Genetic Mechanisms of Sexual Development

Edited by

H. Lawrence Vallet

Ian H. Porter

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PREFACE

At our seventh annual Birth Defects Institute Symposium we confronted critical issues relevant to "Genetic Mechanisms of Sexual Development". This theme allowed for a rare and unique opportunity of interaction between endocrinologists and geneticists who so often travel parallel paths but infrequently sense their common goal.

The purpose of this book is to delineate these recently discovered biological mechanisms which directly effect normal fetal and perinatal sexual differentiation and pubertal development and to describe in detail those instances of *mechanism failure* which result in ambiguity of phenotypic sex and problems of gender identity.

The extent to which growth of knowledge in this field is rapidly expanding can be appreciated through reading the historical presentation found in the first chapter in this volume.

As definitive analysis of any pathophysiologic mechanism is necessary before one can develop an orderly approach to problem-solving, unique etiologic classifications of disorders of sexual development and syndromes are presented; other chapters reveal the sequences necessary to effect progressive normal sexual differentiation in utero. The role of autosomes and the physical characteristics of the Y-chromosome as revealed by computerized videodensitometric studies, new information relevant to X-chromosome inactivation, the X-chromosome map, and patterns of replication in X-chromosomes, are all vital to the understanding of gonadal differentiation, subsequent sexual development, and phenotypic–karyotypic correlations. These sections leave one with a clearer picture of the pathophysiology of Turner- and Klinefelter-like syndromes and other disorders associated with gonadal dysgenesis.

Hormone "imprinting" on the human brain is generally an elusive concept, yet the evidence as seen here adds greatly to our knowledge that in animal models hormonal control of preference for sweets *is sex-specific* and indeed there may also be a sexually dimorphic neonatal pituitary–adrenal axis, with a role for perinatal hormones in feminine sexual development. However, the data on behavioral studies in poly-X and poly-Y syndromes and evaluations of psychosexual adjustment in adolescents in those with congenital sexual organ abnormalities are not entirely in agreement with the animal models presented. These unresolved issues persist in amplifying the need for intensification of research in this new area of scientific progress.

Although a major portion of this volume is concerned with conditions determined by X- and Y-chromosomes, it is the disorders which are under autosomal control, i.e., inborn errors of the adrenal steroid biosynthetic pathways, for which we have accumulated the largest amount of significant biochemical data. In those chapters that deal with adrenal causes of pseudohermaphroditism, one sees (as with the sex-chromosome-related disorders) a great variation in clinical and biochemical expression of these conditions, particularly the 21-hydroxylase defect. This genetic heterogeneity has, in the past, posed problems for the clinician–endocrinologist with regard to early diagnosis, in some instances, and specific mineralocorticoid therapy in others. Now this knowledge of the existence of heterogeneity and the description of compounds unique to the diagnosis of the 3 β-hydroxysteroid dehydrogenase defect should remove some of the insecurities with which we have treated patients in the past. As demonstrated, the prenatal diagnosis of these disorders remains elusive, probably also due to population heterogeneity and points to the need for the development of more sophisticated tools, generally applicable to the entire field concerned with the prenatal diagnosis of all inherited disorders.

We included here, along with these vital presentations, the relevant and lively discussions which greatly enhanced the success of the symposium; we have retained them for our readers as their poignancy gives each presentation a relevance not usually afforded research endeavors.

We believe that the success of the symposium and this resultant volume will be measured by those who will find themselves directly applying much of its authoritative content immediately to clinical problems. For the participants and contributors who silently awaited this belated publication, we know its intended use by students, clinicians, and academicians will more than sufficiently reward their patience.

This preface would be incomplete without the appropriate but inadequate award of gratitude to our editorial assistant, Mrs. Ellen J. Heenehan, whose genetic complement guaranteed this publication.

H. L. Vallet
I. H. Porter

CONTENTS

ANCIENT IDEAS ABOUT SEX DIFFERENTIATION

Hymie Gordon

When I began to review what was known about sex differentiation in ancient times, my first surprise was the extent of the primary sources which deal with this subject. My second surprise was how little use has been made of these sources by modern geneticists, endocrinologists, teratologists and others interested in the mechanisms of normal and abnormal sex differentiation. The subject is too vast to cover in one presentation, so I shall limit myself to a preliminary survey of some of the main sources from antiquity until the 17th century. My studies of these and other sources are continuing and I hope one day to present them in more detail and to bring the history up to a more modern date.

To facilitate the presentation, I have divided the sources into four categories: firstly, the ancient idea that birth defects were portents and that the evaluation of babies with birth defects – specifically with abnormalities of sex differentiation – could be used to foretell the future; secondly, the mythology of intersexuality in ancient Greece and Rome and their extension into travelers' tales during the Middle Ages and later; thirdly, some of the legal problems presented by individuals with ambiguous sexual development; and fourthly, the attempts by ancient biologists and physicians to understand the mechanisms of abnormal sexual development. I will limit myself to Western sources.

ABNORMALITIES OF SEX DIFFERENTIATION AS PORTENTS

The earliest written records of cases of abnormal sex differentiation are in the Babylonian cuneiform tablets found in the remains of the Royal Library at Ninevah. This library had been assembled largely during the reign of King Assurbanipal in the 7th Century before the Christian era. When Assurbanipal's palace was excavated by Henry Layard and George Smith during the 19th century of our era, they found literally thousands of tablets dealing with administrative, political, domestic, academic, agricultural, medical and religious matters. On one of these tablets (K2007 in the collection of the British Museum) there is a list of 62 kinds of birth defects and a brief statement of what each portends for the household or the country. It was believed in ancient Mesopotamia that birth defects were caused by unfavorable conjunctions of the heavenly bodies. It was

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obvious to all that major terrestial events, such as the seasons and tides, related to the positions of the stars and planets. Hence, if a specific astral pattern was the cause of a specific type of birth defect, then it was likely that the same astral pattern could determine the course of domestic and national events.

This cuneiform tablet was translated into English by Ballantyne in 1894.[1] He based his translation on a French translation published by Oppert three years earlier. Among the 62 birth defects, there are four which deal with abnormal sexual differentiation:

> When a woman gives birth to an infant –
>
> 8. whose right ear is round, there will be an androgyne in the house of the newborn.
>
> 21. that has neither nose nor penis, the army of the king will be strong, peace will be in the land, the men of the king will be sheltered from evil influences and the Lilit shall have no power over them.
>
> 34. that has no well-marked sex, calamity and affliction will seize upon the land; the master of the house shall have no happiness.
>
> 44. whose legs are male and female, there will be a rebellion.

The infant that has "no well-marked sex" most likely has severe hypospadias – one of the several etiologic varieties of pseudo-vaginal perineo-scrotal hypospadias. I do not know of a recognized syndrome in which the infant "has neither nose nor penis" nor am I sure what is meant by the infant "whose right ear is round" or by the infant "whose legs are male and female". Some of these difficulties in interpretation may be the fault of the translation. As far as I know, no fresh attempt has been made to translate this tablet since the late 19th century. It is possible that the increased knowledge of cuneiform writings in recent years will lead to improved translations which might facilitate interpretation.

The idea that babies with abnormal sexual differentiation were portents persisted for several centuries and was prevalent in ancient Rome. For example, Livy writing at about the beginning of the Christian era reported that in the year 207 BCE:

> . . . at Frusino, a baby was born who was the size of a four-year old. It was a wonder not merely because of its size but because its sex, whether male or female, was uncertain. In fact, the soothsayers summoned from Etruria said it was a disgusting and disgraceful portent which had to be removed from Roman territory, far from contact with the earth, and drowned in the sea. They put it alive into a chest, carried it out to sea, and threw it overboard.[2]

In modern Western communities, babies with abnormal sexual differentiation or other birth defects no longer are regarded as portents of political or economic disaster; but in at least some Western societies, disregard for the humanity of the baby with birth defects is no better than it was in ancient Rome.

THE MYTHOLOGY OF THE "HERMAPHRODITE"

The word "hermaphrodite" appears for the first time in the writings of Theophrastos of Eresus in Lesbos (about 370-287 BCE). Theophrastos was a pupil of Aristotle and is best known to physicians for his *Enquiry into Plants*, the first detailed review of botany and materia medica. He also wrote a more lighthearted book on human temperaments and personalities, entitled *Characters*. He regards superstitiousness as "a sort of cowardice with respect to the divine". He gives this description of the practices of superstitious characters:

> . . . on the fourth and seventh days of every month he has wine mulled for his house-hold, and goes out to buy myrtle boughs, frankincense, and a holy picture, and then returning spends the livelong day doing sacrifice to the Hermaphrodites and putting garlands about them.[3]

The origin of the first Hermaphrodite is described by many of the classic authors but none does so in more picturesque detail than Ovid (43 BCE-CE 17?). In the *Metamorphoses,* Book 4, Ovid tells the story of the handsome youth Hermaphroditos, the son of Hermes and Aphrodite. One day, when this young man was bathing in a stream, he was spotted by the nymph Salmacis. Immediately, Salmacis was passionately attracted to the young man, but he bashfully resisted her advances. Not to be denied, Salmacis jumped into the stream, seized the youth and wrapped her arms and legs around him so he could not escape. Her enthusiasm is best described in the exalted Victorian style of Henry King's verse translation:

> So clings the ivy to the forest oak: –
> So clutches with encircling tentacles
> The Polypus his prey. . .[4]

What happened next is described rather more prosaically in the modern prose translation by Mary Innes:

> . . . as they lay together, their bodies were united and from being two persons they became one. As when a gardener grafts a branch on to a tree, and sees the two unite as they grow. . . so when their limbs met in that clinging embrace the nymph and the boy were no longer two, but a single form, possessed of a dual nature, which could not be called male or female, but seemed to be at once both and neither.

I would be reading too much into this charming myth if I suggested that it foreshadowed modern ideas of post-zygotic somatic fusion with consequent mosaicism as a cause of true hermaphroditism.

The story of Hermaphroditos and Salmacis is well known and has been repeated in several versions and quite often has been the subject of classical paintings. Less well known is the story of Teiresias – perhaps the most remarkable of all cases of "sex change". Teiresias was the son of Evares and the nymph Chariclo. Teiresias was blind and he had prophetic powers. One of his better-known prophecies is connected with the history of Oedipus. After Oedipus had killed his father Laius and married his mother Iocaste, the city of Thebes was stricken by a plague. Teiresias told Oedipus and the Thebans that Oedipus's patricide and incest had caused the plague and that the plague would not cease until Oedipus had made amends.

There are several versions of what had caused the blindness of Teiresias and how he obtained his gift of prophecy. A widely accepted version was given by Apollodoros the Athenian in about 150 BCE.[6] It relates that on the island of Cyllene, Teiresias observed two serpents coupling. He killed the female – in violation of the Olympian law – so he was himself turned into a female. After living as a female for seven years, Teiresias again encountered a pair of coupling snakes. This time he killed the male and he was restored to manhood. One night, on Mount Olympus, Zeus and his consort Hera argued about who derived greater satisfaction from sexual intercourse. Zeus said that the female had the greatest enjoyment; Hera vehemently argued the opposite. To settle the argument, they consulted Teiresias as the only person who had experience of sexual relations both as a man and as a woman. Teiresias's answer was:

> If the sum of Love's pleasure adds up to ten,
> Nine parts go to women, one only to men.

Hera was so angry because Teiresias had testified against her that she caused him to be blinded. But Zeus was so pleased that he gave Teiresias the gifts of prophecy and longevity.

TRAVELERS' TALES

Myths and other forms of folk legend sometimes are derived entirely from the imagination. Other myths may be created by imaginative attempts to explain bizarre phenomena; the myth of Hermaphroditos and Salmacis may be of this type. Still other kinds of myths develop from the progressive elaboration by successive generations of story tellers of what originally was a real experience. Some of the travelers' stories about strangely-formed peoples probably are of this category.

The elder Pliny (Gaius Plinius Secundus, 23/4-79 CE) in the seventh book of his *Natural History* describes many such monstrous people.[7] For example, the Abarimon peoples who live in the Malayas have their feet turned backwards. It is possible that this story is derived from observations of individuals with severe

club feet. Pliny also described a tribe of Indian nomads, the Sciritae, who have a central hole in their faces instead of nostrils, and the Arimaspi of Scythia who have only one eye, situated in the middle of the forehead. Possibly these stories developed from observations of cases of holoprosencephaly, but one must be careful when one tries to apply modern nosology to some of these ancient descriptions. For instance, Pliny refers to another Indian tribe who have no necks, but before we leap to the the diagnosis of the Noonan syndrome we should note that Pliny also says that these people have their eyes on their shoulders – not characteristic of the Noonan syndrome. He also quotes an ancient account of another Indian tribe, the Monocoli "who have only one leg" and who "move in jumps with surprising speed" – a description not difficult to harmonize with some forms of reduction limb anomalies. But Pliny goes on to say that the Monocoli also are called the Sciapodes – the Umbrella-footed tribe – because when the weather is hot, they lie on their backs and protect themselves with the shadow of their feet! Accordingly, in considering abnormalities of sex differentiation, we must treat with caution Pliny's description of the Machlyes of North Africa. Pliny says that these people ". . . who live beyond and adjacent to the Nasomenes, are Androgyni. They are able to perform the function of either sex alternately. Aristotle adds that their right breast is that of a man and the left breast is that of a woman."[8]

Pliny made no claim to have observed all these different peoples himself; in most cases he cited his authorities. Subsequent writers were not always as scrupulous. Many gave the impression that they had themselved traveled to these far-away parts and observed some of these strange peoples. A well-known example of this class of literature is a book called *The Travels of Sir John Mandeville.*[9] Although "Mandeville" purports to be an Englishman, the book originally was written in French in about 1357. The real author is unknown; he may have been Jean de Bourgogne, a physician of Liege who died in 1372 – but this is an unsupported surmise. There is little original material in this book, which mostly is compilation of previously published travel tales. The anonymous author was sufficiently enlightened to emphasize that the "lond and the see ben of rownde schapp and forme" and he provides the necessary evidence for this.

In parts he is reasonably accurate. For instance, his account of the Holy Land, written as a travel guide, provides good descriptions of Jerusalem with the Church of the Holy Sepulchre, the templum domini and Mount Zion. He also describes adequately the Dead Sea, Galilee, Jericho, and other places of Biblical interest.

In other parts "Mandeville" either is over-imaginative or is gullible; or possibly he is writing only to entertain. His travels took him to the Far East, to the territory of the "Grete Chane of Chatay". On the way, he stopped at Polombe which may be Quilon on the Malabar Coast of South-West India. There he drank the waters of the celebrated well which "Sum men clepen it the Welle of Youthe, for thei that often drynken thereof semen alleways yongly and lyven withouten sykeness."[10]

He also visited the "Gret Yle that is Clept Dondun" and the smaller neigh-