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Karl Peter's fundamental contribution to the structural organization of the kidney

August Heidland [1], Andrè Klassen [1], Gholamreza Fazeli [2], Katarina Sebekova [3], Udo Bahner [4]

[1] Department of Internal Medicine, University of Würzburg, Würzburg - Germany
[2] Institute of Pharmacology and Toxicology, University of Würzburg, Würzburg - Germany
[3] Institute of Molecular BioMedicine, Comenius University, Bratislava, Slovakia
[4] KfH Kidney Centre, Würzburg - Germany

Abstract

Karl Peter provided the first detailed description of the structure and morphology of the human kidney and defined at least 9 major segments of the tubules. He showed that the nephrons were heterogeneous in their structure and could be divided in 2 categories: the short-looped and the long-looped ones. Peter's scheme of the human nephrons was published in many journals and textbooks. Another contribution was the demonstration of a relationship between the relative occurrence of long thin loops (versus short loops) and the maximal urinary concentration capacity. Peter was also the first to describe the cells of the macula densa, which are of fundamental importance in the tubuloglomerular feedback mechanism. Furthermore, Peter gave a detailed description of the principal zones of the human kidney: the cortex, the outer medulla with outer and inner stripes, and the inner medulla.

Key words: *Distal tubule, Human nephron, Karl Peter, Loops of Henle, Macula densa, Proximal tubule, Urinary concentration*

Introduction

Our knowledge of the structure and arrangement of the nephron in the human kidney, as well as that of various mammalian species, is based to a great extent on the fundamental investigations of Karl Peter and his scholars (1). By comparing the findings of various mammals, a better understanding of renal morphology as well as of the structures that the kidneys of these animals have in common could be achieved. For this reason it is rather surprising that Peter's successful research has not received the recognition it deserves. In this light, it seems appropriate to provide a retrospective view of his scientific work, in particular for the clinical nephrologist.

Karl Peter – biography

Born in 1870 in Frankfurt an der Oder, the son of a pedagogue and historian father, and mother, Clara (born Ritschl), Karl Peter began his medical studies in 1890 at the University of Freiburg i.Br., later moving to the universities of Leipzig and Marburg, only to return to

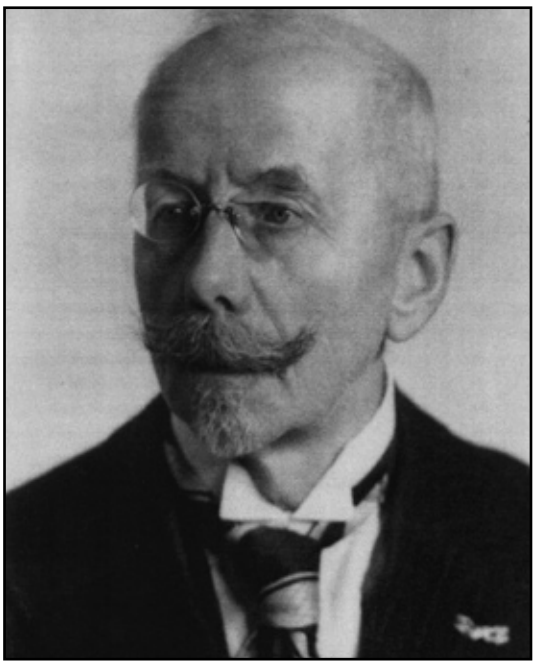

Fig. 1 - Karl Peter (1870-1955). Reprinted with permission from Marion Walther (2003).

Freiburg to complete his doctorate in 1894. Three years later he took up the position of assistant physician at the Institute of Anatomy in Breslau (today: Wroclaw). Peter completed his habilitation in 1898 and moved to Würzburg 6 years later. In the following 40 years, until the end of the Second World War, he was active in the Institute of Anatomy in Greifswald – first as head and later as its director. Although Peter retired in 1935, he maintained his research and teaching activities. In 1946 he moved to Munich where he continued lecturing at the Institute of Anatomy. In 1955 (2), after a full life as a dedicated and popular university professor and a loyal and loving family man, this creative researcher passed away (Fig. 1).

It was during Peter's time at the Institute of Anatomy of the University of Würzburg (beginning in 1904) that he was encouraged by the head of the institute, Prof. Philipp Stöhr, to work on the anatomy of the kidney. This field of research was the focus of Peter's interest also in Greifswald over the next 2 decades. While reviewing the literature, Peter noticed that very little was known about the fine structure of the human kidney. The textbooks of his days presented starkly differing structures of the nephron. This was particularly evident in a publication of Huber (3), who showed 6 different, yet prevalent, schemes of the nephron. Peter further recognized the need to reexamine the kidney structure of various mammals such as the dog, mouse, rabbit, sheep, cat and pig.

Techniques

In his investigations, Peter first applied and improved the method of microdissection of renal tissue after its maceration by strong hydrochloric acid. This technique softens and removes the interstitial substance, leaving the nephron more or less intact and allows the separation of large portions and occasionally a complete nephron structure. The second method employed by Peter was the difficult 3-dimensional reconstruction of the cortical nephron of the kidney, which was prepared by the so-called wax-plate method. This method needs an unbroken series of 150-250 sections. Peter conducted longitudinal and cross-sectional investigations of the fixated kidney after staining with hematoxylin-eosin.

History

As early as 1842, William Bowman (4) observed that the glomerular tufts are surrounded by a capsule which continues into the proximal tubule. Twenty years later, the nephron loops were discovered by Jakob Henle (5). In 1889, Golgi (6) was the first to describe that the final section of the distal limb of Henle's loop attaches to the corresponding renal corpuscle.

Structure of the human nephron

In his microdissection studies, Peter (7, 8) showed that in the human kidney, like that of other mammalian species, the proximal tubule (Hauptstück) could be divided into a convoluted part (*pars convoluta*) and a less convoluted straight part (*pars recta*). The tubule originates at the renal corpuscle, opposite the vascular pole and winds outward to the periphery of the cortex (Fig. 2a). Following various coils and an arcade, it passes close to its own tuft and then continues to the medulla. The transition of the proximal straight tubule to the descending thin limb of Henle's loop is abrupt. The limb of the long loop extends for a variable distance into the inner medulla and subsequently bends. The transition from the thin limb to the thick limb is also abrupt and shows a granular section (Fig. 2b). The subsequent segment is bright and attaches to the vascular pole of its own corpuscle (Fig. 2c). This was without any exception the case in all investigated animals and in adult humans, in accordance with Golgi, but in contrast to other authors. In line with Hamburger, the attachment occurs in the vicinity of the *vas efferens* (9). Peter divided the subsequent convoluted tubule into 3 segments: the intermediate section (Zwischenstück) and proximal and distal segments of the distal tubule. Both

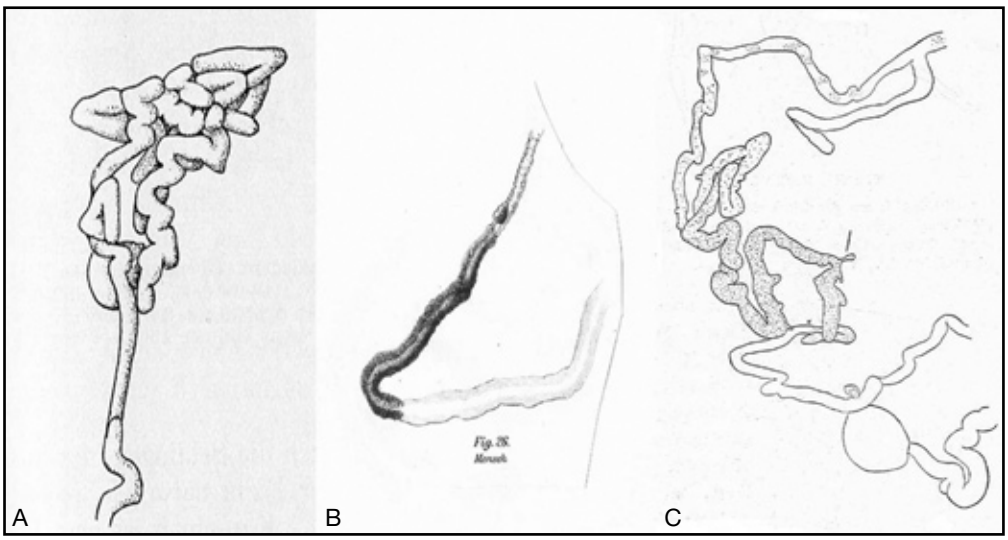

Fig. 2 - Microdisection of different parts of the human nephron. a) Proximal convoluted and straight tubule from the kidney of a 16-year-old girl (Fig. 20 in (8)) (magnification ×40). b) Short loop of a 22-year-old woman (Fig. 26 in (8)). Abrupt transition of the thin descending limb to the granular thick limb followed by the bright thick limb. c) Distal nephron of a 60-year-old man: intermediate section (Zwischenstück) and the proximal and distal tubule segments of the convoluted tubule (Schaltstück) followed by the connecting tubule (Verbindungstück) (magnification ×60).

latter parts are characterized by a cloudier appearance and pursue an irregular course (zigzag course). The diameter of the distal segment appears smaller and less cloudy than the proximal one. The transition to the connecting tubule is gradual and finally ends in the collecting duct, the roots of which are located in the outer regions of the cortex and in the inner medulla.

Short-looped and long-looped nephrons

Peter differentiated 2 structural categories of nephrons: those with loops terminating in the cortex and others in the medulla. The former bend only in the cortex and do not possess a thin limb. In the medulla, the loops are divided into short and long ones. The short loops bend in the outer zone of the medulla, exclusively in their cloudier section (Fig. 2b), while the long loops bend in the entire inner zone of the medulla also in the bright thin section.

Before Peter, it was assumed that the size of the renal corpuscles in the central cortex (juxtamedullary glomeruli) are larger than those of their peripheral counterparts (4). According to the studies of Peter (8) and von Möllendorff (10), this does not apply to the human kidney. However, in some animals (rat, pig and horse), Peter observed larger renal corpuscles in the deep cortex than in the periphery, which was confirmed in rats (11). The cow, in contrast, displays the exact opposite relations – i.e., in the outer cortex there are larger glomeruli than in the central cortex. Corresponding to the anatomical differences of the short- and long-looped nephrons, they differed also in numerous functional aspects, underlining the heterogeneity of the nephrons (12, 13).

Reconstruction of the nephron in the cortex of human kidney

Peter devoted himself in depth to the difficult and time-consuming "reconstruction technique" and performed a 3-dimensional representation of a human cortical nephron (Fig. 3).

Scheme of the arrangement of the human nephrons

By combining microdissection and reconstruction methods, Peter (7, 8) achieved the first diagram of a short-looped and long-looped nephron of the human kidney (Fig. 4).

Peter's scheme of the different types of the nephron structure was published in many journals and medical textbooks. It was also accepted with extensions by Homer W. Smith (14) in his classic book *The Kidney* and in the Netter Atlas (Volume 6, 1973) as well. It is also largely integrated into the standard renal nomenclature of the International Union of Physiological Sciences (15).

Length of the tubule segments in human and various mammalian species

In human, the total length of the tubules averages 55 mm (Tab. I). In all mammals studied, the collecting tubule is the longest part, followed by the proximal convoluted tubule. The length of the tubule is related directly to the size of the renal corpuscles and and correlates to the size of the animals in line with Bowman (4).

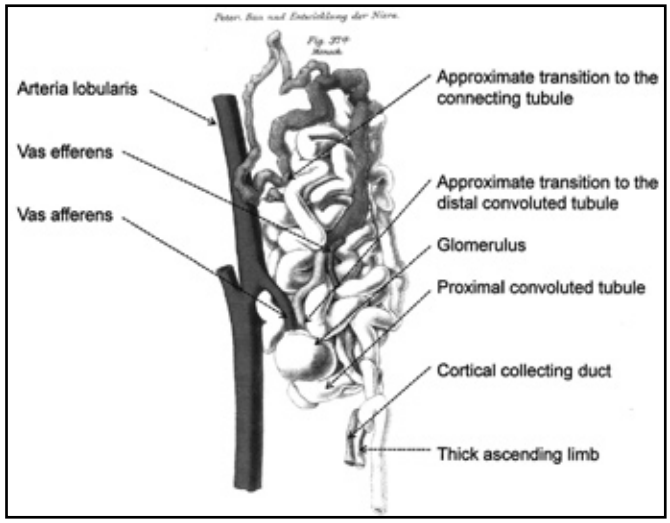

Fig. 3 - Reconstruction of an individual nephron of the kidney cortex from a 26-year-old executed man (Fig. 37a in (8)). The descriptions of the different parts of the nephron have been added to the original picture by the authors for better understanding (magnification 100 x). The centrally located glomerulus shows the vascular pole in the periphery. The diameter of the vas afferens appears larger than that of the vas efferens, in line with Bowman's observation (1842). The proximal convoluted tubule starts at the central side of the glomerulus, winds to the periphery, forms an arcade and then returns nearly to its parent corpuscle. The thick ascending limb reaches the glomerulus after 2 weak bends and is followed by the distal convoluted tubule which extends to the connecting tubule.

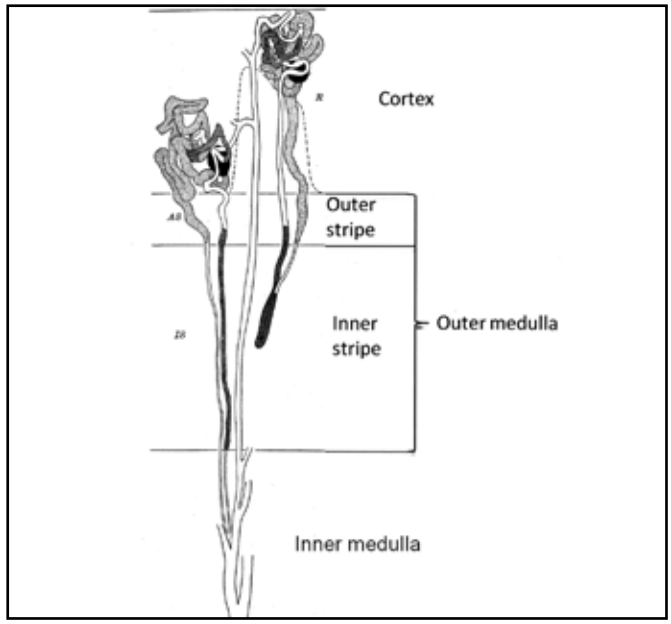

Fig. 4 - Arrangement of the nephron and collecting duct system of an adult human kidney (7). Juxtamedullary nephron (left) and cortical nephron (right) as well as the collecting duct. Black indicates the glomerulus; dotted, the proximal convoluted tubule; dashed, the distal convoluted tubule; crossed, the granular thick ascending limb. The hairpin bend of the long loop is in the inner medulla and that of the short loop in the inner stripe of the outer medulla. The loops then revert to the vascular pole of their own glomerulus.

First evidence for involvement of the long loops of Henle in the urinary concentration mechanism

Peter (8) quantified the incidence of each type of the nephron in the various mammalian species and observed different ratios between long-looped and short-looped ones (Tab. II). The human kidney for example had 1 long-looped nephron for each 7 short-looped ones, corresponding to 15% of the 1 million nephrons in the human kidney. By contrast, the kidney of dogs and cats comprises only long-looped nephrons.

Peter noticed that the relative occurrence of long loops of various mammals correlated with the maximal specific gravity (SG) of their urine. This was very high in dogs, cats and rabbits (SG: 1.060, 1.040 and 1.050, respectively), but lower in pigs and humans (SG: 1.025 and 1.030, respectively). Therefore Peter hypothesized that the frequency of long loops contributes to the fluid reabsorption in their thin segments, resulting in hypertonic urine. In line with this observation it was found later (16) that hypertonic urine is only formed in those mammals and birds, in which the thin segment of long loops is present. Similarly, an elevated ratio of the inner zone/cortex was shown to be associated with the highest urinary concentration capacity in various mammals (17). These findings led to the conclusion that the thin segment of the long loops is involved in the formation of concentrated urine. However, according to micropuncture studies, the fluid absorption in the thin limb of Henle's loop is not an active process. It occurs in a passive manner by the countercurrent multiplication system (18).

First description of the macula densa cells

In his histological investigations of the stained kidney (with hematoxylin-eosin), Peter demonstrated for the first time (8) that the epithelium of the distal thick ascending limb, which is attached to the vascular pole of the renal corpuscle, changes its appearence and forms a plaque of cells with a high nuclei density. This was the first description of the region which was later named the *macula densa* (Fig. 5).

TABLE I
LENGTH OF URINIFEROUS TUBULES: TRANSLATED REPRODUCTION OF TABLE XIII OF PETER (8)

Species	Total tubule, mm	Proximal tubulus contortus, mm	Loop of Henle		Distal convoluted tubule, mm	Collecting tubule, mm
			Thin bright segment, mm	Thick segment, mm		
Mouse	12	2.75	0.8-2.3	1.5	0.65	6
Rabbit	29-37	6.9	1.2-12.3	5-3.6	0.75	16
Sheep	56-65	16	2.6-13	8-6.6	1.9	27.5
Cat	40-52	9	3.6-12.4	6.5-5.2	1.2	20-24
Porpoise	18.6	4.5	1.0-6.5	2.4-2.6		6.2
Cow	70-84	19	4.5-20	11.8-8.9	1.3	20.8-22.4
Man	52-58	14	2-10	9	4.6	21
Pig High	51	15.6	0-3.3	1.6-3.7	1.8	21
Pig Low	75	22.5	9.3	6.4	3.4	33

About 50 years later, it was shown by using micropuncture and microinjection experiments that the cells of the macula densa play an important role in the tubuloglomerular feedback mechanism (19). The macula densa cells sense the fluid composition of the thick ascending limb, which normally has a low concentration of sodium chloride as consequence of the high salt reabsorption in the thick ascending limb (20). A small rise in the salt concen-

TABLE II
RELATIVE OCCURRENCE OF THE DIFFERENT TYPES OF LOOPS IN VARIOUS MAMMALS: TRANSLATED REPRODUCTION OF TABLE XI OF PETER (8)

	Long loops	Short loops	Cortical loops
Cat, dog	+	0	0
Rabbit	3	2	0
Porpoise	1	2	0
Sheep	1	2.3	0
Cow	1	3	0
Man	1	7	+ rare
Pig	1	many	+ many

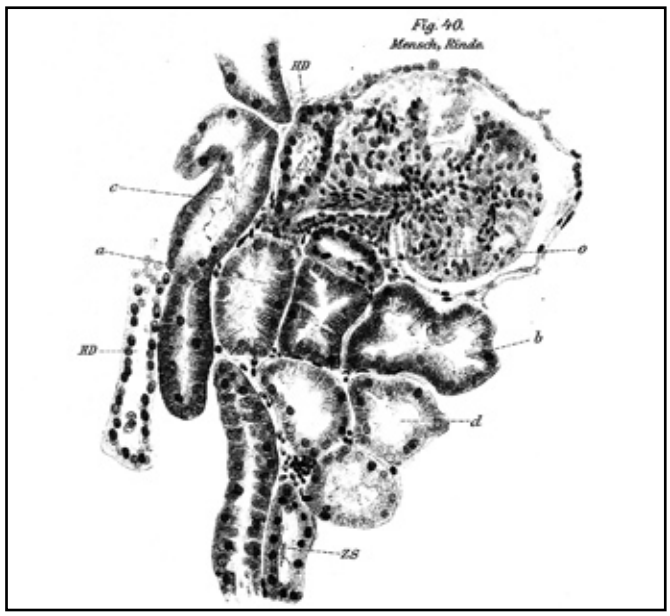

Fig. 5 - Histological section of the kidney cortex of a 20-year-old executed man (Fig. 40 in (8)). Attached to the vascular pole of the glomerulus is the final portion of the thick ascending limb with the macula densa cells (O). The opposite side shows the thin epithelia of the thick ascending limb. Labels a-d: distal convoluted tubule. HD = think limb of Henle's loop and ZS = intermediate section (magnification x260).

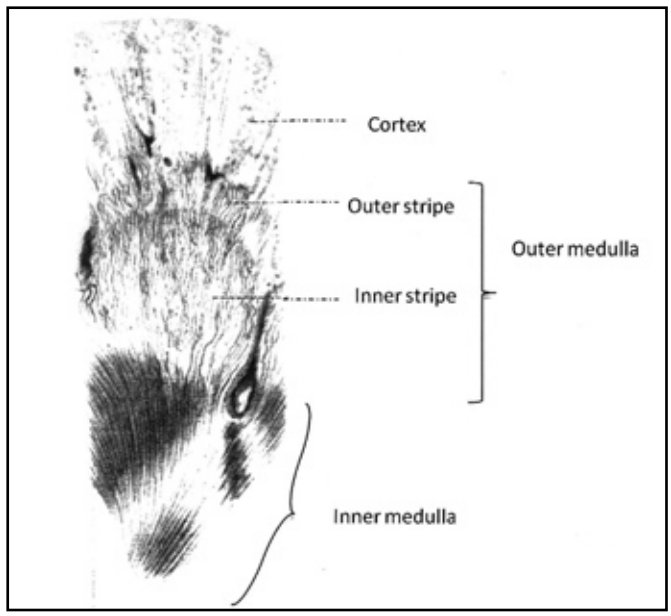

Fig. 6 - Principal zones of the human kidney of a young girl (Fig. 58 in (8)). The zones could be visualized after treatment of the tissue with hydrochloride acid.

tration is detected by the macula densa cells and signaled to the glomerulus, followed by a decline of the glomerular filtration rate (GFR). On the other hand, a lower salt concentration at the macula densa enhances the GFR (20). Thus it is assumed that the function of the macula densa is to protect the organism from the loss of excess fluid and salt (21).

Principal zones of the kidney

Surprisingly, at that time, the macroscopic structure of the kidney, in particular of the medulla, had barely been investigated. Peter reevaluated the structural organization of the nephrons and showed that the human kidney could be divided into 4 different zones: the cortex, the outer stripe of the outer medulla, the inner stripe of the outer medulla and the inner medulla (Fig. 6). These parts were related to the specific structure of the cortical and juxtamedullary nephrons. The kidney cortex contains the labyrinth with the glomeruli, the convoluted parts of the proximal and distal tubules, the connecting tubule as well as the medullary rays with the straight part of the proximal tubules and the distal part of the thick ascending limb. In the medulla, 2 transitions of the nephrons take place: first a transition from the straight part of the proximal tubule to the thin descending limb (Fig. 4). This subdivides the outer and inner stripes of the outer medulla. Second, there is the transition from thin ascending limb to the thick ascending limb. Thereby, the outer medulla is divided from the inner medulla. The inner zone is a straight part containing the thin part of Henle's loop and the straight collecting duct.

Significance of the morphological structures of the distal nephron and collecting duct for functional processes

Peter described at least 9 different segments of the tubules in the various mammalian nephrons. In particular, the structural organization of the distal nephron and collecting duct were carefully characterized by him (22). In the past several years, the corresponding functional processes in these segments have been analyzed by immunostaining. In the thick ascending limb, the local structure matches with the bumetanide/furosemide-sensitive Na-K-2Cl (NKCC2) transporter. The distal convoluted tubule of the human kidney displays the thiazide-sensitive Na-Cl cotransporter (NCC) (23). A feature of the connecting tubule as well as of the cortical collecting duct is the amiloride-sensitive

epithelial Na channel (ENaC). Moreover, major parts of the connecting tubule and the collecting duct coexpress aquaporin 2 (23). Interestingly, in the intermediate section of the distal convoluted tubule, a hormone-dependent adenylate-cyclase activity has been demonstrated, which is limited to this segment (24).

Summarizing, from the historical point of view, Peter's innovative investigations of the architecture of the kidney were a milestone in our understanding of renal anatomy, for which he deserves much more recognition.

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Address for correspondence:
August Heidland, MD
Department of Internal Medicine
University of Wuerzburg and KfH Kidney Center
Hans-Brandmann-Weg 1
DE-97080 Wuerzburg, Germany
August.Heidland@t-online.de

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