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Development, Differentiation and Derivatives of the Wolffian and Müllerian Ducts

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1. Introduction

The Wolffian ducts (pro- and mesonephric ducts) are the most important and earliest structures formed during the development of the urogenital system in vertebrates including humans. The Wolffian ducts originate in the prospective cervical region of the young embryo but later migrate caudally inducing the development of the pronephric and mesonephric tubules along their migratory route. In addition to being the inducers of the first two generations of the kidney, namely the pronephros and mesonephros, the Wolffian ducts also give rise to the ureteric buds which drive the growth and differentiation of the permanent kidneys, the metanephroi. The paired ureteric bud arises as outpouching from the caudal end of the Wolffian duct and induces the epithelialisation of the metanephric blastema leading to the formation of the renal corpuscles and tubular part of the nascent metanephric kidney, while the entire collecting system consisting of the ureter, the renal pelvis, the calyces and the collecting ducts take their origin from the ureteric bud.

Gender specific contributions of the Wolffian ducts amount to the induction and development of the Müllerian (paramesonephric) ducts, the anlagen of the female genital ducts, while in males, the Wolffian ducts elongate to form the epididymal ducts and the vasa deferentia. The seminal vesicles are formed during regression and transformation of the mesonephroi.

The developmental significance of the Wolffian duct for the development of the excretory and genital system can be drawn from the extirpation experiments in vertebrate embryos where the absence of Wolffian ducts showed that neither kidneys, nor male or female genital ducts develop.

Human embryos shown in this article were collected by the late Prof. K.V. Hinrichsen during the years 1970 till 1985. They are from legally terminated pregnancies in agreement with the German law and following the informed consent of the parents. For the description of human embryos the Carnegie stages (CS) are used.

2. Wolffian ducts

The Wolffian ducts are named after the German anatomist Caspar Friedrich Wolff (1733-94) who first described the paired mesonephros, also called Wolffian body and its duct. The

mesonephroi represent the second kidney generation of vertebrates. The first generation, the pronephroi precede the mesonephroi in a temporal and spatial sequence. The pronephric ducts are continuous caudally with the mesonephric ducts. Therefore, we use the term Wolffian ducts for the common pro- and mesonephric ducts.

2.1 Development of the Wolffian ducts

The Wolffian duct anlagen arise from the right and left intermediate mesoderm between somites and somatopleure. They first appear as continuous ridges caudal to the sixth pair of somites at CS 10 in embryos with ten somites. Since the developmental steps are comparable with other vertebrates one can see how the Wolffian duct anlage shown here as a mesenchymal ridge in the scanning micrograph of a chick embryo (Fig. 1a) segregate from the dorsal part of the intermediate mesoderm.

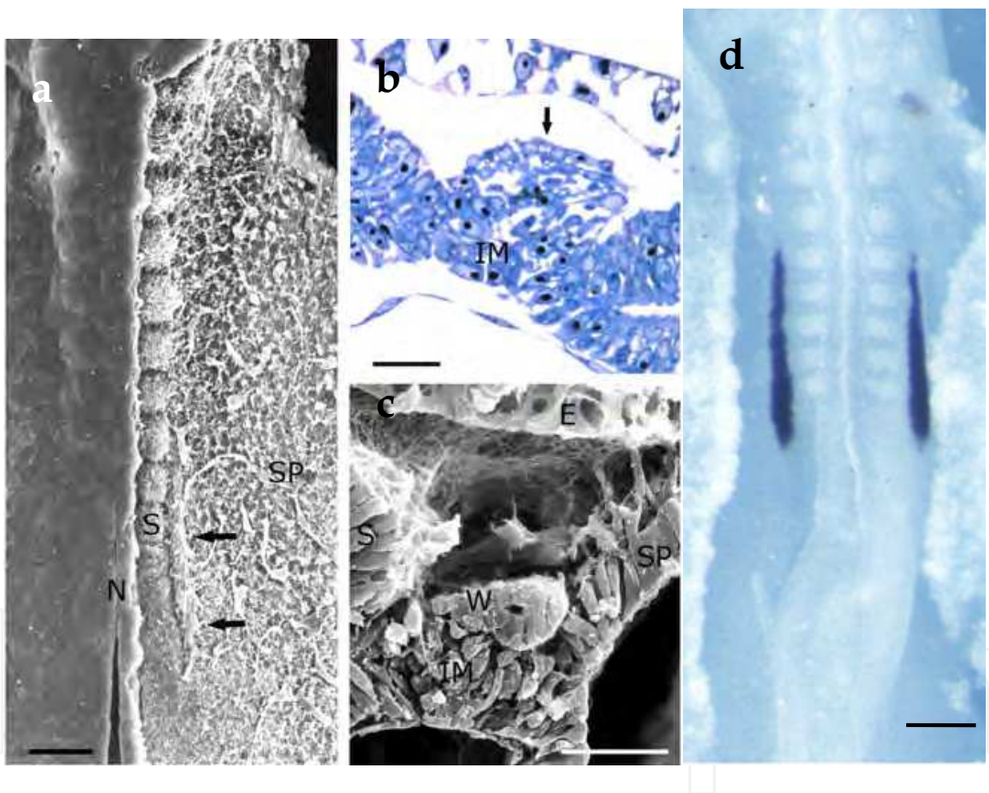


Fig. 1. Formation of the Wolffian ducts
a) Dorsal view of the Wolffian duct at stage 10 HH after extirpation of the ectoderm on the right side. Note the anlage of the Wolffian duct (arrows) adjacent to the last somite (S) and the anterior part of segmental plate. N, neural tube; SP, somatopleure. Bar = 100 µm.
b) Transverse semithin section through the mesenchymal anlage of the Wolffian duct (arrow). IM, intermediate mesoderm. Bar = 25 µm c) Canalized epithelial duct (W) on the ventral part of the intermediate mesoderm (IM). E, ectoderm; S, somite; SP, somatopleure; Bar = 25 µm. d) *Pax2* expression in the Wolffian duct anlagen in a stage 10 HH chick embryo (ten somites) as shown by *in situ* hybridization; Bar = 0.3 mm.

The mesenchymal ridges segregate from the dorsal part of the intermediate mesoderm (Fig. 1b). In human embryos at CS 11, the Wolffian ducts undergo mesenchymal-epithelial transitions and form two epithelial canalized ducts (Fig. 1c), on either side of the somites and segmental plate, however, their caudal tips maintain their mesenchymal identity and help them to migrate caudad on the intermediate mesoderm to join the cloaca at CS 12 (3 to 5 mm, 26 days, 26-28 somites).

The Wolffian duct anlagen can be identified by the expression of the *Pax2* gene (Fig. 1d), a transcriptional regulator of the paired-box gene family (see Torres et al., 1995) that controls the development of the different kidney generations. During urogenital development of vertebrates, *Pax2* appears at first within the Wolffian duct anlagen and in successive order in the other kidney generations and even in the Müllerian ducts. *Pax2* seems to induce the mesenchymal-epithelial transformation of the intermediate mesoderm (Dressler et al., 1990). Pax8 has synergistic effects, but knockout animals reveal no kidney defects.

Other genes have also been found to be important in early kidney development. Kobayashi et al. (2004) documented the expression of the LIM- class homeodomain transcription factor *Lim1* in the Wolffian ducts and knockout animals fail to develop Wolffian ducts. The homeobox gene *Emx2* was proposed to regulate the epithelial function of Pax2 and Lim1 (Miyamoto et al., 1997).

2.1.1 Migration of the Wolffian ducts

Experimental and morphological data suggest that the extension of the Wolffian ducts along their caudal path is not only the result of proliferation, but of active migration of the cells at their posterior tips (Jacob et al., 1992). Furthermore, experiments performed in chicken embryos (Grünwald, 1937; Jacob and Christ, 1978) show the significance of the mesenchymal tip of the Wolffian duct: as following its extirpation, migration of the duct stops and the mesonephros fails to develop on the operated side (Fig. 2). The metanephros

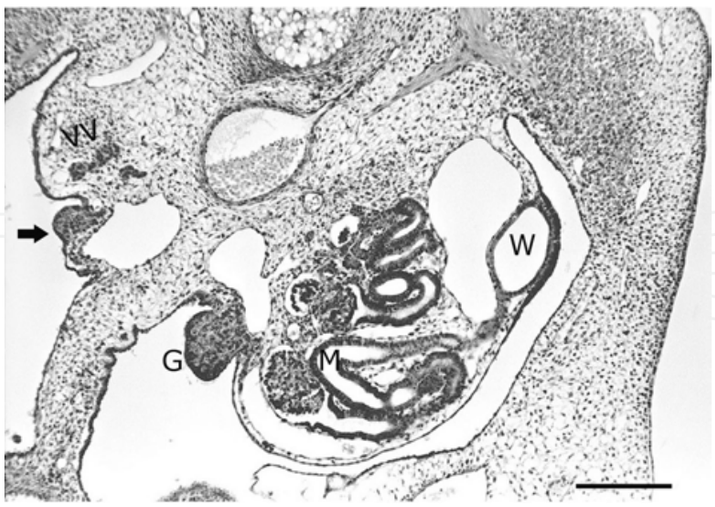


Fig. 2. Extirpation of the caudal tip of the Wolffian duct.
Transverse section through a chicken embryo sacrified two days after extirpation of the caudal part of the Wolffian duct. Control side with well developed mesonephros (M), Wolffian duct (W), and gonadal anlage (G). On the operated side (left) the mesonephros shows only rudimentary tubules (vv) and a smaller gonadal anlage (arrow). Bar = 100 μm.

and the genital ducts of both genders eventually fail to develop. The gonad although appearing normal, is considerably reduced in size on the manipulated side.

The cells at the duct tip extend long cell processes, which are in contact with the extracellular matrix (Fig. 3a). Also required for the caudally directed migration of the Wolffian duct are the special properties of the extracellular matrix through which the duct migrates. Epithelial parts of ducts implanted at the place of the tip cells were able to migrate towards the cloaca even if their cranial end was rotated. Only the intermediate mesoderm caudal to the duct tip induces and guides this migration. Matrix molecules like fibronectin are supposed to be an important component of the special substrate needed for the migration of the Woffian ducts (Jacob et al., 1991). Although fibronectin may be a prerequisite for cell migration, its nearly ubiquitous occurrence rules out a specific role in directed cell migration of this molecule in this context (see also Bellairs et al., 1995). It is suggested that polysialic acid plays a more specific role in the migration of chicken Wolffian ducts. NCAM polysialic acid had a similar distribution as fibronectin, and treatment of the living embryo with Endo-N specifically degrades polysialic acid and stops the caudal extension of the duct.

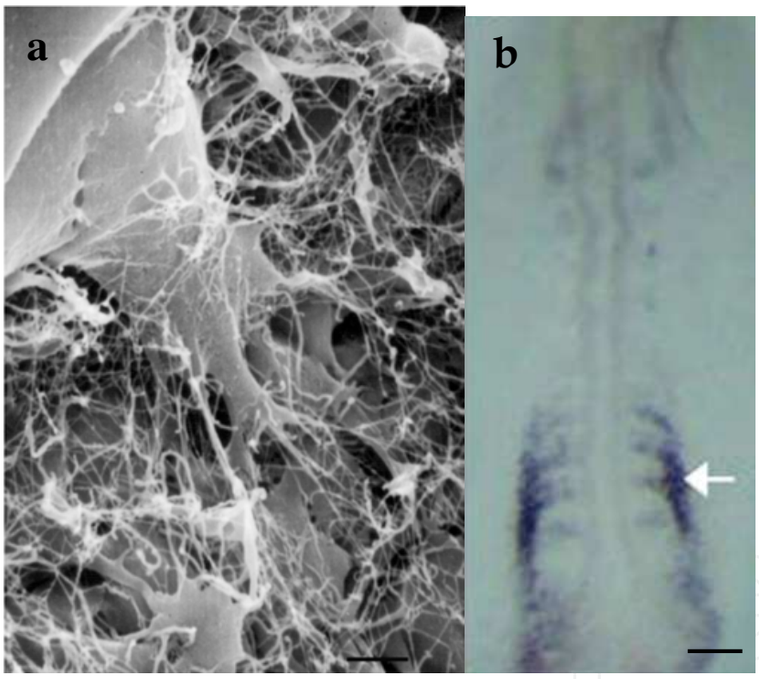


Fig. 3. Migration of Wolffian ducts.
a) Scanning electron micrograph of the tip region from a stage 13 HH (Hamburger, Hamilton) chick embryo Wolffian duct. Note the cell processes, which are in contact with the extracellular matrix. Bar = 10 μm. b) In situ hybridization of a stage 9 HH chick embryo showing *CXCR4* expression domain in the posterior half of the most caudal somites and in the intermediate mesoderm (*white arrow*). Bar = 0.2 mm.

Since the migration of the Wolffian ducts is a crucial step in the development of the urogenital system the search for the molecules that guide migration and regulate insertion of the ducts is still ongoing. Research over the years has brought some molecules to light

that may be involved in guidance of this migration either by adhesion gradients or chemotaxis. A guidance cue identified in Axolotl is GDNF, which activates signaling through the c GFRα1-Ret receptor (Drawbridge et al., 2000). In the chicken embryos, the receptor CXCR4 was shown (Fig. 3b and Yusuf et al., 2006) to be expressed in the region of the developing mesonephros anlage. Furthermore Grote et al. (2006) suggested that Pax2/8 regulated Gata3, which itself controls Ret expression is necessary for Wolffian ducts guidance.

2.2 Development of pro- and mesonephros

During the caudad extension and migration of the Wolffian ducts they induce the formation of nephric tubules within the right and left intermediate mesoderm starting with the pronephros in the cervical region. The characteristics of the pronephroi are that they form

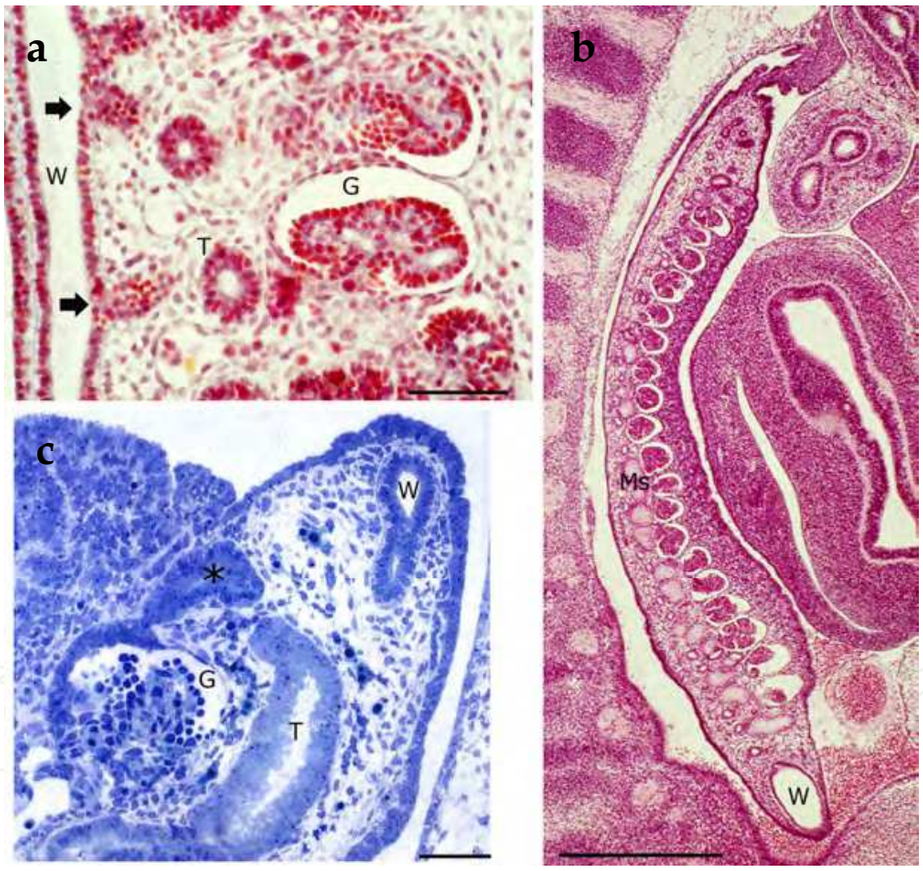


Fig. 4. Development of mesonephros
a) Sagittal section through the cranial part of the mesonephros of a 7.5 mm (CS 14/15) embryo with the longitudinal Wolffian duct (W) on the left side. Arrows, openings of tubules (T) into the duct; G, glomerulus. Azan staining. Bar = 50 µm. b) Sagittal section of the whole mesonephros (Ms) of a 10 mm (CS 16) embryo. Note the serially arranged nephrons with tubules and mesonephric corpuscles. W, caudal dilated part of the Wolffian duct. HE staining. Bar = 500 µm. c) Transverse semithin section of a 14.8 mm (CS 18) embryo W, Wolffian duct; asterisk, secretory part of a tubule; T, collecting part; G, glomerulus; Bar = 50 µm.

external glomerula and their tubules drain into the coelomic cavity via openings called nephrostomata. These structures exist also in human embryos though in higher vertebrates, the pronephroi are only rudimentary with no significant excretory function.

Early in the fourth week follows the successive induction of mesonephric tubules extending from the thoracal to the lumbal region. These tubules drain into the Wolffian ducts (Fig. 4a) and their blind ends form typical renal corpuscles with Bowman's capsule and glomerulus (Fig. 4a-c). Each tubule may be divided in a secretory and a more faintly stained collecting part (Fig. 4c). The secretory part resembles the proximal tubule of the permanent kidney with well-established microvilli.

The formation of tubules is terminated by CS 14 with a total number ranging between 35 to 38.

2.3 Development and differentiation of the ureteric buds

The permanent kidneys, the metanephroi develop by interaction of the ureteric bud with the metanephric blastema in the lumbosacral region of the intermediate mesoderm.

Early in the fifth week (CS 14) ureteric buds branch from the posterior ends of the Wolffian ducts at the level of the first sacral segment (Fig. 5a). According to Chi et al. (2009) the epithelium in the caudal part of the Wolffian duct convert prior to budding from a simple epithelium into a pseudostratified. The exact position and outgrowth in dorso-cranial direction of the ureteric buds is critical to join the metanephric blastema and thus for the development of the permanent kidneys.

The ampulla-like blind end of each ureteric bud is surrounded by a cap of dense mesenchyme, forming the metanephric blastema (Fig. 5a and b). Reciprocal interactions between ureteric bud and metanephric mesenchyme are necessary for the outgrowth and branching of the ureteric bud on one hand and the mesenchymal-epithelial transformation and tubulogenesis of the metanephric blastema on the other hand (Fig. 5b and c).

2.3.1 Branching of the ureteric buds

The contact point of the ureteric bud and the metanephrogenic blastema represents the coming together of two functionally distinct kidney parts, namely the urine conducting and the urine producing system respectively. An appropriate out pouching site of ureteric bud from the Wolfian duct followed by its dichotomic patterning enable not just a formation of a functional urinary tract, but also ensure the viability of the metanephric kidney. Extensive research over the last decades in this field underlines the significance of appropriate ureteric bud outgrowth and patterning as urinary tract malformations are amongst the most common congenital defects accounting to around 1% of all congenital defects. Further impact of faulty ureteric bud branching also affects the absolute nephron number in the kidney which may play out as a predisposition to chronic renal failure.

The correct outgrowth of the ureteric buds and their dichotomic budding is controlled by a network of genes (see for review Constantini and Kopan, 2010) with GDNF/RET signaling as a main factor. GDNF is expressed in the metanephric mesenchyme and the Ret receptor tyrosine kinase and its co-receptor Gfrα1 in the tip of the ureteric bud. It has been experimentally shown that it is not the expression, but the activity of the RET that is decisive

for the site of ureteric bud out pouching selection. Wnt signaling transducter β-catenin (Marose et al., 2008) and Gata3 (Grote et al., 2008), a zinc finger transcription factor, act together and are pivotal in modulating the RET activity at the prospective ureteric bud formation site in the caudal Wolffian duct.

The mode of branching was shown by Osathanondh and Potter (1963) using microdissection. At CS 16 the ampullated tip divides into two branches determing the cranial and caudal pole of each metanephros.

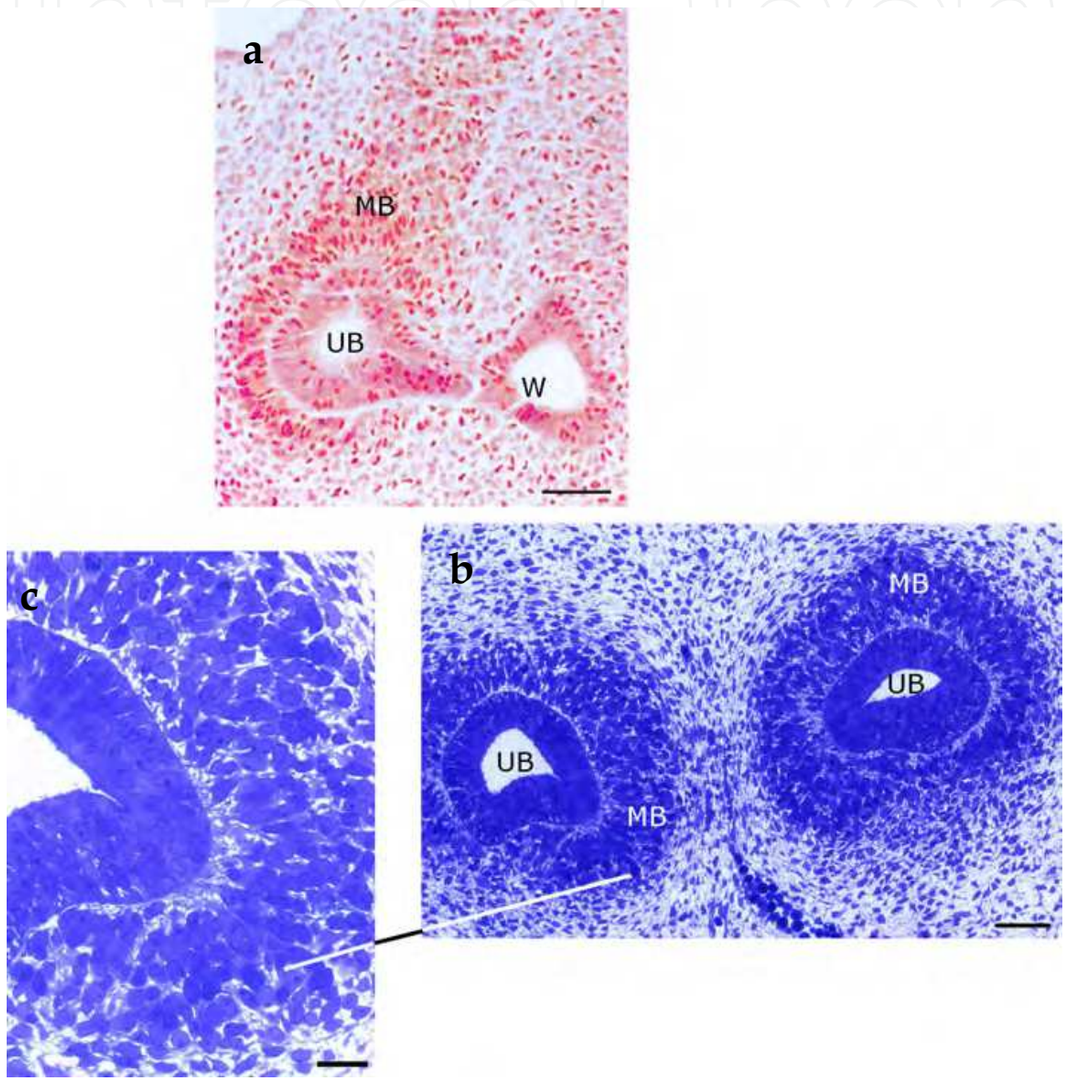


Fig. 5. Ureteric buds and metanephrogenic blastemata
a) Sagittal section from a 6.5 mm (CS 14) embryo with outgrowing ureteric bud (UB). W, Wolffian duct; MB, metanephrogenic blastema. Azan staining. Bar = 50 μm. b) Horizontal section from a 10.5 mm (CS 16) embryo. The tip of ureteric bud (UB) is dilated and starts branching induced by the metanephrogenic blastema (MB). Bar = 50 μm. c) Detail from b marked by the line. The cells of the dense metanephrogenic blastema connect the dividing tip of the ureteric bud with multiple cell processes. Bar = 20 μm.

The mode of branching is unique to the kidney with lateral and terminal bifid branches (Al-Awqati and Goldberg, 1998). The terminal branch can no longer divide since it induces the formation of nephrons.

At CS 19 four to six generations of branching can be observed. Within the metanephrogenic blastema adjacent to the ampulla vesicles form. Each vesicle eventually differentiates into a tubule and the glomerulus (Fig. 6).

The first three generations of division dilate and fuse to form the renal pelvis, the fourth and fifth form the calyces. The further divisions - 6 to approximately 15 - generate the collecting ducts. By the 22nd to 23rd weeks of gestation branching is completed.

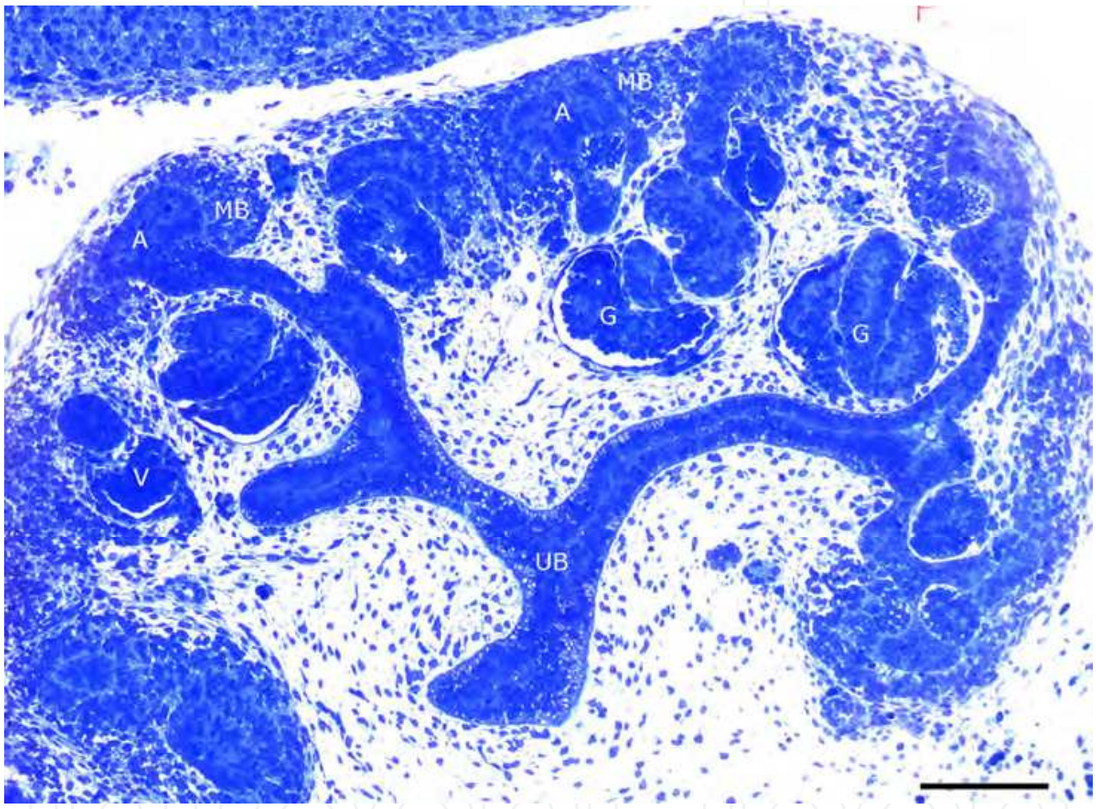


Fig. 6. Branching of ureteric bud.
Semithin-section through the metanephros of a 25 mm (CS 22) embryo. Dichotom branching of the ureteric bud (UB). The ampulla-like blind end (A) induces the formation of vesicles (V) within the metanephrogenic blastema (MB). The vesicles differentiate into tubules and glomeruli (G). Bar = 100 μm.

2.4 Differentiation of the Wolffian ducts in male fetuses

The stabilization and further growth of the Wolffian ducts depend on androgen that is produced in the testes of male embryos starting from the eighth week of gestation. An active stimulation is necessary to prevent regression of the ducts and the mesonephric tubules and to induce the differentiation of epididymides and vasa deferentia. The androgen receptor is first found in the mesenchyme surrounding the duct epithelium and interacts with different

growth factors like EGF (epidermal growth factor) (see for review Hannema and Hughes, 2007). Expression of EGF and its receptor can be increased by androgen treatment and vice versa. EGF modulates sexual differentiation by enhancement of AR-mediated transcriptional activity and not enhancement of AR gene expression receptor (Gupta, 1999).

2.4.1 Development of the epididymis

Epididymal development depends on a cascade of molecular and morphological events controlling transformation and regression of mesonephric nephrons and the persistence of the Wolffian duct (Kirchhoff, 1999). In the male, some of the mesonephric tubuli eventually form the ductuli efferentes located in the caput epididymidis, while the Wolffian ducts differentiate into the right and left ductus epididymidis and the vas (ductus) deferens. During the transformation of the mesonephroi into the paired epididymis, two waves of regression are observed. The first wave of regression occurs in the most cranial nephrons and starts before the caudal parts of the mesonephroi are fully developed and is correlated with an inner descent of mesonephroi and gonads. Felix (1911) found this wave to be terminated in 21mm embryos (about CS 20). The second wave of regression includes the caudal part of the mesonephroi persisting as rudimental paradidymis. In the third month, the surviving mesonephric tubuli unite with the anlage of the rete testis.

The process of transformation from nephrons into ductuli efferentes remains poorly understood. In some vertebrates, a special mode involves the *de novo* formation of ductuli efferentes from the Bowman's capsules in the chicken (Budras and Sauer, 1975) or from the dorsal part of the giant nephric corpuscle of the bovine embryo (Wrobel, 2001). The appearance of the apoptotic p53 proteins and the antiapoptotic bcl-2 in the mesonephros from the seventh week on (Carev et al., 2006) coincide with the regression on one hand and the survival of some tubules on the other hand.

We investigated the development of the epididymis in human embryos from 14,8 mm (CS 18) to a 170 mm fetus. The CS 18 embryo reveals well-developed mesonephroi (Fig. 4c). The structure of the glomeruli is similar to those of the metanephroi with a thin capillary endothelium and podocytes. The structure of the proximal tubules resembles that of the proximal tubules of the permanent kidney, however the distal parts of the mesonephric tubules seem to have only collecting function.

Shortly later, already in the first wave of regression or at the beginning of the second period, degeneration of glomeruli and proximal tubuli starts. According to Felix (1911) only the distal parts of the tubuli adjacent to the testis (epigenital tubules) survive. They elongate to form coiled ductuli, which eventually join the rete testis. In our 26 mm embryo (eighth week) long and straight tubules are found near the developing rete testis. More medial sections (Fig. 7a) show nephric corpuscles with fused or degenerating glomeruli and thickened Bowman's capsule at the testicular side.

The 32 mm fetus (ninth week) exhibits condensed and small glomeruli. Near the anlage of the testicular rete, tubules with narrow or obliterated lumina are visible (Fig. 7b). However their morphological features do not elucidate whether they belong to remnants of degenerating proximal tubules or are new outgrowths from Bowman's capsules. A mesenchymal sheath forms around the wide Wolffian ducts, a prerequisite for the subsequent elongation and coiling of the Wolffian ducts since androgens are supposed to act via mesenchymal androgen receptors.

In a 45 mm embryo the paired Wolffian duct had increased in length and transformation into the ductus epididymidis starts in the proximal region with the characteristic coiling. During the enormous elongation up to six meters in the adult epididymis, the duct twists into another direction and folds onto itself. Constraints of the surrounding mesenchymal tissue are the supposed forces for the coiling and the narrow space which forces the duct to compact in the anterior region especially in the later corpus of epididymis (Joseph et al., 2009).

In a 68 mm fetus, the epididymal duct assumes an increasingly coiled arrangement. The blind ends of the prospective ductuli efferentes are dilated.

The 88 mm fetus, 13th week, shows the rete testis on either side fused with the ductuli efferentes. The epididymal duct is highly convoluted, but the distal part remains straight (Fig. 7c). It is lined by a non-specific cylindrical epithelium and is surrounded by many concentric layers of mesenchyme.

In the 170 mm fetus, 21th week, in the anterior region a dense coiling and an increased mesenchymal sheath are found. The mesenchyme is essential for the maturation of the ducts and especially for the formation of the vasa deferentia. At this stage, testis and epididymis establish contact with the jelly gubernaculum (Barteczko and Jacob, 2000).

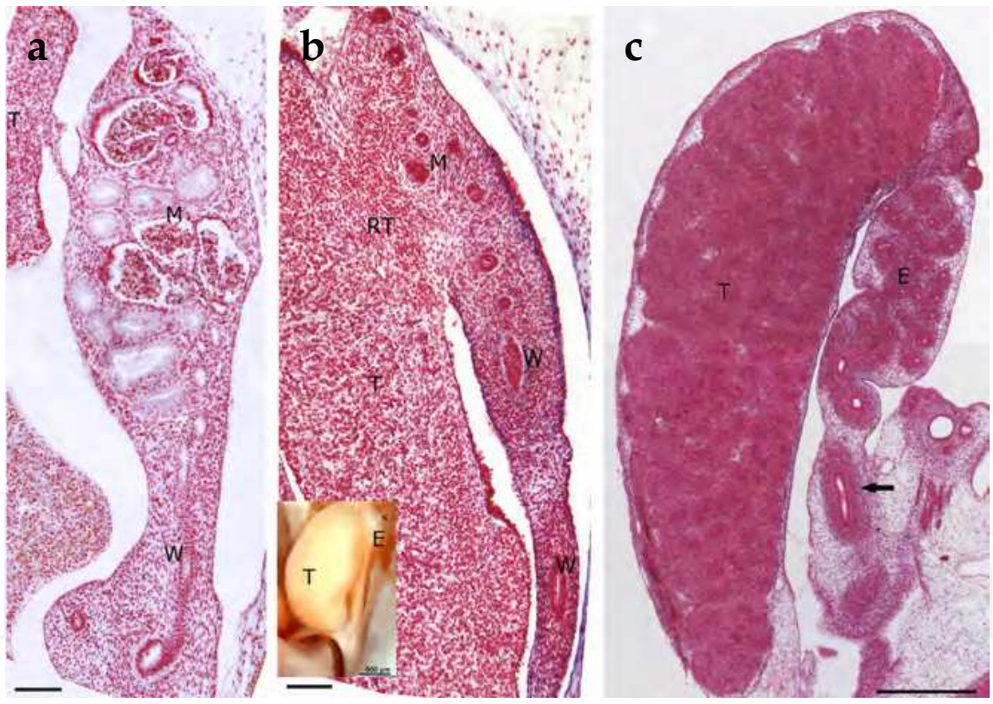


Fig. 7. Development of epididymis
a) Sagittal section of a 26 mm (eighth week) male embryo. In the epigenital part of the mesonephros (M) fused glomeruli and tubules are visible; W, Wolffian duct; T, testis. Azan staining. Bar = 100 µm. b) Sagittal section of a 32 mm (ninth week) male fetus. Tubules of mesonephros (M) with narrow or obliterated lumina are found near the rete testis (RT). T, testis; W, Wolffian duct. Azan staining. Bar = 100 µm. Inset: Testis and epididymis of a 68 mm about 11 weeks, fetus. Asterisk, appendix epididymidis. c) Sagittal section through testis (T) and epididymis (E) of a 88 mm (13th week) male fetus. Note the coiled ductus epididymidis and the straight vas deferens (arrow). HE staining. Bar = 500 µm.

The differentiation of the specific sections of the Wolffian ducts is regulated by the regional expression of Hox genes. In mouse embryos *Hoxa9* and *Hoxd9* are expressed in the epididymis and vas deferens, *Hoxa10* and *Hoxd10* in the caudal epididymis and the vas deferens, *Hoxa11* in the vas deferens, and *Hoxa13* and *Hoxd13* in the caudal portion of the WD and seminal vesicles (Hannema and Hughes, 2007).

2.4.2 Differentiation of the distal part of the Wolffian duct

The secretion of testosterone stimulates also the differentiation of the distal parts of the Wolffian ducts into the vasa (ductus) deferentia and the seminal vesicles. As already mentioned, the regional differentiation of the Wolffian duct is related to Hox genes. E.g. *Hoxa-10* domain of expression in male mice embryos has a distinct anterior border at the junction of the cauda epididymidis and the ductus deferens and extends to the sinus urogenitalis (Podlasek et al., 1999).

The development of the straight ductus deferens is characterized by the formation of the thick coat of circular smooth muscle cells.

The seminal vesicles sprout out of the Wolffian duct close to its entrance into the urethral part of the urogenital sinus between the tenth and twelfth week. The common ducts of vasa deferentia and seminal vesicles are called ductus ejaculatoria.

At around the ninth week of gestation, the ureteric buds have separated from the Wolffian ducts and their openings lie superior to those of the Wolffian ducts into the bladder part of the sinus urogenitalis. The common view that the Wolffian ducts are incorporated into the posterior bladder wall to form the trigone is now questioned and lineage studies have shown that the trigone mesenchyme derives from the bladder musculature (Viana et al., 2007). Apoptosis seems to play a role in ureter transposition. Regulation of the different growth and insertion of ureteric bud and distal Wolffian duct (vas deferens) is unknown.

2.5 Differentiation of the Wolffian ducts in female fetuses

In the female, the Wolffian ducts degenerate due to the absence of testosterone. Only rudiments persist as Gartner's ducts or cysts running in the broad ligament to the wall of the vagina.

3. Müllerian ducts

The Müllerian (paramesonephric) ducts are named after the German physiologist Johannes Peter Müller (1801-58). The formation of the human Müllerian ducts starts in the sixth week when other organs are already functional. They develop in close proximity and by induction of the Wolffian ducts. In male embryos they regress shortly after their formation under the influence of the anti-Müller-hormone produced by the Sertoli cells of the testes. In female embryos they further differentiate and form the oviducts (uterine tubes), the uterus and the vagina.

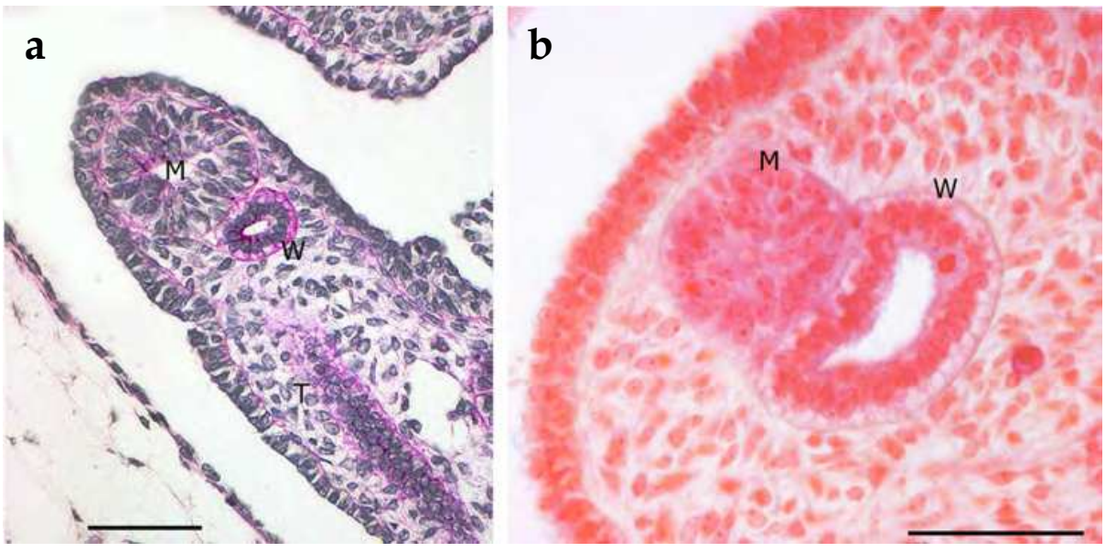
3.1 Development of the Müllerian ducts

The formation of the human Müllerian ducts starts in the sixth week (CS 16) as drop-like aggregations of cells beneath the cranial part of the Müllerian or tubal ridges

corresponding to the thickened stripes of coelomic epithelium located near the Wolffian ducts (Jacob et al., 1999). Here, at the transition zone between pro- and mesonephros a discrete population of cells within the coelomic epithelium gives rise to the epithelium of the paired Müllerian duct as shown by lineage tracing studies (Guioli et al., 2007). In the 11,5 mm embryo ostium-like indentations of the coelomic epithelium were observed determining both so-called funnel-regions. Placode-like thickenings and deepenings of the coelomic epithelium form the anlagen of the Müllerian ducts. In some vertebrates including humans, these cranial parts of the Müllerian duct are supposed to contain remnants of nephrostomes from the last pronephric and the first mesonephric tubules (see for discussion Jacob et al., 1999; Wrobel and Süß, 2000). A solid cord of cells forms from each ostium or funnel region and rapidly grows caudally in close vicinity to the Wolffian ducts. It has been experimentally shown that in vertebrates the Wolffian ducts are required for the induction of Müllerian duct formation and in their absence no Müllerian duct can develop.

Labeling dividing cells with BrdU in chick and mouse embryos provide evidence that high cell proliferation of the Müllerian duct epithelium and the coelomic epithelium of the funnel region can be regarded as the motor of the caudal extension of the Müllerian ducts (Jacob et al., 1999; Guioli et al., 2007) ranging from 330 μm length in a 12.5 mm embryo and between 1440 and 1220 μm in a 17 mm embryo (Felix, 1911). Interestingly, in chick and human embryos two to four accessory openings into the coelomic cavity were observed in the cranial part of the Müllerian ducts (Felix, 1911; Jacob et al., 1999). Since these accessory funnels exist only during the robust expansion phase of the Müllerian ducts development, they probably supply more cells from the coelomic epithelium at the funnel field. Whether they are remnants of pronephric tubules has to be elucidated.

The major part of each Müllerian duct anlage canalizes (Fig. 8a) with the exception of the caudal tip. In 17 to 21 mm human embryos, at the point where the ducts are in close contact no basal lamina is present between each Müllerian and Wolffian duct (Fig. 8b). In this way the Wolffian ducts guide the Müllerian ducts to the lumbal region. However, Müllerian and Wolffian duct epithelium can be distinguished because of their distinctive morphological features (Laurence et al., 1992). The Müllerian ducts are more pseudostratified and reveal



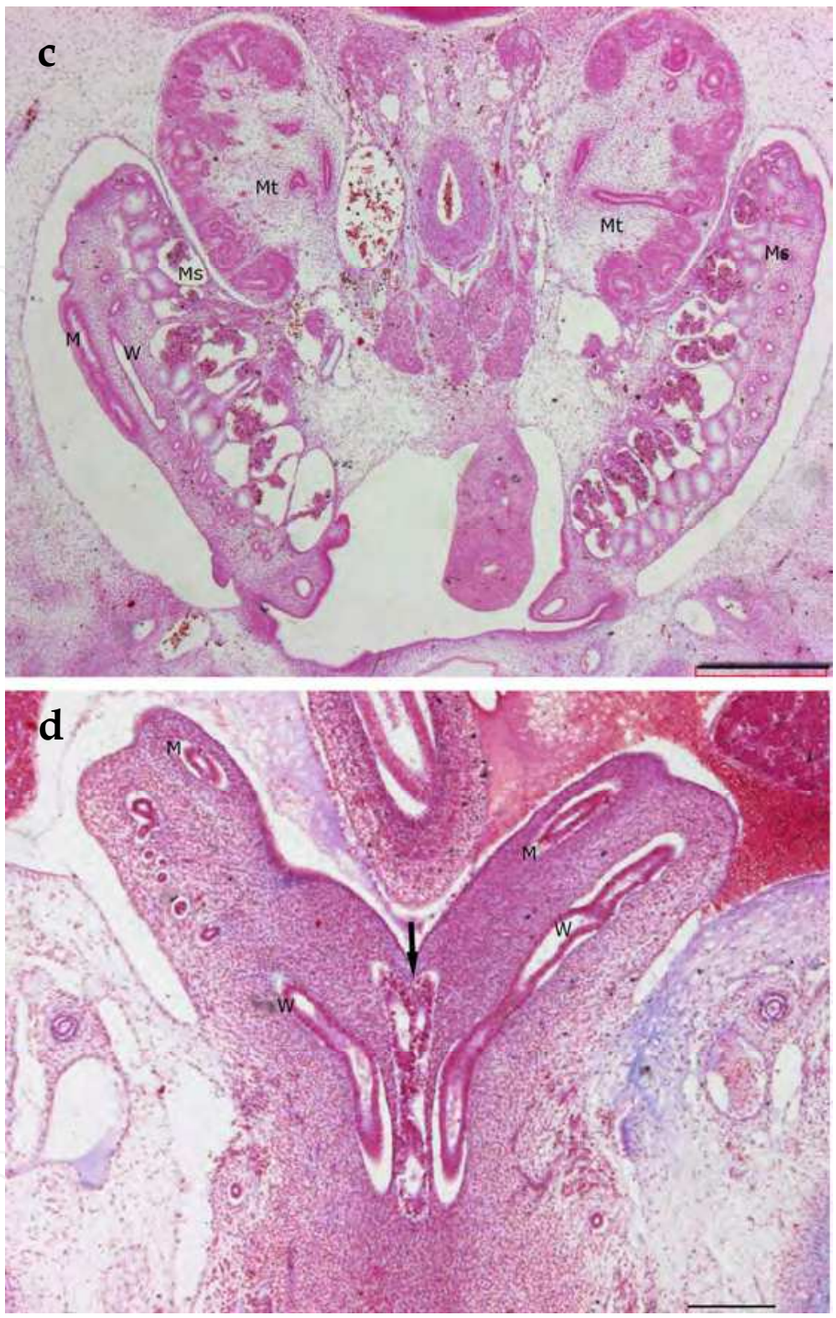


Fig. 8. Formation of the Müllerian ducts
a) Frontal section from a 16 mm (CS 18) embryo. Cranial part of the Müllerian duct (M) adjacent to the Wolffian duct (W). PAS staining. Bar = 50 µm. b) Sagittal section through a 21 mm (CS 20, eighth week) embryo. Note the close relation of müllerian (M) and Wolffian duct (W). Azan staining. Bar = 50 µm. c) Frontal/horizontal section of a 26 mm (CS 22) eighth week with both mesonephroi (Ms) and the developing metanephroi (Mt). W, Wolffian duct; M, Müllerian duct. Azan staining. Bar = 500 µm. d) Frontal section through a 29 mm (CS 23). The Müllerian ducts (M) are fused in the midline (arrow). W, Wolffian duct. Azan staining. Bar = 200 µm.

a larger number of elaborate microvilli at their luminal surfaces. Wolffian ducts exhibit abundant intracytoplasmatic glycogen. Furthermore, immunohistochemical investigations in chick and mouse embryos have also shown that the Müllerian ducts differ from the Wolffian ducts in their expression of the mesenchymal marker vimentin characterizing them as mesothel while the Wolffian ducts are true epithelial tubes expressing cytokeratin (Jacob et al., 1999; Orvis and Behringer, 2007). From this and other experimental and molecular data available any cell contributions from the Wolffian ducts to the Müllerian ducts could be excluded (Jacob et al., 1999; Guioli et al., 2007; Orvis and Behringer, 2007).

While the Müllerian ducts grow caudally, their cranial parts are separated from the Wolffian ducts by circular mesenchymal layers (Fig. 8c) derived from the dissolved tubal ridges.

In the 22 mm embryo (CS 21), the Müllerian ducts cross the Wolffian ducts to extend medially and join each other. In the midline the two Müllerian ducts run caudally and fuse to a single tube, the uterovaginal canal. At CS 22 to 23 this canal inserts at the separated anterior part of the cloaca, the sinus urogenitalis. Here the mesenchyme of the ducts proliferates and protrudes the wall of the sinus urogenitalis forming the Müllerian tubercle.

At first the fusion of the Müllerian ducts is only external with the formation of a common basal lamina, because a septum still separates the fused ducts. A single lumen was found at CS 23 (Hashimoto, 2003).

Genes that are required for Müllerian duct formation are also found in kidney development: *Lim1* specifies cells in the coelomic epithelium (Kobayashi et al., 2004) and *Wnt-4* induces the invagination of these cells (Vainio et al., 1999). The Wolffian duct also induces the expression of *Pax2* in the Müllerian duct although the anterior part of the Müllerian ducts is initially formed in Pax2 mutants (Torres et al., 1995), indicating an autonomy of the funnel region (for review see also Massé et al., 2009).

3.2 Regression of the Müllerian ducts in male fetuses

Regression of the Müllerian ducts in males is due to the production of anti-Müllerian hormone (AMH), also named Müllerian-inhibiting substance (MIS), by the Sertoli cells of the testes. A hormone for development of male reproductive duct different from testosterone was first postulated by Jost (1953). Secretion of AMH, a member of the transforming growth factor-β (TGF-β) family, starts in the eighth week of gestation and provokes the irreversible regression of the Müllerian duct in the eighth and ninth week (Rey, 2005).

AMH induces apoptosis within the Müllerian duct epithelium through a paracrine mechanism binding to the AMH type2 receptor (AMHRII) expressed in the mesenchyme around the epithelial tube. Allard et al. (2000) found a cranio- caudal gradient of AMHRII in the peritubal mesenchyme followed by a wave of apoptosis. They furthermore suggest that β-catenin, playing a role in the Wnt signaling, mediates apoptosis. They also described that beside apoptosis, an epithelio-mesenchymal transformation is important for regression. Apoptosis needs the disruption of the basal lamina correlating with the loss of fibronectin and expression of the metalloproteinase 2 gene (*Mmp2*) (see for review Massé et al., 2009).

The Müllerian ducts do not completely disappear. The most cranial parts are supposed to persist as appendices testis (see below) and the caudal parts as prostatic utricles. However,

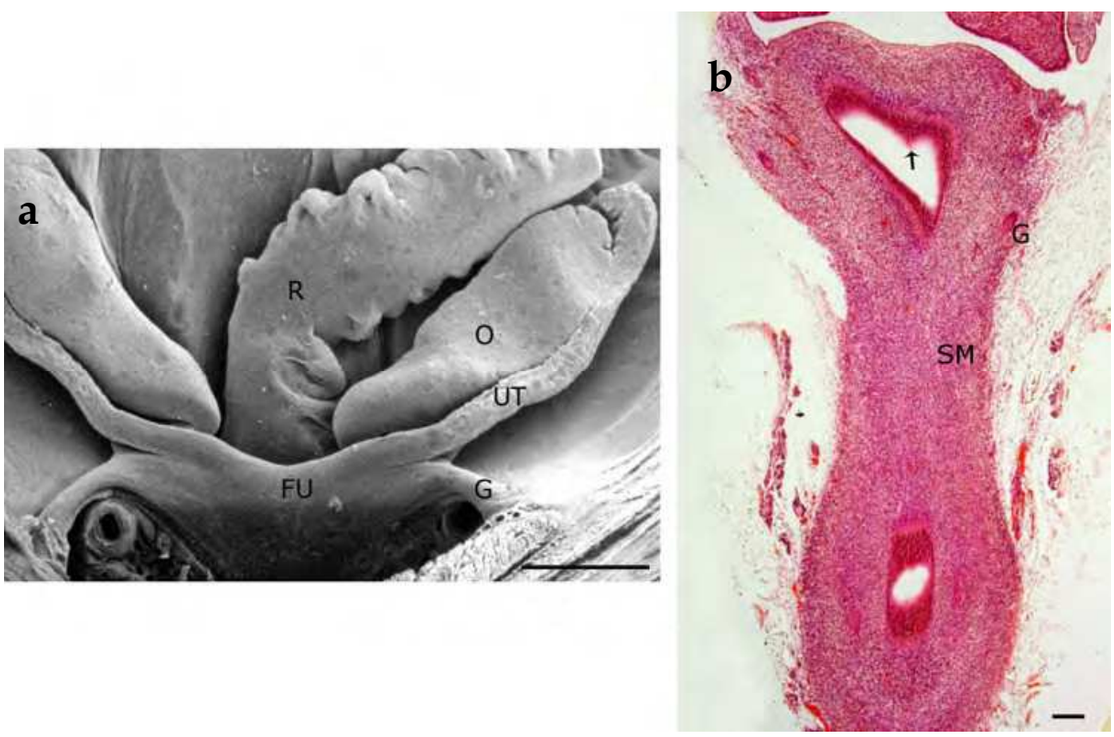
Shapiro et al. (2004) concluded from their immunohistochemical studies that the utricle forms as an ingrowth of specialized cells from the dorsal wall of the sinus urogenitalis.

3.3 Differentiation of the Müllerian ducts in female fetuses

In the female, where AMH is lacking, the uniform Müllerian ducts differentiate in very specific segment to give rise to the uterine tubes (oviducts), the uterus, cervix and the vagina. These specification along the antero-posterior axis is due to a specific *Hox*-code. As during the differentiation of the Wolffian duct in male fetuses, Hox genes are expressed according to a spatial and temporal axis. In the female reproductive tract the *HOXA/hoxa* genes 9, 10, 11 and 13 are expressed (Taylor et al., 1997) and their pattern is highly conserved between the murine and the human. Furthermore members of the Wnt family are necessary for a correct pattern and differentiation of the female reproductive tract. e.g. Loss of function of *Wnt-7a* was reported to result in a partial posteriorization of the female reproductive tract, specifically, the oviduct had acquired characteristics of the uterus and the uterus characteristics of the vagina (Miller and Sassoon, 1998).

3.3.1 Differentiation of the uterine tubes

The non-fused cranial part of the Müllerian ducts form the uterine tubes (oviducts) reaching from the abdominal ostium with anlage of fimbria to the insertion of the gubernacula Hunteri (later round ligaments) (Fig. 9a). During the twelfth week of gestation, the simple columnar epithelium grows more than the surrounding mesenchyme thus forming the characteristic folding of the epithelium lining a stellate lumen (Wartenberg, 1990). The paratubal mesenchyme proliferates and differentiates into the smooth muscle layers and the lamina propria.



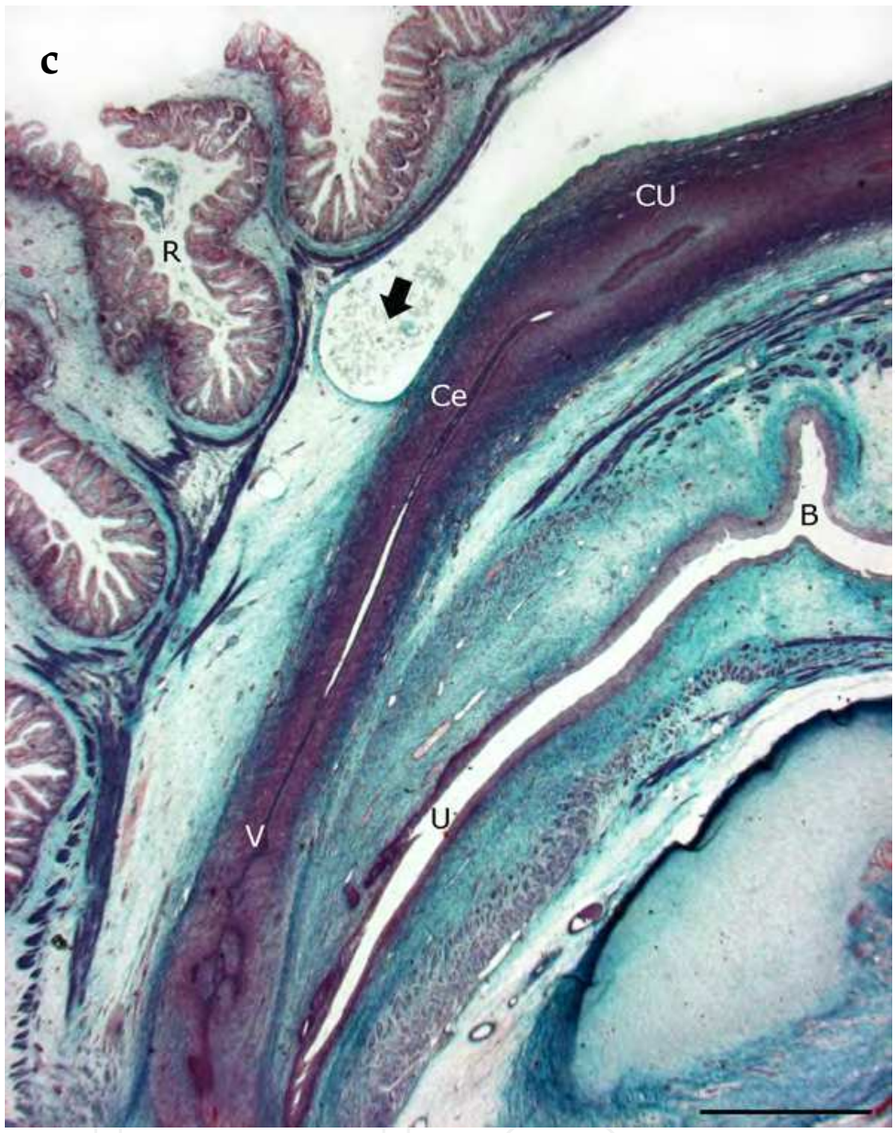


Fig. 9. Formation of oviduct, uterus and vagina
a) Scanning electron micrograph on the broad ligament of a 78 mm CRL (crown-rump length, about 12 weeks) female fetus. The upper border of the ligament is formed by the uterine tubes (UT) and the fundus of the uterus (FU). The insertions of the gubernacula (G) mark the transition from oviducts to uterus. O, ovar; R, rectum. Bar = 1mm. b) Uterus anlage of a 4 month fetus. Note the thick layer of smooth musculature (SM) and the remnant of the septum (arrow). Gartner ducts (G) are found within the uterus wall. Bar = 100 µm. c) Uterus and vagina anlage of a 150 mm (4 month) fetus. CU, corpus uteri; Ce, cervix; V, vagina; R, rectum; B, bladder; U, urethra; arrow, excavatio rectouterina. Bar = 1mm.

3.3.2 Differentiation of uterus and cervix

The uterus develops from the fused upper parts of the Müllerian ducts but the fusion is at first not complete since a thick septum is formed at the fundus of the uterus between week

13 and 20 of gestation (Figs. 9a and b). According to Muller et al. (1967), fusion of the ducts and resorption of the septum begins at the region of the isthmus and proceeds simultaneously in cranial and caudal direction. Incomplete fusion of the Müllerian ducts or incomplete resorption of the septum gives rise to many malformations. Any form of duplicity of the uterovaginal canal may be found from uterus bicornis to complete duplication of uterus and vagina, uterus didelphys with double vagina.

The differentiation of the mesenchymal wall of the uterus into smooth muscle starts as in the uterine tubes during the third months (Fig. 9b and c). Initially the epithelium reveals not as high proliferation as the oviduct epithelium and the uterus lumen is lined by a smooth surface without folds.

The region specific differentiation of the epithelium within oviducts (uterine tubes), uterus, cervix and vagina seems to occur perinatally also under the influence of the above-mentioned hox genes. The last step in differentiation of the epithelium is the formation of uterine glands. According to studies of Meriscay et al. (2004) in the mice, *Wnt5a* from stromal cells provides a specific signal that permits the luminal epithelium to form glands.

3.3.3 Differentiation of vagina

The development of the vagina is a matter of controversy and is under discussion. The solid caudal end of the uterovaginal canal inserts at the sinus urogenitalis between the openings of the Wolffian ducts and forms the Müllerian tubercle. Within this tubercle, the tissue of Wolffian and Müllerian ducts intermingle and make it difficult to define their genesis. Since the classic study of Koff (1933) on the development of the human vagina it is generally believed that the cranial part of the vagina is derived from the Müllerian ducts and the caudal part is formed from the sinus urogenitalis. Morphological studies of Forsberg (1965) argue for this view since the so-called Müllerian vagina has initially a pseudostratified columnar epithelium. Furthermore human males with complete androgen insensitivity syndrome but with functional AMH develop a shortened vagina. New genetic and experimental studies contradict this view (see for review Cai, 2009). In case of the shortened vagina it has been shown that the caudal part of the Müllerian duct is insensitive to AMH and under influence of androgen contributes to prostate development (Cai, 2009). Analysis of the vagina in testicular feminization mutated mice by Drews et al. (2002) demonstrated in male embryos, that the entire vagina arises from the Müllerian ducts growing caudal along the sinus urogenitalis together with the Wolffian ducts. In the male embryo, androgens binding to androgen receptors in the mesenchyme of the caudal Wolffian duct soon stop this caudal migration. Cai (2009) reviewed morphological, genetic and molecular studies and presented a model of the formation of the caudal vagina. The caudal ends of the Müllerian ducts insert into the sinus urogenitalis wall in which BMP4 is strongly expressed after induction by Shh (Sonic hedgehog). BMP4 mediates caudal extension of the uterovaginal canal.

The distal part of the uterovaginal canal, which extends caudad is at first a more or less solid cell plate known as vaginal plate. However Terruhn (1980) has found by injection technique that already at 14th week of gestation, the vagina as well as the uterus revealed a lumen (compare Fig. 9c). Later at the 26th week of gestation a functional plugging of the endocervical canal was observed presumably due to a secretory activity of the epithelium.

4. Remnants of the Müllerian or Wolffian ducts (hydatids) in adults

Hydatids of genital organs were first discovered by Morgagni. They are remnants of the cranial part of the Müllerian ducts and Wolffian ducts. In males, the frequent appendices of the testes develop from the funnel region of the Müllerian ducts. Due to a cranial crossing-over of Müllerian and Wolffian ducts, the Müllerian ducts come close to the upper poles of the testes (see Fig. 11a). They are not pedunculated and contain connective tissue and many blood vessels.

Different types of appendices epididymides are found. They all arise from the cranial ampullated ends of the Wolffian ducts and are in most cases pedunculated (Jacob & Barteczko, 2005). They may be vesicular or solid and often reveal a twisted stalk (Fig. 10a).

Likewise, in females, hydatids are found that are often pedunculated. They may occur at the fimbriae of the Fallopian tubes deriving from the Müllerian ducts, or as paratubular appendices vesiculosae or hydatids of Morgagni deriving their origin from the Wolffian ducts or mesonephric tubules (Fig. 10b).

The clinical relevance of these structures is torsion of pedicle with acute syndrome within scrotum or abdomen. Tumors deriving from these vestigial structures are also described.

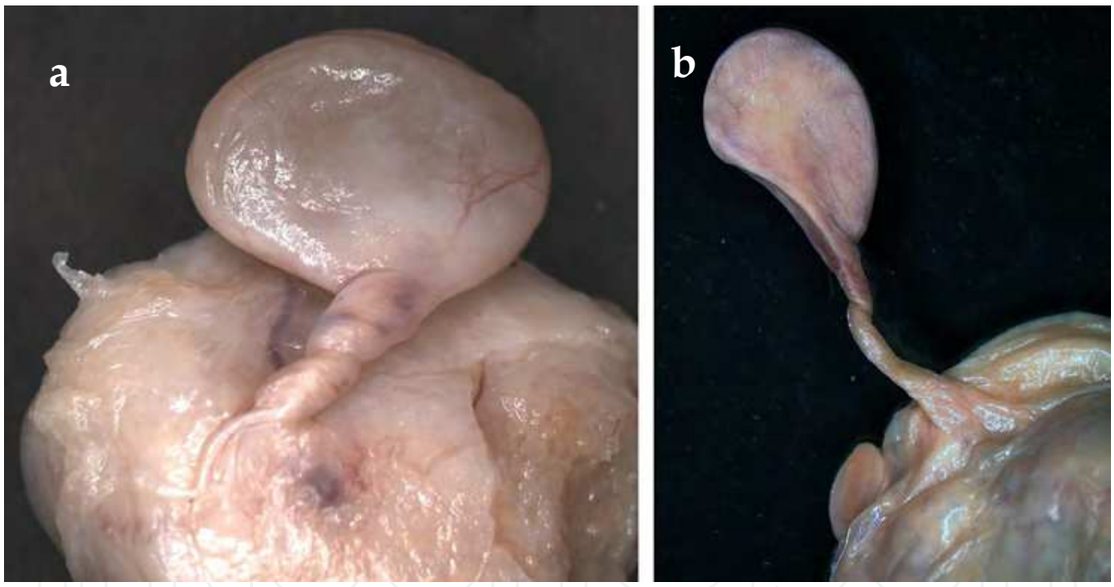


Fig. 10. Remnants of Müllerian or Wolffian ducts in adults
a) Pedunculated twisted hydatid (appendix epididymidis) as remnant of the ampullated blind cranial end of the Wolffian duct. 10.1 x 9 mm
b) Paratubular hydatid with torsion of pedicle. Length with pedicle 12.5 mm.

5. Summary and conclusion

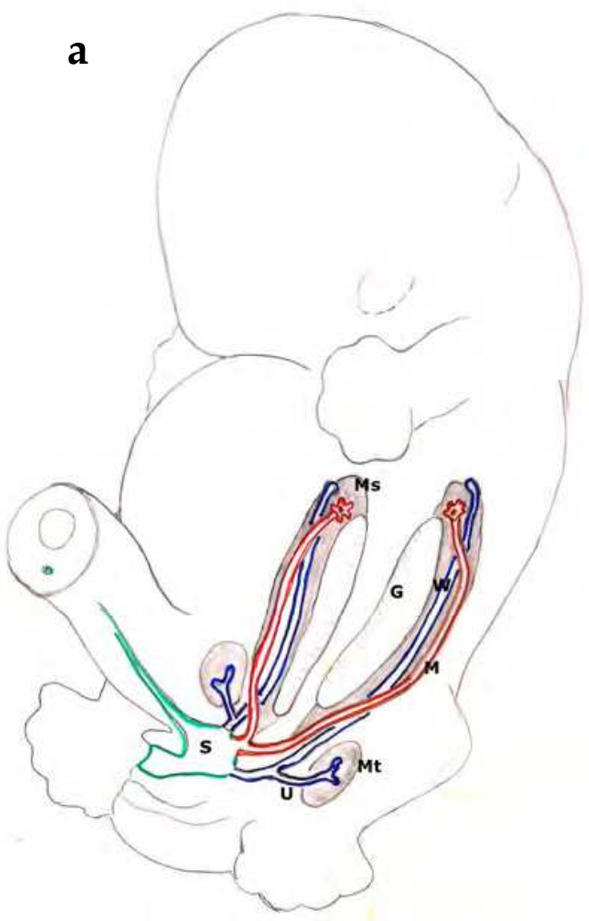
The Wolffian ducts are the first appearing structures of the urogenital system and their migration and inductive properties are critical for the development of the permanent kidneys and the genital ducts in males and females. The development of the gonads, however, occurs independent of the Wolffian ducts.

Shortly after the onset of somite differentiation, the Wolffian duct anlagen separate from the intermediate mesoderm. During caudal migration they induce the pro- and mesonephroi within the ventral part of the intermediate mesoderm. Near the caudal entrance into the cloaca (sinus urogenitalis) an ureter bud sprouts out from each Wolffian duct and grows dorso-cranially to join the metanephric blastema (Fig. 11a). Each ureter bud divides in a special dichotomy manner and forms ureter, pelvis, calyces and collecting ducts of the permanent kidney (Fig 11 b and c).

The Wolffian ducts need androgens for further differentiation. In males, each duct forms a coiled ductus epididymidis and the straight vas deferens (Fig. 11b). Sprouting of the seminal vesicles occurs near the urogenital sinus.

The ductus epididymidis together with some persisting tubules of the mesonephros differentiates into the epididymis, which via the rete testis is in close connection with the testis enabling transport and maturation of spermatozoa. Shortly before birth, the epididymis descends into the scrotum together with the testis.

In females, the Wolffian ducts do not differentiate further, but persists as rudimentary Gartner's ducts in the broad ligament lateral to the uterus. The Gartners's ducts are found generally lateral to the uterus, but might also reach down to the wall of the vagina and can give rise to cysts (Fig. 11c).



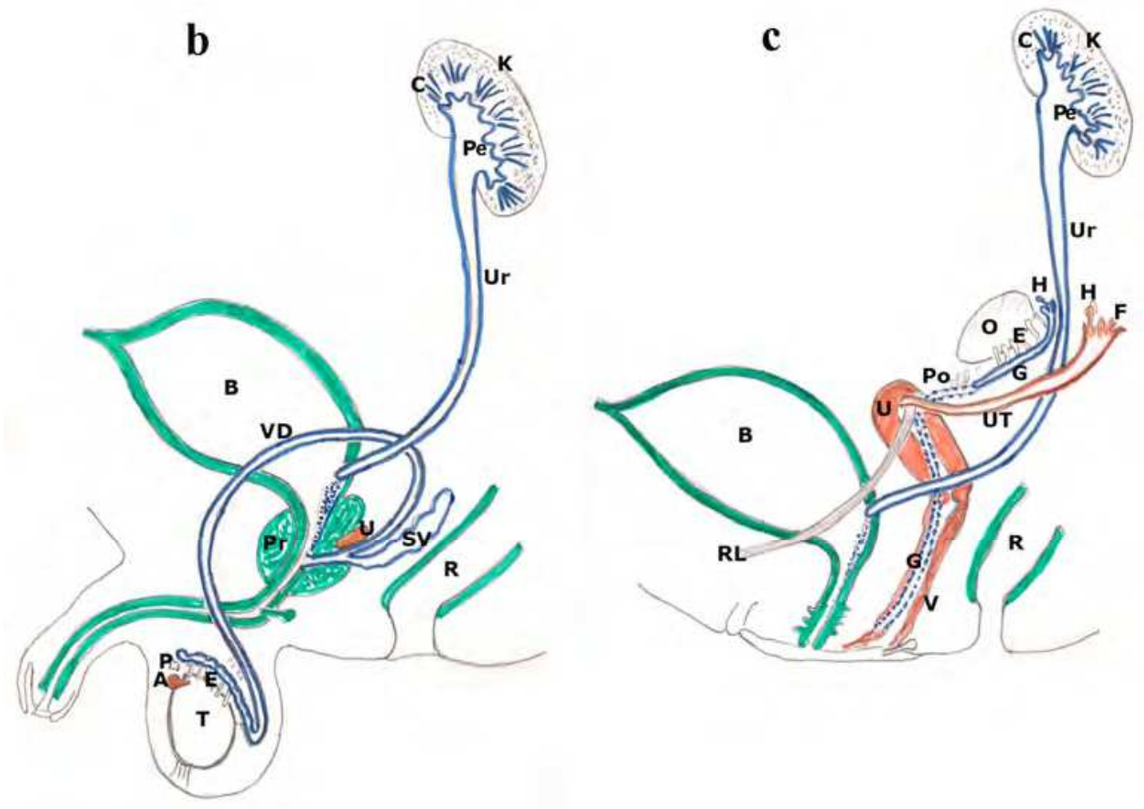


Fig. 11. Schematic drawings of genital ducts
a) Indifferent stage with Müllerian and Wolffian ducts in both genders. G, gonad; M, Müllerian duct; Ms, mesonephros, Mt, metanephros; S, sinus urogenitalis; U, ureter bud; W, Wolffian duct. Modified after Larsen b) Male differentiation of Wolffian duct (blue color). Red, remnants of Müllerian duct = Appendix testis (A) and utriculus prostaticus (U); dotted area, trigonum vesicae, according to classical view of Wolffian ducts origin. Green, derivatives of endoderm. B, bladder; C, collecting ducts; E, Epididymis; K, kidney; P, paradidymis; Pe, pelvis of kidney with calyces; Pr, prostata; R, rectum; SV, seminal vesicle; T, testis; Ur, ureter; VD, vas deferens. c) Female differentiation of Müllerian ducts (red). Differentiation and vestigial structures of Wolffian ducts blue. Green, Derivatives of endoderm. B, bladder; C, collecting ducts E, epoophoron; F, fimbriae; G, Gartner's duct; H, hydatids; K, kidney; O, ovar; Pe, pelvis of kidney with calyces; Po, paroophoron; R, rectum; RL, round ligament; U, uterus; Ur, ureter; UT, uterine tube; V, vagina. b) and c) modified after Hamilton , Boyd, Mossman.

The Müllerian ducts appear later in organogenesis but like the Wolffian ducts they develop at first in a similar manner in male and female embryos (Fig. 11a). The Müllerian ducts need induction of the Wolffian ducts with exception of the most cranial funnel region, which is supposed to include some nephrostomata from the regressing pronephros. The cells of the Müllerian ducts derive from the splanchnopleure exactly from the bilateral thickened stripes of coelomic epithelium, the Müllerian ridges. No cellular contribution from the Wolffian ducts was observed. The Müllerian ducts use the Wolffian ducts as guide to grow caudad, but in the lumbal region they cross the Wolffian ducts in the midline to form the uterovaginal canal (Fig. 11a). In females, they than differentiate into uterine tubes and the fused part forms uterus and vagina (Fig. 11c). New concepts of vaginal development

contradict the classic view that the caudal part of the vagina derives its origin from the urogenital sinus, but is supportive of the view that origin of the vagina can be traced solely back to the Mullerian duct.

In males, AMH induces apoptosis and epithelio-mesenchymal transformation of the Müllerian ducts. Only the most cranial and the most caudal parts frequently persist as appendix testis and utriculus prostaticus (Fig. 11b), demonstrating special properties of these regions.

The differentiation of the indifferent ducts into their special structures in adults is listed in table 1. From this it becomes clear that all anlagen of the urogenital system are identical in the indifferent stage of development. The female differentiation is more passive while male differentiation needs genetic and hormonal factors. Early developing structures leave their trace in the adults as a vestigial organ which might be of clinical interest.

A better understanding of the organogenesis of the genital ducts under their well orchestrated genetic control during critical period of development would greatly help in diagnosing congenital malformations early and would serve as a guideline for designing therapeutic modalities for the treatment of disorders of the urogenital system.

indifferent	male	female
Wolffian duct	Ductus epididymidis	Gartner's duct
	Vas deferens	(Appendix vesiculosa)
	Seminal vesicle	
	(Appendix epididymidis)	
	Ureter	Ureter
	Renal pelvis and calyces	Renal pelvis and calyces
	Collecting ducts	Collecting ducts
Müllerian duct	(Appendix testis)	Tuba uterina
	(Utriculus prostaticus)	Uterus
		Vagina
		(Appendix vesiculosa)
Sinus urogenitalis	Bladder	Bladder
	Urethra	Urethra
	Prostata	Caudal part of vagina?
Tubules of mesonephros	Ductuli efferentes	Epoophoron
	Paradidymis	Paroophoron

Table 1. Anlagen of genital ducts and their differentiation in male and female organs and vestigial structures in parenthesis.

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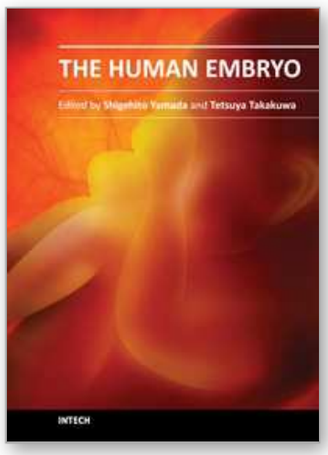

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Human embryology is now rapidly moving to a new phase due to recent innovation and advances of life science including ES and iPS technology. This new era also directs a difficult challenge for scientists in terms of technological and ethical issues for future human embryology. However, human embryology is difficult to research due to ethics involved in the collection of human materials. This book traces the early history and provides knowledge on demonstration of principles from ancient to the most recent embryo studies amidst the unresolved scientific and ethical issues. We hope this book will help the readers to understand human embryo development better.

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