalist dichotomy. To be sure, the error was not so much a failure to describe the dire consequences for the masses of naked capitalism as to wrongly diagnose the cause. By deciding a priori that economy determines behavior, Marx turned the argument on its head. Perhaps the situation for the poor was intolerable to him, so he annulled the role of the intrasystemic budget, declared that the individual is a product of the social conditions, and designated capitalist society as the evil agent causing poverty.

It is interesting to note that another guiding principle of classical economy is making a comeback. Today most of the leading economists are no longer so happy with the notion that greed (a mentalist hypothetical construct) is the single most important mover of socioeconomical behavior. Too many examples of people willing to endure endless hardship, poverty, and torture, as well as to give their lives to defend freedom or cultural identity, disprove the case. The GTC-A/E model provides an alternative account: Optimal tuning of the intrasystemic budget to extrasystemic demands determines who gets the money and the glory. Hormotypes with an intrasystemic budget optimally tuned to extrasystemic requirement will be those that eventually take command and become the leaders. There is no need to posit abstract psychological motives.

Also at a very concrete level is the explosive population growth in many developing contries. The GTC-A/E model predicts that high-numbered hormotypes will have more children than low-numbered types, given equal extrasystemic conditions. There is good reason to assume that extrasystemic conditions are not at all equal, however. Factors like nutrition, health, and infrastructure may have considerable impact on who gets many surviving children. Then again if high-numbered types experience a significant improvement in life circumstances, they may react with a larger population increase than the lower numbered individuals. In fact, over the past century there has been a stagnation or equilibrium in the birth/death ratio in several northern countries and a colossal growth in the Third World. It is difficult

to remain optimistic and believe that this world crisis can be solved by peaceful means. Perhaps we are facing another clash of hormotypes but this time perhaps involving nuclear arms. Einstein once said that he was not sure which weapons the Third World War would be fought with, but he was certain that the Fourth World War would be fought with stone axes. In that opinion he may have been more absolute than relative.

On a much smaller scale, it is important to note that the model neither can nor should be used to defend the bad habit of some members of the ruling classes to favor their own offspring unjustly by channeling them to high positions via connections or money . Quite to the contrary: the model actually predicts that hormotype A4,E4 or A5,E5 offspring will show a tendency to social deroute if born into A1,E1 and A2,E2 families, and that hormotype A1,E1 and A2,E2 offspring will tend to move socially and economically upwards if born into A4,E4 or A5,E5 families, everything else being equal. In that respect the model is used to explain some within-family upward or downward social mobility. It actually speaks against caste and class determination, and cannot be used to justify predestination and keep people in their "proper" place because they are born to be there. Such a mistake would mix "What is" with "What should be." The first aspect refers to the world as it is and to falsifiable hypotheses about why this state of affairs prevails. The second aspect is usually ascribed to the domains of ethics and moral. However, the sex hormonal guidance of body and brain development will not go away, however much we may condemn it. If you must infer morality, I think we behave in a morally justifiable way—and will be better prepared to bring an end to misery—if we examine the way things work instead of remaining satisfied with postulating the idea that greed, the Devil, a preordained order, the ruling classes, economy, or norms and cultural stereotypes are more or less independent agents responsible for misery.

Not only can the GTC-A/E model help us examine the reasons for the increasing division of modern society into survivors and losers, but it can also explain part of the reason for the well-documented North–South differences in national wealth and progress (Nyborg, 1987a). As argued elsewhere (Nyborg, 1994e), the model provides a coherent explanation of why the intrasystemic Neanderthal economy had to give way to the Cro Magnon economy, to modern man's economy. This coherence continues into predictions about which intrasystemic budgets will be favored by future high-tech society. Future selection may favor the services of hormotypes 1s and 2s, and it will work against type 4s and 5s. If southern countries become increasingly industrialized, we can expect many of the 4s and 5s in some of these countries to be pushed out of business. Tomorrow's society will find it increasingly difficult to reward an impulsive, physically and sexually quite active, extroverted, low-ability A5, because he could easily bring disaster if operating one of the planned high-power

plants. This danger would probably be much lower with a restrained, physically and sexually less active, introverted, high-ability A1 at the handle.

We are, of course, talking in general terms here because if a high-ability A1 for some reason became really hostile or disturbed, a consequent well-planned terror action could easily lead to more extensive damage than the one caused by sheer mistake or ignorance on the part of an A5. This century has seen enough examples of this, to be sure. However, I fear that the basic problem touched on in this discussion may easily become larger with the projected future technification of life circumstances and concentration of power. Then the 4s and 5s will be likely losers everywhere in the world. Stress will be imposed on them, and they may find it difficult to cope with this state of affairs by civilized means. Unless we find ways to handle this potentially disastrous problem, we might become involved in a war basically fought among different hormotypes with each having their particular intrasystemic economy budget, desperate to grasp or keep resources. However, if the present analysis of evolutionary continuity is largely correct, there will be nothing new in this. The only difference will be that this time we might be able to look in the right direction and see the nuts and bolts of the conflict, not being distracted by abstract social, economical, or psychological theory.

The economy principle is beyond justice and morality, and evolution in no way guarantees fairness. It is neither fair nor unfair to be a type 1 or 2 born into a 4 or 5 family, nor a 5er trying to cope with the demands of a school system geared mainly to the teachings of 3s, whatever conflicts that is likely to create. It may sound worrisome that evolution probably is completely indifferent with respect to moral values, sin, or shame, but such a concept appears to make sense only within a Christian or Muslim orthodoxy. Selection may actually favor the most devious, perverse, dishonest, crooked individual, if the intrasystemic budget disposes for behavior called so, if it increases the reproduction rate, and if all this fits well into long-term extrasystemic conditions. According to this view, the "worth" of a given hormotype is totally independent of what moral philosophers can dream of because selection favors whatever reproduces stupidity and wisdom alike.

The absolute value-free status of the economy principle suggests that the question of whether Cro Magnon man—our immediate predecessor—was a cold killer who purposely slaughtered an assumed primitive, brutal Neanderthal man is misplaced. None of the parties can be ascribed any moral responsibility because molecules and the flow of energy determined what happened and they assume no responsibility whatever. Isaac Bashevis Singer was once asked whether he believed he has a free will. "Yes," he said, "Of course I have a free will. I have no other choice!" Individuals behave in accordance with inner and outer circumstances, but, luckily, selection seems

to favor intrasystemic budgets that are at least to some extent compatible with coexistence and to select against serial killers. According to physicology, this probably has more to do with concrete molecular constellations than with abstract internalized norms guiding morally acceptable behavior.

Yesterday's optimal intrasystemic adjustment to a particular set of extrasystemic requirements may be tomorrow's minimum adjustment if circumstances change radically. In a constantly changing world, there is always a need for a rich variety of hormotypes to select from, but the circumstances dictate which will be favored. The ancient type 5 Neanderthals were perhaps replaced with the better endowed prehistoric type 4 Cro Magnon successors, which in turn were taken over by or melted into the even later maturing modern type 3s. The past couple of centuries may reflect a trend in which the 3s are being overtaken by 2s, and the near future may call out the 1s. They will probably be bright enough to devise a better society than the present one, as well as to construct the ultimate chemical weapons. Perhaps they may also be stupid enough to use them if pushed beyond limits. Thus, the question of whether this would be an evolutionary trend for the better or the worse blows in the wind. Darwin's advice—never say "higher" or "lower"—applies tomorrow as it did yesterday.

Can the GTC-A/E model and its associated principles be used as tools for changes if deemed necessary? I see three rather different possibilities. First Watson and Crick's observation of the basically simple nature of genetic material and later genetic engineering techniques enabled us to manipulate the physico-chemical DNA foundation for carbon-based systems that was established and selected for during phylogeny. The GTC-A/E model provides an extremely powerful tool for manipulating fundamental aspects of ontogenetic development, for major and systematic redistribution of intrasystemic parameters, and thereby for a change in the relative frequency of particular hormotypes. Obviously, such use of the model in the prime interest of some future dictator or oligarchy would come close to reviving Huxley's "Brave New World," but this time in a more precise form.

The second scenario is the "laissez-faire" approach. Afraid of doing something wrong, quarreling with moral philosophers, humanists, or ethical committees, we just sit down and watch the comings and goings of winners and losers, acting as they must in accordance with their internal economy and fixed budgets, and pushed around by inter- and other extrasystemic conditions. The implication of this scenario is that the best we can do is to weep if the situation becomes too onerous.

I find none of these scenarios acceptable, so I prefer a third future option: Piecemeal physico-chemical engineering, guided by scientifically established principles rather than by principles derived from clerical, political, or economic interests. A combination of mature genetic engineering (and we have certainly not arrived at such a stage today) and well-disciplined hormonal manipulation (also a future goal) will in the foreseeable future

allow us to radically change the course of phylogeny and ontogeny. The basic trick is simple enough: To insert or remove genes, thus remodeling the genotype previously considered an independent variable, and/or to change the expression of the genotype by hormone manipulation. Whether or not we like it, these techniques will soon be here, so we had better begin to discuss which kinds of restrictions such techniques call for if we are to survive and reproduce in a future of a better quality than the past. One of the most important of these obligations is, in my view, to keep a sharp eye on the importance of the individual at the expense of group interests, whether they be generated by religious fanatics, ageists, sexists, racists, or mad scientists. I am convinced that there will be no easy solutions.

Is there at present any good excuse for full-speed implementation of contemporary genetic and hormonal techniques, or should there be exceptions? Let me digress from this serious question with a brief personal role. A substantial part of my professional career has been devoted to the study and treatment of children with developmental disturbances. In the process, I have come to the conclusion that there really are no good reasons for recommending legal abortion of girl fetuses with Turner's syndrome (Nielsen, Nyborg, & Dahl, 1977a). Decisions based on well-tested scientific principles are, in general, to be preferred to decisions based on ignorance, dogma, or laissez-faire, even though the scientific principles most certainly are incomplete. Obviously, decisions of consequence for our fellow human beings must presume informed consent based on solid information about the pros and cons, and must take into account the potentials of all involved parties. If well-informed parents choose to bring up an abnormal child, neither experts nor religious fanatics should be allowed to interfere with reference to more or less idiosyncratic or dogmatic visions. At the same time, the interests of the child should also be made very obvious, and the long-term evolutionary implications should be considered. Now, consider the possibility of hormonal engineering. Just remember the previously mentioned example of chemical "repair" of specific ability deficits. This study took advantage of the fact that Turner girls need hormone substitution therapy to complete stunted SD. As reported in Section 3.7.3, this treatment had the "side-effect" of also removing the spatial ability deficit commonly observed in girls with Turner's syndrome (Nyborg et al., 1994). The encouraging outcome of such studies justifies chemical manipulation of basic body and brain parameters in such cases.

Now, what about nonclinical cases? Should we offer early active remodeling of the intrasystemic budgets of A5s,E5s and of A4s,E4s, so that they can be turned into A1s,E1s, or A2s,E2s, and thus perhaps respond more adequately to the selective pressures of tomorrow's high-tech society? If the GTC-A/E model is basically correct in diagnosing the inhibition of childhood creativity as a function of hormonal overshooting at puberty (3.7.5), we could perhaps make sure that creative as well as not-so-creative children

will not overshoot. The point is that the GTC-A/E model offers an important handle for chemical manipulation of the rate of maturation, extent of SD, or neoteny, if you like. Do we want to take this offer? Are we prepared to pay the price for planned manipulation of the internal budget, ontogenetically as well as phylogenetically?

I do not know the answer to these most important questions about our individual and common future, and I fear that nobody else has the solution. So it might be high time to start a qualified discussion, and an important aim of this book is to pave the way for this discussion. In the meantime I will personally be ready to defend hormonal manipulation of individuals clearly out of tune with the qualities of a good life, as long as *they* want the treatment after having listened carefully to the pros and cons, as long as it can be demonstrated by proper scientific means that there is a good effect of the treatment, with few if any harmful side-effects, that is, as long as the various intra-, inter-, or extrasystemic bills do not run too high. The costs of doing nothing can be very high and may mean sacrifice of the individual, when moving into the brave new world of ample physico-chemical opportunities. There is no such thing as a free lunch!

Chapter 14

Sex Hormones and Individual Variability

3.12. INDIVIDUAL DIFFERENCES AND DIFFERENT INDIVIDUALS

3.12.1. Introduction

> Principle 11: Sex hormones enhance individual phenotypic variability within and across male and female genotypic modal ontogenetic development.
>
> This is *the individuality principle.*

Psychologists who study SD are typically interested in individuals, but they quite often apply statistics based on group means. The reason for this apparent paradox is that SD is seen as a complex, multidetermined psychological phenomenon, arising from the fact that boys and girls are exposed to a multitude of different environmental factors, each making an impact. Accordingly, the best strategy is to study a large number of men and women, examine a variety of social conditions, calculate means, and produce correlation coefficients in order to reveal general trends in the material.

I have previously argued that this averaging approach is less than ideal if our purpose is to learn more about causal factors guiding the ontogenetic development of the single individual. Like psychology, the physicological analysis may take group mean averages as its point of departure, but it is important to note that a preference for working the other way around characterizes the physicological approach. This preference for the person-specific approach springs from two facts. First, physico-chemical processes, such as sex hormonal actions, take place in particular individuals, and not at all in the abstracted average individual, a truism that is often not fully acknowledged. Second, physico-chemical processes running along bio-

chemical continua often show nonlinear effects. Such nonlinear effects may easily be masked by averages and the associated variability considered as noise in the calculations. Physico-chemical continuity may, on the other hand, easily be masked by the tradition of dichotomizing sex-related effects. These problems have often been ignored in traditional research on SD, so I will briefly discuss some details and countermeasures.

3.12.2. SD, Averages, and Individuals

Many traditional studies of SD suffer from two serious methodological problems. First, the data of individual differences in SD are typically treated in terms of nonindividualizing statistics, some of these having first been developed for use in population genetics. Second, the nomothetic study of individual differences can easily be confused with the study of different individuals (Nyborg, 1974, 1977, 1988). A sex-dimorphic nomothetic approach to SD may run into problems because the composition of clusters of traits varies not only between the sexes, but also within one sex, that is, on an individual basis and even within an individual, that is, over the lifespan as indicated by ipsative variations (Nyborg, 1987a). Some of these problems become apparent when we take a close look at the considerable male-female overlap in the distribution of most sex-related traits, at the changes in the pattern of traits in an individual from childhood over puberty to old age, and at the dynamic spatial-verbal tradeoff in menstruating women as compared to a more static tradeoff in men. Application of the nomothetic approach encourages treating all this variability as "noise" to be eliminated statistically, with the unfortunate result that an attempt to establish a genuine general trend on the basis of averaging over different individuals easily results in statistical artifacts. Sex-specific averages may, for example, be deflated by plus and minus within-sex variations. Such deflated measures have been used in the past to argue that sex differences are too small to deserve serious scientific interest (e.g., Jacklin, 1979), to argue against a biological interpretation of sex-related differences, or to defend nonspecific multifactorial social learning, mentalistic, or superorganismic explanations.

To summarize, the nomethetic approach encourages averaging the measurements of a few traits at any given time in a large number of people and then makes distinctions among different types of people. In contrast, the idiographic approach strives to measure many traits at great depth, often over a long period, in a few people. The molecular approach attempts to combine the best of these two worlds by studying processes responsible for the dynamics of covariant trait patterns in a life-span perspective in a large number of individual people. Perhaps the term "idiothetic" is suitable for such an approach.

3.12.3. Sex Hormones and Individuality

An individualized analysis of SD should take into account at least the following three functional aspects of sex hormones. First, sex hormones constrain the originally multipotential organism by selectively suppressing the expression of many genes. For example, sex hormones cut the number of possible mammalian sexes down to two and only two modal phenotypes. Second, sex hormones procure a tremendous variability around these two modal phenotypes by exerting dose-response and nonlinear effects on a number of intrasystemic parameters. Third, as mentioned many times before, a host of inter- and other extrasystemic environmental factors can exert a very significant impact on the actions of sex hormones. Several external factors influence, for example, body and brain growth and timing of puberty and reproduction.

To be fully understood, these various aspects of sex hormone function must be considered together as the establishment and stabilization of dominance hierarchies may illustrate. A male alpha animal makes subordinate animals obedient through entirely physico-chemical means, according to physicology. Thus, the sight of size and assertive display behavior of the dominant alpha animal leads to systematic modulation of neurotransmitter patterns in perceiving beta animals. This may reduce androgen output, which in turn may result in rapid changes in membrane characteristics and slower changes in gene expression, with short- and longterm effects on aggression and reproductive capability. The end result for the submissive beta animals may be decreased aggression, libido, and chances for mating relative to the victorious alpha animal that may even experience a testosterone surge. Such a chain of processes and mechanisms may have important evolutionary implications. Subtle hormone adjustments can, in fact, explain the observation that after initial all-against-all test-fighting and establishment of a stable dominance hierarchy, the fighting lessens to a level where there is no longer a devastating everybody's war against everybody at any time. In other words, hormonal adjustment may explain the eventual establishment of relative individual stability in a dominance hierarchy.

Reorganization of the dominance hierarchy can be explained in the same individually economical way. If the alpha animal's displayed behavior signals weakness, owing perhaps to illness or ageing, the stress on the beta animals would ease. This would be sufficient signal for their endocrine system to raise the level of plasma androgen concentration, aggression, and later muscle potential, enabling then to challenge the alpha animal. If a particular beta animal were successful in dethroning the alpha, his plasma androgen would increase significantly and this would facilitate his presence on the throne. This mechanism would further explain why alpha animals tend to die at a relatively early age, even if unhurt by competitors. High plasma testosterone seems to be a health risk (Ellis & Nyborg, 1992).

There is probably much more to such complex physico-chemical adjustments than described above. But even this simplifying discussion suggests that such complex so-called social phenomena as establishment of leadership, monopolization of females, increased fertility, and the securing of multiple offspring for the future can perhaps be explained in part by fairly straightforward dynamic and temporary suppression of the androgen secretion of beta males. The mechanism would explain how it becomes possible to stabilize and change the complicated power balance in a group—and indeed reach an elegant, economical, purely physico-chemical resolution of the difficult problem of securing intersystemic stability of the social hierarchy, and flexible adaptation to changing circumstances (Archawaranon & Wiley, 1988; Ehrenkranz, Bliss, & Sheard, 1974; Goldfoot, 1979; Hellhammer, Hubert, & Schürmeyer, 1985; Keverne et al., 1984; Mazur & Lamb, 1980; Oettel & Kurischko, 1978; Olweus, 1986; Persky, Smith, & Basu, 1971; Poll, Zanten, & Jonge, 1986; Simon & Whalen, 1986; Van de Poll & Jonge, 1984) by a light turn of a hormone dial. Even more dramatic effects of the physico-chemical regulatory mechanisms can be observed in some species of fish, where a beta animal may change sex when the alpha animal dies (e.g., Shapiro, 1980). There is certainly no need to invoke desires or hate to explain dominance–submission and individual differentiation in the social power structure in subhuman species. It remains to be seen, however, whether the GTC-A/E model can explain dominance–submission by similar mechanisms in humans, too. Nothing in the available data speaks against this possibility; sporadic evidence actually favors it. Stress and hard physical work reduce plasma androgen (Cook et al., 1986; Ellison & Lager, 1986; Kreuz & Rose, 1972; Wurster et al., 1982), whereas winning enhances it (Dabbs, de la Rue, & Williams, 1991; Rose, Holaday, & Bernstein, 1971; Sapolsky, 1985).

3.12.4. Factors That Individualize

In the search for the many sources of individual variability in SD, the following topics may be of particular interest (also see Section 3.1.2). The person-specific timetable for clustering of traits is interesting, because the scheduled unfolding of trait patterns depend on genetic factors, on the availability of a particular sex hormone, on previous and actual receptor activity, and on the environment. Slight temporary changes (however caused) in secretion, binding, uptake, or metabolism may each, or in combination, exert tremendous transient or permanent effects on the unfolding of particular traits, and thus may explain individual variations around modal developmental trends. The diversity of effects further depends on the availability of sex hormones at "critical periods," the timing of which depends on the maturity of the target tissues. An unusual sex hormonal exposure during a sensitive period may lead to a profound, life-lasting

deviation from the modal pattern of development, whereas a similar exposure immediately before or after the "critical period" may have little, no, or the opposite effect. The sensitive periods of the target tissues vary on an individual basis around the mode.

Another set of factors that contribute to individual variability in the patterning of traits is the presence or absence of certain DNA loci, genes, and the substitution of various alleles at a given locus. The truly tremendous number of genetic combinations procured by the sexual reproductive mode introduces the perhaps most important source of further genetic variability. After combination, the karyotypic constellation becomes wide open to the modulatory effects of the sex hormones but within limits, because the phenotypic expression of sex-limited genes depends as much on whether the genes are there to be expressed as on the availability of inhibitors and enhancer substances. For these and other reasons, it must be clear that a fairly complete analysis of the phenotypic effects of systemic exposure to sex hormones includes at least an analysis of the presence of particular DNA material, essential for the potential development of particular traits. At this point the goals of physicology meet with behavior genetics. However, a happy relationship can only be sustained on the explicit understanding that the person-specific experimental approach is better suited for the task of identifying causes and mechanisms than are averaging, anonymous, correlation coefficients and the variance analysis approaches, geared originally toward problems in population genetics.

3.12.5. Constraints and Individual Variation

Sex hormones impose a few distinctively discontinuous sex-related constraints on the development of male and female body, brain, and behavior. These are menstruation, gestation, lactation, and insemination. Most other sex hormone effects are of a more continuous nature such as those influencing ability and personality development. Steroids thus act at one and the same time as sequesters (restraining through organizational and activational effects) and as boosters of individual variation around the mode (but still within the reaction range of male and female options, respectively). This dual role complicates the study of sex hormones. But it is important to realize that the difficulties are of a technical rather than of a principal kind. Sex hormones interact with other substances and structures in accordance with relatively few, fairly simple, circumscribed, and straightforward principles, and their actions can be subjected to ordinary physico-chemical analysis. The physicological approach holds the promise that we may finally be able to fully appreciate the profound dual role of sex hormones as constrainers and promoters of human individuality with the aids of methods from the natural sciences.

Part IV

PERSPECTIVES ON PHYSICOLOGY

Chapter 15

Epilogue

4.1. INTRODUCTION

The two main themes running through this book are the inadequacy of traditional mentalistic, philosophical, and superorganismic approaches to the study of human nature and culture, and the promotion of an alternative research program. In Part I attempted to show that mentalistic and superorganismic positions lack both empirical and heuristic value and that since Plato they have been exceptionally counterproductive, in part because they flourished without the necessary empirical censorship to grade them and in part because they are typically formulated in such a way that no quantitative science can disprove them, much like psychoanalysis. Concepts are reified and are then used as causes or intervening variables to explain quality, behavior, or culture. Part II presented physicology as an alternative research program. Part III sought to demonstrate, via an analysis of SD, that the physicological program constitutes a coherent framework for understanding, what to mentalists may appear as completely incompatible phenomena, in terms of a unifying level of physico-chemistry. During the process I argued that Darwinism is a special case of a more general account of universal selection that for the most is a pruning towards economical, energy efficient, physico-chemical arrangements over long periods of time, and in this way added an evolutionary perspective to the physicology program.

The physicological program is conceptually not very sophisticated, and this is perhaps its major strengths. It is, in fact, deliberately kept as unadorned as possible, and the only way to improve it is to put it to hard experimental work, not to expand theory, as is the common goal of most contemporary approaches. The future of physicology is completely determined by its heuristic and empirical assets. In contrast to mentalistic, rational, or superorganismic analyses, physicology is pragmatic and pro-

spective, and invites testing predictions under the tightest possible experimental control. In this aim, physicology is quite like the traditional natural sciences, but it certainly differs from the new "entangled" physics where speculations once again substitute data rather than provide a rich breeding ground for testable hypotheses. Largely liberated from the fabrication of hypothetical mental agents and the construction of intervening psychic variables, physicology concentrates on localizing and operationalizing physical and chemical causal agents, on elucidating their mechanisms of action, and on identifying the effects on other physico-chemical processes by means of the quantitative methods of natural sciences.

It would be an error to assume that physicology represents an anti-intellectual move. It is still important that economical brains come up with testable hypotheses, but this is in essence a process by which matter deals with matter rather than a process by which mind masters matter. Physicology represents an opposition to the notion of pure reasoning by mental powers. It would be incorrect to state that physicology is eliminative materialism, however, because the starting point of physicology is that it has never been documented that there is anything mental to eliminate in the first case. To avoid misunderstanding, I repeat that science cannot prove that mind stuff (or anything else) does not exist, and this would also be quite beside the point.

It would also be inadequate to claim that physicology is materialism because there are so many varieties of materialism, each with its particular connotations, that it would be a futile philosophical task to identify the one form of materialism that comes closest to physicology. Moreover, most philosophical positions are used to clarify concepts, a priori, and to explain, but the major role of physicology is not at all to explain but to identify ongoing physico-chemical processes, and let them talk for themselves. The point is that physicology strives to account for molecular moves, which requires description, not explanation. A full physicological description makes obvious what happens intra-, inter-, and extrasystemically. Given the affinity and space–time coordinates of molecules and the energy flow, the model predicts what else will happen. Is this pure determinism? Not at all. If something else happens, we have to revise the model because the description must be wrong. Determinism is a philosophical concept.

4.2. NATURE IS SIMPLER THAN WE THOUGHT!

One of the guiding principles behind the physicology program is simplicity. Not long ago,we all believed that the genetic basis of life had to be very complex because it gives rise to so many different forms. It was then realized that nature is more conservative than innovative. Nature's major trick seems to be to recycle with monotonous regularity a few simple and well-tested solutions, and selective pressures favor the most efficient of the combinations. During evolution selection has worked on a variety of elements and

their combinations, but eventually it settled for just four nucleid acids when it comes to the processes we call life. Endless repetition of the various combinations of these few acids is the entire physico-chemical basis from which all living organisms are constructed. The combination of the acids follows the ordinary laws of physics and chemistry, and gives rise to no more than twenty active amino acids. By combining these twenty acids, it is possible to produce all known proteins on earth. Their temporal sequence and folding in space appear to explain the differences between amoebae, scientists, philosophers, and elephants. Obviously, physico-chemical body and brain differences will make for behavioral differences and differences in experiences, and this is part of the differentiation process. Although we still miss many details, I think it is fair to say that we now have a reasonably clear view of the chemical and physical basis of life. But why was it previously so difficult to see nature's inherent simplicity? I think that the almost unlimited variation in form and expression blinded us and made us believe that life is a mystery beyond the grasp of science. Now even a primary school kid easily understands the extraordinary simplicity of the basic elements and principles of living systems.

The brain is most certainly found upstream with respect to complexity. There should not be any reason for despair, however. There is no need to resort to pathetic statements about infinite complexity or to give away the game to eager inventors of nonphysical ideas. We have ample evidence that males and females behave and think (i.e., function) differently. With the arrival of techniques for measuring different aspects of SD, we can now close in on when, where, and how much we differ with respect to sex hormones. We know perfectly well that various sex hormones shape multipotential bodies and brains differently according to ordinary physico-chemical principles and that these actions on the body and the brain can be studied with increasingly tight experimental control as techniques develop. This simplifies matters considerably. The physicological program focuses on the operationalization of the processes that affect the system and provide the structural and functional basis for its behavior. A physicologist dose not have to make a choice among literally thousands of hypothetical mental variables, new ones coming every day. Nor does he or she have to spend the day (or write a thousand books) postulating the effects of untouchable desires, ideas, motives, and beliefs. The physicologist can concentrate on a few hundred chemical species in a more or less open physical system, defined by a finite number of more or less well-defined functional areas. Instead of searching for myriads of symbols, logical rules, attitudes, or representations, and linking them together on an intuitive basis to explain behavior, a physicologist would apply, for example, regional cerebral blood-flow techniques to study oxygen uptake and energy consumption during different brain activities (ad modum Roland & Friberg, 1985). True, brain functions vary, but not at random, and again nature demonstrates simplicity.

The present work used SD to demonstrate basic simplicity. The fairly few species of hormones accomplish a cascade of physico-chemical organizing and activating events during embryonic development, at puberty, and throughout the remaining lifespan. These processes are very sensitive to variations in the extrasystemic physical stimulus pattern over the lifespan, and this sensitivity provides an important piece of evidence to explain how males and females come to differ. Any step in these straightforward endogenous processes is open for experimental investigation, according to physicology, because we are dealing with a limited number of steroids and other chemical messengers, having strictly rule-bound effects on a physical system that can be defined by its time–space coordinates. No doubt we could go further down and study the behavior of the single particle. Fortunately, this does not seem to be required in order to provide a fair description of the principles for molecule–behavior connections. Further illustrating simplicity, at least in principle, is the possibility that social interaction can also be analyzed according to the principles of physics and chemistry. The odds are that we can now throw away the futile ancient search for mental and superorganismic phlogiston. The implication of physicology is, that we can now concentrate on metabolism rather than symbolism, on molecules rather than meaning, on physical parameters rather than premonitions, on physics and chemistry rather than philosophy, on realization rather than instruction, and on synapses rather than cognition.

Keeping the definition and description of bodily, brain, and behavioral (individual as well as intersystemic) processes at the one and only level of physico-chemistry effectively eliminates the risk of committing a category-mistake (Ryle, 1980). A category-mistake is committed when one tries to describe events belonging to one category (e.g., mental) by a different category (e.g., molecular). The impact of the environment (e.g., rearing, learning) is, according to physicology, every bit as physical and chemical in nature as is the intrasystemic effect of, say, sex hormones (Section 2.4). Gibson (1968) argued long ago that perception is the internal processing of effects on perceptual systems of variations in physical parameters in a physical world, and Democritus said that there are only atoms and the void in the world. There is not much new under the sun. Unfortunately, again and again we tend to forget previous insights and to reinvent the wheel. Today there is a certain paradox in the fact that we need quite complex modern machinery to reveal nature's basic simplicity. However, compared to brains modern machines are extraordinarily simple.

4.3. HOW MUCH VARIABILITY DOES SD ACCOUNT FOR?

Not a few researchers insist that sex is a relatively unimportant factor that accounts for only a small percentage of total human variability in cognition, personality, and behavior (e.g., Hyde, 1981; Plomin & Daniels,

1987). This view is simply incorrect and is based on a number of misunderstandings. One of these is that most of the major intelligence tests are deliberately constructed to minimize sex differences and accordingly cannot be used to make a fair assessment of sex differences (Nyborg, 1994a). Another factor contributing to the confusion is that so-called meta-analyses averaging the results of literally hundreds of studies consistently underestimate the sex-related differences by playing plus and minus variation studies against each other. That such studies err can be seen from the fact that sex as such is an excellent predictor for the presence and achievement of males and females in many educational and occupational areas. Helping professions, such as nursing, or areas like theoretical physics or problem solving mathematics at a very high level (e.g., Benbow, 1988) are prime examples, where sex is an almost perfect predictor variable. Almost all chess grand masters and musical composers and maestros are males. The situation is different in literature and in other areas that call for verbal skills, however, as well as in some of the performing arts. It seems to me that the really interesting question in this connection is not so much whether sex is an important variable, but rather why so many psychological measures fail to reflect the overwhelming importance of sex in everyday life. Test constructors, like David Wechsler, originally found quite large sex differences in his classical IQ tests, but they deliberately left out items reflecting a sex advantage in order not to be unfair to one sex. Another important reason is that the common classification of people in terms of type of genitals, the karyotype, or self-reported gender identity lumps together people, who differ within sex in many important respects. Such a procedure tends to level out within-group differences that ends up being camouflaged as noise in an anonymous group mean.

Categorization by individual hormotype (e.g., androgen/estrogen balance; see Nyborg, 1984, 1994a; and Section 3.8.3.2) is preferable for several reasons. First, hormotyping avoids the trap of brutal sex dichotomy. Second, hormotyping identifies the proximate agents and respects individual variability. This is not a trivial matter because SD, and with it sexual reproduction, is a variety-promoting device of tremendous importance for the creation and maintenance of individual differences which promotes an understanding of the course of evolution (Jacob, 1982a, 1983). Third, the sexual reproductive mode provides an important bond by uniting opposite-sex organisms, but some observers consider sex a most disruptive social force (Wilson, 1976). As Jacob (1982b) so pertinently phrased it: "Reproduction is the only function to be performed by an organ of which an individual carries only one half so that he has to spend a enormous amount of time and energy to find another half" (p. 5). Fourth, the leap from describing the origin of the processes behind SD to describing the origin of society is insignificant (Ghiselin, 1974).

The point I want to drive home is that the only way it becomes possible to conclude that biological sex accounts for only a small percentage of the total variation is to statistically average out important within-sex differences, to close our eyes to what men and women demonstrate clearly even to the untrained eye through daily behavior, to believe in the relatively low power of some flawed psychological tests and certain statistics, and, finally, to forget the profound evolutionary implications of sex. The reason for the repeated insistence that sex is an unimportant variable, nevertheless, conveys an important message: Sex should be treated as a dichotomous statistical variable only under a few rather special circumstances or as a point of departure for an in-depth analysis. Identifying causal agents and mechanisms behind the SD of body, brain, intellectual, personal, and interpersonal development cannot be made from group means.

4.4. IS PHYSICOLOGY REDUCTIONISTIC?

The attempt to describe mental phenomena in terms of their materialistic basis is often said to represent an uncalled-for reductionism. By this is meant that, for example, a physico-chemical account of human nature reduces the phenomenon to a level where it becomes meaningless. An analysis of molecules, so the argument goes, can never be developed to a point where it accounts for abilities, desires, or beliefs because such qualities are much more than the sum of their elements, even should their basic elements eventually show up in the final analysis to be molecules. Mentalists would therefore argue that physicological analyses will inevitably destroy or, at best, represent a grave misrepresentation of the complex phenomena of human nature and society that the program is supposed to describe.

The mentalist critique of reductionist approaches is dubious or invalid for several reasons. First, the critique reflects nothing but a pessimistic view of the possibility of ever being able to analyze complexity; it also reflects ignorance of recent research suggesting that nature works in simpler ways than was previously thought. Second, the reductionist critique becomes self-defeating because it is based on a questionable premise. The notion of reduction logically takes its point of departure in the *a priori* assumption that the mental or superorganismic phenomena to be reduced (e.g., abilities, ideas, mind, norms, society, cultural stereotypes) in fact exist and have at least temporal reality. But where is the proof for this? The discussion in Part I led to the conclusion that the existence of these phenomena rather refers to speculations, verbal categories, concepts, hypothetical constructs, and intervening variables beyond empirical reach. The only possible implication is that the reductionist critique reduces to a name game because mentalist ideas about mind, society, and culture can be freely generated to suit any taste but the empirical. That being the case, nothing mentally can

be reduced to something else, and the critique of reductionism becomes absurd. What remains to be done to study human nature and society is exclusively an empirical matter and has nothing to do with philosophical notions. The basic value of the physicology program, therefore, depends less on an a priori denunciation by mentalists and philosophers, fond of the idea of reductionism, than on how well it describes the phenomena in question.

The descriptive term *visuo-spatial ability* has been used often in this book. Let me illustrate how purely physico-chemical descriptions of the intra- and extrasystemic side of this phenomenon, as well as of the interaction, go beyond the realm of reductionism critique and level at the molecular bridge. Inspired by Bischof's work (1974) on vestibular-optic interaction, I reinterpreted visuo-spatial ability as measured by performance in the rod-and-frame test in terms of individual brain differences in interaction of optical and vestibular input (Nyborg, 1977). Briefly, if a separated eye system is suspended in space, there is no way it can determine what is physically upright. All vertical and horizontal lines would appear relative to the tilt of the retinal coordinates. If, however, the eye system is provided with vestibular information, informing the system about the direction of gravity, it becomes able to orient itself relative to physical upright. I then showed that the tremendous individual differences in rod-and-frame test performance could be described as a function of the relative weight each brain system allocated to the potentially illusory optical tilt information emanating from the tilted visual framework of the frame or to the gravitational information from stimulation of the otolith and semicircular canals in the inner ear.

It can further be shown that this neural process of integrating the extrasystemic optical information with intrasystemic oculomotor-vestibular (somesthetic) information depends systematically on the level of plasma sex hormones. In other words, physicology neither describes visuo-spatial abilities as static traits or reified concepts in the head, nor degrades to untestable hypothetic constructs. On the contrary, physicology refers to very dynamic molecular brain processes with intra- and extrasystemic physico-chemical correlates that can be described on both sides in terms of physics and experimentally manipulated under the exclusive application of natural science methodology. A future task is to describe the stimulus situation and related test performance in other tests at this unifying level of physics and chemistry, not being depressed by misguided a priori critiques for reductionism.

4.5. WHAT'S NEW?

Let me stress again that the present work makes no claim to originality. Strong criticism of mentalism had already been launched in Plato's day, and materialism was suggested as one among other alternative positions. Hip-

pocrates and Galenos were fierce advocates of humoral theories nearly two thousand years ago. Watson tried hard to re-prove the concept of mind. Skinner was strongly opposed to ideas of mind and psyche because these concepts lack the dimensions of physics. Ryle has suggested that mental events are "ghosts in the machine," or "horses in the locomotive." Hull saw learning as a purely physical phenomenon and suggested that human and animal learning differ only quantitatively. Eysenck (1967) has repeatedly stressed the biological nature of personality. Before him, Darwin propounded the view that differences between human and animal are quantitative, not qualitative. Ghiselin made a strong case for universal economy. Dawkins has promoted the idea of universal Darwinism. In recent times, Rorty (1970), the Churchlands (1981, 1984, 1986), and others have launched a strong defense of eliminative materialism. The physical aspects of SD and the simplicity of nature have long been acknowledged by Jacob and others. Atkins (1981, 1984) has discussed the physico-chemical basis of life at length. To give full justice to all these economic brains and to all those unnamed here would make for a very long list; for a few of them, see the Bibliography.

4.6. THE TREES AND THE FOREST

The present work does not pretend to provide the reader with a scholarly review of any of the many areas covered. Proper treatment of each of these fields would require establishing a library in close cooperation with multiple specialists. Nobody can be a specialist in all the areas covered here, as this book regrettably documents. Personally, I have no doubt that most experts within the various fields covered will feel rather frustrated when they realize the somewhat cavalier treatment of their specialty. It is hoped that they will gain a perspective from reading other parts of this book, which is intended primarily to build bridges over troubled waters.

4.7. WHAT'S IN A NAME?

As mentioned at the beginning of this book, I decided to use many mentalistic and superorganismic terms throughout the book. I did so because these terms are practical and convenient ways of referring to complex matters that have received extensive treatment in the literature under these references. This procedure is perfectly acceptable as long as it is clearly understood that there is no such thing as consciousness, ideas, or desires, but only neurons, synapses, and physico-chemical processes. However, let there be no mistake: The essence of the present work is that consciousness refers to physico-chemical and not to cognitive processes. Thinking is intrasystemic metabolism more than a flow of ideas. Social communication is systematic intersystemic exchange, not of signs, atti-

tudes, or meanings but of physical stimuli. Culture is communality in the ways a geographically defined group of people function, not behavior shaped by local prescriptions or stereotypes. Learning is the realization of functions within physico-chemical constraints, not limitless accumulation of instructions, norms, or culture, conveyed by significant others.

The only way to realize all this is through physics and chemistry, and not from intuition or pure reasoning. When this point is made perfectly clear, it does no harm to use anachronistic mentalist terms. I have at times spoken against the limitless use of abstractions. Obviously, this warning is valid only where the abstraction leaves the reach of physico-chemical reality. It is, for example, an abstraction to talk about hormones or other molecular species. Permission for using abstractions lies in the physico-chemical address of the abstraction. There is no molecular address on abstractions such as ideas, desires, norms, or culture. They just float around in a frictionless and fantastic mental hyperspace. As new findings are released, a new and more precise terminology will surely emerge, but it would indeed have been awkward or even confusing to fill this book with a whole new vocabulary. Perhaps Part I underlines the importance of keeping Shakespeare's "What's in a name?" in sight. Words are cheap. Data cost, but they are worthwhile.

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