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DEVELOPMENTAL STUDIES ON THE KIDNEYS OF RABBITS

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SUMMARY

The development of the rabbit's kidney was investigated during the pre and postnatal periods. The bilateral mesonephroi appeared in 11 days old fetuses as two masses bulging into the coelomic cavity; one on either side of the developing aorta. Each mesonephric blastema was composed of primitive tubules, corpuscle and duct; supported by vascularized mesenchyme and covered by the coelomic mesothelium. By the 14th day, brush border appeared in some mesonephric tubules. Once the metanephroi appeared; in 15 days old fetuses, degenerative changes began to occur in the mesonephroi. The latter were completely disappeared in fetuses of 22 days of age.

In 15 days old fetuses, the uretric bud appeared in the center of the metanephric blastema. As the fetal age reached 17 days, this bud began to branch. At 20 days, metanephric corpuscles started to develop. Near the end of fetal life, marked maturation of some corpuscles was evident. By the 25th day, the proximal and distal tubules as well as the macula densa began to appear. In 27 days old, the renal pelvis, collecting tubules and the medullary rays became visible. Moreover, thick and thin segments of nephron loop appeared in the medulla.

In newly born rabbits, the production of new nephrons in the subcapsular zone persisted for 2 weeks. From 4 weeks and onward, the collecting tubules became lined by dark and light cells.

INTRODUCTION

Numerous studies had been made on the prenatal development of kidneys in various mammalian species including man (Robert et al., 1962; Al-Awdan and Kandil, 1979; Canfield, 1980; Ammar et al., 1982; Bareedy et al., 1982; Moustafa and Enany, 1985; Moustafa et al., 1986; Dougbag, 1988; Emara, 1989 and Soliman, 1991). Moreover, the postnatal age changes of the same organ was described by many authors (MacDonald and

Emery, 1959; Leeson, 1961; Osathanondh and Potter, 1963; Nash and Edelman; 1973; Speller and Moffat, 1977; Friis, 1980; Zamzam et al., 1989 and Soliman, 1991).

The available literature on the kidney of rabbit fetuses were limited (Leeson, 1957 & 1960; Leeson and Baxter, 1957 and Tiedmann, 1979). However, the postnatal age changes of the kidney of the balady rabbit were only described by Moustafa et al., (1985). For these reasons, the present study was designed to clarify the pre and postnatal development of the kidneys of the Newzealand white rabbits.

MATERIAL AND METHODS

22 Newzealand white rabbit fetuses ranged from 11-30 days of age, in addition to 16 kidney specimens of male and female rabbits, aged 1-120 days, were used in this study. The caudal halves of the fetuses of early ages up to 16 days were taken intact. These samples were fixed in 10% neutral formalin, Susa and Helley's fluids, processed and embedded in paraffin. Cross and/or sagittal stepserial sections 4-6 um thick were cut and stained with Haematoxylin and Eosin (H & E), Crossmon's trichrome stain, Gomori's reticulin method, Weigert's elastic tissue stain, periodic acid Schiff (PAS), alcian blue and Best's carmine (Crossmon, 1937 and Drury and Wallington, 1980).

RESULTS

Mesonephros :

The bilateral mesonephroi appeared in 11 days old rabbit fetuses as two masses bulging into the coelomic cavity; one on each side of the developing aorta (Fig. 1). The gonadal primoridia appeared as a small thickened ridges over the medial side of each mesonephros. On the other side, the mesonephric duct was found to occypy a dorsolateral position within each mesonephros. The main bulk of the mesonephric blastema was made up of primitive tubules separated from each other by mesenchymal cells and limited externally by the coelomic mesothelium (Fig. 2). Such primitive covering epithelium was formed of one layer of cuboidal and/or flattened cells lacking basal lamina. In the section levels, the mesonephric tubules appeared ovoid, rounded, elongated or irregular in shape and sometimes showed inward invaginations. Some of these tubules were lined by low cuboidal cells with ill-distinct borders and spherical or ovoid central nuclei. Other tubules were lined by high cuboidal or truncated pyramidal cells with spherical or ovoid basal nuclei. Moreover, some tubules were invaded by the peritubular mesenchymal tissue that permeated by developing blood capillaries; forming the primordia of the mesonephric corpuscles (Fig. 2).

The right and left mesonephroi of rabbit fetuses aged 13 days were greatly enlarged and bulged more in the coelom due to the increase in the

number and size of their tubules. Many of these tubules became invaginated by a tuft of glomerular capillaries that contained immature nucleated red blood corpuscles. Thus, the mesonephric tubule was transformed into a double-walled epithelial capsule. The epithelial surface facing the blood capillaries was reflected over the glomerulus forming the visceral layer while the other surface formed the parietal layer. Some of the epithelial lining cells of the latter layer began to take the squamous form (Fig. 3). The narrow space between the parietal and visceral layers represented the capsular space of the developing mesonephric corpuscle.

As development proceeded; 14 days old fetuses, an apical PAS positive brush border was observed in some of the mesonephric tubules. PAS reactivities were also seen in the glomeruli and the epithelial cells of the mesonephric duct (Fig. 4). On the other hand, all the mesonephric structural components were alcian blue and Best's carmine negative. However, the coelomic epithelium became rested on a continuous reticular basal lamina. Reticular fibers were alo demonstrated in the basement membrane around the mesonephric tubules (Fig. 5).

As the rabbit fetuses reached 15 days of age, the metanephric primordia appeared as an ovoid body at the ventral concave surface of each mesonephros (Fig. 6). By the same time, features of degeneration began to occur in the mesonephroi. Some tubules appeared dilated with vacuolated cytoplasm and protruded or detached nuclei in the lumen. The lumina of other tubules became partially or completely filled with cytoplasmic sheds and luminal debris (Fig. 7).

By the 17th day, the mesonephros began to reduce in size, so the mesonephric duct became enclosed within a mesenchymal fold and limited externally by the coelomic epithelium. Regression affected also the mesonephric corpuscles. On the other hand, the metanophros as well as the gonads were markedly enlarged in size (Fig. 8). From 18 days and onward, degeneration continued; leading to partial (Fig. 9) then complete distruction of all mesonephric tubules and corpuscles (Fig. 10). This was accompanied by a gradual reduction in size of the mesonephroi till they were completely disappeared in fetuses of 22 days of age.

Metanephros (permanent kidney) :

In 15 days old fetuses, each metanephric blastema appeared to be formed of densely packed mesenchymal cells in its peripheral zone. Some of these cells were aggregated in the form of ovoid solid masses, vesicles and elongated or s-shaped tubules. In the meantime the uretric bud appeared in the more central part of the blastema. It was surrounded by loosely arranged mesenchymal cells (Fig. 6). As the fetal age reached 17 days, this bud began to branch. The uretric bud branches extended between the vesicles and tubules to terminate directly under the covering epithelium of the metanephros (Fig. 8).

At 20 days of age, the aggregation of the metanephrogenic tissue into vesicles and tubules continued in the peripheral zone (Fig. 11). Meanwhile, the intertubular mesenchyme began to differentiate into fibroblasts and erythrocytes. However some of the primordial tubules became invaginated by the developing blood cells and some metanephric cells to start formation of the metanephric corpusles (Fig. 11).

In 23 days old fetuses, the uretric bud branches continued in a dichotomous manner toward the peripheral zone. The dilated ampullar ends of these branches were seen attached to some of the tubules (Fig. 12). Toward the center, there was a marked increase in the vascularity of the previously formed corpuscles together with a relative differentiation in the parietal and visceral layers of their glomerular capsule (Fig. 12). Moreover, some of the mesenchymal cells began to differentiate into mesangial cells.

The covering epithelium of the growing metanephros at 25 days of age began to take the squamous form (Figs 13 & 14). The outer zone beneath this epithelium was quickly occupied by numerous vesicles and tubules. Many of these tubules continued to expand and gave a series of secondary bendings. Besides, different stages of transformation of these tubules into corpuscles were also observed. All these structures had large intensely stained nuclei that gave this zone a marked basophilic appearance. In the same stage of growth, the characteristic features of the proximal and distal tubules began to appear. The prospective proximal tubules showed a narrow lumen. They were lined with high cuboidal or truncated pyramidal cells possessed acidophilic cytoplasm and spherical basal nuclei. The forerunner of the distal tubules were lined by low cuboidal cells with less intensely stained cytoplasm. Their spherical nuclei occupied most of the cells (Figs 13 & 14). Adjacent to the vascular pole of the growing renal corpuscles, the first signs of the macula densa formation was evidenced (Fig. 14). The cells lining the side of the distal tubule facing the glomerulus showed more crowded nuclei than the other side.

At the 26th day, the outer basophilic zone was covered by a primitive capsule, where the subepithelial mesenchme was differentiated into spindle-shaped fibroblasts (Fig. 15). The latter cells were supported by fine reticular network and collagenous fibers.

In fetuses of 27 days old, the caudal end of the uretric bud was dilated to form the primordia of the renal pelvis (Fig. 16). The primitive renal sinus was filled with fibroblast cells and contained developing blood vessels. Numerous outgrowths arose from this pelvic dilatation. These outgrowths represented the straight collecting tubules. The latter extended toward the presumptive site of the renal cortex; inbetween the growing renal corpuscles, to form the medullary rays (Figs

16 & 17). The primitive renal pelvis and collecting tubules were lined by tall columnar cells possessed light acidophilic or unstained cytoplasm and clear margins. Their spherical nuclei situated near the luminal border of the cells. Some of these cells appeared in proper mitotic activity (Fig. 18). In addition to the collecting tubules, thick and thin segments of nephron loop began to appear in the primitive medulla. These structures were supported by fibroblast cells permeated by growing blood capillaries. The thick segments were lined with cuboidal cells; had eosinophilic cytoplasm, ill-distinct cell borders and spherical nuclei whereas the thin segments were lined by a single layer of two or more flattened cells possessed ovoid nuclei bulged into the lumen (Fig. 18).

From 28 days till the end of fetal life, additional generations of corpuscles and tubules were formed in the subcapsular nephrogenic zone. Although most of these tubules and corpuscles appeared immature, marked maturation of some other corpuscles was evident. Their capsules acquired a clear parietal and visceral layers. Between these two layers the capsular space became very obvious. Within the glomeruli, the erythrocytes attained their mature non-nucleated form. At the urinary pole, the flattened cells of the parietal layer were abruptly changed into the high cuboidal cells lining the neck portion of the proximal tubules (Fig. 19).

In newly born rabbits, figures of newly formed corpuscles and tubules continued to appear in the outer nephrogenic zone (Fig. 20). With the increase of the rabbit's age, this nephrogenesis was gradually reduced. At 7 days old, the previously formed corpuscles and tubules appeared more differentiated. They became closely invested by a well-developed, strong PAS-positive basement membrane (Fig. 21). Meanwhile, the proximal convoluted tubules acquired a clear brush borders. PAS reactivity appeared also in the glomerular tuft of capillaries as well as in the intercapillary mesangial tissue.

By 2 weeks old, the production of new nephrons was completely ceased and the differentiation of the already present nephrons persisted. The cortex became interrupted by a clear medullary rays that demarcated the cortical substance into clear cortical labyrinth. These rays showed an increased amount of reticular fibers inbetween their tubular contents (Fig. 22). Reticular fibers became also condensed and more thicker around the renal corpuscles while the interstitial tissue became scanty.

At 4 weeks old and onward, complete absence of the subcapsular basophilic zone was denoted. The capsule showed a progressive increase in its fibrous content especially the collagenic variety. It was covered by adipose tissue (Fig. 23). The supporting stroma was condensed in the renal sinus, under the transitional epithelium lining the renal pelvis and around the dilated blood vessels. It was mainly formed of reticular and collagenous fibers

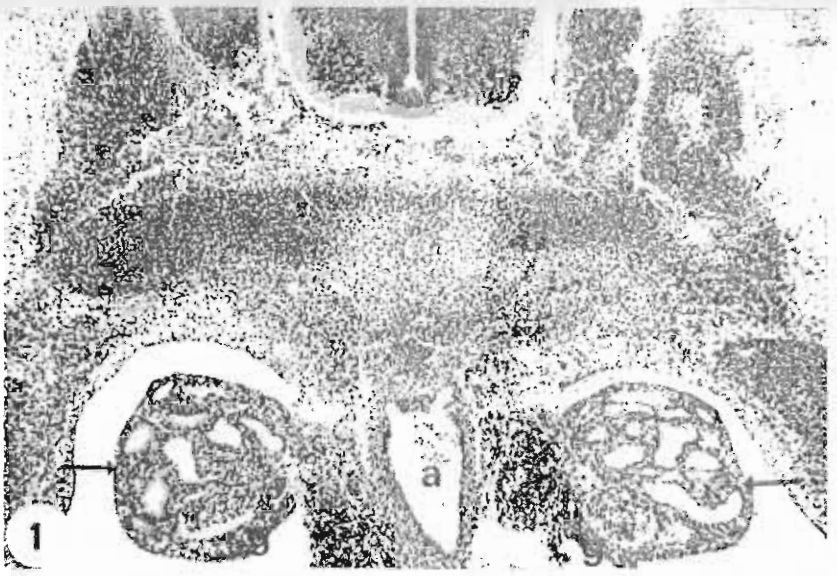

Fig. (1): A section through the caudal half of 11 days old rabbit fetus showing the two mesonephric masses (arrows) on either side of the primitive aorta (a). Notice the gonadal primordia (g). H & E stain, X 65.

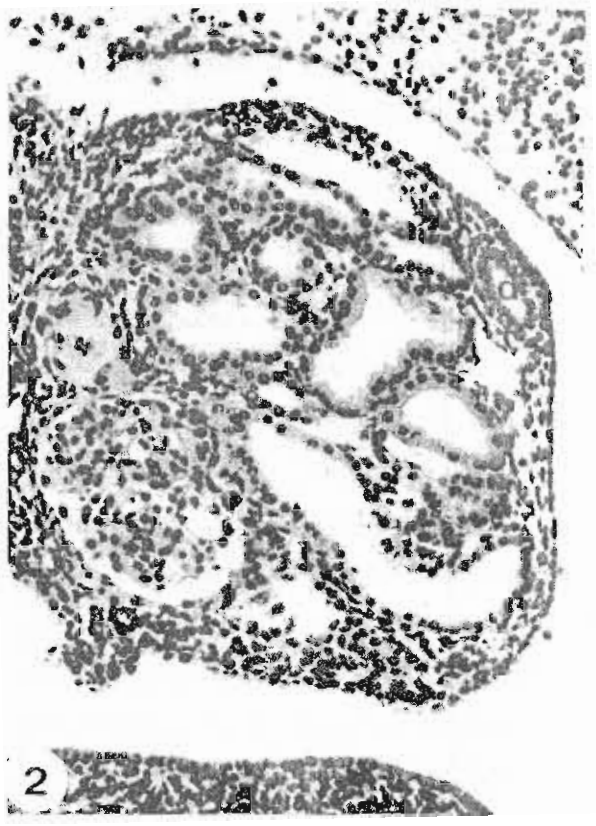

Fig. (2): A high magnification of Fig. (1) to show the coelomic mesothelium, the lining epithelium of the mesonephric tubules and the first appearance of the mesonephric corpuscles. Notice the mesonephric duct (d). H & E stain, X 200.

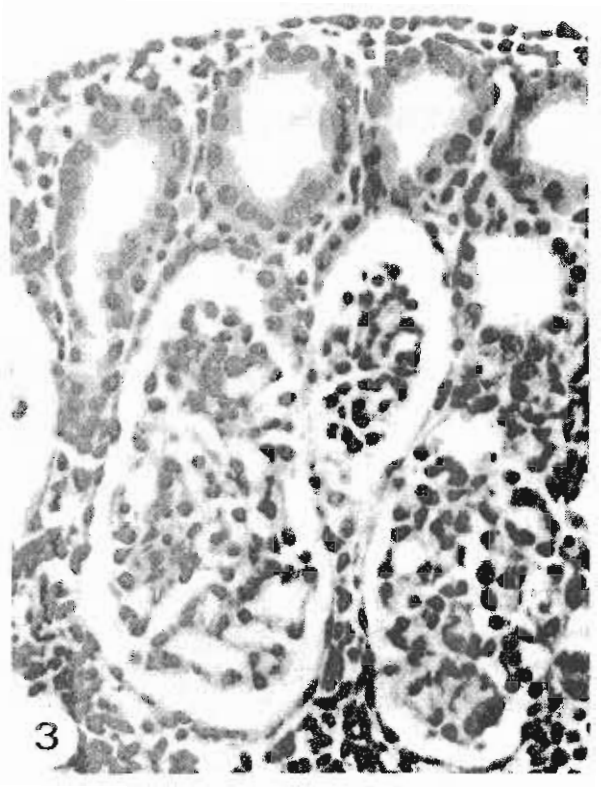

Fig. (3): A section of the mesonephros of 13 days old rabbit fetus showing more differentiated mesonephric corpuscles and tubules. Notice that the epithelial lining the parietal layer of the glomerular capsule began to take the squamous shape. H & E stain, X 320.

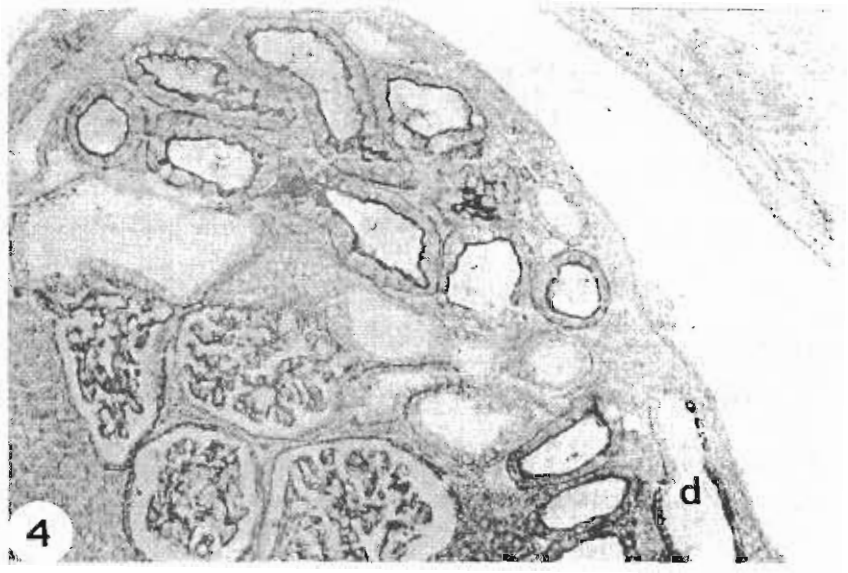

Fig. (4): Mesonephros of 14 days old rabbit fetus showing PAS positive brush border in some mesonephric tubules. Notice the PAS reactivity in the glomeruli and the mesonephric duct (d). PAS technique, X 130.

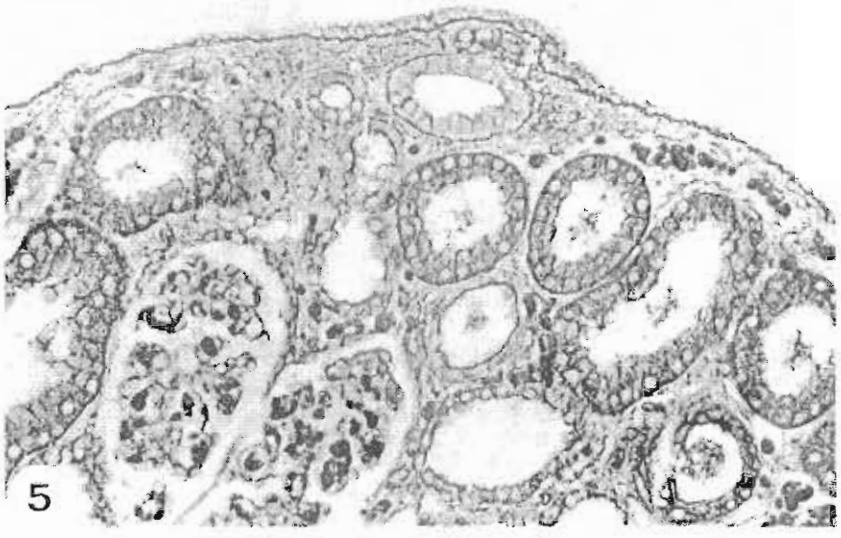

Fig. (5): Mesonephros of 14 days old rabbit fetus to show reticular fibers in the basement membrane of the coelomic epithelium and around the mesonephric tubules. Gomori's reticulin method, X 200.

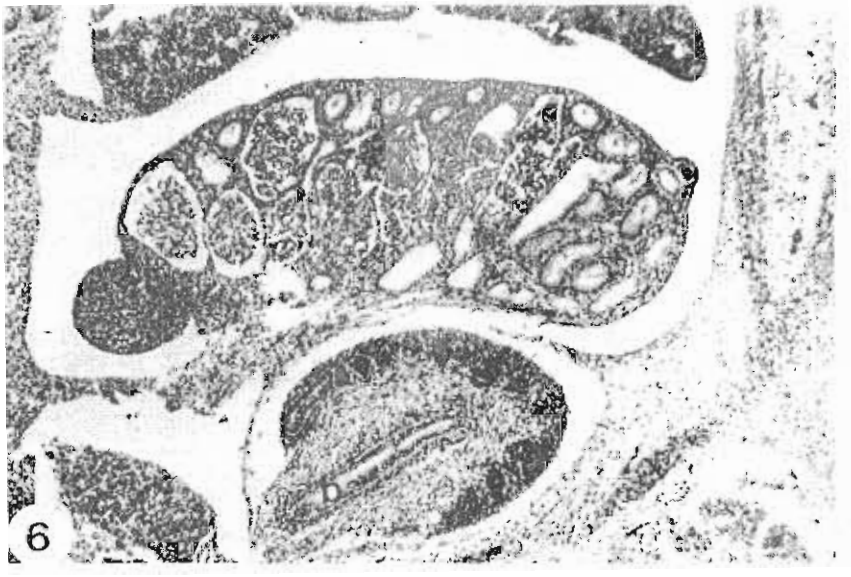

Fig. (6): A section through the caudal half of 15 days old rabbit fetus showing the primordia of the metanephros. Notice the uretric bud (b) in the center and the vesicles and tubules in the periphery. H & E stain, X 50.

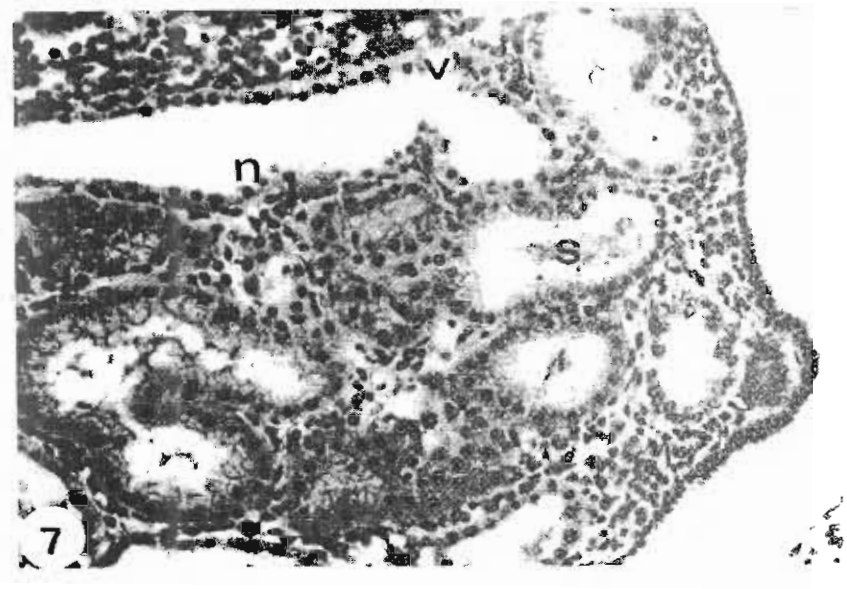

Fig. (7): Higher magnification of the mesonephros at 15 days old fetus showing degenerative changes in the mesonephric tubules. Notice the vacuolated cytoplasm (v), detached nuclie (n) and cytoplasmic sheds (s). H & E stain. X 200.

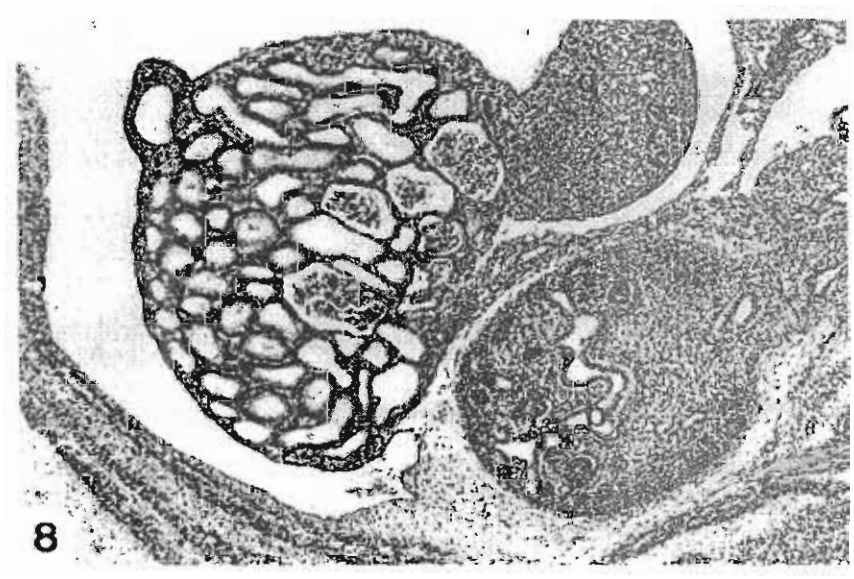

Fig. (8): A section through 17 days old rabbit fetus to show the enlargement of size of the metanephros and gonads (g). Notice the branching process of the ureteric bud (b) in the developing metanephros. H & E stain. X 50.

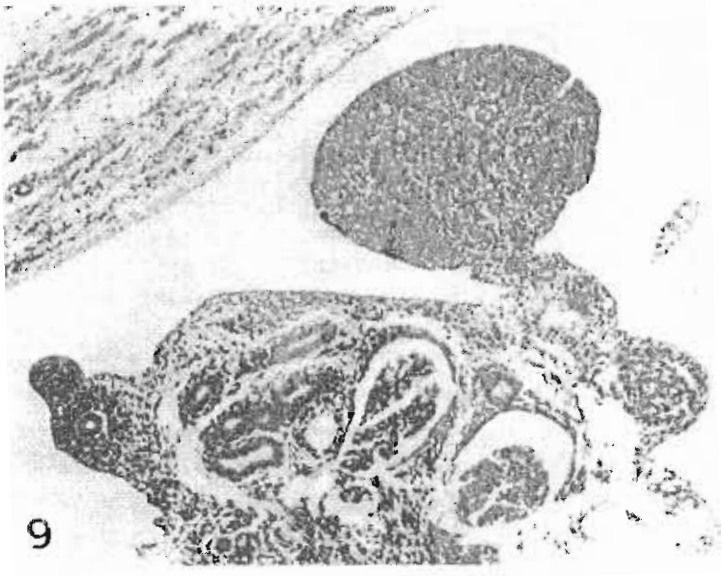

Fig. (9): A section through 18 days old rabbit fetus showing partial distruction of mesonephric corpuscles and tubules. Notice the reduction of size of the mesonephros and the enlarged gonad (g). H & E stain, X 50.

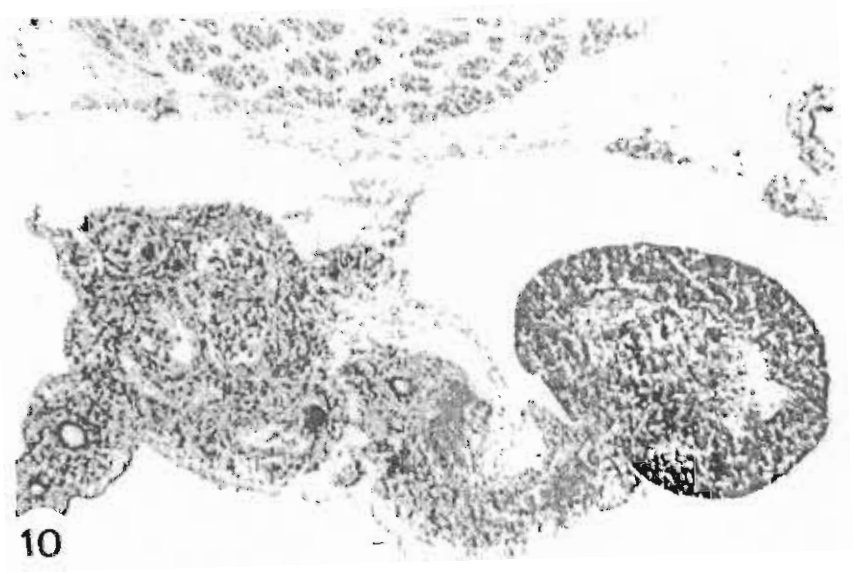

Fig. (10): A section through 20 days old rabbit fetus showing complete distruction of the mesonephric corpuscles and tubules. Notice the reduction of size of the mesonephros. H & E stain, X 50.

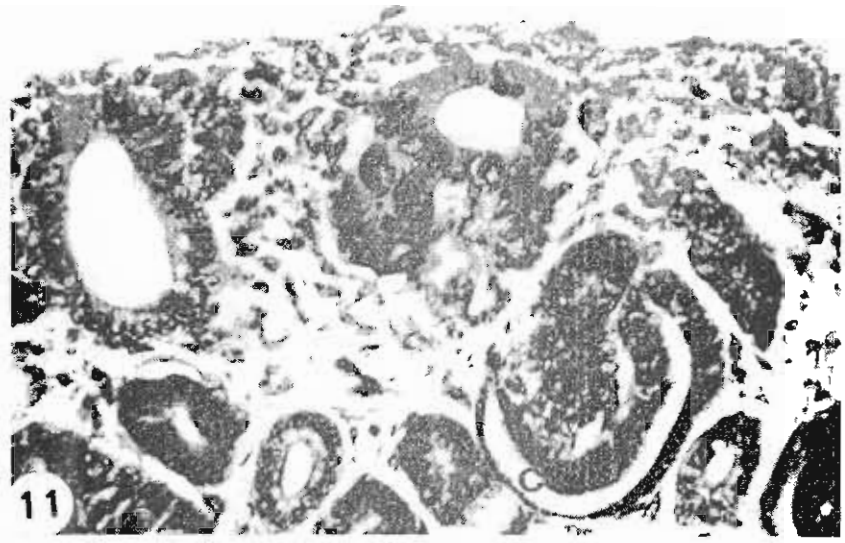

Fig. (11): Peripheral part of metanephros at 20 days old fetus showing the primordia of the metanephric corpuscles (c). H & E stain, X 320.

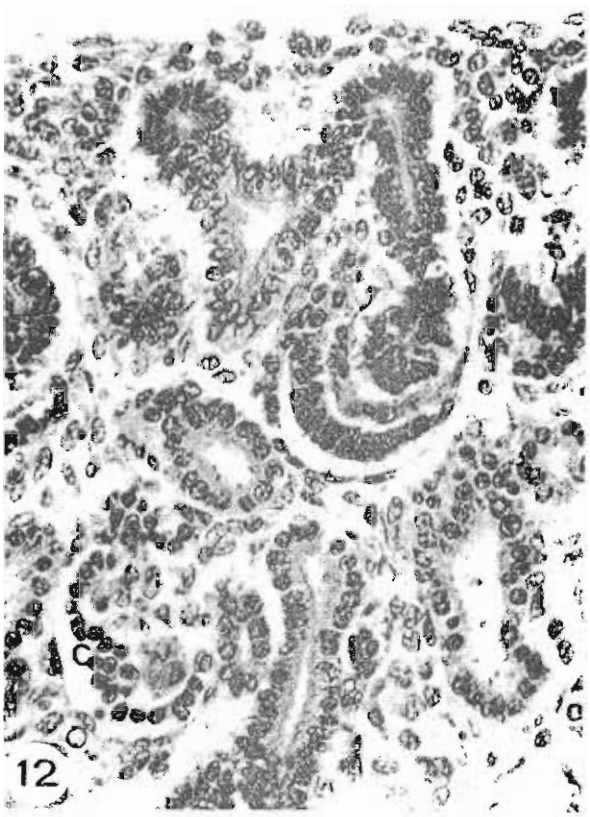

Fig. (12): Metanephros of 23 days old rabbit fetus to show the uretric bud branches in the peripheral part. Notice that the development of the corpuscles (c) was more advanced near the central zone. H & E stain, X 320.

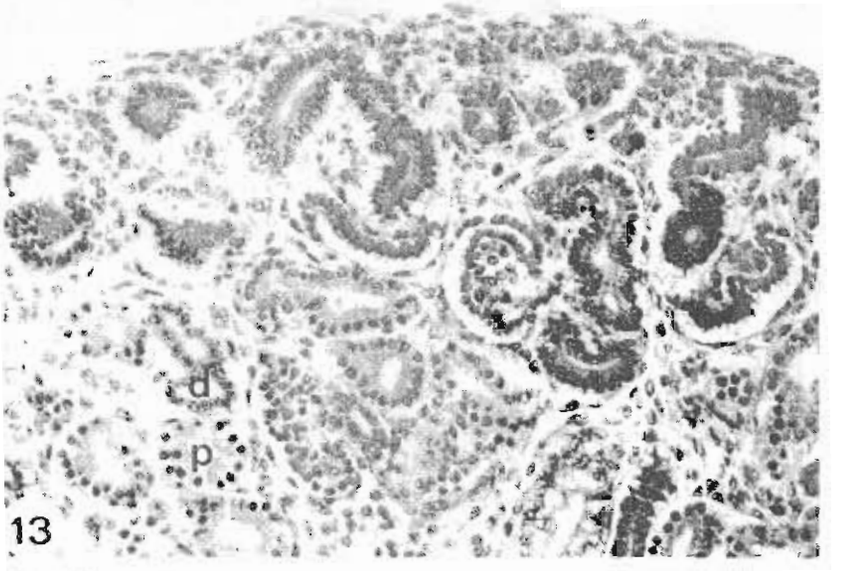

Fig. (13): Metanephros of 25 days old fetus showing the outer basophilic zone under the surface epithelium. Notice the first appearance of the proximal (p) and distal (d) tubules. H & E stain, X 200.

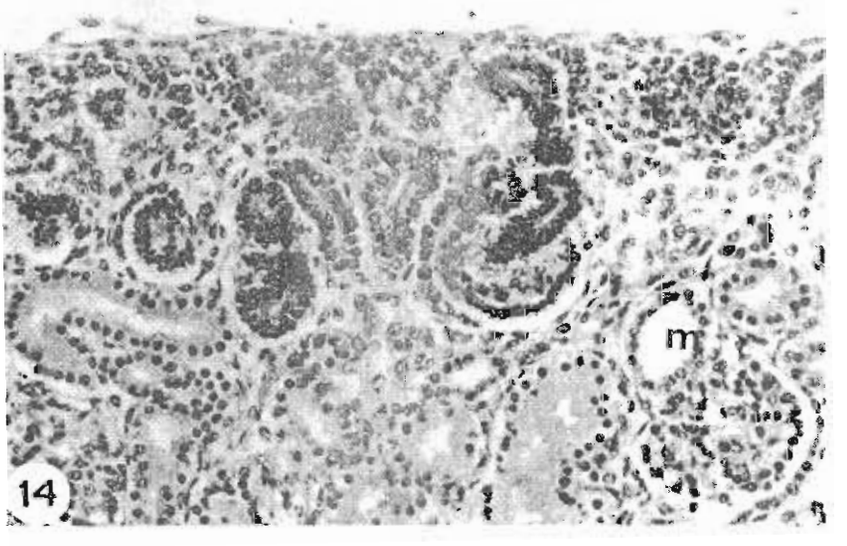

Fig. (14): Metanephros of 25 days old fetus to show the first sings of the macula densa (m) formation. H & E stain, X 200.

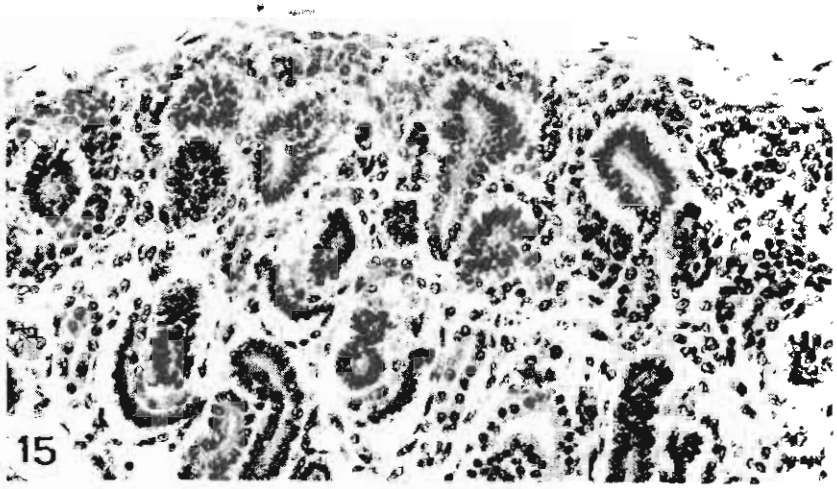

Fig. (15): The outer basophilic zone of the metanephros was covered by a primitive capsule in 26 days old rabbit fetus. H & E stain, X 165.

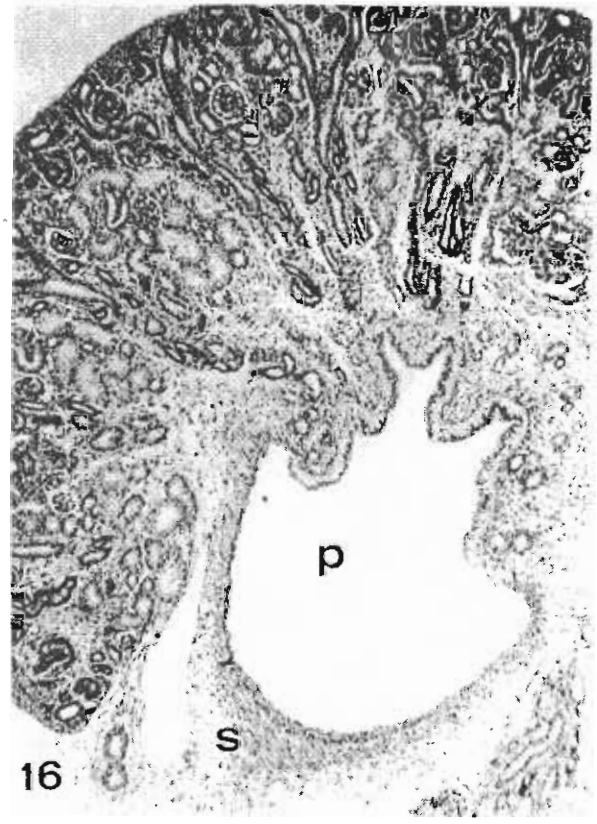

Fig. (16): Metanephros of 27 days old fetus to show the primitive renal pelvis (p) and renal sinus (s). H & E stain, X 50.

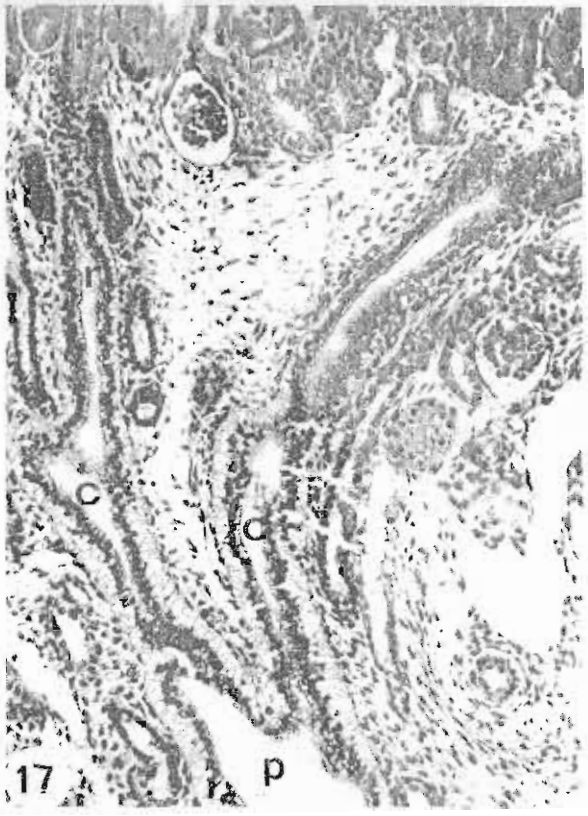

Fig. (17): Metanephros of 27 days old fetus showing the projection of the collecting tubules (c) from the renal pelvis (p). Notice the extension of the collecting tubules toward the cortex to form the primitive medullary rays (r). H & E stain, X 130.

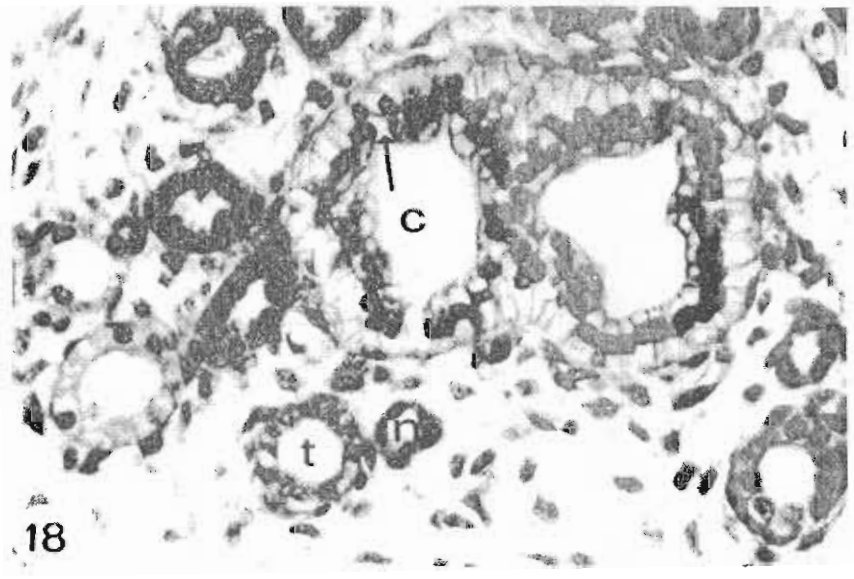

Fig. (18): Central part of the metanephros at 27 days old rabbit fetus to show collecting tubules (c), thick (t) and thin (n) segments of nephron loop in the primitive medulla. Notice the mitotic division (arrow). H & E stain, X 320

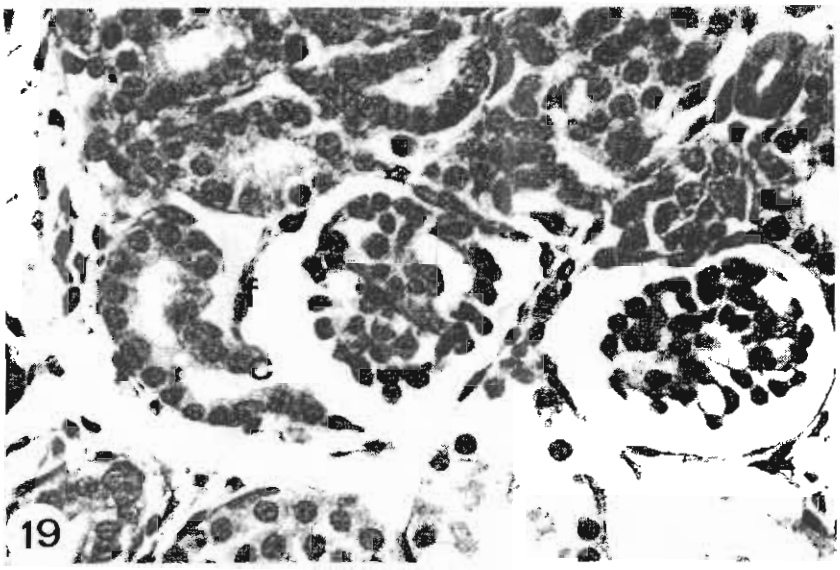

Fig. (19): The subcapsular nephrogenic zone of 28 days old fetus showing marked maturation of some corpuscles. Notice the abrupt change of the flattened cells (f) lining the parietal layer into the cuboidal cells (c) lining the proximal tubule. H & E stain, X 410.

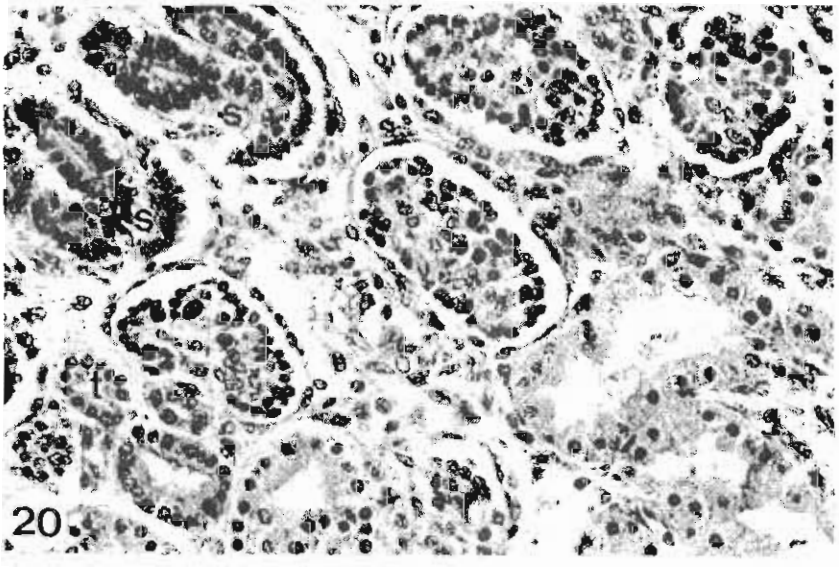

Fig. (20): The subcapsular zone of one day old rabbit showing figures of newly formed corpuscles (s) and tubules (t). H & E stain, X 200.

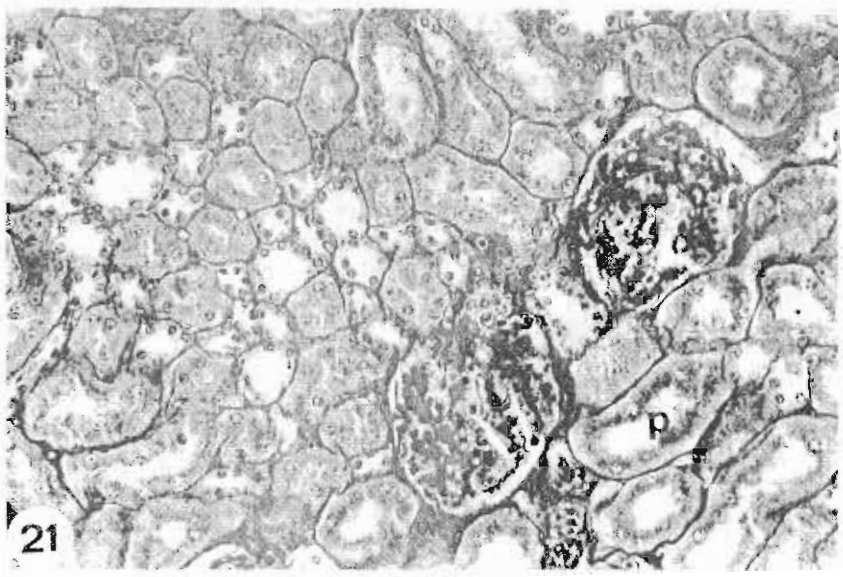

Fig. (21): Renal cortex of 7 days old rabbit to show PAS positive basement membrane of the renal corpuscles and tutules. Notice the PAS reactivity in the glomerular tuft of capillaries and in the brush border of the proximal tubules (p). PAS technique, X 200.

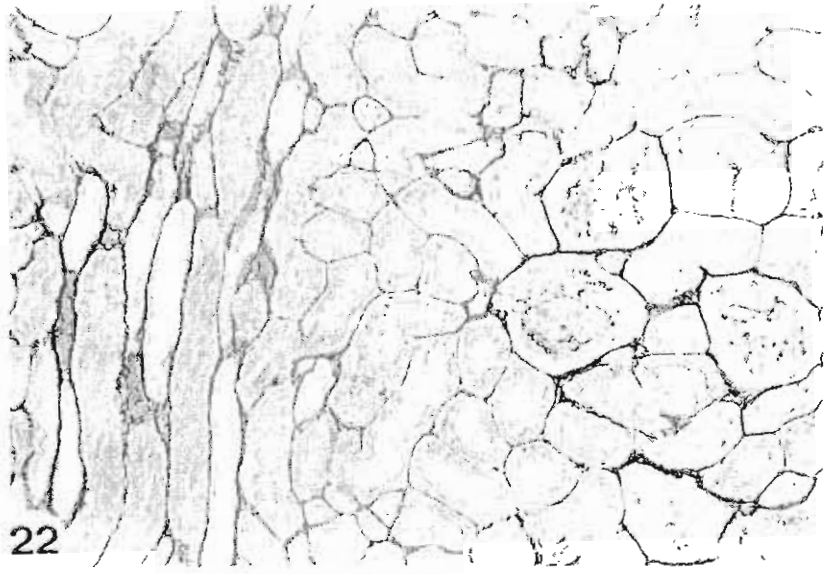

Fig. (22): Renal cortex of 2 weeks old rabbit showing condensation of reticular fibers around the tubular contents of the medullary rays and around the renal corpuscles. Gomori's reticulin method, X 130.

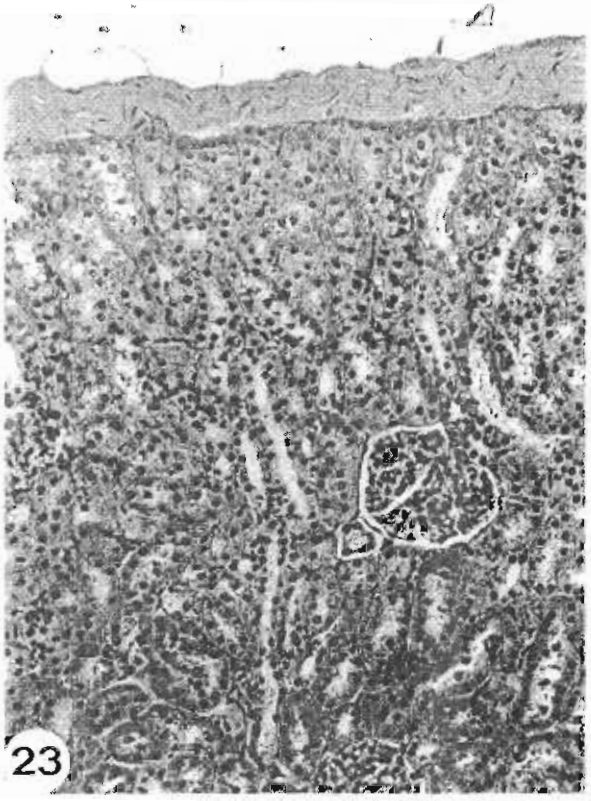

Fig. (23): Renal cortex of one month old rabbit to show the progressive increase of the fibrous content of the capsule. Notice the absence of the subcapsular basophilic zone. H & E stain, X 130.

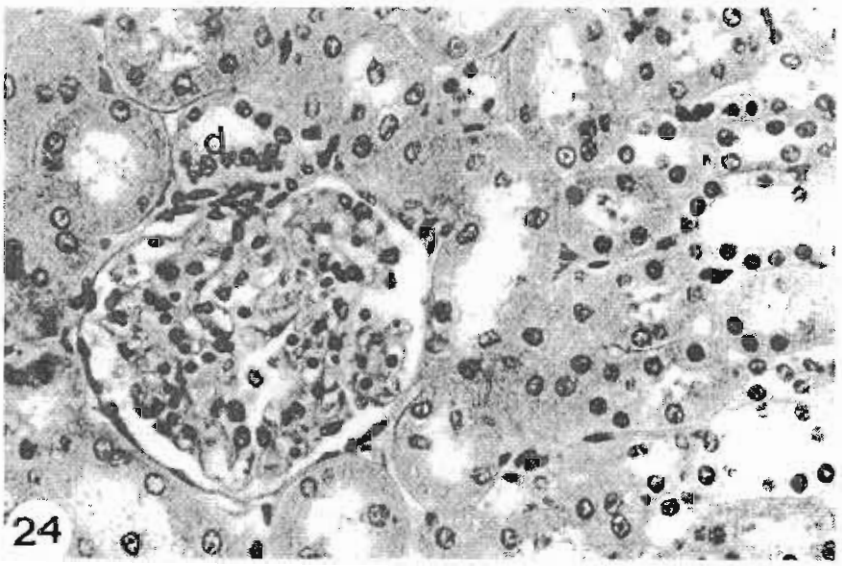

Fig. (24): Renal cortex of 2 month old rabbit showing well-organized renal corpuscle surrounded by numerous cross and oblique sections of proximal tubules. Notice the macula densa (d). H & E stain, X 320.

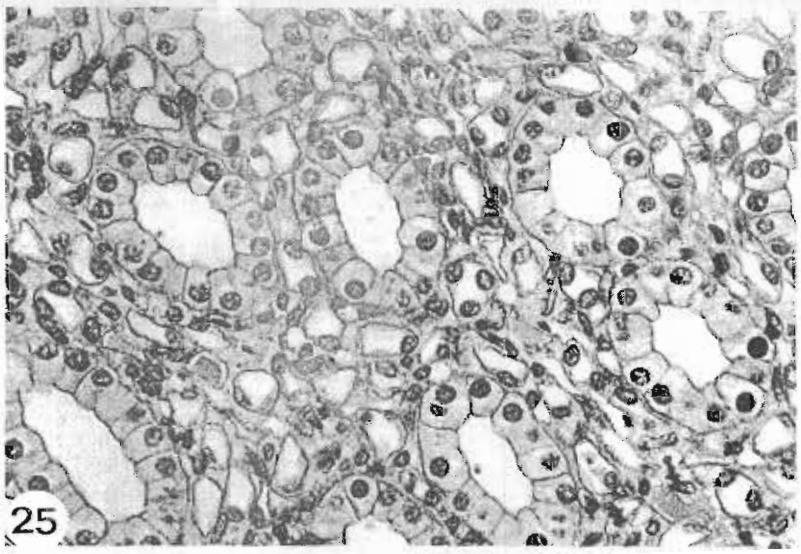

Fig. (25): Kidney of 3 month old rabbit showing collagenous fibers supporting the compartments of the renal medulla. Crossmon trichrome stain, X 320.

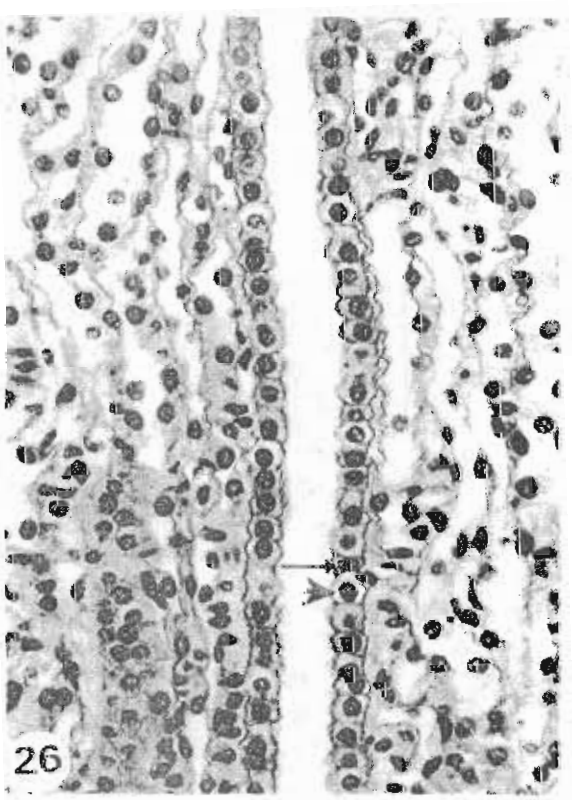

Fig. (26): Renal medulla of 4 month old rabbit to show dark (arrow) and light (arrow head) cells lining the collecting tubules. H & E stain, 320.

whereas the elastic fibers were only demonstrated in the wall of the blood vessels. The typical features of the mature renal corpuscles were seen (Fig. 24). Such corpuscles bear an internal well-organized glomerular tuft with intercapillary mesangial tissue. The nuclei of the mesangial cells appeared small and darkly stained. Around each corpuscle, numerous cross and oblique sections of the proximal tubules were observed. Meanwhile, the macula densa became very obvious. No basement membrane could be detected under the macula densa. Therefore the extraglomerular mesangial cells and the juxtaglomerular cells lay in close contact with the cells of the macula densa.

The compartments of the renal medulla became well-distinct (Figs 25 & 26). They were supported by fine collagenous fibers (Fig. 26) and reticular ones. The peritubular blood capillaries were increased. However, two types of cells; light and dark cells were recognized lining the lumen of the collecting tubules either in the medulla (Fig. 26) or in the cortex.

DISCUSSION

The right and left mesonephroi of the rabbit fetuses appeared in the 11th day as two bodies bulging into the coelomic cavity; one on either side of the primitive aorta. Two types of mesonephric tubules are recognized. One type is lined with high cuboidal or truncated pyramidal cells. The second type is lined by low cuboidal cells. Some of these tubules are transformed into corpuscles as they are invaded by developing blood capillaries. Similar findings were described in rabbits (Leeson and Baxter, 1957 and Leeson, 1960); in human (Bois, 1969 and McCrory, 1972), in mice (Hiura and Fujita, 1977); in camels (Bareedy et al., 1982 and Emara, 1989) and in buffaloes (Moustafa et al., 1986 and Soliman, 1991).

There was a general agreement that the mesonephros was functional during part of fetal life then degenrated, whereas the metanephros persisted permanently as the final kidney. Patten (1964) claimed that the mesonephros was the principal organ of excretion during early fetal life. He added that the mesonephroi depended entirely on their glomerular apparatus for filtering excreta out of the blood and into the tubules. In agreement with Emara (1989) in camels and Soliman (1991) in buffaloes, the mesonephric tubules were increased in number and size and acquired a distinct brush border. Besides, the corpuscles became more differentiated. Also the reactivity of these tubules and corpuscles to PAS was also increased. Judging from these results it seems probable that the mesonephroi are functionally active in the early fetal life.

As soon as the metanephric primordia appeared, in 15 days old fetuses, features of degeneration began to occur in the mesonephroi. Leeson and Baxter (1957) observed these degenerative changes in 17 days old rabbit fetuses. The finding that

the mesonephroi showed gradual regression while the metanephroi became more developed was in accordance with those described in buffaloes by Soliman (1991). On the other hand, Patten (1964) found that the mesonephros underwent rapid involution when the metanephros became well-developed.

The mammalian kidney was of double origin : the uretric bud and the metanephric blastema. The interaction between these two primorida drive the division of the uretric bud to produce the collecting duct system and induce the metanephric mesenchyme to undergo a series of differentiation steps that lead to the formation of the nephron (Potter, 1972; Canfield, 1980 and Davies, 1996). In 15 days old rabbit fetuses the mesenchymal cells in the peripheral part of the metanephric blastema are aggregated in ovoid solid masses, vesicles and elongated or s-shaped tubules whereas the uretric bud appears in the central part. As the fetal age reached 17 days, this bud begins to branch. The blind ends of these branches are swollen formed ampullae. Osathanondh and Potter (1963) in human reported that the nephron induction was initated by the ampullar ends of the uretric bud branches. Soliman (1991) in buffaloes noticed that the division of the uretric bud started after reaching the metanephric blastema.

In fetuses of 27 days old, the renal pelvis primordium appeared as a dilated caudal end of the uretric bud. In buffaloes, Soliman (1991) found that the caudal extension of the uretric bud was the forerunner of the major calyx which later divided into minor calyces, but in camel fetuses, Emara (1989) noticed that these caudal extensions rebranched continuously to form the papillary ducts without formation of calyces.

The present study revealed the same observations of Dougbag (1988) and Emara (1989) in camels and Soliman (1991) in buffaloes that the metanephric corpuscles developed by invagination of the vesicles or s-shaped tubules by the vascularized mesenchyme. Such mesenchyme will later develop into endothelial and glomerular capillaries as well as mesangial cells. The observations on the general development of the corpuscle from the renal vesicle to the s-shaped tubule and further on to the mature corpuscle was confirmed by Potter (1972) in human; Larson (1975) in rat and Friis (1980) in pig. Moreover, El-Hadidy (1997) in rat divided the development of the corpuscle into 4 stages : renal vesicle, s-shaped tubule, appearance of capillary loop and the mature stage.

In all examined metanephroi, a characteristic basophilic nephrogenic zone was observed in the subcapsular area. This zone showed figures of newly formed corpuscles and tubules. MacDonald and Emery (1959) recorded that the presence of this zone indicated the activity of nephron induction. After birth, the formation of new corpuscles and tubules persisted for 2 weeks of rabbit's age. Similar observations were reported in rabbits by

Moustafa et al., (1985); in mice by Johonson and Barrows (1980) and in rat by Zamzam et al., (1989). Thus it could be emphasized that the incomplete nephrogenesis in the late stage of fetal life and at birth resulting in a relatively lower efficiency of the kidney in newborn animals than in adults. On the contrary, McCrory (1972) in human; Moustata et al., (1986); Emara (1989) in camels and Soliman (1991) in buffaloes noticed that the production of new nephrons was completely ceased prior to birth and the metanephros took the picture of the functional kidney.

The characteristic features of the proximal and distal tubules begin to appear in 25 days old rabbit fetuses. After birth the proximal tubules form the main bulk of the renal cortex. They appear more tortuous than the distal tubules as indicated by their numerous cross and oblique sections. Similar results were reported in rats by Maunsbach (1964) and El-Hadidy (1997) and in buffaloes by Soliman (1991). Therefore it could be concluded that the proximal tubules are highly functional in the process of reabsorption and ionic exchange process than the distal tubules.

The macula densa is first recognized in the 25th day of fetal life. After birth they become more differentiated but no basement membrane could be detected under the macular cells. Latta (1973) in rats and Soliman (1991) in buffaloes noticed that the extraglomerular mesangial cells were in intimate contact with the cells of the macula densa. Moreover, there was an effective fluid transport between the lumen of the distal tubule in this region and the extraglomerular mesangium (Gomba et al., 1967).

As it was also observed by Moustafa et al. (1985), the lining cells of collecting tubules of 4 weeks old rabbits are demarcated into light and dark cells. According to Myers et al., (1966) the dark cells might represent a different functional state of the light cells. Evan et al. (1980) and Nicholson and Kendall (1983) suggested that the dark cells might be involved with protein and potassium pumping and control of urinary buffer concentrations. Fawcett and Ronald (1997) confirmed that these cells participate in acid base balance by resorption of bicarbonates. On the other hand, El-Bargeesy et al. (2000) anticipated that the dark cells might represent one of the prominent cellular events (apoptosis). Appearance of apoptotic cells in the renal collecting tubules is a normal physiological phenomenon (Gobe and Axelsen, 1991 and Thomas et al., 1999).

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