HISTOLOGICAL STUDIES OF HUMAN FETAL URINARY TRACT

THESIS

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By

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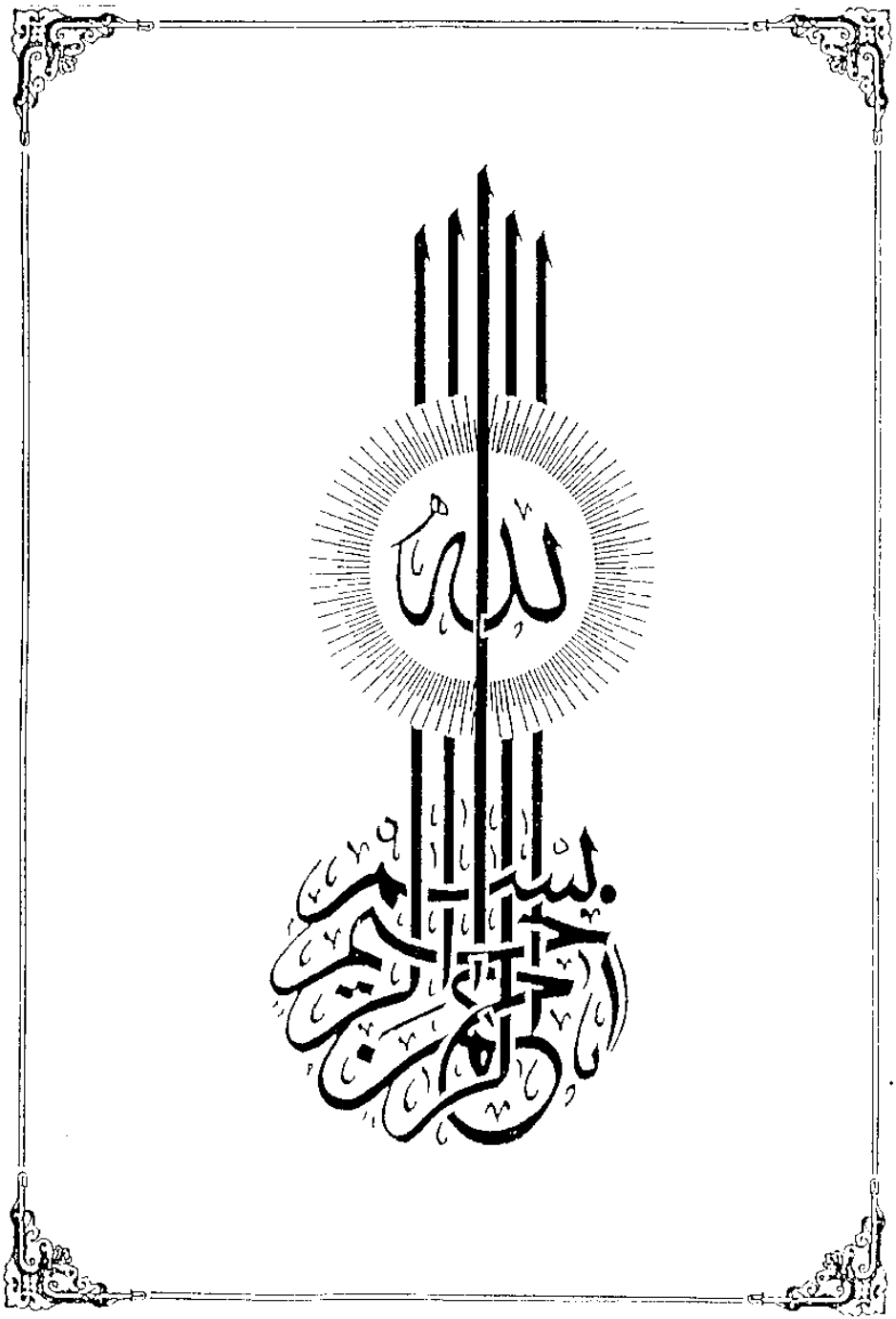

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Recent technological advances in ultrasonography has made it possible to examine fetal organs in great details. The fetal kidney can be visualized with high resolution equipment as early as 12th week of pregnancy ***(Granum, Brannum, Bracker, Silverman and Hobbins, 1980).***

Diagnostic ultrasound is now widely used as a tool to evaluate fetal anatomy ***(Sagi, Vagman, David, Van Dongen, Goudie, Butterworth and Jacobson, 1987)*** and it is accepted in many parts of the world as a routine screen in most perinatology centres. ***Sampio and Aragao (1990)*** found it possible to define kidney size at different periods of gestation and could use the kidney length to correlate between fetal growth and gestational age. This facilitated the determination of renal anomalies and gestational age.

While there are an endless number of studies dealing with the light microscopical and the ultrastructure of the normal adult urinary tract, there is a paucity of the morphological studies during fetal life ***(Newman and Antonakopouls, 1989)***. This stimulated us to carry on histological studies of the human urinary tract spanning early and late in fetal life.

REVIEW OF LITERATURE

EMBRYOLOGY OF THE KIDNEY

The kidney is composed of several units called the uriniferous tubules. The tubules arise from the mesoderm of the intermediate cell mass or nephrogenic cord. During development of vertebrates, they developed three kidneys;

(a) Pronephros : Is the first and simple kidney to appear and its degeneration is complete in 4^{th} week embryo.

(b) Mesonephros : It replaces the pronephros and it is considered as the second kidney. It appears later in the 4^{th} week at a lower level from the middle part of the nephrogenic cord. Its degeneration is complete at the 4^{th} month of gestation.

(c) Metanephros : It is the last kidney to appear. It is the permanent kidney of mammals. It has double origin being derived from :

1- Ureteric bud which gives rise to the renal pelvis, major calyces, minor calyces and the papillary ducts and the straight collecting tubules of the medulla.

2- Metanephric cap from the lower part of the nephrogenic cord which is differentiated forming the different parts of the nephros.

As new orders of collecting tubules arose progressively each mass of metanephric tissue not only increased in amount, but also subdivided in the same rhythm.

EMBRYOLOGY OF THE URETER

At the fourth week of intra-uterine life, the Wolffian duct had reached the cloaca and joins it at the level of the first sacral vertebra at right angle. At his point, the ureteric bud appeared as a dorsal bud growing from the Wolffian duct and turns into the undifferentiated mesonephric mesenchyme. By the sixth week of intra-uterine life, the tip of the ureteric bud had elongated cranio-dorsally and produced several secondary buds which would form the primitive pelvis and calyces. The lining epithelium of the pelvis, calyces and the ureter was mesodermal in origin, and they became invested with coats of smooth muscle and connective tissue produced by specialization of the surrounding mesenchyme ***(Moor, 1982)***.

EMBRYOLOGY OF THE URINARY BLADDER

The urinary bladder was derived from the cranial part of the primitive urogenital sinus, which is continuous with allantois. The lining epithelium develop from the endoderm of the vesico-urethral canal. The lamina propria, muscularis and serosa developed from the adjacent splanchnic mesoderm ***(Moor, 1982).***

As the bladder was taking shape, the allantois above it involuted to form a thick tube, the urachus. After birth, the urachus became a fibrous cord, the median umbilical ligament, extending from the apex of the bladder to the umbilicus.

REVIEW OF THE KIDNEY

Gruenwald and Popper (1940), examined the human fetal metanephros histologically. They found that the most advanced nephrons, which were juxtamedullary in position, had a continuous visceral glomerular epithelium which appeared as an inextendable sac reducing blood flow and causing adhesion between adjacent glomerular loops and reducing the filtration surface. They believed that rupture of this continuous epithelium occurred at birth allowing function to commence, but before birth, there was a mechanical obstruction to metanephric glomerular filtration.

Potter and Thierstein (1943), studied the prenatal development of the human fetal kidney. They claimed that further differentiation of subcapsular glomeruli were continued until about 35 weeks of gestation, and the development of new glomeruli was ceased at about 35^{th} weeks from the last menstrual period when the fetus has reached a weight of 2100 to 2500 gram and 46-49 cm crown-rump length. So, they reported that, production of new glomeruli was dependent primarily upon body weight and secondarily upon gestational age.

Baxter (1950), examined the metanephros in a series of human fetuses from 80 mm crown-rump length until the full-term, and in several babies up to 12 days old, for the detection of cytoplasmic alkaline phosphatase activity. He observed the enzyme in the cells of the proximal tubules only when the luminal surface of the tubules had became modified to

a brush border. He also examined two additional embryos, 20 and 26 mm crown-rump length, and in each cytoplasmic alkaline phosphatase was present in the proximal secretory segment of the intact mesonephros.

Robbins (1950), showed that the periodic acid-Schiff technique demonstrated the presence of polysaccharide in the mammalian kidney. It was present in the basement membranes of the glomeruli and tubules. The cytoplasm of the proximal tubules was stained slightly, but with marked staining of their brush borders.

Allen (1951), studied serial sections from the various developmental stages of fetal kidney. He found that the metanephric diverticulum did not abruptly cease its branching with formation of collecting and distal tubules, but ramified into the nephrogenic tissue. He added that the multipotent cells of this nephrogenic tissue were progressively added as epithelium corresponding to the cells of the advancing tubular buds until the entire length of the tubule was formed. He decided that, in the development of the nephron, proximal and distal portions of the nephron did not develop as separate units with final union of their lumina, but only a single advancing lumen appeared to exist on the developing nephron.

Ross, Ely, and Archer (1951), studied the alkaline phosphatase enzyme activity in the fetal and newborn rat kidneys. They observed that the alkaline phosphatase enzyme was present at very high concentrations in the proximal tubules. They reported that the enzyme level was low in the

fetal stage and increased rapidly just before and a few days after birth. They suggested that the enzyme activity was correlated with kidney function and not with rate of kidney growth. They thought that the change of this enzyme in the developing rat kidney might be correlated with the quantitative change in other enzymes of known function.

Davies (1952), found P.A.S. positive granules in the fetal kidney tubules. He suggested that these granules represented protein which had crossed the glomerular vessels, and was reabsorbed by the proximal tubules as evident by their large number in the fetal kidney and the presence of protein in the fetal urine. He also detected protein precipitate in the fetal renal pelvis and the ureter, and were also P.A.S. positive. Their presence indicated the extreme permeability of the immature glomeruli to protein and the failure of the tubules to reabsorb it completely. He also found in sections which were previously treated with saliva before P.A.S. staining, P.A.S. positive granules in the collecting tubules, and ureters of fetuses and newborn.

Hall and Roth (1954), studied the ultrastructure of the developing glomerulus and introduced the terms lamina fenestrata or attenuata for the endothelial lining of the glomerular capillaries, the lamina dense for the extracellular basement membrane, and the podocytes for the visceral epithelium. He described the podocytes as having large processes, from which small foot processes or pedicles extended to be attached to the outer

surface of the lamina densa. These terms which he had applied, became accepted.

Wachstein (1955), found, with histochemical studies of the kidney, that non-specific alkaline phosphatase reaction was regularly present in fresh frozen sections of all species in the proximal portion of the proximal convoluted tubules. The reaction was concentrated in the brush borders. He also observed varying degrees of this enzymatic reaction in the glomerular capillaries.

Lewis (1956), showed that there was a striking similarity between the glomerular and the spleen development. In both organs, a thick proliferative mesodermal epithelial surface gave rise to a dense mass of cellular angiogenic tissue. In this tissue, spaces appeared giving rise to the various components of the vascular system in the spleen, and to the capillaries of the glomerulus in the kidney.

Leeson and Baxter (1957), studied the mesonephros and metanephros of the rabbit histochemically. They observed positive both alkaline phosphatase and P.A.S. reactions in the brush borders of the proximal tubules, in both mesonephros and metanephros.

Kurtz (1958), studied the development of the human renal glomerulus. He found that the renal corpuscle developed as a mass of epithelial cells in continuity with the convoluted tubule and it was surrounded by a sparse

incomplete layer of basement membrane. He stated that the capsular space developed by cleft formation when the primitive glomerular tuft appeared leaving a single layer of Bowman's capsule on one side. The visceral epithelial cells rapidly differentiated in appearance from the parietal cells. He decided that the red blood cells were developed in situ in the glomerulus. He also concluded that, at birth, the kidney was not fully differentiated.

Lewis (1958), studied the development of the blood vessels of the metanephros after injection of latex-like material into the renal circulation and subsequent microdissection. He demonstrated that capillary spaces were formed within glomerular tuft prior to connection of these spaces with branches of the renal artery. He also concluded that the capillaries were formed in situ from components of the renal vesicle rather than by ingrowth of branches of the renal artery.

Bloom, Hartmann and Vernier (1959), measured the width of normal renal glomerular basement membrane. By comparison of electron micrographs of biopsy specimens obtained during life with autopsy specimen from both human and experimental animals, they found that little change in basement membrane width occurred postmortem. They recorded that the mean width of the normal basement membrane in infants and young children (1100 A°) was much less than the mean value in older children and adults (2700 A°). They also found that the basement membrane was thickened gradually in early childhood, but was changed little with increasing age in the adult.

Harkin (1959), utilized the electron microscope to study the development of the renal glomerular basement membrane of the newborn mouse. He demonstrated glomeruli at various stages of maturation from a clump of undifferentiated cells to a fully mature glomerulus. He observed a distinct basement membrane.

Leeson (1959), studied the mesonephros and metanephros of the rabbit histologically. He showed that there was a similarity between the mesonephros and metanephros both in morphology as well as in function. The mesonephros differed from the metanephros in the absence of juxta-glomerular apparatus, the absence of tunica media in the afferent and efferent arterioles, and the absence of loops of Henle.

Macdonald and Emery (1959), described histologically three phases in the maturation of glomeruli. First a period up to about 36th week of gestation, during which new glomeruli were formed. Second, a period extending until the 3rd to 5th year of age, where the glomeruli, although mainly immature, were present in numbers similar to those in adults. Finally, a period extending from the 3rd to 12th years of age, during which full maturation of glomeruli occurred. They also classified the maturation of glomeruli into six stages starting from the most primitive S-shaped proglomerulus, and ending with the full mature glomerulus. They concluded that the most primitive glomeruli were not found after the 44th week of gestation, while some immature forms might persist until 4-6 months of age after birth.