Renal Pathology

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RENAL PATHOLOGY

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Foreword

Renal Pathology typifies the modern trend to system specialization that is affecting pathology a decade or so later than the clinical specialties. Neuropathology led the way to the pathology system specialties but it has been followed, perhaps reluctantly, by specialization in the pathology of many limited systems. Pulmonary pathology, osteopathology and gastro-enterological pathology are well-established subspecialties, while renal, cardiac and hepatic pathology are developing along similar lines.

Any pathologist working in a hospital in which a renal unit is established will now find himself required to produce a refinement of investigations beyond the level expected by general physicians and surgeons. Recruits to the ranks of hospital pathologists must, therefore, be ready to upgrade their work in renal pathology to match the requirements of the specialist clinicians. In the present volume of the *Postgraduate Pathology Series* Professor Darmady and Dr MacIver have treated the subject in depth sufficient in every way to provide for this upgrading.

This volume further demonstrates the erosion of the boundaries between histopathology, chemical pathology and immunopathology that occurs when 'system pathology' becomes closely linked with system-based clinical specialties. The importance of basic training in these subjects during the early years of postgraduate work is self-evident.

Sir Theo Crawford

Contents

1

The Development of the Normal Kidney

The complex structure of the adult kidney can only be achieved if every stage of its development and regression is complete, and overlaps correctly both in type and construction. It is important, therefore, to understand how the kidney develops, as the failure of any stage may result in a recognizable malformation.

To simplify matters the elaborate development of the kidney is considered under five stages, bearing in mind that each stage will overlap with the next. These stages are the formation of:

1. Pronephros.
2. Mesonephros.
3. Metanephros.
4. Ureters, calyces and pelvis.
5. Nephrons.

They are shown in *Figure 1.1.*

PRONEPHROS

The first element in the development of the kidney is the formation of a *pronephros*; this is recognizable about three weeks after conception. It is formed from a mass of mesenchymal cells starting first at the cephalic end of the nephrogenic cord at the level of the seventh somite (which corresponds roughly to the upper end of the thorax). It produces approximately seven pairs of primitive nephrons (nephrotomes), bilaterally. Adjacent to each nephrotome, a branch of the aorta provides the blood supply to each primitive glomerulus. Between the fourth and fifth weeks, the nephrotomes begin to degenerate starting at the cephalic end, while the pronephros itself forms a tubule (pronephric

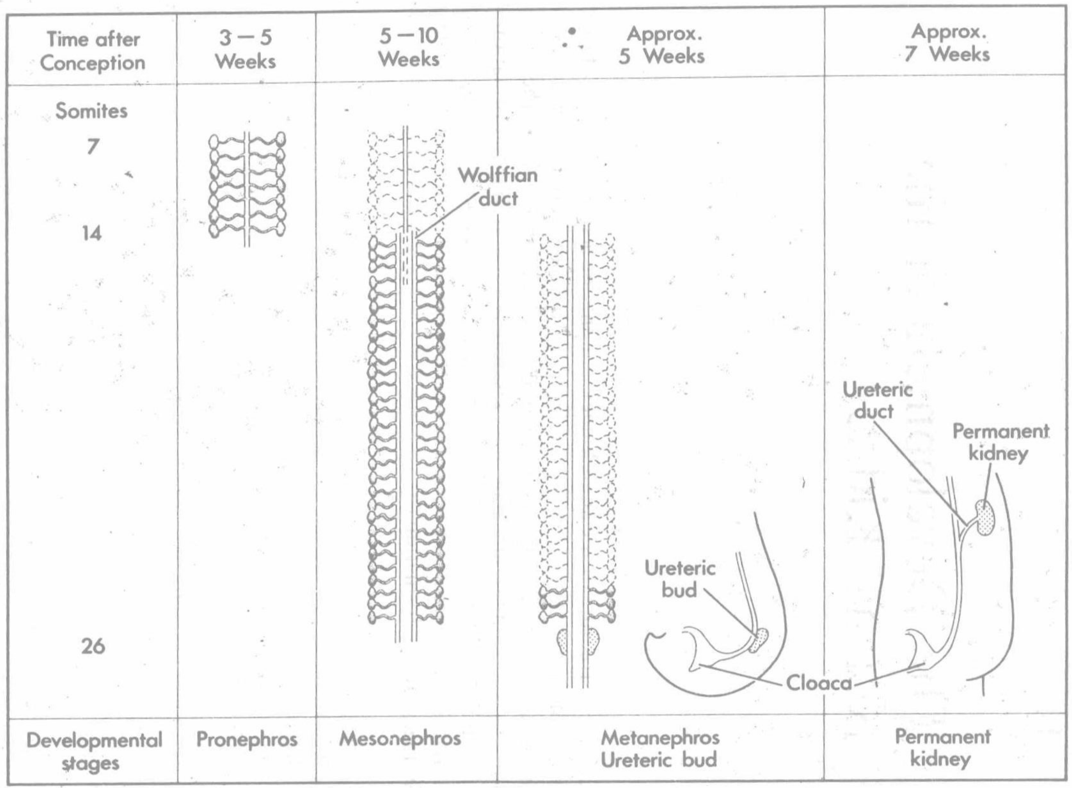

Figure 1.1 *The development and regression of the three primitive kidneys (pronephros, mesonephros, metanephros), during early fetal life. The area of regression is shown by dotted lines*

duct) which grows caudally to join the cloaca. At about this time, all the nephrotomes have regressed and have been replaced by the mesonephros. In the human, the pronephros must be considered as a transitory excretory organ, while in fish and amphibians it is a primitive but functional kidney. In man it is believed that the failure of formation of pronephros and mesonephros will prevent the subsequent development of an adult kidney (*see* Chapter 4).

MESONEPHROS

At about the fifth week, the pronephros has almost completely regressed and has been replaced by the *mesonephros*, lower in the embryo. Again, development commences at the cephalic end of the nephrogenic cord but caudally from the pronephros. About 40 pairs of primitive nephrons or nephrotomes are developed, although only about 30 are functional at any one time. These nephrons are more completely developed than those seen in the pronephros. The glomerulus of each nephrotome is formed by invagination of the end of the tubule by an afferent arteriole derived from a branch of the aorta. This forms the characteristic plexus of capillaries which subsequently surrounds the tubules. The glomerulus is attached to the tubule in an 'S' shape and divides into two distinct sections, the proximal tubule leading into the distal portion which, in turn, drains into the pronephric duct.

As the mesonephros forms, two longitudinal swellings appear on either side of the spinal column in the upper posterior abdominal cavity – an area called the *urogenital ridge.* Each ridge divides longitudinally with the medial portion forming the genital, and the lateral forming the mesonephric ridges. The former develops into the gonads, while the latter forms a transitory excretory system as described above.

At about the fifth week, the nephrotomes start to regress from the cephalic end, and are replaced by more mature nephrotomes caudally. As cephalic nephrotomes regress, the pronephric duct fuses with the remaining excretory tubule and forms the mesonephric or *Wolffian duct.* By the end of the tenth or eleventh week the majority of previously functioning nephrotomes have undergone degeneration and are replaced by the *metanephros*, which is the kidney proper.

The genital ridge develops differently in each sex. In the male, the tubule at the upper end of the mesonephric ridge becomes the efferent ductules of the testes which communicate with the seminiferous tubules and epididymis, while the lower end becomes the ductus deferens and the ejaculatory duct. At about the seventh week the cortical portions of the developing adrenal glands are close to the genital ridge of the mesonephros, and occasional fragments of adrenal tissue may persist and be found in either the kidney or the epididymis. In the female, the upper end of the mesonephric tubules may persist as vestigial remains known as the epoöphoron, paroöphoron and Gartner's duct.

METANEPHROS

The metanephros is developed from two sources: the ureteral bud and the metanephric blastema, and these ultimately form the permanent kidney.

Ureteral bud

The ureteral bud is formed at about five weeks and arises from a diverticulum of the mesonephric duct at about the level of the 28th somite, just above the entrance of the mesonephric duct into the cloaca. Subsequently, it develops into the ureter, renal pelvis, calyces and collecting tubules. At the tip of the bud is the actively growing portion which is known as the *ampulla*. This starts to grow both dorsally and cephalically into the dense mesenchyme of the nephrogenic ridge (metanephric ridge or metanephric blastema) at about the seventh week. At the same time, the ureteral bud branches and carries the cells of metanephric blastema with it. These cells surround the growing point of each ureteric division and subsequently develop into nephrons and renal interstitial tissue.

As the ureteric bud continues to grow and divide, the major and minor calyces appear, so that the metanephric cells form separate tubules around the growing ureteric buds. These, at birth, give the kidney the characteristic 'fetal lobulation' – which may persist, in varying degree, into adult life.

At about the seventh week, as the fetus continues to grow, it straightens out from its curled posture so that the kidneys rotate medially and take up their final position on either side of the spinal cord. Since the caudal end of an embryo develops more rapidly, the lower poles of the kidney tend to come closer together and if they fuse they form the well-known developmental error of the 'horseshoe kidney'.

Microdissection studies by Oliver (1968) and by Osathanondh and Potter (1963, 1966) have clarified the development of the ureteral bud and the sequence of events which leads to the formation of the pelvis, major and minor calyces and the nephrons. The ureteral bud grows and divides rapidly, but the speed of division is greater at the poles or outer segments than in the central or interpolar area. For example, although the number of divisions is variable, usually five or so are found at the upper and lower poles with only two or three in the interpolar areas.

Division of the ureteral bud continues to about 10–12 weeks, but now the earlier-formed third or fourth generation of branches fuse together to form the renal pelvis. This probably occurs as the result of the excretion of urine from primitive nephrons which causes the ureteral buds or branches to dilate, the back pressure then brings the branches into contact with each other so that they fuse. During the next 12–16 weeks, the next 3–5 generations undergo

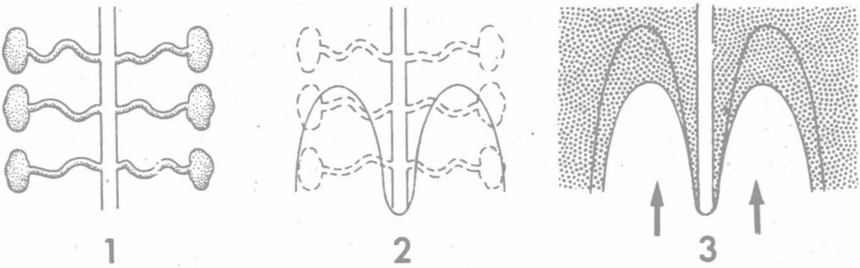

Figure 1.2 The three stages of the formation of the renal calyx and papillae. 1: The first three or so generations of nephrons degenerate and are reabsorbed. 2: Pressure from the secretion of urine by the primitive kidney causes the degenerate tissue to collapse. 3: Increasing urinary pressure causes the calyx to dilate further and the papillae to become cone-shaped

rapid division and coalesce in a similar way to form the major calyces. After this, the rate of division of the ureteral buds slows down and the tubules elongate to form the minor calyces while the next few generations form the cribriform plate which covers each papilla. With the further production of nephrons and interstitial tissue, back pressure of the urine on the calyces causes the papillae to project into the cavity thus producing its well-known conical shape (*Figure 1.2*). Subsequent growth of tubules and nephrons results in the production of papillary ducts (ducts of Bellini), and extrusion of the renal papillae.

In man, as distinct from other mammals with the exception of whales and bears, there is a series of papillae and associated lobes. Each lobe is hemispherical, and from each papilla arise the papillary ducts with associated collecting tubules and nephrons (*Figure 1.3*). Although the exact number of ducts per papilla is

Figure 1.3 The development of a papilla and calyx in an 11.5 cm fetus. Haematoxylin and eosin: x140. (Reduced to two-thirds in reproduction)

still open to conjecture, Oliver (1968) gives a range of 20–72, while Osathanondh and Potter (1963, 1966) give only 10–25. As the kidney develops, so the surfaces of the lobes come together to form the columns of Bertin. According to Bloom and Fawcett (1968), 8–18 papillae are found in the renal pelvis and each papilla is related to a lobe. Oliver, who gives an average of 8 papillae, and Potter (1972), state that at 10 weeks there are 3–4 lobes but that the formation of further lobes increases the number to 14–16 by the end of 4 months. However, Warwick and Williams (1973) found that, in an examination of 375 kidneys, there were only 5–11 papillae in 89 per cent, with 8 papillae being the most frequent number (26 per cent of kidneys).

Collecting tubules

The formation of the renal pelvis, calyces and cribriform plate occupies 7–11 branches (generations) of the ureteral bud. The subsequent 5–7 additional generations form the collecting tubules. Such branches are often long and carry attached nephrons with them. After the formation of the seventh or eighth generation the growth of new branches is rapid, which may account for the absence of nephrons in the medullary area. An alternative explanation is that primitive-formed nephrons become detached during the rapid growth of the ampulla, and subsequently degenerate. In the final stages of development, the formation of additional branches slows down and eventually ceases at about 34 weeks, as does new nephron production.

As a result of microdissection studies, Osathanondh and Potter (1963, 1966), and Potter (1972) have divided the development of the nephrons into four periods.

Period I (5–14 weeks)

This period lasts from 5 to 14 weeks when the ureteral bud grows rapidly into the metanephric blastema, carrying the ampulla with it. The ampulla then divides rapidly and each branch gives rise to a single nephron. During this stage, the earliest-formed nephrons become detached and degenerate.

Period II (15–22 weeks)

During this period, the growth of the ampulla into the metanephric blastema slows down, and there is no active division. Instead, a number of nephrons are

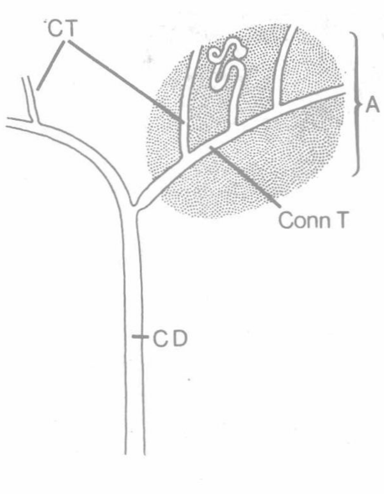

Figure 1.4 Diagram demonstrating the rapid growth of the collecting tubule. Each connecting tubule gives rise to three or more nephrons: an arcade. Only one nephron is shown in the arcade while the remaining two are represented by collecting tubules. A: Ampulla. CT: Collecting tubule. Conn T: Connecting tubule. CD: Collecting duct

formed from each ampulla and, as a result, several nephrons are formed from each connecting tubule to form an arcade (*Figure 1.4*). This drains into the collecting tubule from which it has been formed. The number of nephrons on each arcade varies from 3 to 5, and very occasionally a second arcade is formed from one ampulla.

Period III (20–34 weeks)

At 20–22 weeks, the ampulla continues to grow peripherally into the blastema beyond the attachment of the arcades, and there is a change in the form of development. Branching of the ampulla and collecting tubule stops and the nephrons are now formed singly, from the point where the ampulla joins the

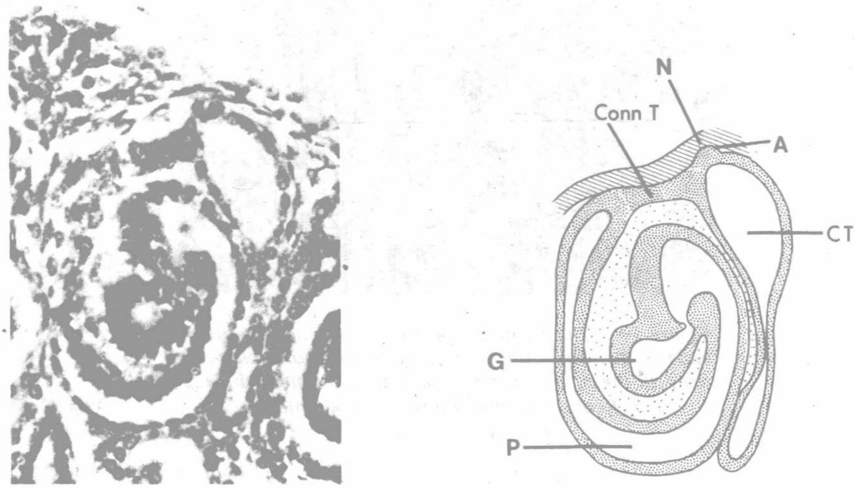

Figure 1.5 The primitive nephron is shown in the 'S' stage of development. The accompanying diagram shows the ultimate divisions. A: Ampulla. N: Nephrogenic blastema. Conn T: Connecting tubule. CT: Collecting tubule. G: Primitive glomerulus. P: Proximal tubule

collecting tubule (*Figure 1.5*). As the ampulla gradually advances, the last portion of the collecting tubule is formed and this grows into the cortical area, leaving 4–6 nephrons at points of juncture between ampulla and tubules. These nephrons also differ in their structure and begin to differentiate (*Figures 1.6* and *1.7*).

Period IV (32–36 weeks)

At 32–36 weeks, the ampulla becomes inactive and disappears at the same time as the production of nephrons and further branches of collecting tubules also ceases. Instead, the nephrons enlarge, especially the proximal tubules which