Urinary system

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The system consisting of the kidneys, urinary ducts, and bladder. These structures will be discussed in this article in terms of their comparative anatomy, embryology, and physiology.

Comparative Anatomy

Similarities are not particularly evident among the many and varied types of excretory organs found among vertebrates. The variations that are encountered are undoubtedly related to problems with which vertebrates have had to cope in adapting to different environmental conditions.

Archinephros

It is now generally believed that the primitive vertebrate ancestor possessed an excretory organ referred to as an archinephros or holonephros (**Fig. 1**). This probably consisted of a pair of dorsally located ducts extending the length of the body cavity. Each duct was joined by a series of segmentally arranged tubules, one pair to each segment. The other end of each tubule opened into the body cavity by a ciliated, funnel-shaped aperture. Close to each opening was a small knot of arterial blood vessels called an external glomerulus. From this type of kidney with its archinephric duct the various kidneys of forms living today may originally have been derived. The larval form of the hagfish and the larvae of certain amphibians, the caecilians, are present-day vertebrates possessing kidneys of this type.

Anamniote kidneys

The anterior portion of the archinephric kidney persists only in the adult stage of the hagfish and of certain teleost fishes in which it is called the head kidney, or pronephros. It appears in the embryos of most vertebrates as a transitory structure that usually degenerates soon after it has formed. The remainder of the kidney posterior to the pronephros is known as the opisthonephros.

Pronephros. The importance of the pronephros lies mainly in the part it plays during development in forming the archinephric duct which persists even though the pronephros appears only as a transient structure. In some larval forms the pronephros may be important in getting rid of wastes at a time when the opisthonephros is being formed. Even in the hagfish, the head kidney has become modified from the primitive condition. Here the openings of the tubules connect with the pericardial cavity, and the fluid drained by the tubules passes into a

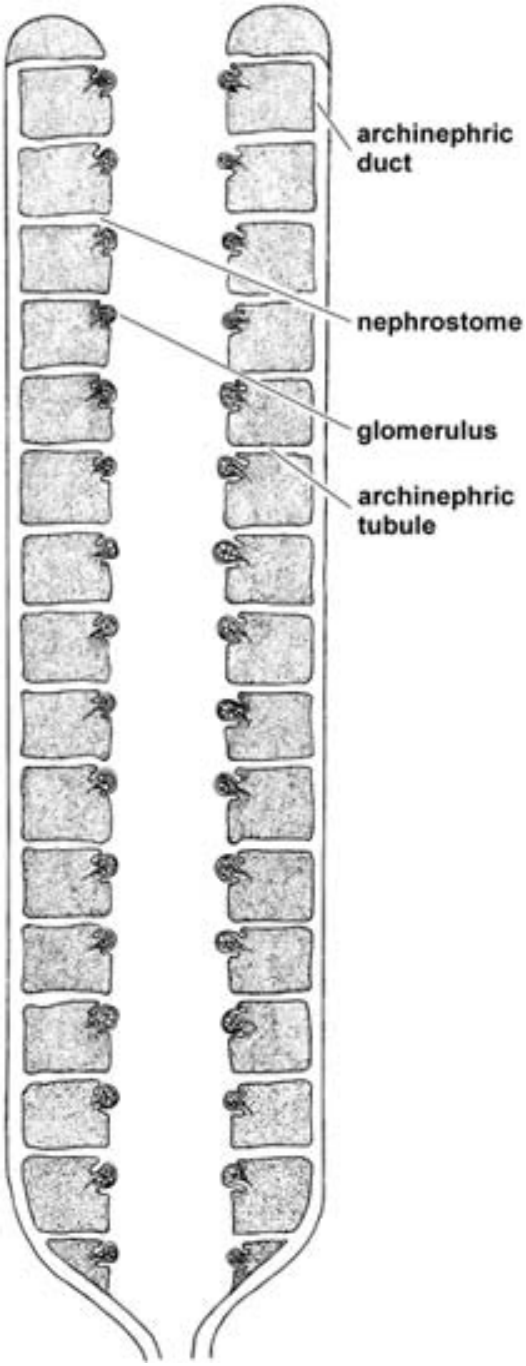

Fig. 1 Hypothetical structure of archinephros. (*After C. K. Weichert, Elements of Chordate Anatomy, 3d ed., McGraw-Hill, 1967*)

nearby vein instead of entering the archinephric duct. Pronephros and opisthonephros become completely separated by degeneration of the portion between them.

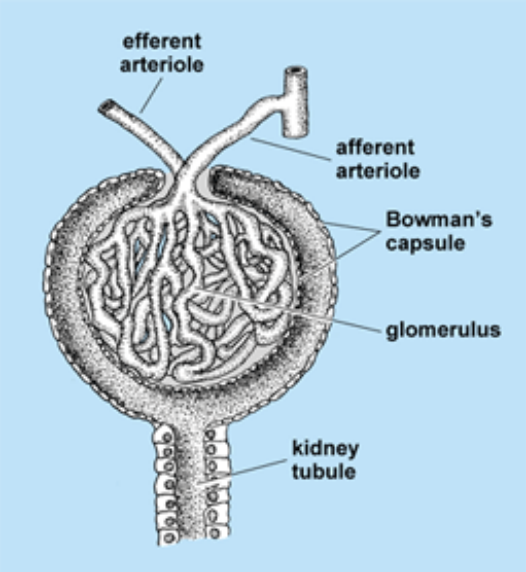

Fig. 2 Renal corpuscle. (*After C. K. Weichert, Anatomy of the Chordates, 4th ed., McGraw-Hill, 1970*)

Opisthonephros. Because the pronephros is usually a transitory structure, the opisthonephros is the more important of the two. It serves as the adult kidney in lampreys, most fishes, and amphibians. The opisthonephros differs from the pronephros in several respects. A main distinction is that the segmental arrangement of the kidney tubules is lost and many tubules may lie within the confines of a single segment. Furthermore the connection of the opisthonephric tubules with the body cavity is usually lost, and renal corpuscles with internal glomeruli are typically present. These are small knots of arterial vessels, each surrounded by a double-walled cup called Bowman's capsule; the two together form a renal corpuscle (**Fig. 2**). The internal, or visceral, layer of Bowman's capsule is actually very complexly arranged, folded, and interdigitated to follow the configurations of the individual glomerular capillaries which exhibit extensive anastomoses. The cells, called podocytes, are not squamous in type and do not furnish a continuous covering of the capillaries.

In some forms the anterior tubules of the opisthonephros lie in the same segments as posterior pronephric tubules. This indicates the transitional nature of the two. A typical opisthonephric tubule consists of a narrow neck adjacent to the renal corpuscle, followed in turn by secretory and collecting portions. The collecting portion joins the archinephric duct. The ends of several collecting tubules may unite to form a common duct which either opens into the archinephric duct or establishes an independent connection with the cloaca. Several such accessory ducts may be present.

Cyclostomes. The opisthonephros of the adult hagfish differs basically from the original archinephros only in the loss of peritoneal connections of the posterior tubules. In the adult lamprey the opisthonephros on each side consists of a long, strap-shaped body without peritoneal connections. The kidneys lie on either side of the middorsal line from which each is suspended by a mesenterylike membrane. The archinephric duct lies along the

free edge of the kidney. The ducts of the two sides unite posteriorly to open into a urogenital sinus which leads to the outside through an aperture at the tip of a small urogenital papilla. Two slitlike genital pores connect the urogenital sinus with the coelom. The condition is similar in both sexes. Eggs or spermatozoa leave the body cavity by way of the genital pores, the urogenital sinus, and the urogenital aperture. Only here are the reproductive and urinary systems associated.

Fishes. There is much variation in shape of the opisthonephric kidneys of fishes, but they are fundamentally similar in structure. In some they extend the length of the coelom; in others they are short and may show various degrees of fusion. Peritoneal funnels rarely occur. Some marine teleosts lack glomeruli and thus possess aglomerular kidneys. In elasmobranchs the anterior ends of the kidneys of the male have been appropriated by the reproductive system. Modified kidney tubules, called efferent ductules, connect each testis with the archinephric duct which lies on the ventral surface of the kidney and serves as a ductus deferens for sperm transport. Accessory urinary ducts are usually present. In teleost fishes there is no connection between the testes and the opisthonephric kidneys. The posterior ends of the archinephric ducts of female fishes enter a common urinary sinus inside a small urinary papilla. The latter enters the cloaca in elasmobranchs and dipnoans, but in most other fishes it opens directly to the outside, a cloaca being absent.

Amphibians. In common with other amphibians, adult caecilians possess an opisthonephros. The kidneys of the tailed amphibians are much like those of elasmobranch fishes, the anterior ends in males being concerned with genital rather than urinary functions (**Fig. 3**). The archinephric duct courses along the lateral edge of the kidney a short distance outside the kidney proper. Numerous collecting ducts or tubules leave the kidney at intervals to join the duct. The two ducts in both sexes open separately into the cloaca. In frogs and toads the opisthonephric kidneys lie toward the posterior part of the abdominal cavity. A yellowish adrenal gland is located along the ventral surface of each. The kidneys of females are not related to the reproductive system but in males an intimate connection exists. Modified tubules, or efferent ductules, from the testes connect with kidney tubules which lead to the archinephric duct. This duct is located within the kidney along its lateral margin. Peritoneal funnels are present on the ventral sides of the kidneys in some frogs but they connect with veins rather than the kidney tubules. A thin-walled urinary bladder opens into the amphibian cloaca. It has no connection with the archinephric ducts.

Amniote kidneys

In reptiles, birds, and mammals three types of kidneys are usually recognized: the pronephros, mesonephros, and metanephros. These appear in succession during embryonic development, but only the metanephros persists in the adult. Mesonephros and metanephros actually represent different levels of the opisthonephros of lower forms, the metanephros being equivalent to the posterior portion.

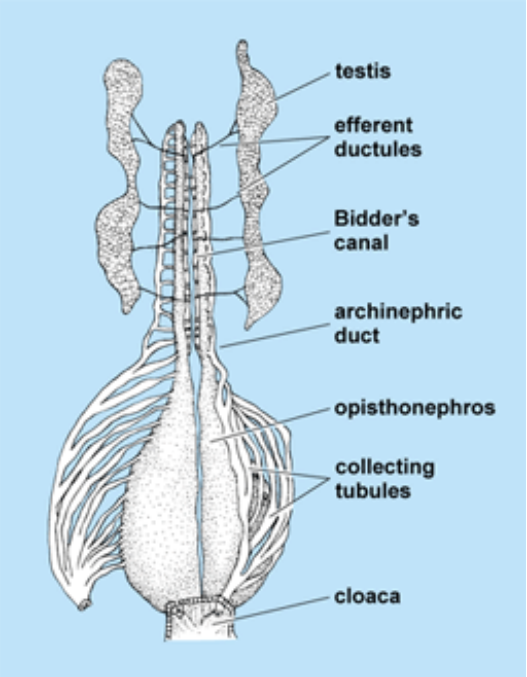

Fig. 3 **Urogenital organs of male salamander, ventral view. The collecting ducts on the left are shown detached from the cloaca and spread out for clarity. (*After C. K. Weichert, Elements of Chordate Anatomy, 3d ed., McGraw-Hill, 1967*)**

The anteriorly located pronephros appears during very early development, but it soon degenerates and the more posterior mesonephros then develops. The duct of the pronephros, however, persists to become the duct of the mesonephros. This is actually the same as the archinephric duct but is usually referred to as the Wolffian duct.

The mesonephros persists for a time and then degenerates. In the meantime the metanephros has begun to develop from the region posterior to the mesonephros. A few mesonephric tubules and the Wolffian duct persist to contribute to the reproductive system of the male or to remain as vestigial structures.

Mesonephros. The tubules of the mesonephros develop in the same manner as opisthonephric tubules. Some of the anterior tubules may even form peritoneal connections. In some forms the mesonephric kidneys become voluminous structures; in others they amount to very little. In reptiles, spiny anteaters, and marsupials the mesonephros may even persist for a time after birth.

Metanephros. A metanephric kidney develops on each side posterior to the mesonephros. It is composed of essentially the same parts as the mesonephros and contains renal corpuscles, secretory tubules, and collecting tubules. No peritoneal connections are present. Each kidney has a twofold origin. An outgrowth from the posterior end of the Wolffian duct grows forward into the tissue posterior to that from which the mesonephros was derived and which is called the metanephric blastema. The outgrowth is destined to form the ureter and the

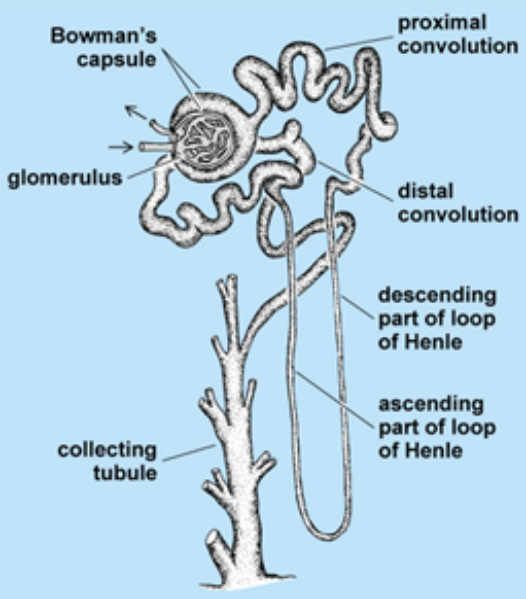

Fig. 4 **Mammalian metanephric tubule, showing the renal corpuscle and secretory and collecting portions.** (***After C. K. Weichert, Elements of Chordate Anatomy, 3d ed., McGraw-Hill, 1967***)

collecting portion of the kidney. It branches and rebranches many times to form ultimately large numbers of fine collecting tubules. At least in mammals at the point where the outgrowth undergoes its primary divisions an expanded region forms the pelvis of the kidney.

From the blastema adjacent to the collecting tubules arise secretory tubules. Each tubule grows and becomes S-shaped. One end establishes connection with a collecting tubule; the other expands and becomes invaded by a vascular glomerular tuft so that a typical renal corpuscle is formed. Each tubule differentiates into several regions (**Fig. 4**).

Reptiles. The metanephric kidneys of reptiles lie in the posterior part of the abdominal cavity, usually in the pelvic region. They are small, compact, and often markedly lobulated. The posterior portion on each side is somewhat narrower. In some lizards the hind parts may even fuse. The degree of symmetry varies, being most divergent in snakes and limbless lizards which have notably long, narrow, lobulated kidneys in correlation with the shape of the body. One kidney may be entirely behind the other.

Snakes and crocodilians lack a urinary bladder, but most lizards and turtles have well-developed bladders which open into the cloaca. Except in turtles the ureters open independently into the cloaca. In turtles they connect to the bladder. Some turtles possess a pair of accessory urinary bladders which open into the cloaca. They may be used as accessory organs of respiration. In females they are reported to be filled with water which is used to soften the soil when a nest is being prepared.

Birds. The kidneys of birds are situated in the pelvic region of the body cavity; their posterior ends are usually joined. They are lobulated structures with short ureters which open independently into the cloaca.

Except for the ostrich, birds lack urinary bladders. Urinary wastes, chiefly in the form of semisolid uric acid, are eliminated through the cloaca along with the feces.

Mammals. The rather typical mammalian metanephric kidney (**Fig. 5**) is a compact, bean-shaped organ attached to the dorsal body wall outside the peritoneum. The ureter leaves the medial side at a depression, the hilum. At this point a renal vein also leaves the kidney and a renal artery and nerves enter it. The kidney is surrounded by a capsule of connective tissue under which lies the cortex. The renal corpuscles and the greater part of the secretory tubules lie entirely in the cortex. The portion of the kidney surrounded by the cortex is the medulla. It is partly composed of large areas, the renal pyramids. The outer borders of the pyramids are divided into smaller units called lobules. The collecting tubules lie within the pyramids but may extend well up into the cortex. The inner portion of each pyramid, in the form of a blunt papilla, projects into an outpocketing of the pelvis known as a minor calyx. Several minor calyces join together to enter major calyces which in turn open into the renal pelvis. The pelvis leads to the ureter which empties into the bladder, except in monotremes in which it enters the urethra. Urine, which is stored temporarily in the bladder, passes to the outside through the urethra. In males the urethra opens at the tip of the penis; in females the condition varies, for in some, as the rat and mouse, the urethra opens independently to the outside, passing through the clitoris. It usually, however, enters a vestibule which is the terminal part of the genital tract. The kidneys of mammals are markedly lobulated in the embryo, and in many forms this condition is retained throughout life. *See also:* KIDNEY.

Charles K. Weichert

Comparative Embryology

The kidney, or nephros, of vertebrates is made up of many individual structural and functional units known as nephrons. The nephrons are derived from that portion of the embryonic mesoderm designated as the intermediate mesoderm. Ideally, this material becomes segmented, with each segment being termed a nephrotome (**Fig. 6**). Any given nephrotome contains a coelomic chamber, the nephrocoele, which opens to the adjacent body cavity via a peritoneal funnel.

The conversion of nephrotome to nephron involves the following events. There arises from the dorsolateral wall of the nephrotome a tubular outgrowth, the principal tubule, which communicates with the nephrocoele via a nephrostome; the medial wall of the nephrotome thins, flattens, and bulges inwardly coincidently with its invasion by arterial capillaries derived from the nearby dorsal aorta. The skein of capillaries makes up a glomerulus, and the wall of the nephrotome investing the glomerulus is known as a renal, or Bowman's, capsule (**Fig. 7**).

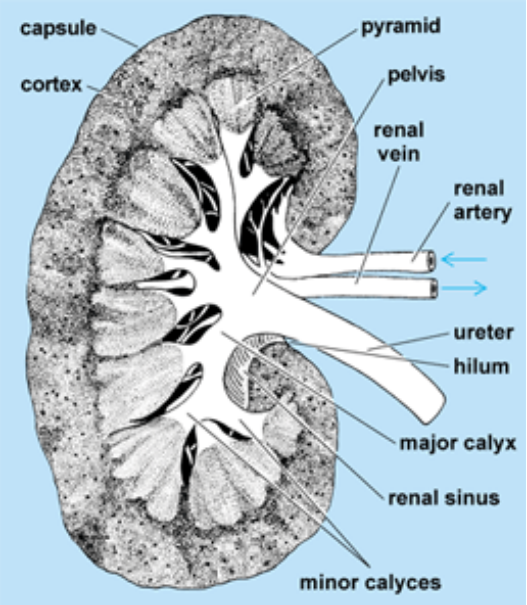

Fig. 5 Sagittal section of metanephric kidney of a human (semidiagrammatic). (*After C. K. Weichert, Elements of Chordate Anatomy, 3d ed., McGraw-Hill, 1967*)

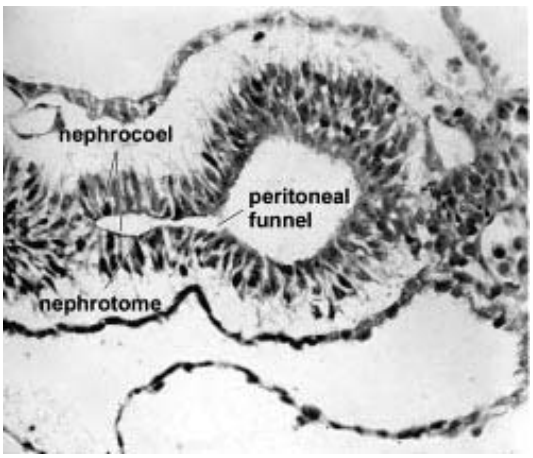

Fig. 6 Nephrotome of human embryo.

The original vertebrate nephros presumably consisted of similar nephrons throughout the length of the organ with each opening independently to the exterior. However, this arrangement is only hypothetical, for in all known vertebrates the nephrons empty into a common drainage, or nephric, duct which passes back alongside the nephros to terminate in the cloaca, the chamber which also receives the digestive tract. The situation is also complicated in present-day vertebrates by four variables. First, in the embryos of higher vertebrates, typical hollow nephrotomes are seldom formed; instead, nephrons differentiate without segmental arrangement within a

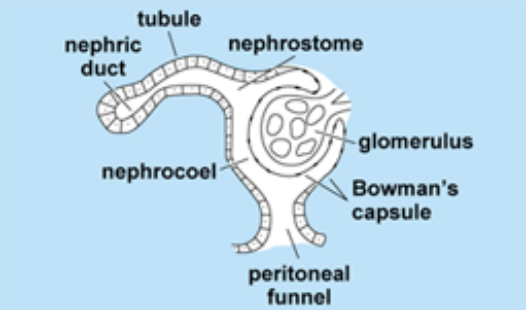

Fig. 7 **Basic design of a nephron.**

continuous cord, the nephrogenic cord, of intermediate mesoderm. Second, as the nephros develops embryonically, its entire length does not appear at one time; instead, the nephrons appear in sequence from front to rear and the first-formed anterior ones tend to disappear before the posterior ones arise. Third, the nephrons become progressively more complex from anterior to posterior. Fourth, the manner of establishment of the nephric duct is not consistent in all vertebrates. The results of these four variables follow.

Nephros of fishes and amphibians

Embryonic development of the nephros is inaugurated within the most anterior reaches of the mesomere. This intermediate mesoderm becomes segmented into nephrotomes from each of which a nephron forms in the general manner already described. The number of these first-formed nephrons varies with the species, but is always relatively small, usually three to five. These nephrons, because of their anterior position and because they are the first to appear, form the head kidney, or pronephros. Accordingly, the nephrons themselves are termed pronephric tubules, or pronephrons. As the first and most anterior pronephric tubule arises, it first extends dorsolaterally and then turns backward to join the one forming immediately behind. This one in turn joins the one behind it, and so on, thus producing a common drainage duct designated the pronephric duct. The pronephric duct, once initiated, extends itself backward along the still undifferentiated intermediate mesoderm until it joins the cloaca (**Fig. 8***a*).

With the exception of the hagfishes and some bony fishes in which it persists throughout life, the pronephros has a temporary existence. In the sharks, for instance, it is present only during early embryonic stages and has little or no functional significance, but in those forms having an active free-living larval stage, such as amphibians and lampreys, it persists in the larva as a functional organ and the individual pronephrons possess ciliated peritoneal funnels opening to the adjacent coelom. This provides for the uptake of certain materials directly from the coelom as well as from the bloodstream. Direct demonstrations of the functional capacities of pronephric tubules have come from a variety of tests. For example, the pronephrons of the larval lamprey will take up quantities of coloidal carbon which may be injected into the coelom; and through their ability to accumulate the dye phenol red, the pronephrons of frog larvae and certain bony fishes have also revealed their functional capabilities.

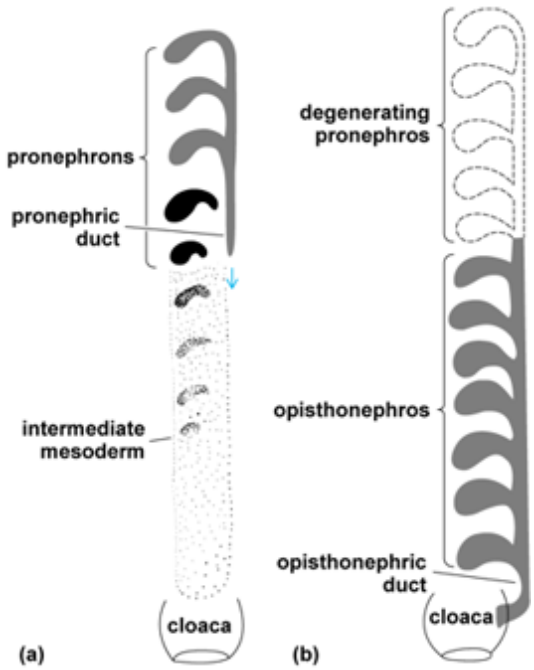

Fig. 8 Diagram of (*a*) developing pronephros and (*b*) opisthonephros.

Whatever the length of its existence, the pronephros is supplemented and succeeded by a second generation of nephrons derived from the remainder of the intermediate mesoderm. Although they arise in basically the same manner and exhibit the same fundamental structure, these later-formed nephrons tend to be longer and more complex in their makeup, and ordinarily lack peritoneal funnels. Unlike their pronephric forerunners these nephrons fail to establish their own drainage duct; they join the already existing pronephric duct. Eventually, as noted, the earlier-formed pronephros disappears, leaving this later generation of nephrons to constitute the final, definitive kidney. This organ, distinctive to fishes and amphibians, is the opisthonephros, or back kidney, and the former pronephric duct which its nephrons have taken over is the opisthonephric duct (Fig. 8*b*).

Nephros of reptiles, birds, and mammals

The embryonic initiation of the nephros of higher vertebrates is customarily described as involving the establishment of a pronephros and pronephric duct as in fishes and amphibians. Although this may be true for reptiles and birds, in mammals pronephric tubules rarely if ever appear. In humans, for example, that level of intermediate mesoderm equivalent to the pronephros never gets beyond the point of conversion to a few rudimentary nephrotomes. Because definitive pronephric tubules are never provided, the pronephric duct must arise in some fashion other than by junction of the ends of pronephrons. The original nephric duct is initiated as a solid rod which splits off the dorsolateral side of the nephrogenic cord (**Fig. 9**). Once established in this fashion, the solid duct then frees itself from the parent material and as a tapering rod extends itself backward by

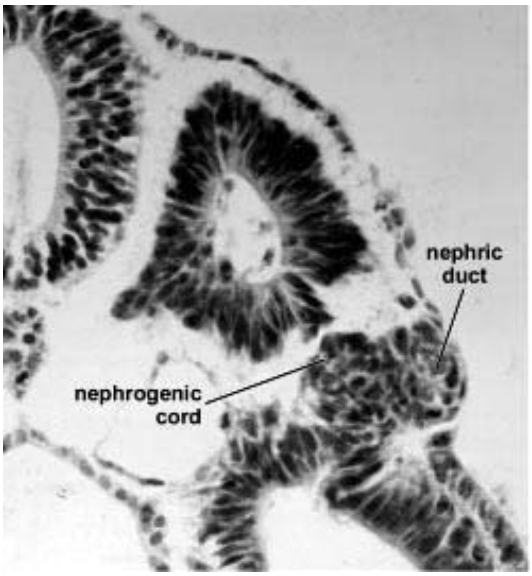

Fig. 9 **Origin of nephric duct in human embryo.**

independent terminal growth, ultimately contacting and fusing with the wall of the cloaca. The solid rod gradually hollows out and within a few days after its original establishment becomes tubular throughout.

Wolffian duct. As the nephric duct, or Wolffian duct, is being formed the first of two generations of nephrons appears. The first generation consists of a series of nephrons derived from the middle level of the intermediate mesoderm. The details of their manner of development and final form vary from one category of animals to another, but in general they conform to the pattern described above. The human embryo may be used as a specific illustration. Briefly, the nephrogenic cord paralleling the growing Wolffian duct provides an increasing number of serially arranged spherical bodies known as nephric vesicles (**Fig. 10**). These are solid at first, but become hollow, and as they do so each vesicle sends a principal tubule dorsolaterally to join the Wolffian duct. The vesicle proper will provide the capsule surrounding the later-developing glomerulus. Elongation and twisting of the principal tubule and the acquisition of a capillary network complete the nephron (**Fig. 11**).

Wolffian body. These nephrons are known as mesonephric tubules, or mesonephrons, and collectively they make up the mesonephros, or Wolffian body. This kidney is well developed in reptiles and birds, but in mammals exhibits considerable variation. In the rat embryo, for example, it is quite rudimentary and only a dozen or so abortive nephrons arise. At the other extreme is the pig embryo whose mesonephros is large and bulky and involves several hundred long and convoluted nephrons. The human mesonephros lies between these two extremes.

Embryonic function. The variable status of the mesonephros, especially in mammals, raises the interesting question of the functional role it plays in the economy of the embryo. It is reasonable, of course, to infer function from

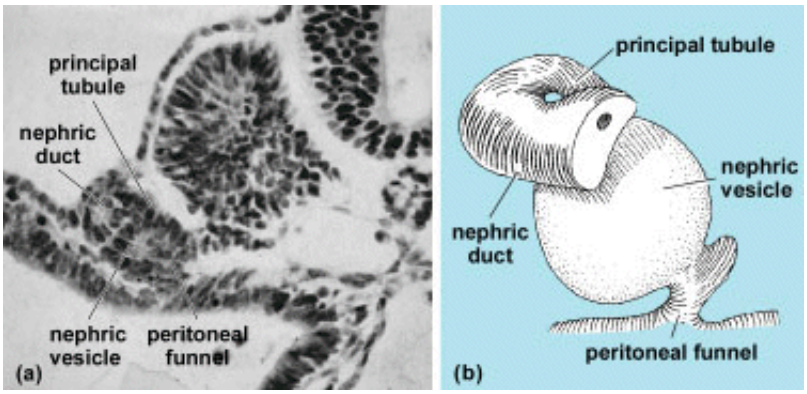

Fig. 10 Early human mesonephron. (*a*) Section. (*b*) Reconstruction.

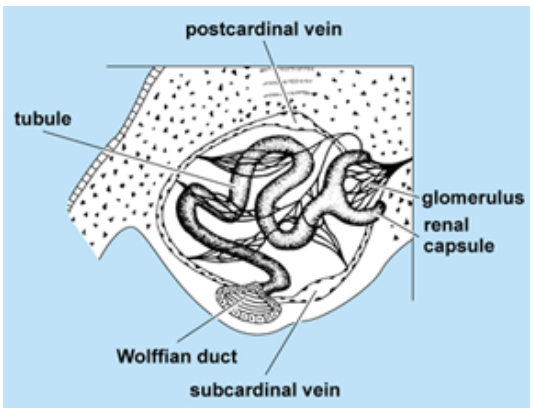

Fig. 11 Fully differentiated human mesonephron. (***After T. W. Torrey, Morphogenesis of the Vertebrates, 2d ed., John Wiley and Sons, 1968***)

exhibited structure. More convincing, however, are the direct experimental demonstrations of functional capacities of the mesonephrons. To this end, certain techniques employed to assess kidney functions in adult forms have been applied with profit.

The chick embryo has been a common subject for such tests. Solutions of indigo red and trypan blue injected into the vascular system ultimately appear in the mesonephrons. Another approach has been that of cultivating a fragment of mesonephros in a suitable culture medium to which an indicator such as phenol red has been added. The proximal portions of the tubules pick up the indicator and transport it to their lumina; the distal portions resorb water. Still another method has been the direct identification of nitrogenous wastes deposited in the embryonic bladder, the allantois. *See also:* ALLANTOIS.

Similar experiments on mammals are complicated by the intrauterine location of the embryo and its association with a placenta. Nevertheless, it has been possible either to inject suitable indicators directly into the embryonic

body or to introduce them secondarily by transmission via the placenta from the maternal bloodstream. Such tests on embryos of the rabbit, cat, pig, and pouch-young opossum have provided positive demonstrations of the functioning of both the glomerular filter and the tubule proper.

Metanephros. As the mesonephros is attaining its maximum development, a second generation of nephrons is inaugurated. The history of this group is considerably more complicated than the former and runs briefly as follows. A tubular outgrowth from the Wolffian duct, the ureteric diverticulum, appears close to the entrance of the Wolffian duct into the cloaca and pushes itself anteriorly into the undifferentiated intermediate mesoderm behind the mesonephros. The distal end of this diverticulum enlarges, and the intermediate mesoderm coincidently begins to condense around the enlargement. **Figure 12***a* shows that the proximal segment of the original diverticulum is the ureter, or metanephric duct; the expanded distal end of the diverticulum is the primitive renal pelvis; the condensed mesoderm around the pelvis is the metanephric blastema.

Subsequent events pertain primarily to the pelvis and blastema. The former subdivides first to form the two future major calyces (Fig. 12*b*). These divide and subdivide until several generations of branches are produced. The earlier generations come to represent the minor calyces; the later generations become the collecting tubules (Fig. 12*c* and *d*). As the primitive pelvis carries on this program of subdivision, the blastemal tissue subdivides into a corresponding number of masses. Thus there results a nodule of blastema in association with the end of each prospective collecting tubule (**Fig. 13**). Each such nodule or sphere is the forerunner of a metanephric or uriniferous tubule. The solid sphere first becomes a vesicle which, by elongation, is transformed into a tortuous tubule (Fig. 13). The thinner-walled, blind end of the tubule becomes the capsule surrounding the glomerulus forming concomitantly. Coincidentally, the tip of the prospective collecting duct grows out to meet the end of the tubule and the two unite (Fig. 13). The uriniferous tubules, collecting tubules, and calyces are the definitive kidney or metanephros of the late embryo and adult. In terms of gross anatomy, the convoluted portions of the uriniferous tubules, with their glomerular capsules, collectively form the cortex of the kidney. These tubules lead into the collecting system and calyces making up the medulla of the kidney. All drainage ultimately converges upon the renal pelvis, which in turn leads to the ureter.

Developmental interdependence. Experimental analyses have revealed important developmental interdependencies within the mesonephric and metanephric systems. The original nephric duct grows back from the level of its origin to join the cloaca. In the normal course of events it is joined along the way by mesonephrons and thus becomes the Wolffian duct. If the backward extension of the duct alongside the prospective mesonephros-forming area is prevented, little or no development of the mesonephros will occur. This can be accomplished readily in the chick embryo by producing a minute wound or inserting some block in the pathway of the duct. This is interpreted to mean that the duct serves as an inductor of the mesonephric tubules; that is, differentiation of the mesonephrons depends upon some kind of stimulus provided by the nephric duct. Another consequence of such a blockage of the nephric duct is the elimination of the ureter which normally grows from it. This in turn leads to a failure of the blastema to produce metanephric tubules. The ureter is the inductor of

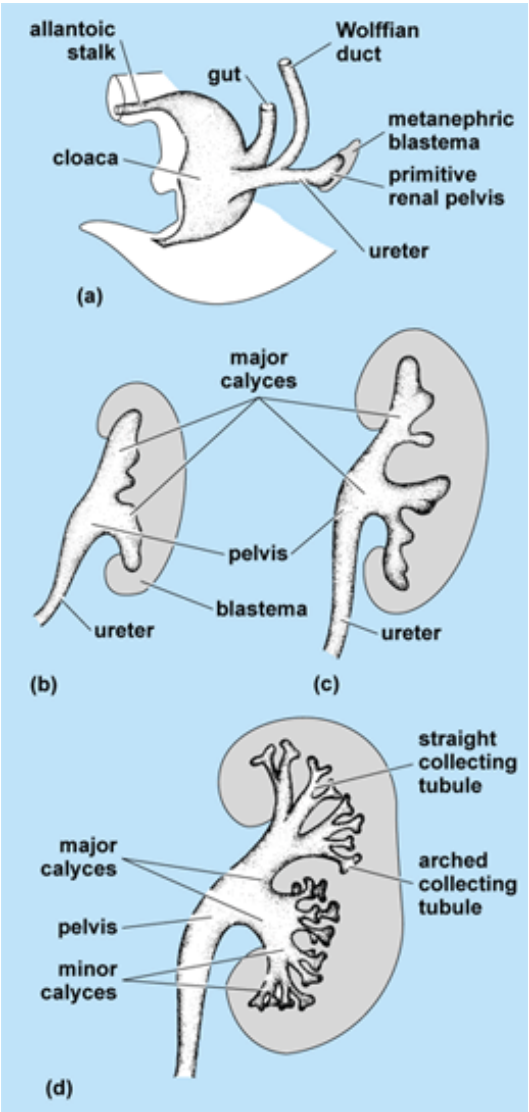

Fig. 12 Stages *a–d* in development of metanephric pelvic and blastema. (*After T. W. Torrey, Morphogenesis of the Vertebrates, 2d ed., John Wiley and Sons, 1968*)

these tubules. Development of the nephros is thus revealed as a series of steps, each dependent upon the one before, with the original nephric duct playing the starting role.

During the latter part of embryonic life the mesonephros and metanephros function simultaneously. Gradually, however, the mesonephros regresses and the metanephros assumes full responsibility for excretion. In females, the mesonephros disappears almost entirely; in males, parts of it are incorporated in the reproductive system. As a consequence of straightening and elongation of the fetal body, the kidneys come to be displaced relatively far forward in the body. *See also:* REPRODUCTIVE SYSTEM.

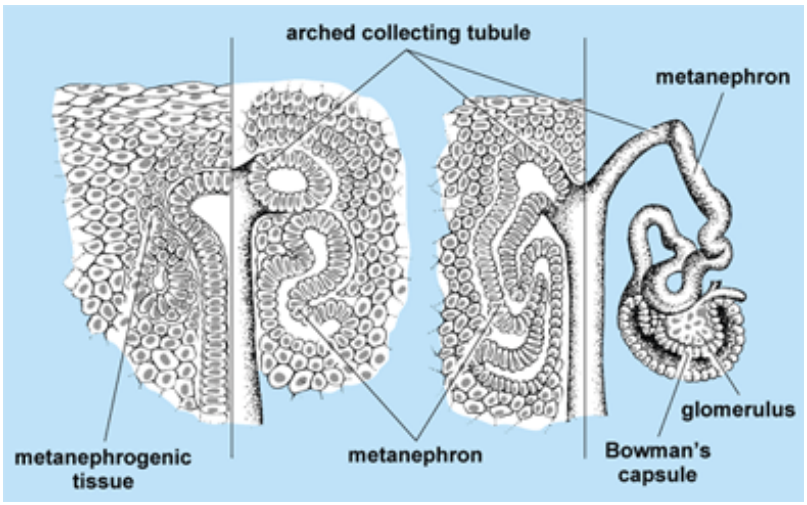

Fig. 13 Differentiating metanephron. (*After T. W. Torrey, Morphogenesis of the Vertebrates, 2d ed., John Wiley and Sons, 1968*)

Urinary bladder

At or near the posterior ends of the nephric ducts there frequently is a reservoir for urine. This is the urinary bladder. Actually there are two basic varieties of bladders in vertebrates. One is found in fishes in which the reservoir is no more than an enlargement of the posterior end of each urinary duct. Frequently the urinary ducts are conjoined and a small bladder is formed by expansion of the common duct. The far more common type of bladder is that exhibited by tetrapods. This is a sac which originates embryonically as an outgrowth from the ventral side of the cloaca. Present in all embryonic life, it is exhibited differentially in adults. All amphibians retain the bladder, but it is lacking in snakes, crocodilians, and a few lizards; birds, also, with one or two exceptions, lack a bladder. It is present in all mammals. Because much of the developmental history of the tetrapod bladder is linked to the history of the cloaca, it will be considered in this conjunction.

Amphibians. The basic pattern is exemplified by the Amphibia. All retain the cloaca as adults and the urinary bladder arises as a diverticulum from the floor of the cloaca (**Fig. 14**). Commonly it is bilobed. There is no direct connection between the excretory ducts and the bladder. Instead, urine first passes into the cloaca and thence into the bladder. Urine is expelled by the intermittent opening of the cloacal orifice and the coincidental contractions of the muscular wall of the bladder.

Reptiles and birds. In reptiles and birds the cloaca is partly subdivided so that the intestine and urogenital ducts open into separate compartments which then join in a common outlet. In the embryo a pouch develops from the floor of the urogenital portion of the cloaca and expands to form a prominent sac known as the allantois. Ultimately the allantois enlarges to extend beyond the confines of the embryo and to fuse broadly with the outermost membrane, the chorion, surrounding the embryo (**Fig. 15**). The combined chorioallantoic membrane

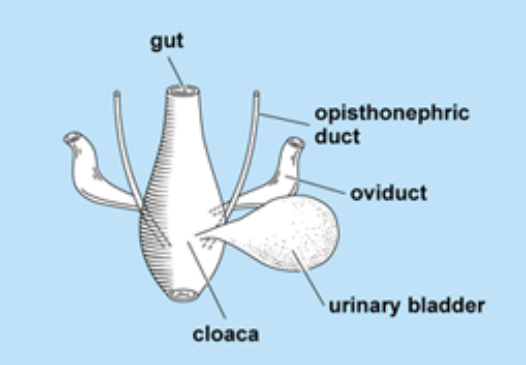

Fig. 14 Cloaca and urinary bladder of a female amphibian. (*After T. W. Torrey, Morphogenesis of the Vertebrates, 2d ed., John Wiley and Sons, 1968*)

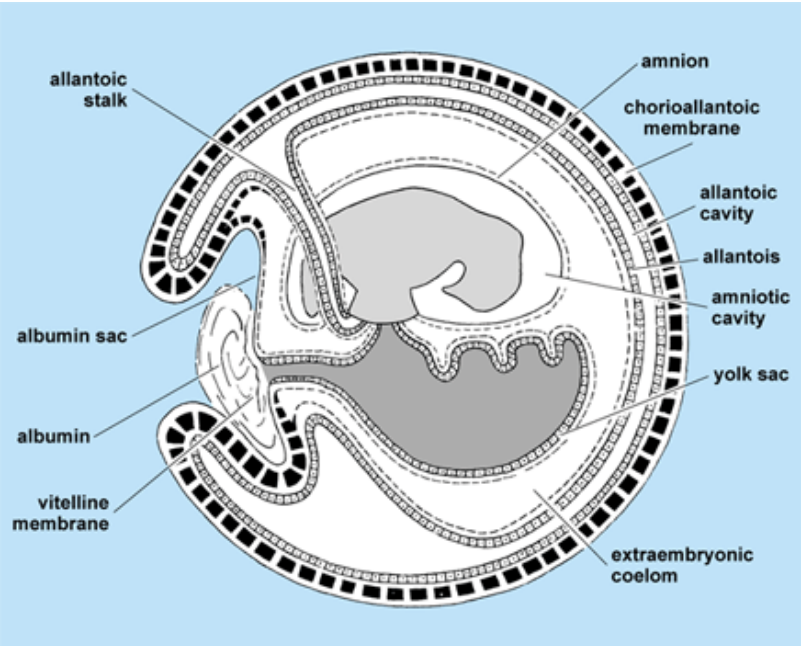

Fig. 15 Fully matured extraembryonic membranes of the chick. (*After T. W. Torrey, Morphogenesis of the Vertebrates, 2d ed., John Wiley and Sons, 1968*)

ultimately makes broad contact with the membrane lining the inner surface of the shell. This fusion and spreading of the allantois serves to bring an extensive blood supply adjacent to the shell and thus sets up a medium for respiratory exchange. The allantois, therefore, serves not only as a reservoir for urine but also plays a major role in embryonic respiration. *See also:* FETAL MEMBRANE.

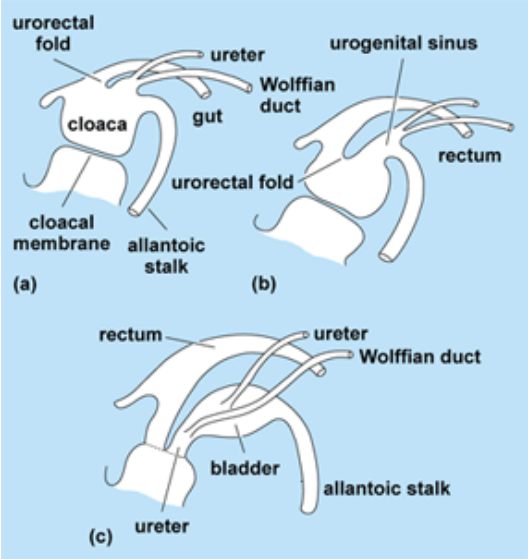

Fig. 16 **Development of cloaca and urinary bladder. (*a*) Formation of cloacal membrane. (*b*) Urorectal fold formation. (*c*) Urethra formation.**

In birds the entire allantois is discarded at hatching and no adult urinary bladder is retained. This is also true for most reptiles although some, notably the turtles and certain lizards, retain the base of the allantois as an adult bladder, and the remainder atrophies.

Mammals. Among mammals, only a few primitive forms retain a cloaca as adults. In all the others it is modified in such a way as to be eliminated. Concomitantly, the openings of the excretory ducts are shifted and the urinary bladder is established. The pig embryo may serve to illustrate the usual events.

Almost as soon as the cloaca is established, an allantois arises from its floor. As in reptiles and birds, the allantoic sac, complete with blood vessels, expands greatly and fuses with the chorion. This association enables it to serve not only as a urinary bladder, but also to provide a major component of the placenta, so important in fetal economy. In the meantime the cloaca itself is modified. The cloaca initially ends blindly, its ventroposterior floor making contact with the embryonic skin to form the cloacal membrane (**Fig. 16***a*). A division of the cloaca into two parts, a dorsal rectum and ventral urogenital sinus, then follows. This division is effected by the urorectal fold, a crescentic fold which works backward from the angle where the allantois, excretory ducts, and gut meet until it meets the cloacal membrane (Fig. 16*b* and *c*). Not only is the cloaca itself subdivided, but the cloacal membrane is likewise divided into an anal and urethral membrane. Both these membranes eventually rupture so that the two parts of the cloaca open independently to the exterior.

The next step is the enlargement of that portion of the urogenital sinus receiving the neck of the allantois. The enlargement may involve a part of the allantoic stalk itself. This enlargement is the beginning of the definitive urinary bladder. As the bladder expands, the terminal ends of the Wolffian ducts which open to the urogenital

sinus at this level are absorbed into the bladder wall. In consequence, the ureters, which stemmed initially from the Wolffian ducts, come to open directly to the growing bladder while the Wolffian ducts open somewhat behind into that part of the sinus which remains narrower and gives rise to the urethra (Fig. 16*c*). The ultimate fate of the Wolffian ducts and the final form of the urethra differ between the two sexes. The allantois per se is discarded at birth.

Theodore W. Torrey

Physiology

Urine is produced by individual renal nephron units which are fundamentally similar from fish to mammals (Fig. 4); however, the basic structural and functional pattern of these nephrons varies among representatives of the vertebrate classes in accordance with changing environmental demands. Kidneys serve the general function of maintaining the chemical and physical constancy of blood and other body fluids. The most striking modifications are associated particularly with the relative amounts of water made available to the animal. Alterations in degrees of glomerular development, in the structural complexity of renal tubules, and in the architectural disposition of the various nephrons in relation to one another within the kidneys may all represent adaptations made either to conserve or eliminate water. The urinary systems of fishes, amphibians, reptiles, birds, and mammals will be compared to see how they respond to demands imposed by various freshwater, marine, amphibious, terrestrial, and desert environments that influence their development and differentiation.

General principles

Certain basic principles underlie excretory processes in all animals, from protozoa to humans. These are regulation of volume, electrolyte balance, movement of water across cell membranes, and the elimination of nitrogenous substances.

Regulation of volume. Paleontological evidence strongly suggests that early vertebrates evolved in freshwater, or at least that progenitors of modern fishes had a long history of dwelling in freshwater. Kidneys of living vertebrates bear the imprint of this early evolutionary history. Except for the primitive marine cyclostome *Myxine*, all modern vertebrates, whether marine, freshwater, or terrestrial, have concentrations of salt in their blood only one-third or one-half that of seawater (**Fig. 17**). The early development of the glomerulus can be viewed as a device responding to the need for regulating the volume of body fluids. Hence, in a hypotonic freshwater environment the osmotic influx of water through gills and other permeable body surfaces would be kept in balance by a simple autoregulatory system whereby a rising volume of blood results in increased hydrostatic pressure which in turn elevates the rate of glomerular filtration. Similar devices are found in freshwater invertebrates where water may be pumped out either as the result of work done by the heart, contractile vacuoles, or cilia found in such specialized “kidneys” as flame bulbs, solenocytes, or nephridia that extract excess water from the body cavity rather than from the circulatory system. Hence, these structures which maintain a constant water content for the

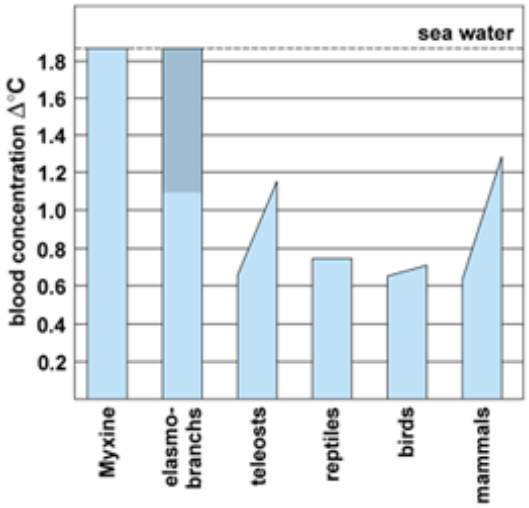

Fig. 17 **Solute concentrations in blood of various marine vertebrates. Only *Myxine* and the elasmobranchs have blood isosmotic with seawater. Note the significant contributions of organic solutes, urea, and trimethylamine oxide (shaded) to the total osmotic concentration of elasmobranch blood. (*After A. P. McLockwood, Animal Body Fluids and Their Regulation, Harvard University Press, 1964*)**

invertebrate animal by balancing osmotic influx with hydrostatic output have the same basic parameters as those in vertebrates that regulate the formation of lymph across the endothelial walls of capillaries.

None of the marine invertebrate phyla seem to have had a freshwater ancestry. Members of the phylum Echinodermata, generally regarded as the closest relatives of the protovertebrate ancestors of fishes, have body fluids that are isosmotic with seawater, and they have no trace of any structure that resembles a kidney or other kind of excretory organ. *See also:* OSMOREGULATORY MECHANISMS.

Electrolyte balance. A system that regulates volume by producing an ultrafiltrate of blood plasma must conserve inorganic ions and other essential plasma constituents. The salt-conserving operation appears to be a primary function of the renal tubules which encapsulate the glomerulus. As the filtrate passes along their length toward the exterior, inorganic electrolytes are extracted from them through highly specific active cellular resorptive processes which restore plasma constituents to the circulatory system. The ability to form a urine hypotonic to blood is related to the length of the tubule. Animals, such as freshwater fishes and amphibians, that produce a urine almost as dilute as distilled water have very long tubules with specially developed distal segments that are impermeable to water while they extract and restore to the blood almost every trace of salt from tubular urine before it enters the bladder. Proximal segments can also actively resorb salt, but their cells are freely permeable to water so that proximal tubular fluid is always isosmotic with respect to blood. Urine of marine fishes is always approximately isotonic with blood, and their renal tubules are short, with the specialized distal segment absent. Proximal tubule cells of all vertebrates also actively resorb glucose, amino acids, and other organic compounds from filtrate. Additionally they actively secrete foreign substances from blood into proximal tubular fluid.

Movement of water. Concentration gradients of water are attained across cells of renal tubules by water following the active movement of salt or other solute. Where water is free to follow the active resorption of sodium and covering anions, as in the proximal tubule, an isosmotic condition prevails. Where water is not free to follow salt, as in the distal segment in the absence of antidiuretic hormone, a hypotonic tubular fluid results. A special case is examined below of hypertonic urine formed when water is free to diffuse into a solution of high salt concentration surrounding mammalian collecting ducts when the cells are not correspondingly permeable to solute.

Nitrogenous end products. Of the major categories of organic foodstuffs, end products of carbohydrate and lipid metabolism are easily eliminated mainly in the form of carbon dioxide and water. Proteins, however, are more difficult to eliminate because the primary derivative of their metabolism, ammonia, is a relatively toxic compound. For animals living in an aquatic environment, ammonia can be eliminated rapidly by simple diffusion through the gills. It is formed by relatively simple biochemical processes of deamination and transamination, which do not require the expenditure of free energy. However, when ammonia is not free to diffuse into an effectively limitless aquatic environment, its toxicity presents a problem, particularly to embryos of terrestrial forms that develop wholly within tightly encapsulated eggshells or cases. For these forms the detoxication of ammonia is an indispensable requirement for survival. During evolution of the vertebrates two energy-dependent biosynthetic pathways arose which incorporated potentially toxic ammonia into urea and uric acid molecules, respectively. Both of these compounds are relatively harmless, even in high concentrations, but the former needs a relatively large amount of water to ensure its elimination, and uric acid requires a specific energy-demanding tubular secretory process to ensure its efficient excretion. *See also:* EXCRETION.

Methodology

The comparative physiological approach can be justified solely for information about the nature of the human's world, but it often contributes also to the solution of practical problems. For example, studies on the peculiar aglomerular kidney of the American anglerfish or goosefish (*Lophius*) led directly to the development of clinical renal clearance tests; micropuncture techniques that took advantage of the unusually large nephrons of the mudpuppy (*Necturus*) proved the hypothesis of glomerular filtration and identified specific sites along the renal tubule as loci of discrete secretory and resorptive processes; and observations on the structural and functional modifications in kidneys of the desert rat and other mammalian forms of arid regions showed how the countercurrent multiplier system operates in the renal medulla to concentrate urine. These examples show where an exploitation of experimental variables provided by nature led directly to new methods or information of general significance in renal physiology and pathology.

Rate of glomerular filtration. Following the disclosure that certain carbohydrates could not be excreted by aglomerular kidneys, a search was then undertaken to find some freely filterable nonmetabolizable carbohydrate which was also not resorbed by the renal tubules of glomerular kidneys. This led eventually to employment of the polysaccharide inulin in an application of the Fick principle to measure the rate of glomerular filtration. Knowing

the total number of milligrams of inulin appearing in bladder urine per minute, one could determine the number of milliliters of filtrate needed to supply this amount by dividing the total number of milligrams excreted per minute by the number of milligrams of inulin in 1 ml of glomerular filtrate. This technique is applied to any intact animal or human patient by quantitatively collecting bladder urine, usually with the aid of a urethral catheter, and simultaneously sampling the inulin content of arterial blood. The latter is used in place of glomerular filtrate, which is virtually impossible to obtain, because the inulin contents of arterial blood and filtrate are identical. Only red blood cells and proteins are retained during the process of ultrafiltration. Hence the glomerular filtration rate (GFR) is determined by Eq. (1),

$$\mathrm{GFR} = \frac{U_{\mathrm{in}} V}{P_{\mathrm{in}}} \tag{1}$$

where U_{in} is the amount of inulin in 1 ml of urine, V the number of milliliters of urine formed per minute, and P_{in} the amount of inulin in 1 ml of arterial plasma (filtrate).

Tubular resorption and secretion. Knowing the volume of filtrate formed per minute, one can measure the amount of any freely filterable plasma constituent being filtered as GFR $\times P_x$, where P_x is the amount of plasma glucose, urea, amino acid, or other constituent in 1 ml of arterial blood (glomerular filtrate). The amount of this plasma constituent either resorbed or secreted by the tubules is then determined as the difference between the amounts filtered and that finally appearing in urine. For glucose, which is resorbed subsequent to filtration, this would be GFR $\times P_{\mathrm{G}} - U_{\mathrm{G}} V$. For penicillinic acid, which is profusely secreted into urine by the renal tubule cells from postglomerular blood that supplied the tubules, it would be $U_{\mathrm{Pa}} V -$ GFR $\times P_{\mathrm{Pa}}$.

For most organic compounds actively secreted or resorbed by the renal tubules subsequent to being filtered, there is a maximal limit imposed on the tubular transport rate (T_{m}). This maximal rate of transfer may be dependent upon the saturation of carrier capacity or upon a limitation in the amount of free energy available for moving these compounds across barriers against their own concentration gradients. Analogous compounds that are secreted or resorbed simultaneously may compete with one another for common carrier; raising the concentration of one will depress the transport rate of the other.

Renal plasma flow (RPF). The Fick principle is used to measure the amount of blood or plasma flowing through the kidneys per minute. For example, if the total milligrams of inulin excreted per minute ($U_{\mathrm{in}} V$) is determined and divided by the number of milligrams removed from 1 ml of plasma as it traverses the kidney (arterial-venous difference or art. P_{in} − ven. P_{in}), then one knows the number of milliliters of plasma that was delivered to the kidneys per minute in order to account for the total number of milligrams of inulin excreted per minute.

However, use of inulin for this purpose calls for separate sampling of blood from the renal artery and the renal vein. Arterial blood from any part of the body can be used for concentrations of plasma constituents in renal

arterial blood, but samples for venous blood must be from the renal vein, and this poses a serious problem in studies on intact animals or patients. Fortunately, certain foreign substances are secreted so profusely by the tubules that, when they are infused into the circulation slowly, only low concentrations accumulate in arterial blood, and they are completely extracted while traversing the renal circulation. Inulin, excreted solely by glomerular filtration, is only 20% extracted in most mammals, but some compounds such as penicillin and *para*-aminohippuric acid (PAH) are almost completely removed by tubular secretion subsequent to glomerular filtration. So with low art. P_{PAH}, the value for ven. P_{PAH} may be assumed to be zero in the Fick equation, and the RPF is determined from Eq. (2).

$$\text{RPF} = \frac{U_{PAH} V}{\text{art. } P_{PAH}} \tag{2}$$

Thus the total number of milligrams of PAH extracted from the circulation by the kidneys per minute, divided by the number of milligrams of PAH extracted from each milliliter of plasma, gives the total number of milliliters of plasma that came to the kidneys per minute in order to account for the number of milligrams of PAH extracted (excreted) per minute. The small amount of nonextracted PAH in venous blood probably represents that fraction of blood which supplies nontubular tissue. Hence, RPF measurements made by this method are sometimes referred to as "effective" RPF, to represent that which is selectively supplied to active tubular tissue; other extraglomerular blood goes to inert fat, connective tissue, and the renal capsule.

Filtration fraction. When both GFR and RPF are known, one can obtain another hemodynamic parameter. Alterations in the fraction of plasma filtered, FF = GFR/RPF, can give insight into whether vasomotor arteriolar changes occur mainly afferent to the glomeruli or as alterations in the diameter of efferent arterioles leading away from the glomeruli. If constriction occurred solely in the afferent glomerular arterioles, one would expect both GFR and RPF to fall correspondingly, and the FF would remain constant. If, however, resistance increased exclusively in the efferent arteriole, RPF would fall as before but the effective glomerular filtration pressure would be expected to rise, thereby increasing the fraction filtered.

In most mammals an average of about one-fifth of the plasma delivered to glomeruli is filtered. Lower vertebrates have much lower filtration fractions because of the separate renal portal (venous) circulation that bypasses the glomeruli and goes directly to the tubules. Hence, the high-pressure arterial blood supply that exclusively sustains glomerular filtration in all vertebrates constitutes a relatively small fraction of the total amount of blood delivered to the kidney in inframammalian forms.

Micropuncture. With the development of exquisitely delicate techniques that enable one to deal quantitatively with nanoliter (10^{-9} liter) fluid samples, physiologists turn to direct micrurgical techniques to study specific secretory and resorptive processes in assignable loci of renal tubule and collecting ducts. Minute samples of urine can be obtained either while urine is flowing freely within the tubular lumen, while tubules are being perfused with

various solutions, or while flow is stopped by injections of oil at selective sites in "split-drop" experiments. Simultaneously, blood samples can be obtained from adjacent regions, and methods are available to measure electrical potential differences and flow of current across tubule cells or across separate cell membranes on the vascular and luminal sides of tubular epithelium.

Stop-flow technique. It is also possible to localize specific secretory and resorptive processes in intact animals by clamping the ureters to allow a stationary column of tubular urine to be held in contact with the tubular epithelium for several minutes. This permits cells in the various segments to operate on the urine in the column, thereby exaggerating processes that modify the composition of tubular urine in specific regions. The clamp is then released; and while urine spurts out under pressure, several dozen serial samples are collected and subjected to chemical analyses. The first samples come from the pelvis, collecting ducts, and distal segments of the tubule; later samples are from segments more proximal to the glomerulus; and finally filtrate and urine formed after release of the clamp are sampled. Some substance excreted solely by glomerular filtration is used as a marker, and its concentration reflects reabsorption of water by the tubule segments. Any urinary component whose concentration rises with reference to the marker is assumed to be secreted in that area; and when its relative concentration falls, it is assumed to be resorbed in the segment corresponding to that particular serially collected sample. **Figure 18** shows a stop-flow analysis in which the site of reabsorption of the amino acid glycine AN is identified as being in the same proximal region in which PAH is secreted. Ammonia (NH_4^+) is secreted distally. In this case creatinine was used as a marker, and the urine/plasma (U/P) concentration ratios of PAH and NH_4^+ were factored by the corresponding U/P ratio of creatinine to correct for reabsorption of water which occurred at varying rates along the nephron during the stoppage of flow.

Culture methods. Isolated renal tubules and thin slices of kidney in suitably oxygenated, balanced salt solutions containing substances capable of being secreted continue to carry on their cellular transport activities for several hours. In the simplest preparations a colored organic compound such as phenol red can be directly observed under the microscope as it is progressively concentrated to a very high degree within the lumen of renal tubules. Such studies have thrown considerable light on carrier-mediated transport competition and the nature of energy dependence. More complicated techniques involve use of chemical analyses and techniques for microperfusing isolated tubules with synthetic solutions of known composition. Fish kidneys, especially of the marine flounder, are particularly useful for tissue culture because they contain little cementing substance and the individual tubules can be easily teased apart. *See also:* TISSUE CULTURE.

Patterns of excretion

Nephrons of primitive protovertebrates probably were supplied exclusively with venous blood, and the open-ended tubules had nephrostomes that drained fluid directly from the body cavity. With the assumption of a freshwater habitus and the need for osmoregulation, it is thought that fishes acquired a glomerulus that at first was perhaps only loosely associated with the coelomostome, as in the embryonic pronephros of present-day vertebrates. Eventually a dual blood supply became possible when the glomerulus supplied with arterial blood

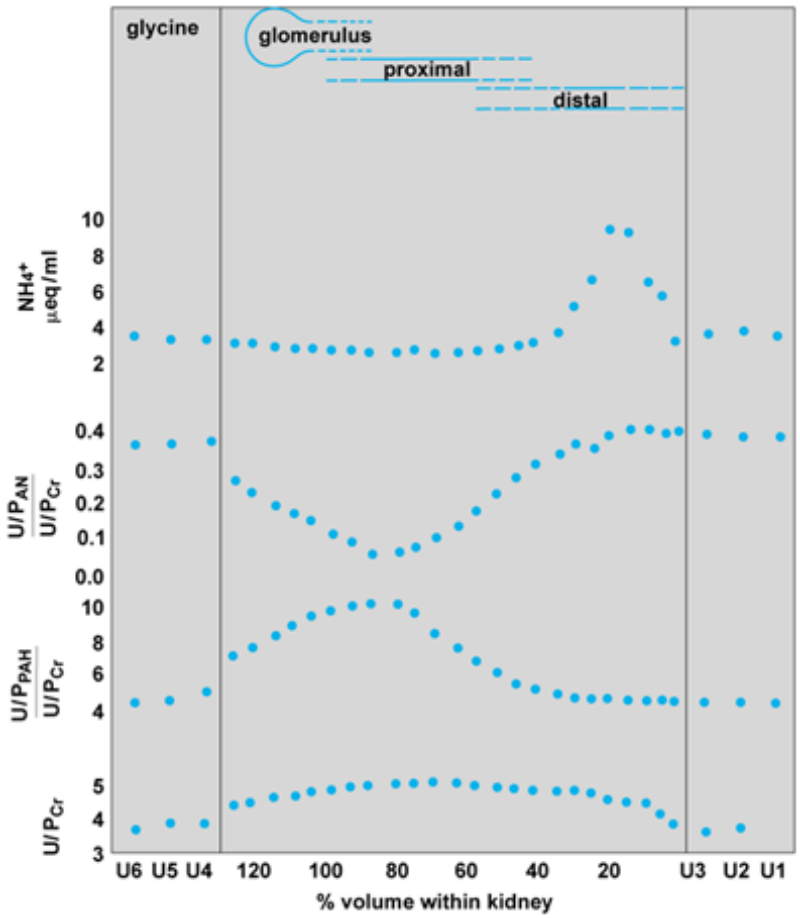

Fig. 18 **Stop-flow analysis of the sites of ammonia secretion, aminonitrogen resorption, and PAH secretion.** (***After R. F. Pitts, Physiology of the Kidney and Body Fluids, Year Book Medical Publishers, 1963***)

became tightly encapsulated within the end of the tubule, but the open coelomostome persisted in some lower vertebrates. With the evolution of a homeostatically regulated internal environment and the guarantee of constant high-pressure filtration at the glomerulus, the renal portal system disappeared in mammals leaving the renal tubule solely with an arterial postglomerular bloody supply (**Fig. 19**).

The functional significance of the venous renal portal supply in a cold-blooded form such as the frog, for example, probably derives from its ability to maintain tubular secretory activity under environmental conditions that would tend to reduce arterial blood pressure to the point where glomerular filtration ceases. Glomerular activity generally is more labile in cold-blooded vertebrates than in mammals. Rates of filtration rapidly fall in fishes and amphibians when they are stressed either by evaporation or osmoregulatory water deprivation, or by cold. Lower vertebrates also rely more on tubular secretory processes for sustenance when glomerular filtration is diminished or ceases entirely and when the low-pressure venous supply of the renal portal system may be the sole source of blood for the kidney.

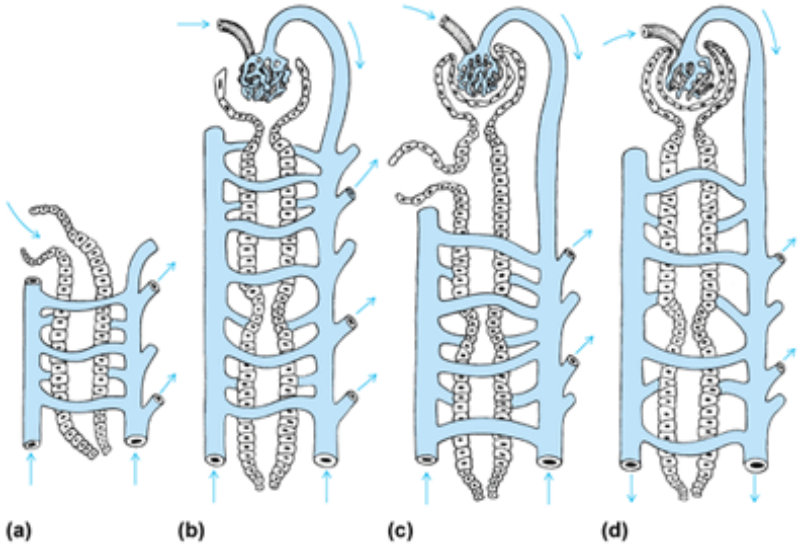

Fig. 19 **Probable stages in the evolution of the vertebrate nephron; arrows indicate direction of flow. (*a*) Hypothetical protovertebrate tubule drained the body cavity through an open coelomostome with only a venous blood supply. (*b*) In earliest vertebrates the coelomostome was brought into loose association with knots of arterial blood vessels capable of filtering fluid under hydrostatic pressure. (*c*) Later evolution sealed Bowman's capsule in the glomerulus. (*d*) In mammals the renal portal venous supply and coelomostomes disappeared. (*After H. W. Smith, From Fish to Philosopher, Little, Brown, 1959*)**

Teleost fishes. The urinary system of fishes plays only a secondary role in the excretion of nitrogenous waste products. As much as 90% of the nitrogen that comes from the deamination of amino acids is usually excreted at the gills in the form of ammonia. Fish in freshwater form large quantities of glomerular filtrate, and this is desalinated by their characteristically long renal tubules which eventually produce copious volumes of essentially salt-free urine. Freshwater fishes excrete urine equivalent to 30% of their body weight per day, and the dilute urine may have freezing point depressions as low as Δ 0.07°F (Δ 0.04°C). Anadromous forms such as the salmon and steelhead trout show markedly reduced urine flow and glomerular filtration rates when in their seawater habitat.

Marine teleosts need to conserve free water in maintaining solute concentrations in blood that are only about half that of seawater (average is approximately Δ 1.62°F (Δ 0.9°C); seawater freezes at 28.54°F (−1.86°C). Production of urine is scanty; glomeruli are reduced in size and totally absent in some 20 species of marine teleosts. After intake of seawater and following intestinal absorption, blood is desalinated to maintain water balance by the gills, which remove the monovalent sodium and chloride ions, and the kidneys, which extract divalent magnesium, calcium, and sulfate ions. These ion transfers are carried out by specific energy-demanding active transport processes, which operate in opposite directions in similar branchial and renal systems of freshwater fishes. Distal tubules are absent in marine fishes, and the urine of both the glomerular and aglomerular forms is roughly isosmotic with that of blood.

Cyclostomes. Primitive hagfishes such as *Myxine* resemble marine invertebrates and are unique among vertebrates in that their blood is isosmotic with seawater, due almost entirely to the accumulation of inorganic ions (Fig. 17). Hence no osmoregulatory mechanisms are required. Freshwater and brackish lampreys such as *Lampetra*, on the other hand, produce copious flows of dilute urine, and their renal function resembles that of freshwater and diadromous teleosts.

Cartilaginous fishes. Sharks, skates, rays, and chimeroids living in the sea prevent water loss to the marine environment in a way that is totally different from that of marine teleosts. They have relatively large glomeruli and they do not drink seawater; instead the renal tubules have specialized processes capable of extracting urea and trimethylamine oxide from glomerular filtrate, and the active resorption of these organic compounds raises the osmotic concentration of their blood and body fluids to equality with seawater (Fig. 17).

Lungfishes. Urinary systems of freshwater dipnoans function similarly to those of freshwater teleosts. However, during estivation all urinary functions stop, and potentially toxic ammonia is then converted by the liver to urea which may accumulate in body fluids to extremely high levels without causing damage. When floods occur after periods of drought sometimes lasting several years, water is rapidly taken up osmotically, and the resulting increase in blood volume and pressure restores glomerular filtration; then a copious production of urine rapidly removes urea and other waste products accumulated during estivation. It is interesting that of the three surviving lungfishes, the Australian lungfish (*Neoceratodus forsteri*), which cannot estivate or survive out of water, is the only one incapable of synthesizing urea via the so-called ornithine cycle that accounts for the production of urea in the African and South American lungfishes, both of which can estivate.

Amphibians. The purely aquatic urodeles, such as *Necturus*, and the tadpole stages of anuran frogs and toads have patterns of urinary excretion similar to that of freshwater teleosts. However, during metamorphosis when anurans change from gill to lung breathing, nitrogen is excreted principally in the form of urea rather than ammonia. Urea is actively secreted by the tubules of the more aquatic frogs, but it does not appear in terrestrial toads or in the unusual crab-eating frog (*Rana cancrivora*) of Southeast Asia that lives in marine mangrove swamps. Such retention of urea could serve the same osmoregulatory function that it does in marine cartilaginous fishes, that is, to help toads in an arid environment to absorb water quickly through the skin during brief showers, and to provide a more favorable free-water gradient for the marine toad in its hyperosmotic environment. Renal accommodations to semiterrestrial life in amphibians, which involve glomerular recruitment, facultative tubular reabsorption of water, and alterations in the synthesis and secretion of urea, are undoubtedly implicated also in such amphibious fishes as the tree-climbing perch (*Anabas*), the mudskippers, many gobies, and such reptiles as the aquatic turtles, alligators, and many water snakes which may alternately live in and out of an aqueous environment.

Terrestrial reptiles and birds. These egg-laying forms have adapted to "uricotelism," which effectively provides for detoxification of ammonia and also for extremely efficient conservation of water. In addition to having relatively low rates of glomerular filtration, uric acid can be actively secreted by the tubules to form a urine practically

saturated with urate. Actual precipitation of solid urate occurs in the allantoic bladder of embryos and in the cloaca of adults, and masses of white crystals are found as residues in hatched eggshells and feces, respectively.

Mammals. The placental form of embryonic development in mammals guaranteed an aquatic environment for the fetus which permitted retention of the "ureotelic" habitus. The renal portal system disappears in mammals, whose tubules are supplied solely with blood that has previously traversed the arterial glomerular capillaries (Fig. 19). The unique functional feature of the mammalian kidney is its ability to concentrate urine. Human urine can have four times the osmotic concentration of plasma (1200 milliosmoles/liter), and some desert rats that survive on a diet of seeds without drinking any water have urine/plasma concentration ratios as high as 17 (6.34 Δ osmoles/liter, more than six times that of seawater). More aquatic forms such as the beaver have correspondingly poor concentrating ability.

The concentration operation depends on the existence of a decreasing gradient of solute concentration that extends from the tips of the papillae in the inner medulla of the kidney outward toward the cortex. The high concentration of medullary solute is achieved by a double hairpin countercurrent multiplier system which is powered by the active removal of salt from urine while it traverses the ascending limb of Henle's loop (**Fig. 20**). The salt is redelivered to the tip of the medulla after it has diffused back into the descending limb of Henle's loop. In this way a hypertonic condition is established in fluid surrounding the terminations of the collecting ducts. Urine is concentrated by an entirely passive process as water leaves the lumen of collecting ducts to come into equilibrium with the hypertonic fluid surrounding its terminations.

Urine more dilute than plasma is formed when hypotonic urine delivered by the ascending limb to the cortex traverses the lengths of distal tubules and collecting ducts and it is not free to come into equilibrium with the progressively more salty interstitial fluids of the cortex, outer medulla, and inner medulla, respectively.

Another countercurrent exchange system operating in the straight blood vessels (vasa recta) that parallel the loops of Henle prevents washout of the hypertonic interstitial fluid of the inner medulla where the blood is in osmotic equilibrium with the surrounding interstitial fluid. Because of the hairpin arrangement of the vasa recta, salt and other solutes are trapped and kept from being carried away from the medulla (left side of Fig. 20). As solute diffusing from the ascending capillary limb comes into equilibrium with more dilute interstitial fluid nearer the cortex, it enters the descending vessel to be redelivered to the inner medulla. This entirely passive process involving exchange of solute is the same as that operating in countercurrent heat exchangers.

Removal of most of the salt from glomerular filtrate takes place in the proximal convoluted tubules of the renal cortex. Sodium is actively resorbed from tubular fluid, and chloride then passively follows down an electrical gradient. Removal of solute effects the simultaneous isosmotic entry of water into the cortical interstitial fluid. This solution, containing about 300 milliosmoles of solute, is then rapidly restored to the general circulation by blood perfusing the cortical capillaries. In humans, about 80% of the glomerular filtrate is withdrawn by the time tubular fluid enters the descending limbs of Henle's loops. During water diuresis the distal tubules and collecting

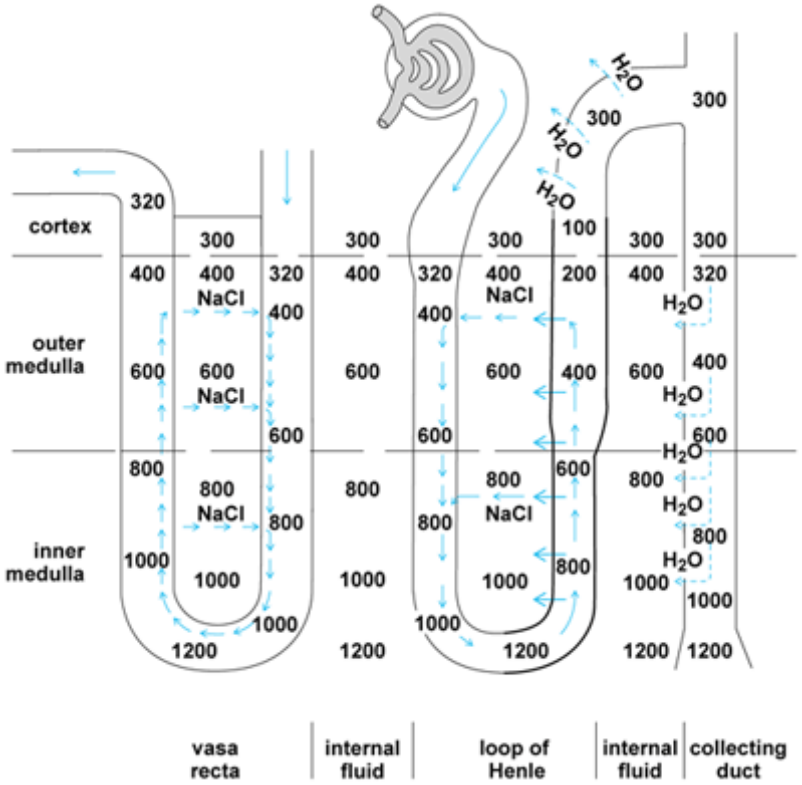

Fig. 20 **The tubular countercurrent mechanism for concentrating the urine, and the exchange system in the straight hairpin blood vessels of the medulla, which minimizes loss of solute from medullary interstitial fluid. Arrows indicate direction of movement of solute. (*After A. C. Guyton, Textbook of Medical Physiology, Saunders, 1966*)**

ducts are relatively impermeable to water, and the hypotonic urine then leaving the loops of Henle is made even more dilute by continued active extrusion of ions, finally resulting in the elimination of large volumes of urine containing little solute. In contrast, during conditions demanding conservation of water antidiuretic hormone (ADH) is released by the posterior pituitary gland, and the distal tubules and collecting ducts are then rendered freely permeable to water. Urine in the presence of ADH is isotonic by the time it reaches the middle of the distal segment, and its volume has been drastically reduced by the continued active extrusion of sodium and the associated passive diffusion of water. The small amount of isosmotic urine entering the collecting duct is progressively concentrated as it gives up water to the hypertonic medullary interstitial fluid and finally achieves a maximal concentration of solute equivalent to that of fluid surrounding the collecting ducts at the papillary tips.

Regulation mechanisms

Many years ago it was shown that injection of crude extracts of pituitary glands into frogs and toads caused rapid weight gain by accumulation of water. Now a whole family of octapeptides is known to be secreted by neurons of the hypothalamus of the brain and then transported by axons to the pituitary gland where they are stored in

the neurohypophyseal lobe. Two of these, arginine vasotocin and vasopressin, oppose diuresis in terrestrial and semiterrestrial vertebrates, and they are frequently referred to as ADH. ADH increases water uptake by opening pores in the skin and urinary bladders of anurans and diminishes urinary output both by increasing the extraction of water from distal tubular urine and by reducing the rate of glomerular filtration. Secretion of ADH is regulated by osmoreceptors in the hypothalamus. Among teleosts secretions of a neurosecretory system in the posterior region of the spinal cord are passed along into a neurohemal organ, the urohypophysis, via a structural and functional arrangement similar to the hypothalamic-neurohypophyseal system of the terrestrial forms.

Renal regulation of electrolytes is accomplished by steroid hormones produced by the adrenal cortex or by homologous tissues in the lower vertebrates. In the absence of cortical steroids kidneys cannot adequately retain sodium and chloride; serum potassium levels are elevated; and there is a marked reduction in blood volume with death inevitably ensuing. Aldosterone is the most potent cortical steroid in mammals. Its release is regulated by changes in the electrolyte level of blood flowing through the brain and kidney. It also promotes sodium retention and potassium loss in sweat and gastrointestinal glands. *See also:* STEROID.

In the frog, however, aldosterone induces the renal tubule to retain potassium and lose sodium. Its effect on the kidney is just the opposite of that in mammals; nevertheless, the frog recovers sodium even more efficiently from bladder urine, and the net result in conserving salt is the same.

Renin is a proteolytic enzyme probably produced by specialized secretory cells in the afferent glomerular arteriole. It reacts with a plasma component to produce a nonprotein substance called angiotensin II which is capable of raising arterial blood pressure. There are several lines of evidence that suggest that the kidney's renin-angiotensin system is a prime regulator of the secretion of aldosterone by the adrenal cortex. Apparently some kind of feedback regulation mutually controls these two important secretions that regulate blood pressure, renin by affecting peripheral resistance in the arterioles, and angiotensin II by controlling retention of salt, hence blood volume and pressure. A negative feedback mechanism could be triggered by hemorrhage or some other factor, causing a temporary decrease in renal arterial blood pressure and renal blood flow. The resultant hypotension could activate the renin-angiotensin system causing the release of aldosterone, which in turn would induce the renal tubules to retain sodium and to increase blood volume, and consequently to raise blood pressure. Such a negative feedback path would then be the afferent signal needed to inactivate the renin-angiotensin system. This is speculative, but the system is of interest to both clinicians and comparative physiologists.

There is also a feedback regulatory system within the kidney itself that apparently coordinates tubular and glomerular function. The juxtaglomerular apparatus which is found in all classes of vertebrates consists of specialized tubular epithelium at the end of Henle's loop (macula densa) and of renin-containing cells in the afferent arterioles. These two separate types of specialized cells come into intimate contact with one another, and the two apposing parts always belong to the same nephron. There is considerable evidence to support the hypothesis that an increased concentration of salt in tubular urine at the macular densa site activates a sodium-sensitive feedback system which operates through the juxtaglomerular apparatus to reduce the rate of

glomerular filtration and thereby adjust the tubule's load of filtered salt to the sodium reabsorptive capacity of this particular nephron. *See also:* ENDOCRINE MECHANISMS; URINE.

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