Proteinuria and function loss in native and transplanted kidneys

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Appendices

Color Figures

Curriculum vitae

Publications

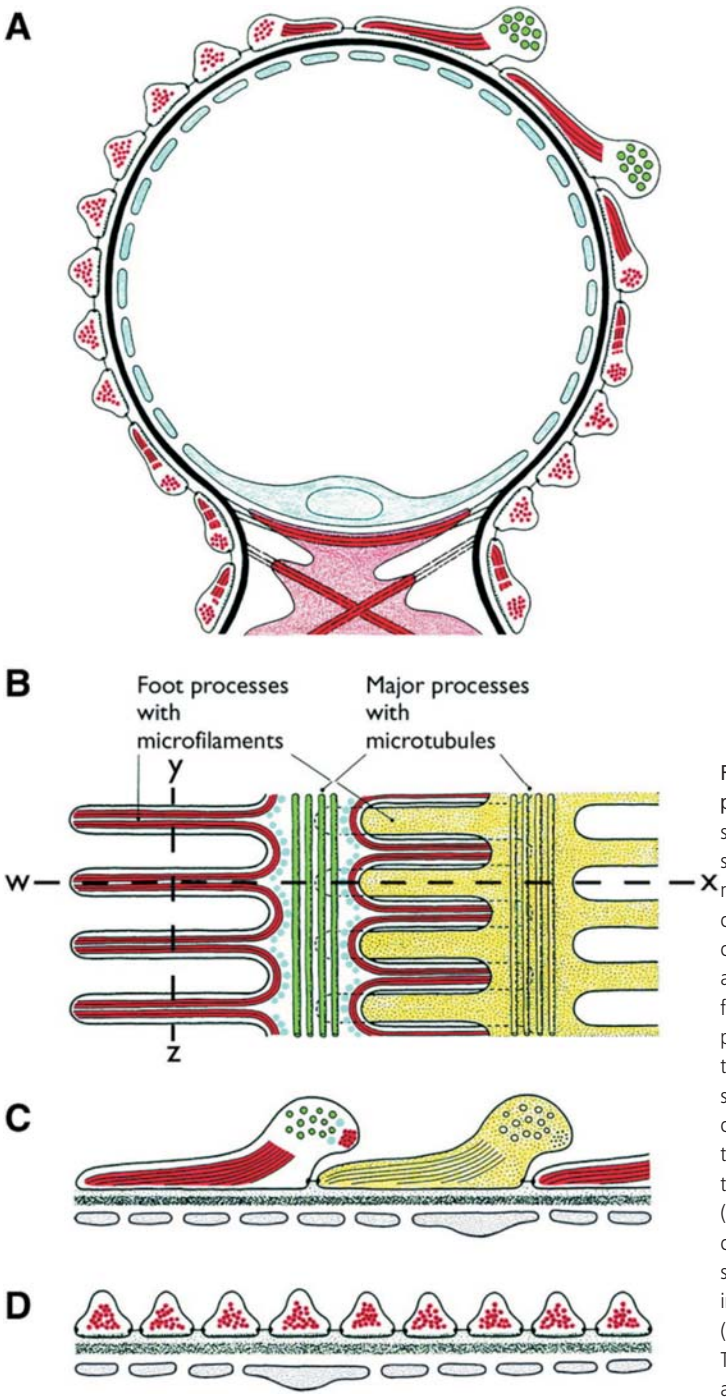


Figure 2. Organization of the podocyte cytoskeleton. A cross section through a capillary loop shows that the capillary is surrounded by podocyte foot processes. At the base of the capillary, contractile mesangial cell filaments are attached (a). A schematic view from above shows that the foot processes sprout perpendicular to the major processes. The cytoskeleton of the major processes is composed of microtubuli, to which the actin-based cytoskeleton of the foot processes is attached (b). In (c) and (d) the lateral view capillary wall is depicted, corresponding to the w-x and y-z line in (b), respectively. Adapted from (14), used with permission from The American Physiological Society and the author.

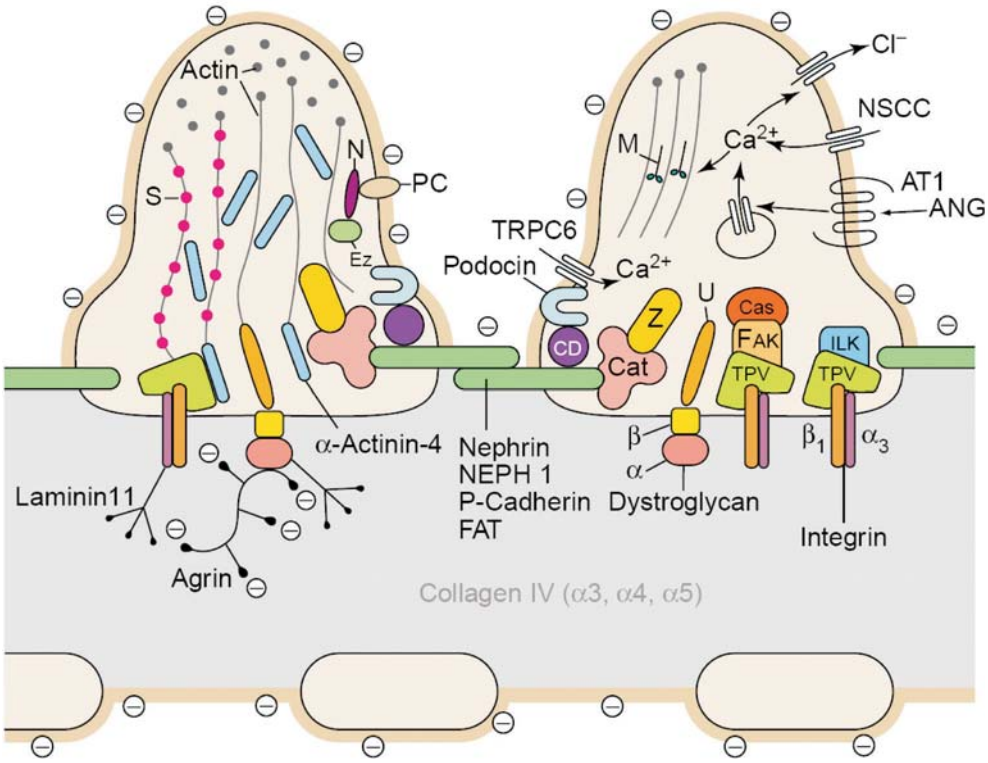


Figure 3. Molecular organization of the podocyte foot process. Two podocyte foot processes with the bridging slit diaphragm are depicted, resting on the glomerular basement membrane (GBM). The central part of the foot process is the actin cytoskeleton (indicated in the left foot process with grey dots), which is reinforced by synaptopodin and α-actinin-4, and has contractile properties as a result of myosin fibers (M). Connected to the cytoskeleton are several molecules that reside in the negatively charged apical membrane, including podocalyxin (PC) via NHERF2 (N) and ezrin (Ez), and podoplanin (not depicted). At the basal membrane, the actin cytoskeleton is connected to the GBM via dystroglycan (linking utrophin (U) to agrin), and the integrin-complex (integrin, talin-paxillin-vinculin (TPV), integrin linked kinase (ILK), focal adhesion kinase (FAK)). The slit diaphragm is composed of nephrin, NEPH-proteins, P-cadherin, and FAT, and the slit diaphragm domain contains several molecules that play a role in the anchoring and signaling of the slit diaphragm (TRPC6, podocin, CD2AP (CD), β-catenin (cat), and ZO-1 (Z)). The podocyte has several receptors, including the angiotensin II receptor AT1. See text for further details. Adapted from (505) and (506), with permission from Elsevier, Lippincott Williams & Wilkins, and the author.

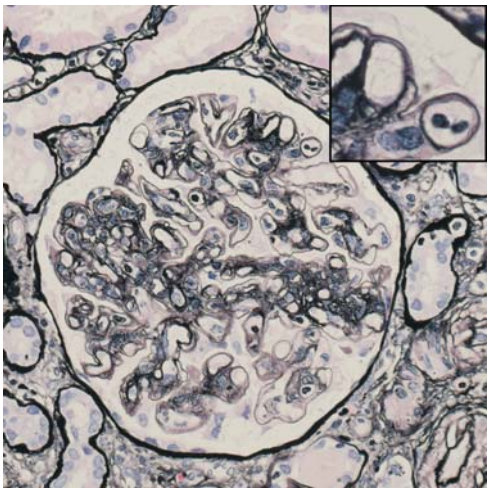


Figure 4. Transplant glomerulopathy. Transplant glomerulopathy is seen in chronic rejection. This glomerular lesion is characterized by a duplication of the glomerular basement membrane (inset).

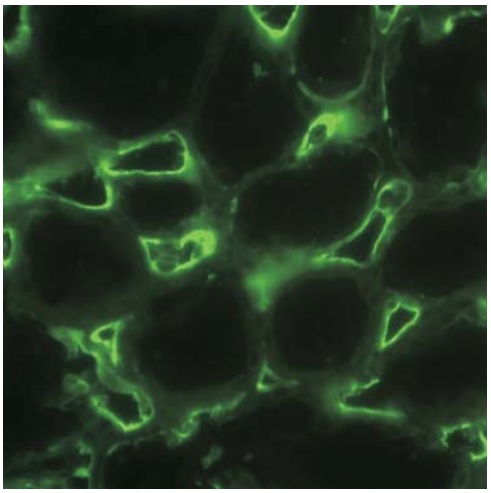


Figure 5. C4d deposition. In chronic humoral rejection, the complement split product C4d remains covalently bound to endothelial cells. This picture shows widespread deposition of C4d in peritubular capillaries.

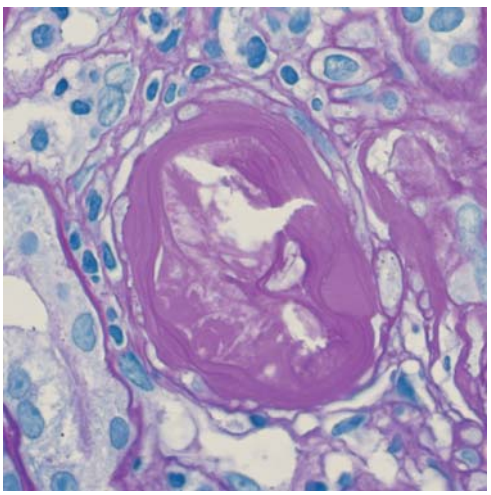


Figure 6. Arteriolar hyalinosis. Nodular depositions of hyaline material are seen in the media of arterioles, indicating the presence of chronic CNI toxicity.

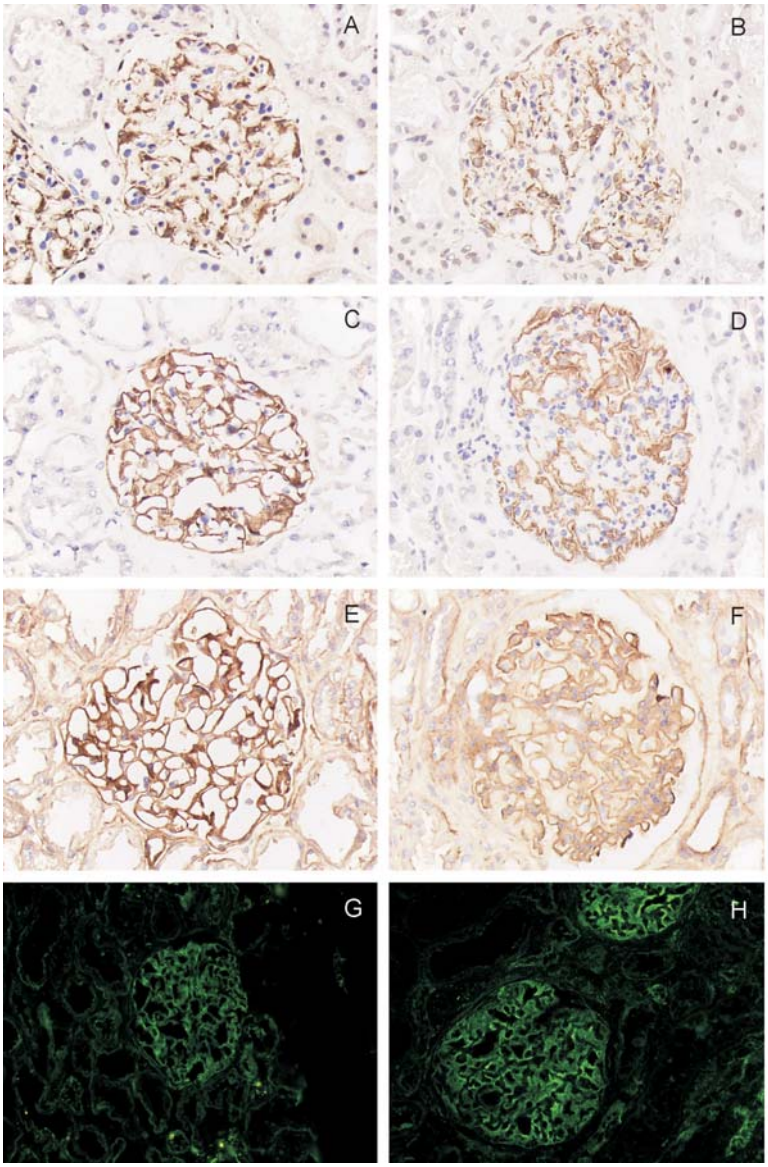


Figure 2. Staining pattern of nephrin, podocin, podocalyxin, and CD2-associated protein (CD2AP) in normal and diseased human kidney sections. Nephrin (A), podocin (B), and podocalyxin (C) show a podocyte-like staining pattern in normal glomeruli as visualized by an immunohistochemical diaminobenzidine staining. The staining pattern of nephrin is more dispersed than that of podocin and podocalyxin, which show a fine glomerular basement membrane (GBM)-like line along the capillary loops of the glomerulus. CD2AP, visualized with immunofluorescence, shows a GBM-like staining pattern (D). In diseased situations, the staining for nephrin (E; minimal change disease), podocin (F; focal segmental glomerulosclerosis [FSGS]), and podocalyxin (G; FSGS) is less intense, and nephrin and podocin stainings show a more granular staining pattern. CD2AP staining shows no clear differences between control (D) and diseased tissue (H; diabetic nephropathy). Magnification x 400.

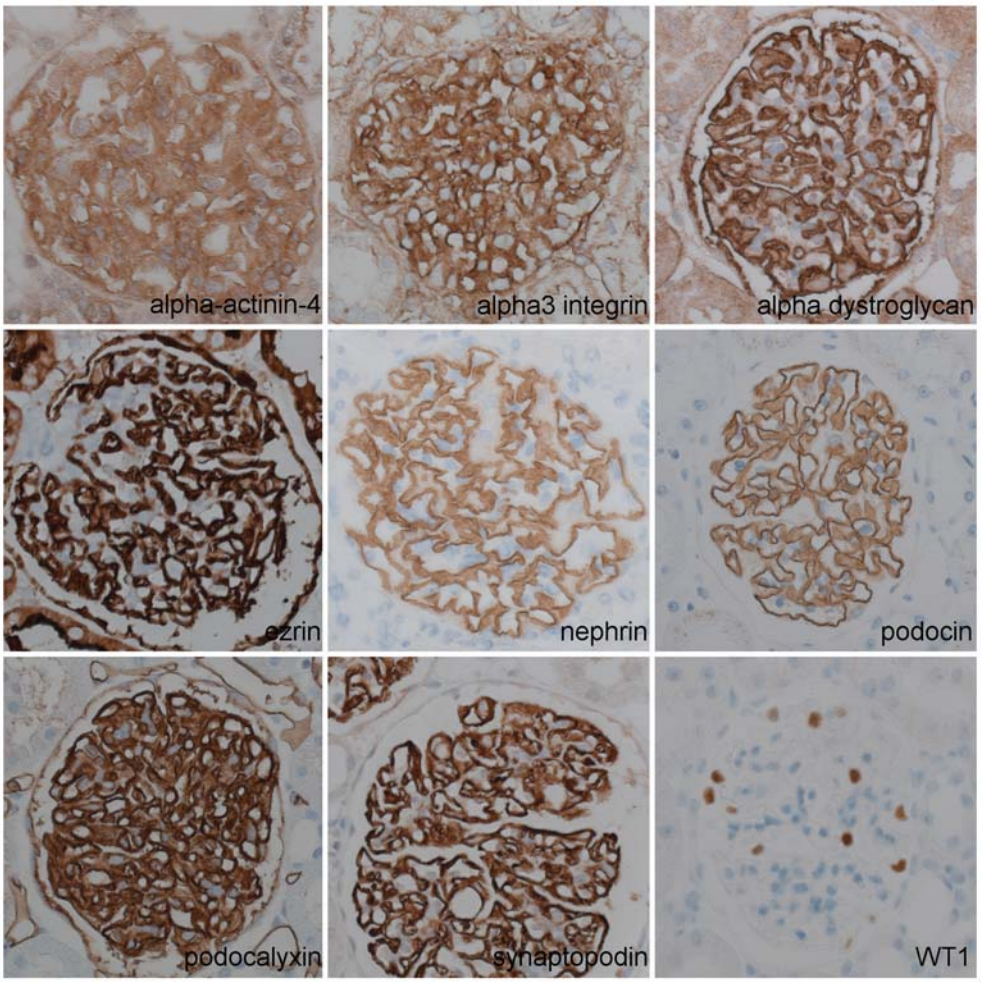
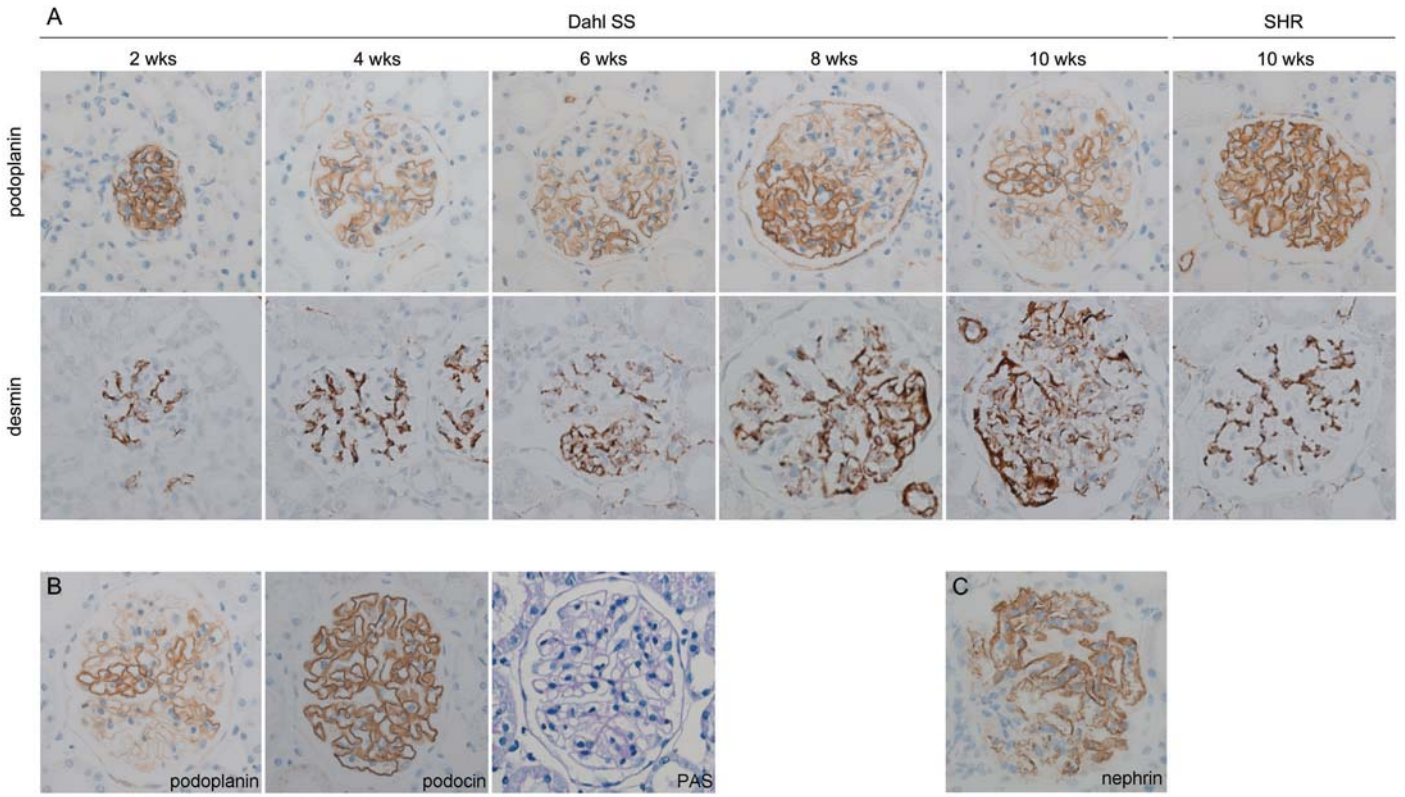


Figure 4. Immunohistochemistry of podocyte proteins. Despite marked proteinuria, 10-week-old Dahl SS rats showed normal expression of α-actinin-4, α3 integrin, α-dystroglycan, ezrin, nephrin, podocin, podocalyxin, synaptopodin, and WT1. Original magnification: x 400.

Figure 5. Podoplanin protein expression in Dahl SS glomeruli was progressively lost in a focal and segmental fashion. Loss of podoplanin protein expression was first seen in 4-week-old Dahl SS rats and increased thereafter. In contrast, podoplanin protein expression remained normal in SHR rats throughout the time course of the study. The upper row of images in A shows podoplanin staining in Dahl SS rats at the indicated time points and in a 10-week-old SHR rat. The lower row of images in A shows desmin staining in Dahl SS rats at the indicated time points and in a 10-week-old SHR rat. Starting at 6 weeks, desmin expression was visible in the extramesangial areas of Dahl SS glomeruli. Expression level increased with age. No change in desmin expression was observed in aging SHR rats. Sequential sections of the kidney of a 10-week-old Dahl SS rat stained with anti-rat podoplanin antibodies, anti-podocin antibodies, and with PAS show that loss of podoplanin is not related to morphological alterations observed by light microscopy or to alterations in podocin expression (B). Nephrin expression was diminished sporadically in segmental parts of glomeruli, but only in 10-week-old Dahl SS rats (C). Original magnification: x 400.


A
Dahl SS
SHR
2 wks
4 wks
6 wks
8 wks
10 wks
10 wks
podoplanin
desmin
B
podoplanin
podocin
PAS
C
nephrin

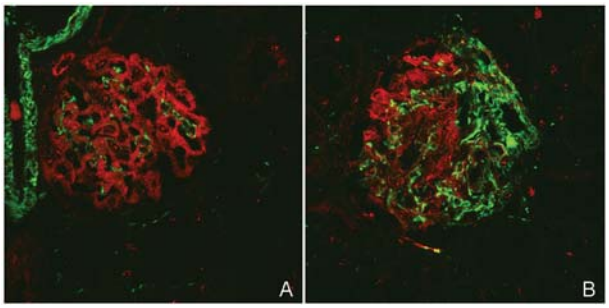


Figure 7. Podoplanin (red) and desmin (green) were costained in kidney sections from 8-week-old Dahl SS rats. Normal glomeruli show desmin expression in renal blood vessels and glomerular mesangium and podoplanin expression in podocytes. Desmin and podoplanin did not colocalize (A). In glomeruli that showed segmental loss of podoplanin expression, increased desmin expression was observed in the podoplanin-negative areas (B). Original magnification: x 630.

Chapter 4

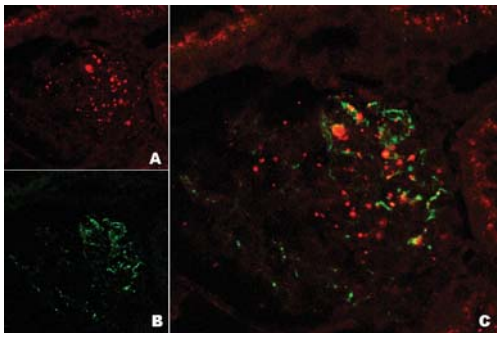
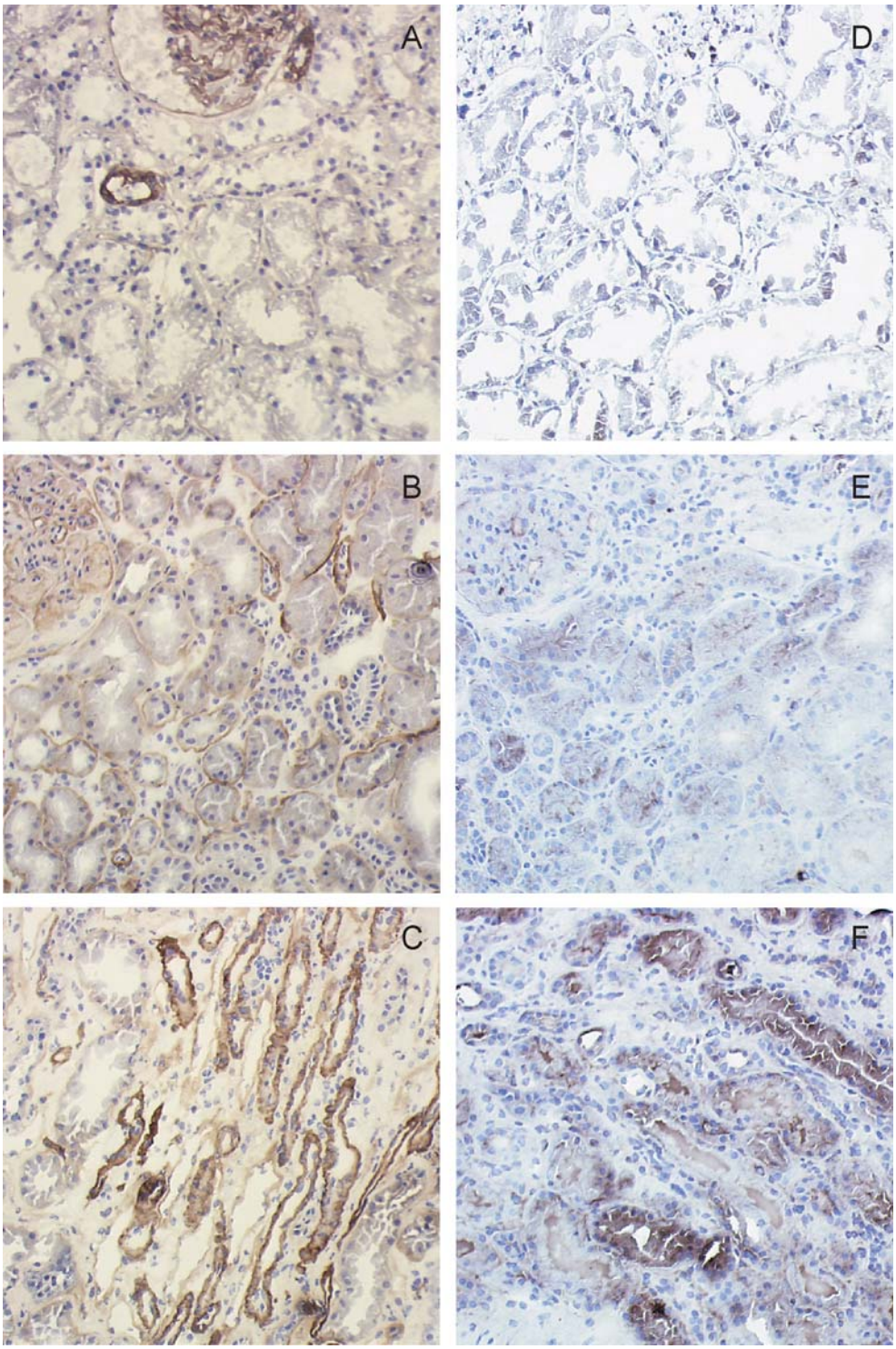


Figure 4. Co-immunostaining of desmin (green) and albumin (red) in a section of an 8-week-old proteinuric Dahl SS rat. Increased desmin expression is seen mostly in areas with extensive albumin accumulation. Desmin (A), albumin (B), merge (C).

Chapter 5

Figure 3. Immunohistochemical stainings for laminin β2 (A to C) and transforming growth factor-β (TGF-β) (D to F). In control tissue laminin β2 staining was observed in the glomerular basement membrane and in cortical vessels (A). In chronic rejection (B) and cyclosporine A (CsA) toxicity (C), expression of laminin β2 was observed in the tubular basement membrane. TGF-β staining was sporadically observed in glomeruli and tubuli of controls (D). In chronic rejection (E) and CsA toxicity (F), some tubuli showed a very intense staining for TGF-β.


A
D
B
E
C
F

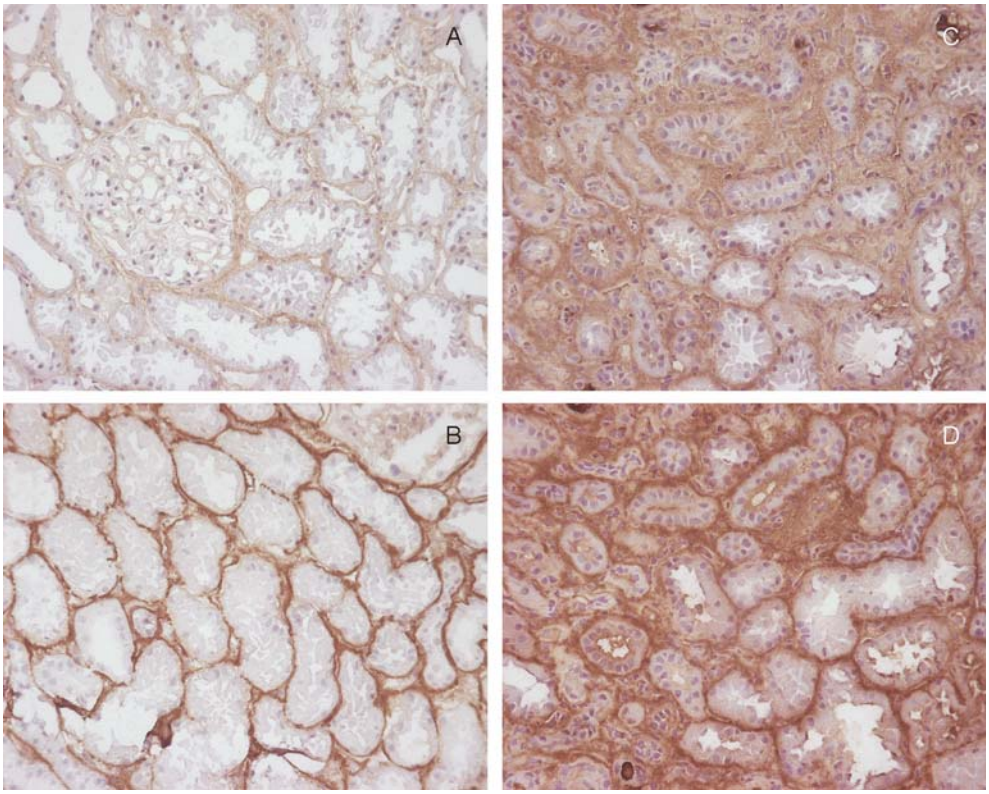


Figure 2. Immunoperoxidase staining for cortical collagen I (A and C) and III (B and D). Representative images of a normal control sample (left) and a kidney allograft with CR (right) are shown.

Curriculum vitae

De auteur van dit proefschrift werd in 1979 geboren in 's Hertogenbosch. Hij doorliep het Voortgezet Wetenschappelijk Onderwijs aan het Greijdanus college te Zwolle, waar hij in 1997 eindexamen deed. Datzelfde jaar ving hij de studie Geneeskunde aan, een jaar later behaalde hij de propedeuse (cum laude), in 2001 voltooide hij het doctoraal examen en in 2004 behaalde hij het artsexamen. In 2005 legde hij het doctoraal examen Biomedische Wetenschappen af. Voortbouwend op onderzoek begonnen tijdens zijn studie werd van 2004 tot 2007 het onderzoek verricht waarvan de resultaten zijn beschreven in dit proefschrift. Dit vond plaats op de afdeling Pathologie van het Leids Universitair Medisch Centrum (hoofd prof. dr. G.J. Fleuren) onder leiding van prof. dr. J.A. Bruijn, dr. E. de Heer en dr. M. Eikmans, in samenwerking met de afdeling Pharmakologie und Toxikologie van de Freie Universität Berlin onder leiding van prof. dr. Reinhold Kreutz. In 2007 begon de auteur met de specialisatie Tropengeneeskunde, achtereenvolgens in het Groene Hart Ziekenhuis te Gouda (opleider dr. H. van Huisseling) en in het Havenziekenhuis te Rotterdam (opleider dr. K.H.A. van Eeghem).

Hij is getrouwd met Gerdien van der Horst, samen hebben zij een zoon, Loek.

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