

Rochester Institute of Technology

RIT Digital Institutional Repository

Theses

1996

Exploring the human frontier

Kevin Olsson

Follow this and additional works at: <https://repository.rit.edu/theses>

Recommended Citation

Olsson, Kevin, "Exploring the human frontier" (1996). Thesis. Rochester Institute of Technology. Accessed from

This Thesis is brought to you for free and open access by the RIT Libraries. For more information, please contact repository@rit.edu.

EXPLORING THE HUMAN FRONTIER

Sexual Development of the Male in Human Embryos

by SRY Gene Expression

BY

KEVIN MICHAEL OLSSON

Submitted in Partial Fulfillment

for the Degree

MASTER OF FINE ARTS

Supervised by Professor Robert Wabnitz

and Professor Glen Hintz

School of Fine and Applied Arts

Rochester Institute of Technology

Rochester, New York

1996

Approvals

Chief Advisor: Glenn Hintz _____

Date

5-16-98

Associate Advisor: Robert Wabnitz _____

Date

5-19-98

Associate Advisor: Nancy Wanek _____

Date

May 7, 1998

Chairperson: Thomas Lightfoot _____

Date

5/19/98

I, Kevin Olsson, hereby grant permission to the Wallace Memorial Library of RIT to reproduce my thesis in whole or in part. Any reproduction will not be for commercial use or profit.

Signature _____

Date

5-19-98

ACKNOWLEDGEMENTS

I am thankful to my parents who instilled important noble ideals, high standards, essential values and worthy goals.

My parents taught that persistence, education, self-confidence and hard work lead to success.

I extend my appreciation to professors Robert Wabnitz and Glen Hintz who gave me invaluable knowledge and confidence not only in the Medical Illustration profession but in life also. Their time, personable friendship and professionalism provided an excellent atmosphere in which to learn. As a team they provided the education on the most up to date computer skills while still teaching the invaluable classical applied techniques necessary to be a competent well-rounded artist.

I am grateful to my friends and family especially to my brother Dave and my sister Kristen for reinforcing in me the importance of education and following one's goals to the end.

Without their support and prayer it would have been all too easy to get lost along the way.

ABSTRACT

The primary purpose of the study is to explain using text and illustration the sexual differentiation and development of the human embryo. The thesis will explain in detail known aspects of crucial and intermediate events that occur during the development of an indifferent human embryo to a sixteen week male fetus. Specific attention will be given to molecular events that occur at week seven and the results of those processes on a gross level.

It is the aim of this thesis to define and address all known and relevant aspects in a manner that enables the most complicated events to be clear even to people with minimal scientific background. In order to bring the reader to the level of research discussed throughout the dissertation, a brief exploration of specific chemical and biological properties, genetic structure and function and other various molecular and cellular events are discussed in detail.

The thesis study was divided into two main categories. First, an illustrative show was held at R.I.T.'s Bevier Gallery. The illustrations were created using both traditional rendering and computer graphics. Second, the written thesis that encompasses the aspects of both molecular and cellular and tissue and organ development.

The 1995 graduate student spring quarter show used traditional rendering to depict on a gross level the stages of development from a four week undifferentiated (indifferent) embryo to a sixteen week fully differentiated and developed male fetus. In addition, a poster size computer color schematic was printed to show the pathway of sexual determination initiated by SRY and MIS molecules which are essential to produce male offspring.

CONTENTS

Chapter	Title	Page
PART ONE		
Chapter I	Embryonic Sexual Development.....	I
I.i	Introduction	
I.ii	The Purpose	
I.iii	The Nature of the Problem	
Chapter II	SRY Protein	IV
II.i	Covalent Bonds	
II.ii	SRY Protein Structure	
Chapter III	Structure and Function of DNA.....	VII
III.i	Nucleotides	
III.ii	Phosphate	
III.iii	Function	
Chapter IV	SRY protein Function.....	IX
IV.i	HMG Box	
IV.ii	Isoleucine	
Chapter V	Gene Expression.....	XI
V.i	Chromosomal Mapping	
V.ii	Gene Activation	
V.iii	Gene Expression	

Chapter VI	Hormones.....	XV
VI.i	MIS	
VI.ii	Steroids	
Chapter VII	Sex and Inheritance.....	XVIII
VII.i	Inheritance	
VII.ii	Discovery of SRY Gene	
VII.iii	Response Mechanisms to SRY.	
VII.iv	SRYIF's	
VII.v	General Embryonic Development	
VII.vi	Male Development	

PART TWO

Chapter VIII	Experiment.....	XXIV
VIII.i	Experiment I	
VIII.ii	Experiment II	
VIII.ii	Experiment III	
VIII.iv	Experiment IV	
Chapter IX	Development of the Testes.....	XXVII
Chapter X	Development of the Genital Ducts.....	XXIX
Chapter XI	Development of External Genitalia.....	XXXII

PART THREE

Chapter XII	Mutations.....	XXXIX
XII.i	Susceptible Period	
XII.ii	Genetic	
XII.iii	Enviromental	
Reference	List.....	XLII
Appendix A	List A.....	XLV
	List B.....	XLVI
Illustrations And Graphics		XLVII
Glossary		XLVIII

LIST OF FIGURES

Figure	Title	Page
I	SRY Structure.....	VI
II	SRY Schematic.....	XIV
III	Week Four.....	XXXIV
IV	Week Seven.....	XXXV
V	Week Nine.....	XXXVI
VI	Week Twelve.....	XXXVII
VII	Week Sixteen.....	XXXVIII

PART ONE

CHAPTER I

AN INTRODUCTION TO THE TOPIC

I.i Introduction:

The objective of this thesis is to explain the complicated processes involved in the journey of human embryonic sexual development. The developmental process has four important aspects: 1. differentiation, 2. morphogenesis, 3. growth and 4. reproduction. Differentiation and morphological change will be the focal point of this study.

The determination of the embryo to be male or female is dependent on several intricately intertwined series of events that involve: fertilization, differentiation, gene activation and expression, SRY protein synthesis, hormone production (Mullerian Inhibiting Substance (MIS) and testosterone), cellular induction and development of internal genital ducts, and external genital organs.

Many of the intricate processes of life occur at the molecular level of science and thus it is important to understand the basic molecular science. Therefore, the thesis will begin with a description of basic genetic, biological and chemical processes as a basis of life that pertain to male development.

There are three mechanisms and three results to keep in mind when mentally dissecting the progress of sexual development of the embryo and fetus. The mechanisms of action include: DNA as genetic material, SRY as the vital protein and Mullerian inhibiting substance (MIS) and

testosterone as the key hormones. The three results that are seen on a gross level are differentiation and development of the genital ducts, the gonads and the external genitalia.

The scope of this thesis will cover generalities from the fertilized egg through a fetus of sixteen weeks, with specific attention to the embryonic stages that involve sexual morphological differentiation at week seven.

I.ii The Purpose:

The purpose of this thesis is to study the biological process of male sexual differentiation and development. The reader should be able to understand how an indifferent human embryo arrives at a specific sex. The embryo genetically is either a male or female from the moment the egg is fertilized. However, the term "indifferent," is used because the embryo's sex in its early stages cannot be distinguished visually.

I.iii Nature of the Problem:

The premise that underlies this thesis is understanding the biological processes that produces offspring of both sexes to insure reproduction and survival of the species. This raises several important questions. How is sex determined? What biological elements are necessary to create a male as opposed to a female when nature otherwise dictates that an indifferent embryo develop as a female?

An egg (ovum) and sperm must fuse to create a unicellular entity, this divides and develops through several stages but, how, why, when and where does sex determination take place? Is the necessary genetic information contained in the sperm or the egg, or both? How is

that genetic code translated to the select cells? How do nucleic acids in DNA tell cells and tissues to develop in a male direction? Does this process happen by default? Does an embryo naturally develop into a female unless acted upon by some "outside" source? Is there an environmental influence on sex determination, i.e. temperature?

Scientists understand that a human develops from a single cell through cleavage, division, gastrulation and organogenesis and that these steps require the ability of differentiation, morphogenesis and growth to reach full development. This process is what allows nature to create from a single cell a multicellular organism with hands, feet, a face, nose and ears.

CHAPTER II

SRY PROTEIN

II.i Covalent Bonds:

Chemical bonds play an essential role as they allow for interaction between the atoms of specific elements in close proximity. There are several types of bonds. The study will focus on the covalent bond because that is the bond that allows for protein to DNA interaction which is the key element and will be discussed later. Covalent bonds involve sharing of electrons between two or more atoms. This is important because it allows two different organic elements to bond together in a temporary fashion and allows formation and glycosylation of all proteins and hormones.

The source of the vast molecular diversity in living things lies in the carbon atom and the ability to bond covalently. Carbon's versatile structure allows it to form covalent bonds with up to four other atoms to create an indefinite variety of carbon-based organic molecules. Organic chemistry bases itself on the carbon atom and the endless variety of carbon based molecule structures. Both protein and nucleic acid structure are built around a carbon molecule "backbone."

II.ii SRY Protein Structure:

Proteins are fundamental to both the structure and function of living material and are directly responsible for the delicate chemistry of the cell. Proteins are not flat but are three dimensional structures made up of primary, secondary tertiary and quaternary dimensions.

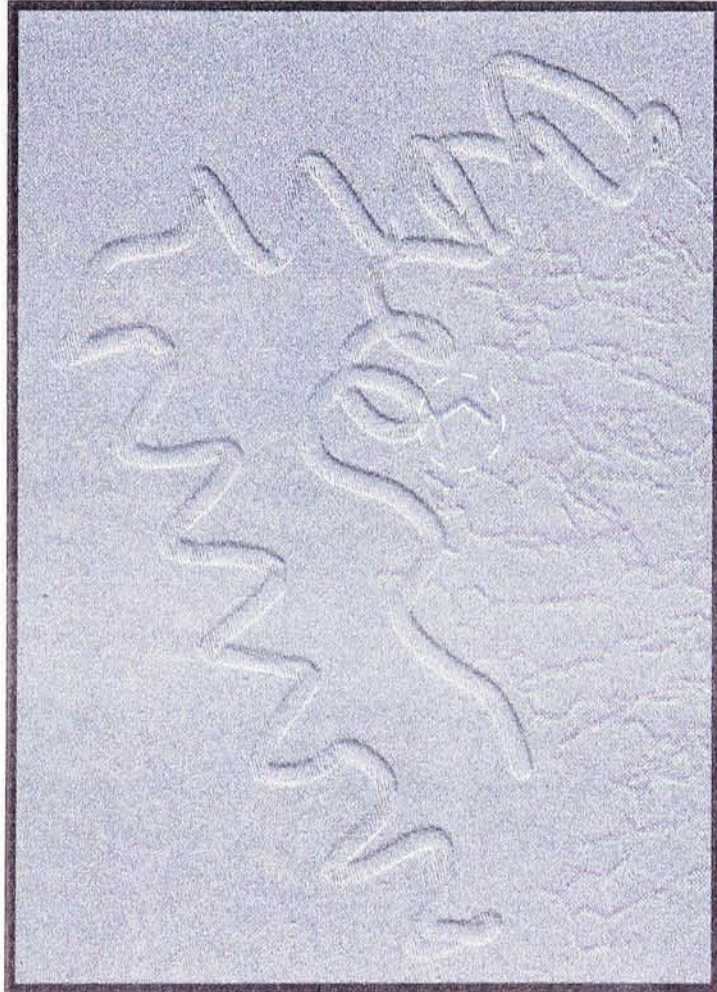
Proteins are long, complex polypeptide chains made from the twenty common amino acids. The sequence of amino acids is referred to as the primary structure of a protein. The SRY protein is the focal point of this thesis. SRY stands for Sex Region Y and the primary sequence of the protein is made up of 223 amino acids.

Amino acids are simple building block compounds comprised by these four elements: carbon, hydrogen, nitrogen and oxygen. These elements form a single carboxyl group (-COOH) a single amino group(-NH₂) and a side chain designated R. These elements allow amino acids to combine together to form thousands of different proteins. Take the SRY protein for example, the 68th amino acid is Isoleucine because the R-group is an Isoleucine side chain, (I68). The term I68 refers to Isoleucine at position 68 of a full-length SRY protein.

Another dimension to proteins that is important to understand is the secondary structure. The three alpha helices of the High Mobility Group box or (HMG box), on the SRY protein are an example of the secondary structure of a protein. The alpha helices demonstrate an ordered arrangement beyond the linear sequence of amino acids. The secondary dimension gives the protein structural integrity while at the same time allowing it to be flexible enough to interact with other molecules such as DNA.

The L-shaped orientation of the three alpha helices is an important example of tertiary structure. This convex shape of the HMG box acts as an important template for DNA recognition, bending, partial unwinding and widening of the minor groove, to allow for protein-DNA interaction. Structural determination of this region was performed by distance geometry and simulated annealing via experimentation (Havel, 1991). Refer to Figure I. of the following page.

SRY Protein Structure



SRY protein DNA binding complex with Isoleucine intercalation (white circle).

Figure I.

CHAPTER III

STRUCTURE AND FUNCTION OF DNA

Deoxyribose Nucleic Acid (DNA) is a double helical structure made up of four different nucleotide building blocks. Each nucleotide is made up of a phosphate group and a nitrogenous base which are attached to deoxyribose, a five carbon sugar. The helical structure contains all the hereditary information necessary to allow life to proceed in an organism. There are approximately three billion bases that make up the human genome. By arranging the four different bases in an infinite and various sequential order, endless genetic codes can be formed. When DNA is viewed in its classical form we see it coiled tightly on protein molecules called histones. DNA in this condensed form is termed chromosome. A human somatic cell normally possesses 23 pairs of chromosomes, including one pair of sex chromosomes. For a human male, an X and a Y chromosome are present. The gene of interest to this study lies within the Y chromosome (See VII.ii, page XVIII). Through a complex process of transcription and translation, the genetic code gives directions to the cell which allows it to perform various assignments.

III.i Nucleotides:

Two of the nucleotide bases adenine (A) and guanine (G) are purines and are double ring structures. Cytosine (C) and thymine (T) are the other two bases and are named pyrimidines and consist of a single ring structure. Each pyrimidine from one strand is paired with one purine from the other strand. The helix is made up of two complimentary strands, adenine pairs up with thymine (AT) and guanine lies across from cytosine (GC). In this way each "cross rung" is made

of one pyrimidine and one purine to allow for regular helical coiling. This also creates consistent major and minor grooves on the helical structure. The width of the double stranded molecule is 2.0 nm permitting vast information to be stored in a small space.

III.iii Phosphate:

Phosphate groups are also present. These groups consist of a phosphorus atom with a hydroxyl and double bonded oxygen attached to it. The phosphate group is part of the DNA backbone structure and is attached to the 5' deoxyribose sugar. The phosphate groups contribute to the protein-DNA interaction. The phosphate groups link the nucleotides together to form single DNA chains. Each phosphate contacts the HMG box to form phosphodiester links. Nuclear Magnetic Resonance (NMR) studies have shown partial unwinding of the DNA to allow for proper alignment of the phosphate contacts (Weir, 1993).

III.ii Function:

The structure of DNA allows for a variety of functions and physical capabilities. For example the structure of DNA allows it to decondense, to be "unzipped" and to be read. The physical properties permit it to bend and bind to proteins such as SRY. The phosphate groups direct precise phosphate contact between the DNA and the binding protein. Bends in the DNA organize a higher order of promoters for protein-protein interaction. This allows for additional downstream transcriptional events to transpire.

CHAPTER IV

SRY PROTEIN FUNCTION

The structure of the SRY protein is multifaceted. Each structural part plays an important role and is directly related to the function of the molecule and its ability to recognize, bind and activate DNA for successful gene expression. The two key elements to the protein and the most well defined are the High Mobility Group and the isoleucine structures.

IV.i HMG Box:

The HMG box is the conserved DNA binding domain located on the SRY protein. Scientists know that the tertiary structure of the HMG box consists of three alpha helices with L shaped orientation and an angular surface. The function of the HMG box is to provide a template to allow DNA to bend. The HMG box was found to be concave in nature causing the DNA to bend away from the protein . As the complex comes together the SRY acts as a template to bend the DNA and to open the minor groove. Bending of the DNA allows for protein binding and side chain insertion. The DNA binding domain has been constructed based on experiments that use nuclear magnetic resonance, distance geometry and simulated annealing (Jones 1994). Mutations of the HMG box on the SRY protein result in sex reversal [see Appendix A].

IV.ii Isoleucine:

In addition to and attached to the HMG box is an amino acid Isoleucine I68. The function

of I68 is to act as a "side chain" allowing for DNA- protein interaction. Isoleucine alignment and insertion is absolutely necessary for DNA recognition by the SRY protein. Intercalation of the Isoleucine occurs when the side chain enters the DNA between a specific AT base pair of the "TATA" box in the minor groove. This causes the minor groove to widen and the DNA to lock into position. Isoleucine causes interruption of base stacking but not base pairing. Any one single base change in the nucleotide sequence ATTGTT especially, at the "TATA box" site (central TT) where the I68 side chain penetrates results in decreased binding. In addition to intercalation of the Isoleucine side chain phosphodiester links assist in the alignment the SRY-DNA complex. This process marks the beginning of transcription and thus gene expression. The function of the SRY protein is to regulate transcription and expression of specific genes. SRY induces gene expression of MIS.

CHAPTER V

GENE EXPRESSION

V.i Chromosomal Mapping:

Chromosomes are contained within the bounds of the nucleus of the cell and are the site on which the genes are located. There are hundreds even thousands of genes for each chromosome. There are approximately eighty thousand genes on the twenty three pairs of human chromosomes. Chromosomal mapping has led to determination of euchromatin (active DNA) and heterochromatin (inactive DNA). Many regions of the heterochromatin were not always inactive but active during certain stages of growth and development. For example, genes used during embryonic development transform into heterochromatin in adults. Extensive regions of heterochromatin indicate functionally related genes to be grouped loosely together. For example, genes specifically involved in embryonic development are loosely grouped because they were once activated or repressed in a "group" fashion. This is important for two reasons; it is a way to categorize or file select genes to be used once and it is a way to expedite gene expression in an efficient and succinct manner.

A gene has been generally defined as a portion of DNA which encodes a specific action. This involves synthesizing RNA's, enzymes, structural proteins, or various polypeptide chains. Genes are encoded on DNA of the eukaryotic chromosomes which are wrapped tightly on histones (protein cores). The histones are wound into tight coils and organized into loops forming the nucleo-protein material called chromatin. Non-histone proteins also exist but do not

binding to certain DNA control regions. This leads to the decondensation (unraveling) of the nucleosomes.

V.ii Gene Activation:

Gene activation occurs in two steps; the unwinding of a particular region of a nucleosome and the binding of an activator to the promoter domain to activate the gene or group of genes in that particular area of uncoiled DNA. It is important to note that scientists do not yet know what sets the SRY protein into action because it has no recognized transcriptional activation domain. While most HMG box proteins contain a transcription activation domain SRY does not appear to. Scientists do know however, that once activated in the seventh week the “SRY gene,” produces the SRY protein.

Once the promoter of a gene is activated the genetic code is interpreted in a two step complex process that involves transcription and translation. The genetic code for building (i.e. growth and differentiation) a new cell or organism in the form of DNA needs to be encoded (transcribed), into the form of messenger RNA (mRNA), and then interpreted (translated), to form chains of amino acids (proteins) via tRNA.

The portion of DNA that contains the gene decondenses, transcription of DNA into mRNA is then accomplished. The DNA remains within the nucleus at all times and is able to transfer its information via mRNA because the mRNA is able to cross through the nuclear membrane and move to sites of protein construction. At these sites mRNA is able to take the genetic information and use it for translation with the help of rRNA located on the ribosomes.

The tRNA carries the amino acids to the ribosomes. Here, tRNA reads the mRNA in

The tRNA carries the amino acids to the ribosomes. Here, tRNA reads the mRNA in groups of three (codon). Each codon represents three base sequences of DNA and these codons are translated into one amino acid. Chains of amino acids are known as polypeptide sequences and it is these sequences that make up proteins.

V.iii Gene Expression:

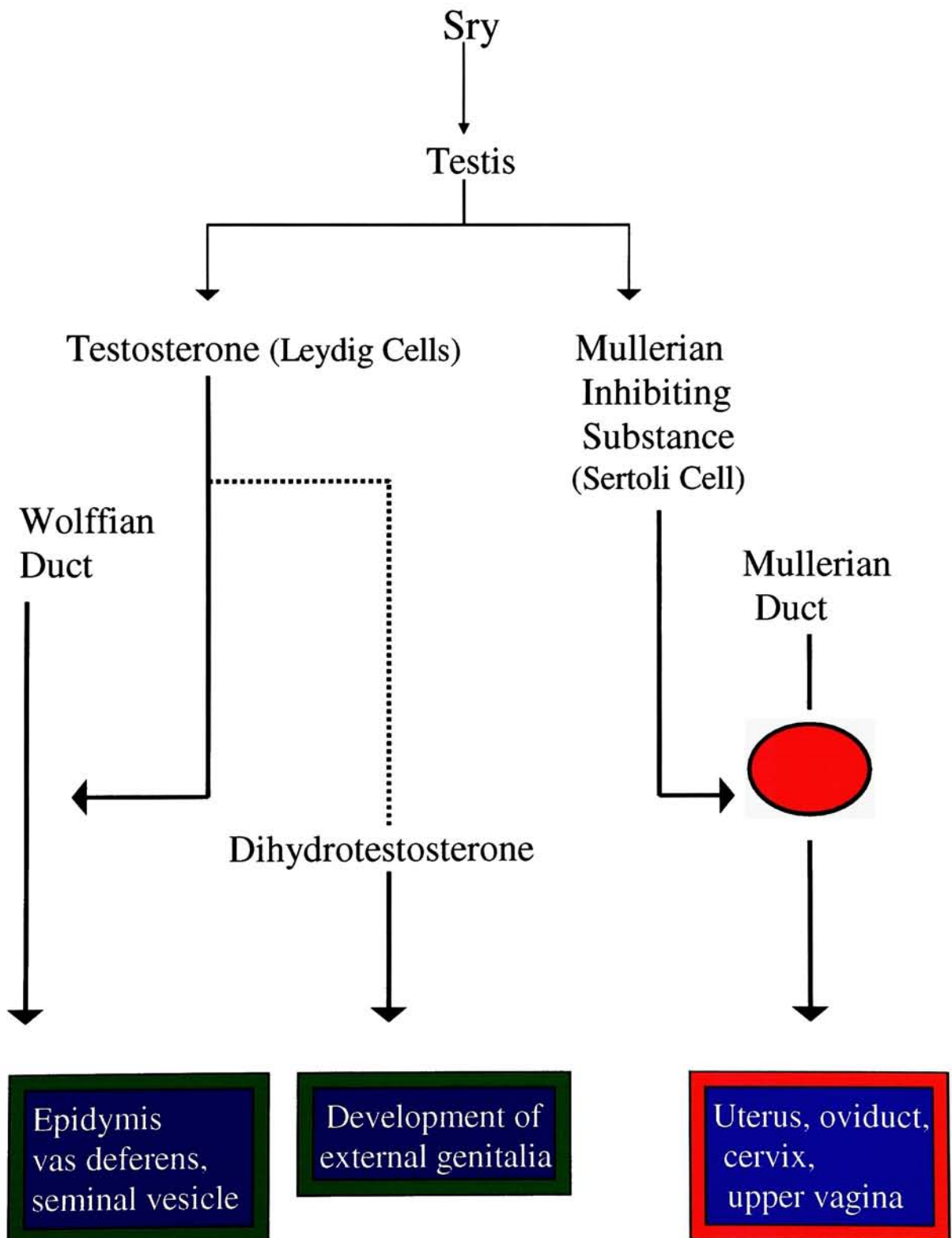
Gene expression is a complicated event that requires activation and then expression via transcription and translation. Without this ability development on any level would not be possible.

The whole process of gene expression for sexual differentiation and development includes protein synthesis and binding of proteins to DNA to allow for downstream processing of essential hormones, imperative for growth and development of the organism. Genes for SRY, MIS and testosterone are expressed in the way described.

It is important to understand that DNA synthesizes SRY protein in sufficient abundance. The SRY proteins then bind to DNA in the seven week embryo which causes downstream processing of Mullerian inhibiting substance (MIS). Cells in the gonadal ridge of the embryo then respond to the MIS hormone to prevent further development of female primordia. Understand, that both male and female primordial structures exist in early male embryos and it is not until production of MIS that the female structures regress.

Refer to Figure II. of the following page to view MIS and testosterone dependent pathway via SRY gene expression.

Sex Determining Region Y



CHAPTER VI

HORMONES

Hormones are substances produced by specialized organs and are transported through the circulatory system toward a specific target tissue. The role of hormones is to regulate gene expression by entering a cell nucleus and binding to the DNA. The three essential hormones necessary for an embryo to develop phenotypically into a male are testosterone, Mullerian inhibiting substance and 5 alpha-dihydrotestosterone. The two separate groups of cells which produce testosterone and MIS reside within the developing gonads (testicles).

VI.i MIS:

Mullerian inhibiting substance is produced in the developing gonads by the Sertoli cells in the seventh week. Mullerian inhibiting substance is a 560 amino acid glycoprotein that is fundamental in the course of regression of female gonadal primordia that leaves behind only the female vestigial structures (paramesonephric ducts/mullerian ducts). These structures would otherwise develop into uterine tubes, uterus, cervix and upper portion of the vagina. It is the response of the Sertoli cells on the developing gonadal ridge at week seven to SRY-DNA binding and in turn production of MIS that is the first key step to male sexual differentiation. The first step of male development takes place at this point, followed by the production of testosterone (Figure II. p.XIV).

VI.ii Steroids:

Steroids are produced only by the adrenal cortex, gonads and other reproductive structures. The two steroid hormones of importance to this study are testosterone and 5 alpha-dihydrotestosterone. Testosterone is produced in the testes and like all steroids has the same basic unit of four interlocking carbon ring structures with various side group configurations. Dihydrotestosterone is converted from testosterone in the urogenital sinus and labioscrotal swellings.

Leydig cells of the testes are the actual cells that produce testosterone. The testes begin secreting small amounts of testosterone during embryonic development but only after the bipotential gonad is realized as a developing testicle. Production of testosterone follows gene activation of MIS. Depending on the genotype of the embryo the gonads can develop into either the testicles or the ovaries. The presence of testosterone is crucial to the differentiation of male structures because it is this hormone that will masculinize the developing fetus. Testosterone is able to enter a specific tissue and the actual cells that make up that tissue. For example, testosterone is synthesized in the developing gonads and then leaves to enter male accessory reproductive structures. The steroid then enters each cell and links itself with a cytoplasmic protein receptor. The complex then moves into the nucleus where it binds directly to the DNA to affect gene expression by regulating the transcription process, in affect causing production of specific and necessary proteins.

Nature dictates that in the absence of these two hormones the indifferent embryo will develop "by default" into a female phenotype. It is important to understand both MIS and testosterone are expressed due to the presence of the SRY protein. For successful male

development MIS and testosterone in addition with 5 alpha-dihydrotestosterone must work in conjunction with each other (Figure II. p.XIV). The testosterone allows the fetus to further develop male traits in two ways. It directs differentiation of the mesonephric duct and when it is converted to 5 alpha dihydrotestosterone, it directs development of the external genitalia. MIS induces regression of nascent female structures. If a divergence in either pathway occurs malformations will result, (Moore, 1983) [Malformations, See Chapter XII].

CHAPTER VII

SEX AND INHERITANCE

VII.i Inheritance:

Of the twenty three pairs of chromosomes in the human genome there are two types. They are the sex chromosomes and the autosomes. There are two types of sex chromosomes; an X and a Y chromosome. Females carry one pair of X chromosomes while the male carries one X and one Y chromosome. As the female produces eggs through meiosis (oogenesis) all eggs receive an X chromosome. When the male goes through spermatogenesis, half of the sperm cells receive one X chromosome while the other half receive a Y chromosome. When fertilization takes place the egg can be fertilized by a sperm that contains either an X or Y chromosome. If two X chromosome pronuclei fuse the result is a zygote that will develop into a female. If fertilization involves a Y chromosome then a male will result. Therefore, the sex of an individual is determined by the sperm at fertilization when the egg and sperm fuse with an equal fifty percent probability for either sex. No other factors including environmental, exist to determine the genetic sex for the human species under normal circumstances. Normal sperm with proper genes on the Y chromosome are the only biological factors for the beginning of male development. However, abnormal genetic and environmental circumstances occasionally do occur resulting in sexual misidentity, see Chapter XII.

VII.ii Discovery of SRY Gene:

Genes unique to the Y chromosome are termed holandric. The phenotypic traits they

control appear only in males. The SRY gene is an example of a holandric gene and is located on the short arm of the Y chromosome. Near the end of the short arm is a 35,000 base pair region that comprises the testicular determining factor or TDF. Within this region lies the gene for SRY.

Published in the December of 1994 issue *Science*, it was revealed that a group of scientists in Boston located the SRY gene. Before Weiss and colleagues discovered the SRY gene scientists could only speculate about its existence. Prior to the experiment that led to the location of the SRY gene scientists referred to the 35,000 bp TDF region as the sex determining region on Y.

VII.iii Response mechanisms to SRY:

The tissue of the gonadal ridge prior to testicular morphogenesis most likely contains the tissue specific mechanics necessary to respond to SRY. Scientist know that SRY protein binds to DNA and activates an ensuing transcriptional process resulting in the development of the testes and hence production of MIS by the Sertoli cells.

As described earlier, the SRY and MIS gene expression go hand in hand and like the SRY gene the MIS gene belongs to a conserved gene family. The MIS gene has a 114 bp promoter with a SRY protected region (-45 to -75) to allow response of SRY downstream processing. Subsequent expression of MIS after SRY expression in the indifferent gonad led scientists to conclude that MIS is evidence of the male specific gene transcriptional process (Crate, 1986).

VII.iv SRYIF's:

Experiments have shown that SRY does not act alone to activate the MIS gene. In fact

there are intermediate factors that are involved to help promote MIS gene expression. Mutation in the 30 base pair region of the MIS promoter does not cause transcriptional interference even though SRY binding is annulled leading one to believe that SRY induced factors (SRYIF's) are present. Just what these SRYIF's are exactly is not yet known, but they act to transduce the signal from the upstream SRY binding signal to the MIS promoter. Scientists do not yet know the exact number of intermediate factors and all their possible roles (Maxwell, 1989).

VII.v General Embryonic Development:

As we have seen, the processes of life are guided by an elaborate series of information transfers. The genes of DNA contain all the information necessary to give life to an organism. The information is capable of orchestrating all the complex events involved in development from a single cell into a complex corporation of cells, tissues and organs that constitute a human.

We know DNA is able to direct development and differentiation through transferring its genetic code via transcription and translation to create enzymes which direct biochemical events. The question is: when and where do these events take place for sexual differentiation? Only certain genes at select times are undergoing this process in accordance with what the cell/organism is doing. As previously stated, SRY and MIS expression occur in the seventh week of the embryo. But what significant developmental events lead to expression of the genes?

The first step toward development of a multicellular animal is the process of fertilization, where the pronuclei of two gametes fuse to form a zygote. Development begins as the unicellular zygote begins to divide into several cells. Even though cell cleavage occurs and more cells are created the relative size of the mass remains the same during the first few days after conception.

Between the eight to sixteen cell stage the cell mass is referred to as a morula. The morula undergoes several cell divisions, and is referred to as a blastocyst. The blastocyst possesses a cell mass and a blastocoele (cavity). The embryo proper is made up of cells from the inner cell mass. The cell mass completes the first of many steps toward differentiation as it divides into two layers to become the epiblast and hypoblast.

In week three the embryo proper begins the process of gastrulation as the bilaminar disc is converted into three germ layers. The ectoderm is the outer layer; the endoderm is the inner layer; and the mesoderm is the middle layer. After this third week the embryo enters the embryonic period (week four to week eight). In week four the embryo undergoes rapid growth. Morphogenesis commences and is highlighted by the process of organogenesis giving rise to all major structural development by week eight.

VII.vi Male Development:

There are three gross anatomical aspects to male sexual differentiation and development; 1. the internal gonads 2. the ducts carrying the gametes from the testes to the penis and, 3. the external genitalia. As stated, three weeks after conception the cell mass undergoes further morphological changes. At week four the mesonephros, gonads and a genital tubercle form and become evident. The mesonephros function as temporary kidneys during embryonic development. As the embryo develops into a male the mesonephros are then referred to as the wolffian ducts of the male reproductive system (week 9).

How do the cells of the gonads, genital ducts and external genitalia arrive? It is from the middle mesodermal layer that the intermediate mesoderm is formed. It is this layer that gives rise

to the mesonephric and Mullerian ducts, gonads and external genitalia. How do all of these events transpire? Scientists do not know or understand all of the steps that are required but do understand the essentials. Scientists do know that cellular induction, chemicals, hormones and DNA acting as the foreman with blue prints are the basic and essential ingredients. Development and differentiation rely not only on specific gene expression at specific times but also on the chemical and electrical signals from nearby cells. Developing cells are influenced via contact (i.e. contact inhibition) and by environmental factors such as diffusible chemicals and hormones. For example, medullary cells in the indifferent gonad will form testicles when induced via the hormone testosterone. In the absence of this hormone a XY genetic male embryo will develop phenotypically into a female.

Assuming, however, that no gross errors have occurred from the point of fertilization to week seven the first step toward embryonic male development would be the establishment of gonadal sex from an indifferent urogenital cell line. This would involve gonadal ridge formation and then testicular development. The gonadal ridge appears in week four and remains indifferent until week seven when it becomes sensitive to testosterone until week eight. In the presence of testosterone the gonad that lies under the mesothelium and is continuous with the mesonephros (Wolffian duct) starts to differentiate on the ventral side of the mesonephros. The gonadal ridge then becomes a developing gonad (testicle) connected to a Wolffian duct.

Growth and further development of the three critical areas (gonads, genital ducts and genitals) continue from week eight into the fetal period of development. The fetal period exists from week nine to birth. Growth of the fetus occurs rapidly causing the length of the fetus to double by week twelve.

The external genitalia continue to develop further. The male and female genitalia look similar in week nine but the sex of the fetus becomes visibly evident at week twelve. At this point, the cloacal membrane has receded and fused to form the scrotal raphe. The labioscrotal swellings begin to resemble the scrotum and the urogenital fold is now characterized as the body of the penis.

The testes at week nine are made up of Leydig, Sertoli, myeloid and germ cells that provide an environment for elaboration of growth, differentiation and spermatogenesis.

The ducts at week nine are still referred to as the Wolffian ducts but by week twelve the ducts begin their own differentiation and are known as the vas deferens. By week sixteen the epididymis is obvious and the formation of seminal vesicle buds appear, (See Chapter's IX, X and XI for more on male development).

PART TWO

CHAPTER VIII

EXPERIMENT

Scientists have tried to answer the questions nature has put before us. The question of sex determination dates back to Aristotle as he hypothesized that heated passion would provide for male offspring. Until 1900 when Mendel's work was reinvestigated it was thought that the environment was the contributing factor for the determination of sex. Further collaboration that pointed to genetics as the sole factor was the rediscovery of the sex chromosomes and the identification of the XX female and the XY male in 1905.

Numerous experiments have been performed in order to understand the structure and function and to find the location of mechanisms responsible for sexual differentiation. Sometimes in order to understand how a normal human functions it best to study the abnormal.

VIII.i Experiment I:

In 1953, Jost experimented with rabbits. He discovered that nature fosters development in the female direction unless acted upon by a male genetic factor. The results were based on the fact that all rabbits developed into females when the indifferent embryo gonads were completely removed prior to differentiation.

VIII.ii Experiment II:

Results in 1984 from studies by McLaren showed that the first step in male sexual determination occurs in the Sertoli cells of the developing testes. This was concluded when McLaren fused XX and XY blastomeres together to produce XX/XY chimeric mice (McLaren 1984). Experiments showed that the Leydig cells consisted of both XX and XY cells and the Sertoli cells were made up solely of XY cells. Since the sex factor resides on the Y chromosome that meant that the beginning of sexual development was most critical in the Sertoli cells (Refer to page XXVII).

VIII.iii Experiment III:

In the 1980's, biotechnological and clinical studies combined to locate a region on the short arm of the Y chromosome that contained the necessary genetic information for male development. The studies involved analysis of sex reversed XX males and XY females in conjunction with DNA hybridization techniques. Studies showed that these XX men had a 35,000 base pair sequence that scientists referred to as region 1 translocated onto one of the X chromosomes. In addition, XY females were found to be missing the same region 1 of the Y chromosome. After further study scientists determined that the 35,000 base pair sequence of region 1 encoded the testis determining factor (TDF) (Page, 1984).

VIII.iv Experiment IV;

The experiment that confirmed prior speculation that a conserved gene on the short arm of the Y chromosome encoded a SRY DNA binding protein was performed by a team of scientists

from Massachusetts General Hospital and Harvard Medical School. The experiment focused on molecular analysis of human subjects with mutations in SRY resulting in pure gonadal dysgenesis. These patients were studied to identify molecular events that occur in testicular differentiation. Results of tests showed the location of the SRY gene to be on the short arm of the Y chromosome within the 35,000 base pair region. Within this gene was found to be a site specific sequence (ATTGTT), for protein-DNA recognition and gene activation. Results also showed a SRY binding protein with a high mobility group and an Isoleucine side chain for precise recognition of the specific nucleotide sequence. Structure of the protein molecule was identified by distance geometry simulated annealing and nuclear magnetic resonance. The team also investigated gene expression by injecting human SRY into a urogenital cell line immortalized in tissue culture (Haqq, 1994). Results showed a male specific pathway that involved SRY recognition of DNA and followed shortly after by MIS gene expression. Strong evidence for an intervening factor or factors also indicated the presence of SRYIF's, (see p.XVIX).

CHAPTER IX

DEVELOPMENT OF THE TESTES

This chapter discusses the results of the SRY and MIS directed pathways for sexual development of the internal gonads. The gonad is a unique embryological entity because it is bipotential. It has the potential to develop into the testes or the ovaries. Normally, organ rudiments are predestined to differentiate into a specific organ type. Evidence of the gonads is seen as the gonadal rudiment sets up in the medial aspect of the mesonephros. At the end of the fourth week it is visible as a bulge under the coelomic epithelium. The rudiment remains indifferent until week seven at which time it begins to differentiate. The gonads of both male and female embryos consist of an inner medulla and an outer cortex. For males the inner medulla differentiates as the cortex regresses to form a thin envelope around the testes.

The signal event for male development is differentiation of the indifferent gonad. Epithelial, finger-like projections, known as the primary sex cords of the indifferent gonad, grow into underlying mesenchyme to form two layers, the cortex and the medulla of the gonad. During the seventh and eighth weeks when levels of SRY protein are in abundance, the sex cords respond and develop into the seminiferous or testis cords. The seminiferous cords in the connective mesenchymal tissue (medulla) eventually develop into seminiferous tubules and are used to house the germ cells. As the tubules form in the medulla the cortex surrounding it slowly regresses.

The developing gonads consist of two main sets of cells. The Leydig cells arise from the interstitial mesenchyme and are responsible for the production of testosterone. The Sertoli cells arise from the sex cords to produce the hormone MIS (only at week seven). The gonads continue

their development and by week twelve are referred to as the testes. Since, the gonad is bipotential it has a rather indistinct amorphous shape for the first few weeks. However, by week twelve they begin to take their final shape.

The function of the gonads is to act as a storing chamber for the sex cells. The primordial sex cells migrate from the yolk sac of the embryo along the hind gut in the dorsal mesentery to the gonadal ridge and are incorporated into the sex cords. The germ cells enter the gonad around week six and later develop into sperm or ova in accordance with the developed gonad by way of induction. To view the developing gonads (G), the Wolffian ducts (H), and the epidymis (L) refer to Figure V. and Figure VI. on pages XXXVI and XXXVII. Also, refer to the **LEGEND** on page XXXIII.

CHAPTER X

DEVELOPMENT OF THE GENITAL DUCTS

Development of the ducts follows in accordance with the differentiation of the gonad.

Initially there are two sets of ducts present in the indifferent embryo. The mesonephric (Wolffian) ducts arise at week four as part of the mesonephric kidney, the temporary kidney for the embryo. The paramesonephric (Mullerian) ducts form by week six. Their function is to develop into the uterus, fallopian tubes and upper vagina unless acted upon by MIS.

If development of the embryo is to be male the mesonephric ducts will remain while the female counter parts degenerate. The hormone testosterone produced by the Leydig cells of the testes allows the mesonephric ducts to persist and directs differentiation of those ducts to become the ductus epididymis, the ductus deferens, the seminal vesicles and the ejaculatory duct. By week twelve, the epididymis forms at the junction of the testes and the mesonephric ducts. Caudal to the epididymis, the mesonephric ducts invest a smooth muscle layer that is referred to as the vas deferens. The seminal vesicles begin to bud off of the main mesonephric ducts at week sixteen (Figure VII.). The ejaculatory duct is located between seminal vesicles and the urethra.

Mullerian Inhibiting Substance (MIS) secreted in week seven by the Sertoli cells suppresses development of the paramesonephric ducts which form vestigial remnants by week twelve. The Mullerian ducts are sensitive to MIS only at week seven. Both testosterone and MIS must act in conjunction with one another at the start of week seven until differentiation and normal development are completed. Without cooperation malformations may occur in these ducts. Upon maturity, the function of these ducts is to transport the sperm from their place of

storage in the testes.

Refer to Figure V., VI. and VII., pages XXXVI thru XXXVIII. The Mullerian ducts (I) and the Uterovaginal primordium (J) are present at week nine (Figure V.). However, by week Twelve (Figure VI.) The Mullerian ducts have atrophied and only the vestigial remnant of the uterus (J) remains. The male ducts at this time have developed an epididymis (L) and a Vas Deferens (H). In (Figure VII.) budding of the seminal vesicles (H) is illustrated.

CHAPTER XI

DEVELOPMENT OF EXTERNAL GENITALIA

The development of the external genitalia is an indirect result of the SRY gene. The SRY/MIS pathway causes the gonads to develop into testes. Once formed, these testicles produce the androgen, testosterone, and when converted to 5 alpha dihydrotestosterone stimulates growth and development of the genital tubercle. In the absence of these hormones, two results occur. The tubercle develops into the clitoris and the urogenital and labioscrotal folds do not fuse (Figure's III. and IV.).

If development is to be in the male direction the genital tubercle will become the penis through a series of steps. In week four, the undifferentiated genital tubercle forms above the labioscrotal and urogenital folds that form alongside the cloaca membrane. In week seven, (Figure IV.) the organ is now referred to as the phallus. The genital tubercle elongates and differentiates as a urethral tube forms on the ventral surface.

In week nine, after further development, the phallus is referred to as the glans penis. Testosterone produced by the fetal gonads is converted to 5 alpha-dihydrotestosterone by the tissues of the genitalia to induce further masculinization. Results are evident as the urogenital folds close to form the body of the penis. The scrotum then forms as the two labioscrotal folds meet and fuse with each other at the midline. Development continues and by week sixteen the glans penis is referred to as the penis.

Malformations of the external genitalia may occur and are referred to as intersexuality. Some examples of sexual misidentity are; hermaphroditism, pseudohermaphroditism, female

androgen insensitivity (testicular feminization), hypospadias and epispadias [See Appendix A].

Refer to figures III. thru VII. on pagesXXXIV-XXXVIII.

LEGEND

This legend is for the Illustrations on the following pages. Illustrations week four through week 16 are on pages (XXXIV-XXXVIII). Each illustration is labeled with capital letters emphasizing the important features.

Week Four (Figure.III)

- A. Genital tubercle
- B. Urogenital folds
- C. Labioscrotal swellings
- D. Cloacal membrane
- E. Tail

Week Seven (Figure.IV)

- A. Phallus
- B. Urogenital folds
- C. Labioscrotal swellings
- D. Cloacal membrane
- E. Tail (receding)
- F. Anus

Week Nine (Figure.V)

- A. Glans penis
- B. Urogenital folds
- C. Labioscrotal swellings
- D. Cloacal membrane
- E. Bladder
- F. Anus
- G. Developing gonads (testes)
- H. Wolffian ducts (male)
- I. Mullerian ducts (female)
- J. Uterovaginal primordium
- K. Kidneys

Week Twelve (Figure.VI)

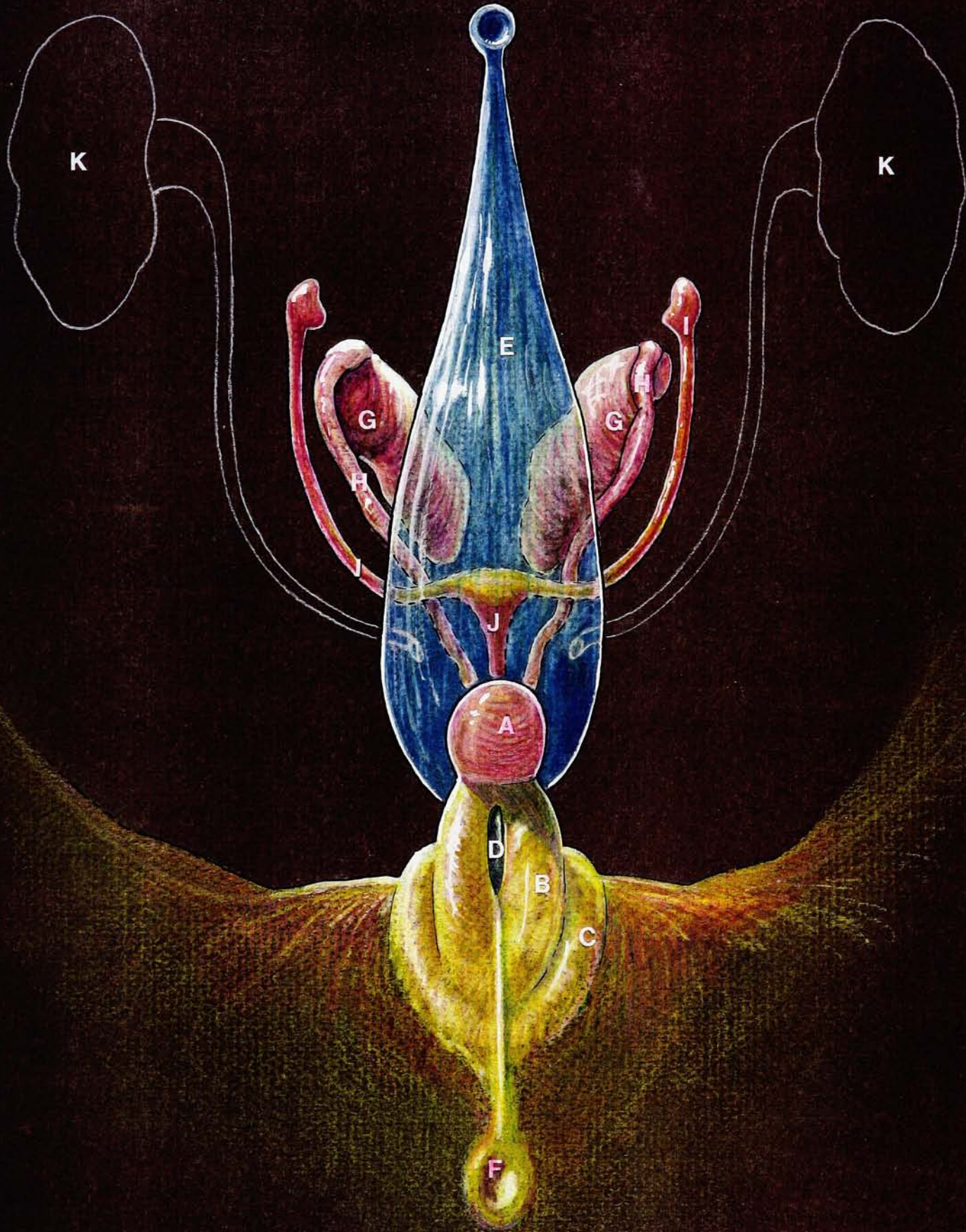
- A. Glans penis
- B. Body of penis
- C. Scrotum
- D. Scrotal raphe
- E. Bladder
- F. Anus
- G. Testicles
- H. Vas Deferens (smooth muscle of)
- I. Mullerian ducts (atrophied)
- J. Vestigial remnant of uterus
- K. Kidneys
- L. Epididymis

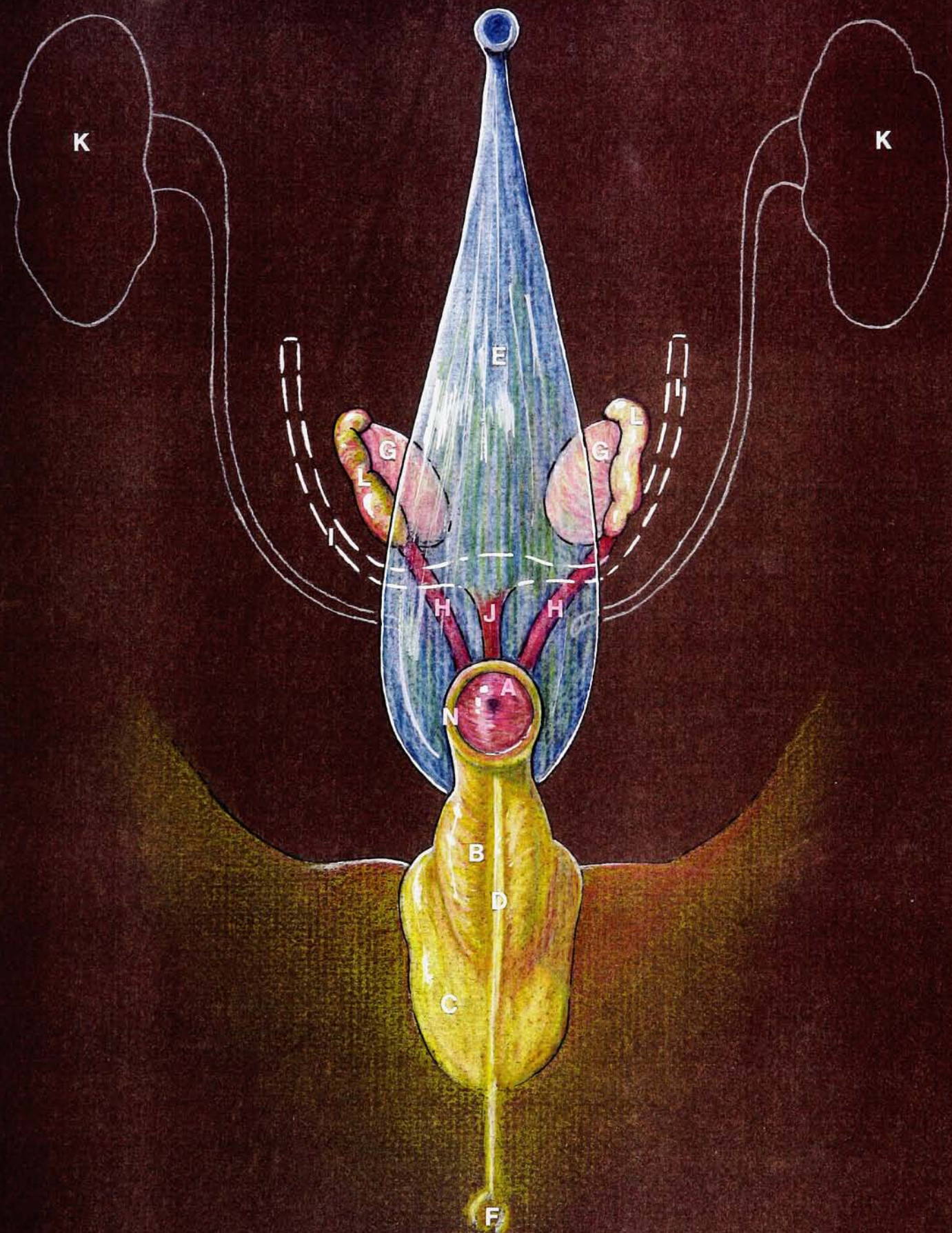
Week Sixteen (Figure.VII)

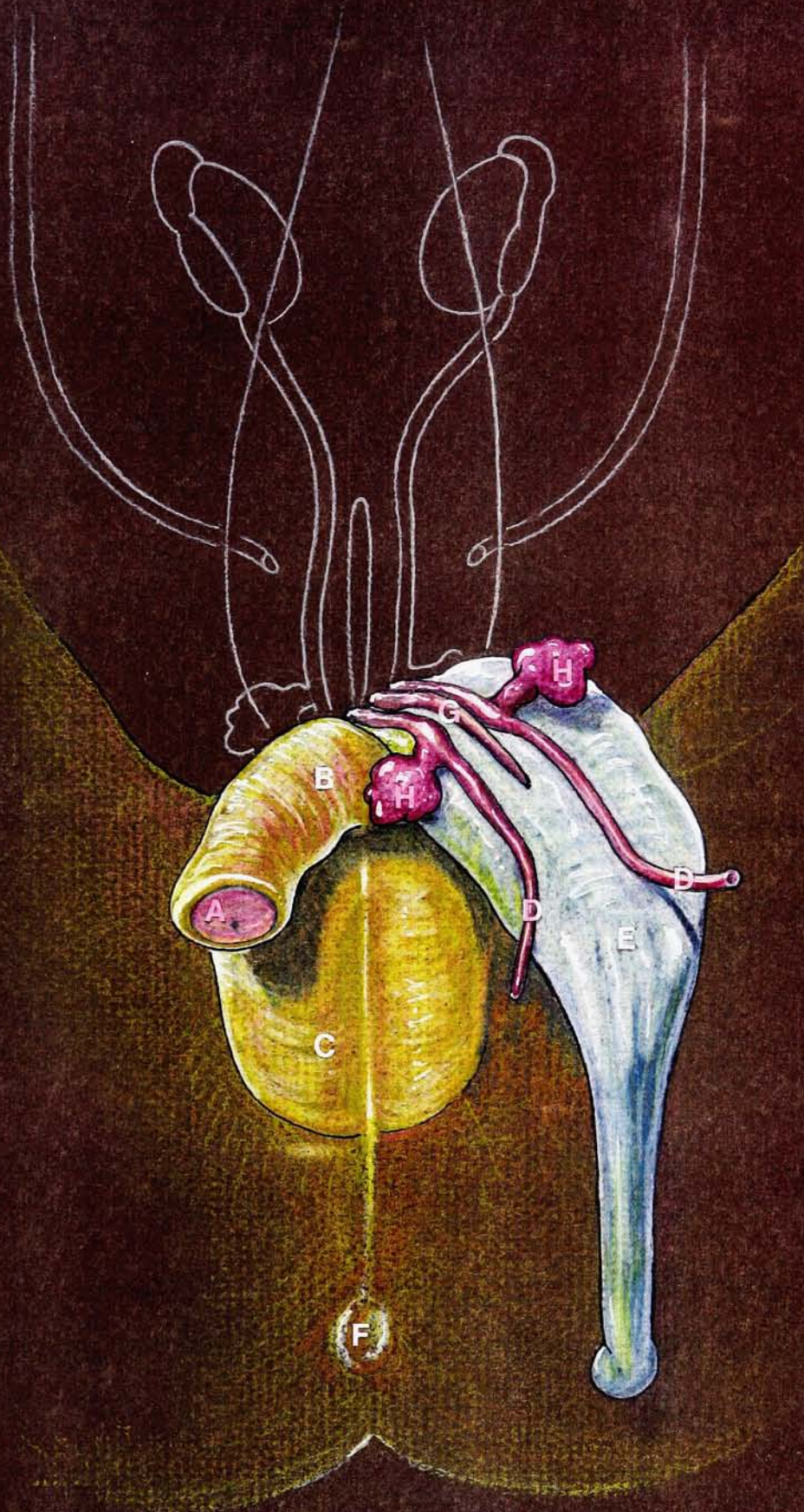
- A. Penis
- B. Body of penis
- C. Scrotum
- D. Vas Deferens
- E. Bladder
- F. Anus
- G. Vestigial remnant of uterus
- H. Seminal vesicles (buds)











PART THREE

CHAPTER XII

MUTATIONS

Sexual misidentity or malformations do occur and can be life threatening. Malformations may occur on a genetic level or stem from the environment but are most commonly caused by a combination of the two.

Even though an embryo on a genetic level may be a certain sex this does not preclude that the embryo will become fully or properly differentiated and developed. This is due to possible errors that can occur in the complex process of development. Mistakes on a molecular, cellular, (cell to cell interaction and induction) and environmental level (mutagens and carcinogens) may occur.

XII.i Susceptible Period:

Several malformations can cause adverse affects in the stages of sexual differentiation and developmental processes. There are critical periods in embryonic development where specific developing body parts of the embryo are highly susceptible to malformations. In general, major morphological abnormalities occur between weeks two and ten when the embryo is most sensitive to teratogens. For example, the external genitalia are highly sensitive to teratogens from early week seven of the embryonic period to late week nine of the fetal period. A lower sensitivity of this part of the anatomy to teratogens continues through week thirty eight.

XII.ii Genetic:

Genetic mutations occur at a rate of approximately one half of one percent in newborns. Genetic mutations are the result of chromosomal abnormalities. Variation in structure and number are the two types of chromosomal alterations that may occur in either the autosomes or the sex chromosomes.

Numerical deviations of the sex chromosomes are in most cases the product of paired chromosomes that fail to separate during cell division. Several examples of aneuploidy exist. Turner syndrome is an example of monosomy and is represented by females with an unpaired X chromosome (XO). Trisomy of the sex chromosomes occurs in both sexes at a rate of one in a thousand. Klinefelter syndrome (XXY), XXX females or XYY males are examples of trisomy.

Structural mutations of chromosomes do occur and are present in individuals due to inheritance or environmental factors. The mutations are usually represented by breaks in the chromosome, translocation of the genes or a complete or partial loss of the gene or group of genes. Translocation of region 1 from a Y chromosome to a X chromosome results in XX males. This anomaly has been the basis of experimental study for location of the SRY gene.

XII.iii Environmental:

Environmental malformations are caused by teratogens and in many cases are preventable. A teratogen is any environmental agent that can induce congenital mutations. Radiation, viruses, drugs, alcohol, food additives, pesticides and a host of chemicals all can lead to malformation of the embryo and the fetus. The embryo is most susceptible to these malformations when it is

undergoing differentiation and rapid cell division. Therefore, the organs involving sex would be most highly sensitive to teratogenic agents early in week seven to late in week nine.

REFERENCES

- Alberts, B. and Dennis, B.** 1989. *Molecular Biology of THE CELL*.
New York: Grand Publishing, Inc.
- Berta, P.** 1990. *Nature*.
348:448-450.
- Burgoyne, P.S.** 1988. *Development*.
102:443-450.
- Cate, R.L.** 1986. *Cell*.
45:685-698.
- Corliss, C.E.** 1976. *Patten's Human Embryology*.
McGraw-Hill, Inc.
- Crate, R.** 1986. *Cell*.
45:685
- Eicher, E.M.** *Annual Review of Genetics*.
20:327-360.
- Eicher, E.M.** *Recombinant DNA and Medical Genetics*.
Academic Press, New York, pp.57-71.
- Gilbert, S.** 1991. *Developmental Biology*. Third Edition
Sinauer Associates, Inc.
- Gubbay, J.** 1990. *Nature*.
346:245-250.

- Haqq, C.M. and King, C.** 1994. *Science*.
Vol.266.
- Havel, T.F.** 1991. *Journal of Molecular Biology*.
217:1
- Jones, D.N.M.** 1994. *Structure*.
2:609
- Keeton, W.T. and Gould, J.L.** 1986. *Biological Science*.
New York: W.W. Norton and Company, Inc.
- Langman, J.** 1982. *Pathology of the Female Genital Tract*.
Springer-Verlag, NewYork, pp.1-20.
- Maxwell, I.H.** 1989. *Biotechniques*.
7:276
- McLaren, A.** 1988. *Trends in Genetics*.
4:153-157.
- McLaren, A.** 1984. *Nature*.
312:552-555.
- Moore, Keith L.** 1983. *Before We Are Born*.
Philadelphia: W.B. Saunders Company.
- Moore, Keith L.** 1982. *The Developing Human*.
W.B. Saunders Company, pp.227-295.
- Page, D.C.** 1985. *Nature*.
315:224-226.

Sinclair, A.H. 1990. *Nature*.

346:240-244.

Tran, D. and Joss, N. 1977. *Nature*.

269:411-412.

Vernaud, G. 1986. *American Journal of Human Genetics*.

38:109-124.

Washburn, L.L. 1983. *Nature*.

303:338-340.

Weir, H.M. 1993. *Developmental Biology*.

12:1311

APPENDIX A

A.i List A:

This list of mutations involves the SRY protein and the DNA, MIS and SRY genes as follows:

1. MUTATION: The HMG box is highly sensitive, any mutations in this area result in human sex reversal because specific DNA binding decreases.

2. MUTATION: Site specific base changes in the consensus sequence (ATTGTT) resulted in decreased binding specificity of the SRY protein, especially when point mutations occurred at the central TT site.

3. MUTATION: Structural alteration of the isoleucine side chain via length and polarity inhibits transcription.

4. MUTATION; Mutation or translocation of the SRY gene causes complete sex reversal.

5. MUTATION: Mutation of the MIS gene in the 114 base pair (-45 to -75) protected region causes retainment of female parts in a male due to abrogation of SRY binding to the promoter.

A.ii List B:

This list comprises various malformations of sexual identity as follows:

1. True hermaphrodites: The genotype is XX, an ambiguous external genitalia and the presence of both ovarian and testicular tissue from error in the indifferent stage of development.

2. Male pseudohermaphroditism: The genotype is XY. The cause is due to low androgenic production or formation of structures after the tissue sensitivity period is over.

3. Female Pseudohermaphroditism: The genotype is XX. This is usually a result of excessive production of androgens.

4. Androgen Insensitivity: The genotype is XY, but the individual appears as a normal female due to the insensitivity of the external genitalia to androgens produced by the testicles which are present in the inguinal canals.

5. Hypospadias: Urethral opening on the ventral side of the glans tip is a result of insufficient androgen production by the fetal testes.

6. Epispadias: Urethral opening on the dorsal side of the penis is a result of improper fusion of the midline.

ILLUSTRATIONS & GRAPHICS

New and creative illustrations depicting sexual development of the human embryo was the main objective for this thesis. The illustrations and graphics were created by using either traditional rendering or computers.

Figure I. was created on the computer using software applications Adobe Photoshop and Quark Express. It was printed out at 400dpi using a MacIntosh printer. The intention was to provide a theoretical and graphic view from an electron microscope of the SRY protein-DNA binding complex.

Figure II. was created on the computer using software application MS Word. The printer used was a HP800 series. The figure acts as a schematic depicting the various pathways that are induced in response to the presence of a SRY/DNA binding complex. When present this complex allows male development to proceed indicated by the green boxes at the bottom. SRY induces MIS which prohibits further development of the female primordia, indicated by a red circle and a red box at the bottom of the schematic.

Figures III.-VII. were created with multimedia on 11" by 16" illustration board. Each illustration shows on a gross level the changes that occur in regard to the external genitals, the internal gonads, and the genital ducts. In this way the internal and external development can be viewed simultaneously. Color pencil was used to render all aspects of the illustration. A white latex paint was then applied with a brush to accentuate the highlights and black pen and ink was applied to sharpen edges and define separate shapes. These were then copied for the presentation of this written thesis using a Canon color copier.

GLOSSARY

The glossary contains the most prevalent and commonly used terms used throughout the paper. Understanding the definitions of these key terms is essential in order to fully comprehend the thesis.

amino acid The building block for proteins, most importantly it possesses an amine group (-NH₂).

autosome Any non-sex chromosome.

bipotential The ability to develop from one of two possible pathways.

blastocyst Forms in week one as 256 blastomeres surround a central cavity called a blastocoel.

chromatin DNA wound on histone cores made of protein.

chromosome Genetic units made up of nucleotide sequences.

cortex Pertaining to the exterior shell of organs.

cortical cords Epithelial finger-like projections from the cortex into the medulla. Also known as primary or sex cords.

decondensation The process of DNA unwinding in order to be read.

development Includes differentiation, morphogenesis, growth and reproduction.

differentiation The generation of cellular diversity.

DNA Deoxyribonucleic Acid

ductus deferens Ducts in the male that lead from the epididymis of the testes to the ejaculatory duct.

embryo Week four to week eight development in the uterus.

epididymis A single, complex, coiled tube attached to the testes in which the sperm are stored.

euchromatin Portion of DNA that is able to be transcribed.

fertilization Fusion of pronuclei of sperm and egg.

fetus Period of development from the ninth week until birth.

gastrula A two and later a three layered embryonic stage.

gene Portion of DNA that codes for a particular molecule.

genetic code The sequence of nucleotides that comprises genes.

genital tubercle Occurs in week four, is indifferent until it develops into a glans penis or a clitoris.

glycoprotein A protein that has had a covalent addition of a sugar molecule while in the endoplasmic reticulum.

gonadal ridge (genital ridge), It is the portion of the mesonephros that differentiates into the male gonads.

heterochromatin Transcriptionally inactive DNA.

HMG box High mobility group that belongs to a family of self-activated transcription factors.

histone Protein core that provides structural support to the eukaryotic chromosome.

holandric Of or relating to the Y chromosome.

hormone A chemical secretion for specific target tissues.

indifferent Cells or tissues prior to differentiation.

induction Ability of cells to stimulate differentiation of proximal cells or tissues to form an intended structure.

Leydig cell A cell that resides within the testes and produces the hormone testosterone.

medulla The inner layer of organs underneath the cortex.

mesonephros Temporary kidney for the embryo. It possesses the mesonephric duct which is retained as the vas deferens.

MIS Mullerian Inhibiting Substance.

morphogenesis Organization of the differentiated cells.

mutation Changes in the chemical structure of a gene.

nucleosome A complex of histones around which DNA is wrapped.

nucleus A membrane-bound organelle that contains the chromosomes.

organogenesis The generation of organs during morphogenesis.

oogenesis Meiotic division of the ovum.

ovaries Organs that store the developing oocytes.

paramesonephric ducts (Mullerian Ducts), become fallopian tubes.

phallus Stage of development after the genital tubercle.

polypeptide A sequence of amino acids that comprises a protein.

primordial Rudiment, from the earliest stages of development.

promoter Region of DNA that is bound by the transcription domain.

pronuclei Nuclei of the sperm and egg

seminal vesicle Outgrowth of the caudal end of the vas deferens.

Sertoli cell A cell that resides in the testes and produces the hormone MIS via downstream expression.

sex chromosome X or Y chromosomes that determine the gender of an individual at fertilization.

SRY Sex Region Y.

spermatogenesis The meiotic division of the spermatogonium.

testis Organs that store the developing Spermatocytes.

TDF Testicular Determining Factor.

transcription Synthesis of RNA from DNA.

translation Synthesis of a polypeptide from a mRNA template.