GENETICS IN RELATION TO UROLOGY

Thesis

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OF MASTER DEGREE IN **UROLOGY**

PRESENTED By :

NAGY SAAD FARAG

M.B., B.Ch.

SUPERVISED BY :

Prof. Dr. HATEM EL-BIALY

Prof. of Urology

FACULTY OF MEDICINE

AIN SHAMS UNIVERSITY

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A C K N O W L E D G E M E N T

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Nagy Saad.

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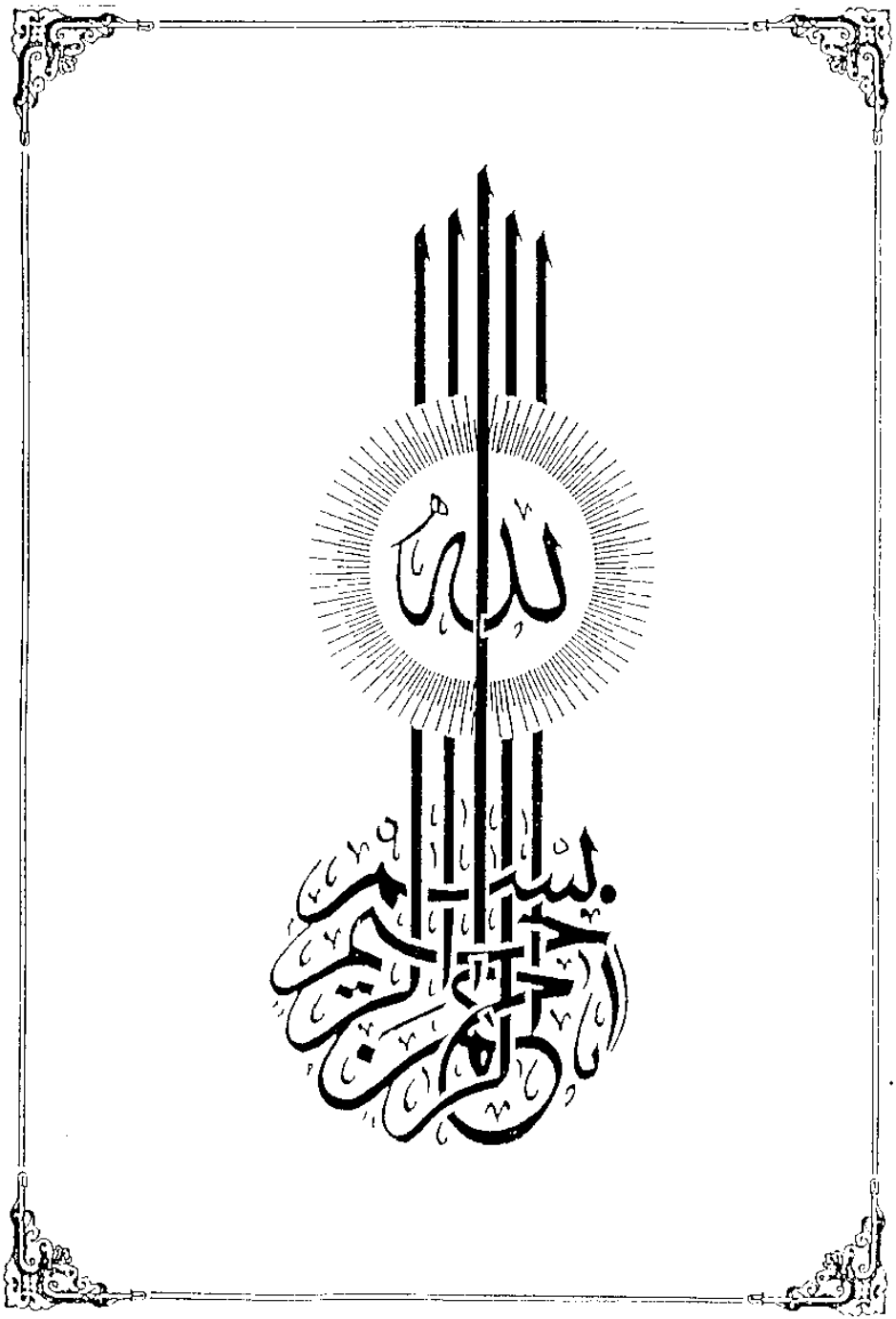

TO MY

PARENTS

C O N T E N T S

I N T R O D U C T I O N

The reduction in the number of patients seen with infectious diseases has contributed to a relative increase in the number of patients who have either genetic disorders or congenital abnormalities.

Genetic defects are present in more than 1 per cent of all newborns, although some of these are not diagnosed in the neonatal period. Congenital abnormalities of the genitourinary tract are among the more common and more important birth defects. Unfortunately many of these malformations are not diagnosed in the neonatal period because they are overlooked in the standard "inspection and palpation" physical examination.

The rapid expansion of medical genetics during the past 15 years has included a corresponding increase in knowledge regarding the genetics of urologic disorders and malformations.

The urologist will be treating patients having genetic disorders that can result from (1) chromosome abnormalities, (2) single-gene defects (Mendelian inheritance), or (3) the interaction of genes with environmental factors or other genes.

EMBRYOLOGY OF UROGENITAL SYSTEM

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Functionally, the urogenital system can be divided into two entirely different components.

1. The urinary system, which excretes waste products and excess water by means of an intricate tubular system in the kidneys.
2. The genital system, which assures continuation of the human race by the production of the germ cells.

Embryologically and anatomically, the two systems are intimately interwoven. Both develop from a common mesodermal ridge along the posterior wall of the abdominal cavity, and the excretory ducts of both systems initially enter a common cavity, the cloaca.

With further development, the overlapping of the two systems is particularly evident in the male. Here, the primitive excretory duct first functions as a urinary duct, but later is transformed into the main genital duct. Moreover, in the adult, the urinary as well as the genital organs discharge their products to the outside through a common duct, the penile urethera.

In most vertebrates, the development of the urogenital system from its inception to its completion occupies a time-span that is long in comparison to that

of other organ systems. (Muecke, 1979).

Despite tne close association of the two systems with regard to their development and adult anatomical relationship, for purposes of description the two systems will be discussed separately.

EMBRYOLOGY OF THE URINARY SYSTEM

Formation of the excretory unit.

In the third week of development, the intra - embryonic mesoderm differentiates into three distinct parts.

1. Paraxial portion which forms the somites.
2. Lateral plate which splits into the somatic and splanchnic mesoderm layers lining the intra - embryonic coelom.
3. Intermediate mesoderm which temporarily connects the paraxial tissue and the lateral plate (Fig. 1.A).

In the cervical region the intermediate mesoderm loses its contact with the somite and forms segmentally arranged cell clusters, known as the nephrotomes (Fig. 1-B). The nephrotomes grow in lateral direction and obtain a lumen. The newly estaolisned tubules, the nephric tubules, open medially into the intra-embryonic coelom, while at their lateral ends they grow in a caudal direction. During the caudal growth the tubules of

succeeding segments unite and form a longitudinal duct on each side of the embryo. While this occurs small branches of the dorsal aorta cause invaginations in the wall of the nephric tubule as well as in that of the coelomic cavity, thus forming the internal and the external glomeruli, respectively (Fig. 1-B). Together the glomeruli and the nephric tubule form the excretory unit.

In the thoracic, lumbar and sacral regions the intermediate cell mass loses its contact with the coelomic cavity. The external glomeruli, therefore, fail to develop. In addition, the segmentation disappears and the unsegmented tissue, the nephrogenic cord, forms two, three or even more excretory tubules per segment.

Three different, slightly overlapping kidney systems are formed during intra- uterine life in man. The earliest and simplest of these is the pronephros, a vestigial structure found in the cervical region. It is replaced by a more advanced system, the mesonephros, which extends from the lower cervical to the upper lumbar segments. This system in turn is replaced by the permanent kidney or metanephros, which arises in the lower lumbar and sacral regions.

1. PRONEPHROS:

In tne human embryo the pronepnros is a transitory structure. It is represented by 7 to 10 pairs of solid or tubular arranged cell groups opposite the seventh to fourteenth somites, between the fifth cervical and third thoracic region.

Each tubule opens into the dorsal part of the coelom by means of its proximal end, the nephrostome canal. The free caudal ends bend caudally, and all of them unite together and then become canalised forming a longitudinal duct termed the pronephric duct (Wolffian duct), on primary excretory duct. The duct continues its growth caudally beyond the level of the tubules until it eventually opens into the ventral part of the cloaca.

The first formed vestigial nephrotomes regress before the last ones are formed, and at the end of the fourth week all indications of the pronephric system has disappeared, except for the pronephric duct which persists as the excretory duct of succeeding mesonephros. (Langman, 1977).

II. MESONEPHROS:

During regression of the pronephric system, the first excretory tubules of mesonephros begin to appear. In human embryo mesonephric tubules are

numerous 70 - 80, in number. They start to develop during the fourth week from the intermediate mesoderm.

They appear as masses of cells opposite the fourteenth somite (sixth cervical) and proceed caudally to about the twenty- eighth somite (third lumbar).

During the fifth week these mesonephric masses appear spherical, then they become hollowed into vesicles. Each of these vesicles develops a solid cranio-caudal cord-like mass of cells, at its lateral part, which extends to unite with the mesonephric duct or wolffian duct. Again this pedunculated vesicle is canalised, then grows into an S-shaped duct and lastly becomes associated at its medial end with a glomerulus.

The medial end of the vesicle enlarges and its wall becomes thin-walled as it is invaginated by blood cappillaries to form an internal glomerulus or Bowman's capsule.

In the middle of the second month (5^{th} week), while the caudal tubules are still differentiating, the cranial tubules and glomeruli show degenerative changes and by the end of the second month the majority has disappeared (Altschule, 1930).

A few of the caudal tubules, however, persist and are later found in close contact with the testis and

the ovary. The fate of the longitudinal mesonephric duct differs with the sex of the embryo. In the male it persists as the ductus deferens or the vas deferens, but in the female it disappears almost entirely. (Langman, 1977).

III. METANEPHROS

During regression of the mesonephric system, a third urinary organ known as the metanephros or permanent kidney appears. Its excretory units develop from the metanephric blastema. (Fig. 2). The excretory units develop in the same manner as in the mesonephric system. The development of the collecting ducts, however, differs from the other kidney systems.

The development of the metanephric kidney depends upon chemical interaction of the newly formed ureteric bud with the metanephric blastema. If the ureteric bud fails to appear, there can be no kidney. (Muecke, 1979).

Furthermore, the appearance of the ureteral bud seems to depend upon proper chemical interaction of the terminal portion of the wolfian duct with the entodermal cloacal wall (Wolff, 1969).

COLLECTING SYSTEM

The development of the collecting ducts of the permanent kidney begins with the formation of the ureteric bud, an out growth of the dorsomedial wall of the mesonephric duct close to its entrance into the cloaca (Fig. 2).

The bud penetrates the metanephric blastema, which as a cap is molded over its distal end. This end subsequently dilates forming the primitive pelvis; simultaneously it splits into a cranial and caudal portion, the future major calyces (Fig. 3).

Each calyx, while penetrating deeper into metanephric tissue, forms two new buds. The newly formed buds continue to sudivide until 12 or more generations of tubules have been formed. While at the periphery more tubules are continously formed until the end of the fifth month, the tubules of the second order enlarge and absorb those of the third and fourth generations , thus forming the minor calyces of the renal pelvis. During further development the collecting tubules of the fifth and successive generations elongate considerably and converge on the minor calyx, thus forming the renal pyramid.

The total number of collecting ducts entering a minor calyx may vary from 10 to 25. Hence, the ureteric

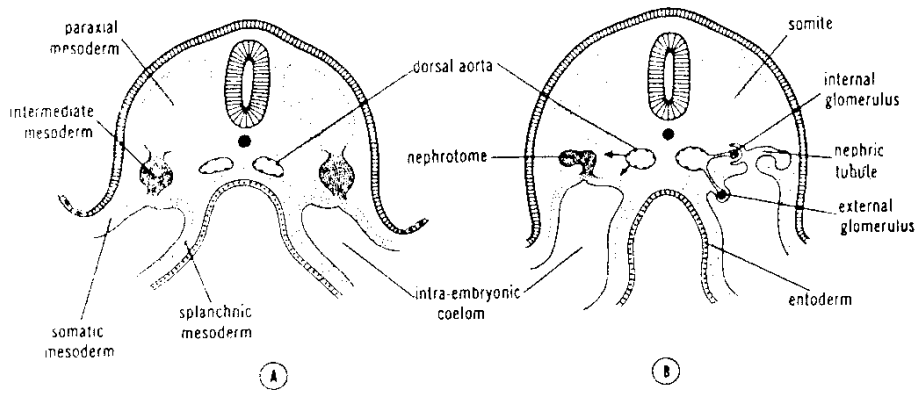

Figure 1. *Schematic transverse sections through embryos at various stages of development to show the formation of the nephric tubule. A, At 21 days; B, at 25 days. Note the formation of the external and internal glomeruli, and the open connection between the coelomic cavity and the nephric tubule (modified after Heuser).*

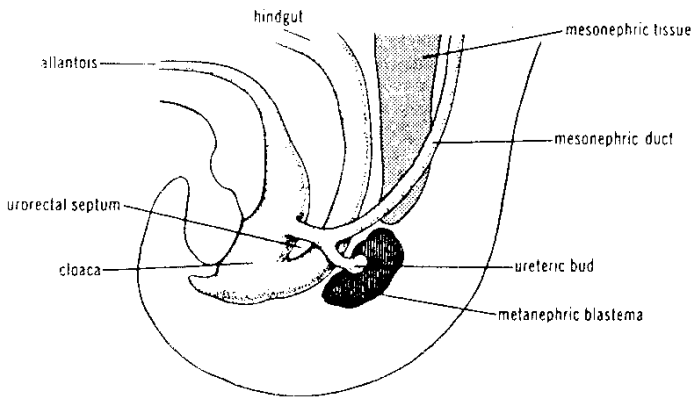

Figure 2. *Schematic drawing to show the relationship of the hindgut and cloaca at the end of the fifth week. The ureteric bud begins to penetrate the metanephric blastema.*

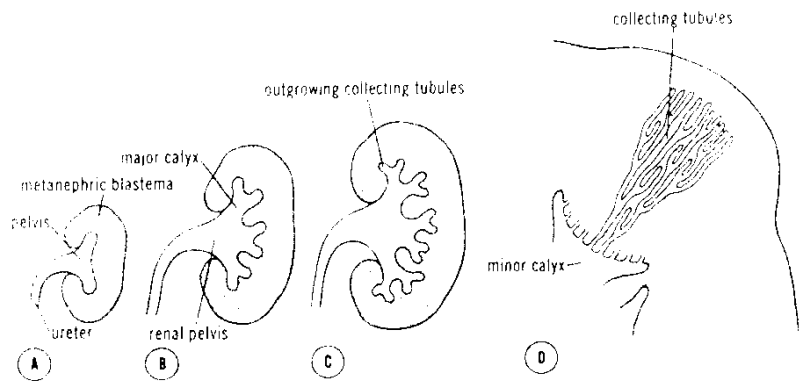

Figure 3. *Schematic drawings showing the development of the renal pelvis, calyces and collecting tubules of the metanephros. A, At 6 weeks; B, end of sixth week; C, 7 weeks; D, newborn. Note the pyramid form of the collecting tubules entering the minor calyx.*