Personal Opinion

Change of paradigms in nephrology— a view back and a look forward

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‘Verlernen ist oft schwerer als lernen.’ (Arthur Koestler)
(To forget is often more difficult than to learn.)

Scientific revolutions by change of paradigms

In his book The structure of scientific revolutions, T. S. Kuhn [1] distinguished between great and small revolutions in science and subjected such revolutions to more detailed analysis. He came to the conclusion that normal science is based upon a set of concepts or paradigms. Normal science has cumulative character, i.e. involves collecting facts and unravelling problems which confirm the consistency and correctness of existing paradigms. By necessity, groundbreaking innovations will shake the foundations of such tenets and are usually suppressed by normal science. Nevertheless, according to Kuhn, on certain occasions normal science yields results which appear to be anomalous and cannot be reconciled with the predictions based on existing paradigms. Such anomalies can then

Fig. 1 a–d. Glomerular changes in decompensated benign nephrosclerosis. (a) Segmental sclerosis and hyalinosis; (b) advanced sclerosis and pseudotubules; (c) almost complete obliteration of all the glomerular capillaries, pseudotubules, and fat droplets in the hyalinized capillaries and endothelial cells; (d) complete destruction of the glomerulus, fat droplets still being identifiable in the areas of subendothelial hyalinosis. Periodic acid–Schiff reaction.

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competing paradigms. Thus, an anomaly in the results does not lead to a crisis, but to the birth of a new paradigm.

My scientific career was dedicated to renal pathomorphology. More than 45 000 renal biopsies were interpreted in the context of clinical data. Based on this experience I wish to propose some thoughts that illustrate how in-depth clinicomorphological analysis forced changes in some paradigms concerning the pathogenesis of renoparenchymal diseases.

The change in concepts concerning vascular lesions of the kidney

Franz Volhard [2] and Theodor Fahr [3] analysed vascular diseases of the kidney and distinguished between benign nephrosclerosis and malignant nephrosclerosis. Later, Theodor Fahr distinguished between a compensated and a decompensated form of benign nephrosclerosis. By decompensation he implied that renal function was altered [4]. As a case in point, he described a 55-year-old hypertensive patient who presented with proteinuria and erythrocyturia and died in renal failure. Apart from benign nephrosclerosis

Table 1. Clinical data of a case of primary malignant nephrosclerosis. Patient, a 39-year-old male, suffered 10 days of cough, nosebleeds, and diarrhoea

<table>
<thead>
<tr>
<th></th>
<th>Dialysis</th>
<th>Histology I</th>
<th></th>
<th>Histology II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g %)</td>
<td>4.5</td>
<td>140/80</td>
<td>165/85</td>
<td>230/140</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>35</td>
<td>140/80</td>
<td>Anuria</td>
<td>170/120</td>
</tr>
<tr>
<td>LDH</td>
<td>1380</td>
<td>1710</td>
<td>Onset of polyuria</td>
<td>1710</td>
</tr>
<tr>
<td>Platelets</td>
<td>108 000</td>
<td>28</td>
<td>40</td>
<td>56</td>
</tr>
<tr>
<td>Bilirubin (mg %)</td>
<td>1 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg %)</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN (mg %)</td>
<td>187</td>
<td></td>
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<tr>
<td>Blood pressure</td>
<td>140/80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output (ml)</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up (days)</td>
<td>1</td>
<td>28</td>
<td></td>
<td>61 +</td>
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</tbody>
</table>
Fig. 4 a–d. Interlobular arteries in secondary malignant nephrosclerosis. (a) Early changes, stenosing intimal oedema; (b) stenosing intimal oedema and subendothelial necrosis; (c) late changes, intimal fibrosis and fresh haemorrhages; (d) Late changes, obliterating endarteritis. All the blood vessels are from the same kidney. Goldner’s trichrome stain.

Fig. 5 a–f. Examples of severe isolated glomerulopathy with normal serum creatinine concentration. (a) Control kidney; serum creatinine concentration 1.2 mg%, periodic acid–Schiff reaction. (b) Acute endocapillary glomerulonephritis with mild acute renal failure; serum creatinine concentration 1.29 mg%, urinary output 2450 ml/24 h. (c) Membranoproliferative glomerulonephritis type I; serum creatinine concentration 1.2 mg%, creatinine clearance 90 ml/min, periodic acid–Schiff reaction. (d) Membranoproliferative glomerulonephritis type I plus chronic membranous glomerulonephritis; serum creatinine concentration 1.06 mg%, creatinine clearance 172 ml/min, periodic acid–Schiff reaction. (e) Severe nodular diabetic glomerulosclerosis; serum creatinine concentration 1.2 mg%, periodic acid–Schiff reaction. (f) Perireticular renal amyloidosis; serum creatinine concentration 0.8 mg%, periodic acid–Schiff reaction.
Fahr found glomerular lesions with focal thickening of capillaries without cellular proliferation and circumscribed adhesions between glomerular capillaries and Bowman's capsule. Glomerular obsolescence was strikingly frequent and the renal interstitium was fibrosed, particularly in the deep cortex.

Despite such precise description by this pioneer of renal pathology, decompensated benign nephrosclerosis had been completely forgotten as a cause of renal dysfunction. We had great difficulty in drawing attention to this entity [5], which is not infrequent. We have observed this constellation in more than 250 cases [6]. Figures 1 and 2 show the characteristic lesions. The glomerular changes (Figure 1) first appear in the juxtamedullary glomeruli, which are not subject to autoregulation (Figure 2) and spread out into the cortex. Interstitial fibrosis and tubular atrophy are also seen. With the aging of the population and longer survival of patients with hypertension, this lesion will be recognized more frequently, particularly since end-

**DIABETIC GLOMERULOSCLEROSIS**

Correlations between relative area of postglomerular capillaries and serum creatinine concentration at time of biopsy

![Graph](image1)

Fig. 6. Diabetic glomerulosclerosis. Correlations between relative area of postglomerular capillaries and serum creatinine concentration at time of biopsy.

**RENAL AMYLOIDOSIS**

Correlations between relative area of postglomerular capillaries and serum creatinine concentration at time of biopsy

![Graph](image2)

Fig. 7. Renal amyloidosis. Correlations between relative area of postglomerular capillaries and serum creatinine concentration at time of biopsy.
stage renal failure is by no means infrequent in the elderly hypertensive patient [7].

Another example for revision of past pathogenetic concepts is malignant nephrosclerosis. F. Volhard had assumed that the characteristic obliterative preglomerular vascular lesions are exclusively the result of malignant hypertension. Based on one single case, i.e. a young normotensive patient with normal cardiac size who exhibited malignant nephrosclerosis at autopsy, Fahr [8] proposed that the vascular lesions were primary and that hypertension was a secondary consequence. Volhard’s opinion was based on the observation of numerous patients with malignant hypertension and appeared perfectly convincing. We were satisfied with Volhard’s concept until we examined the renal biopsy of a 39-year-old patient who had been normotensive as documented by daily blood-pressure measurements over a 4-week period. Nevertheless he had the characteristic histological lesions of malignant nephrosclerosis (Table 1 and Figure 3). Currently we have collected more than 200 cases of malignant nephrosclerosis who had documented normotension at the start of their disease. We designated this entity ‘primary malignant nephrosclerosis’ to distinguish it from ‘secondary malignant nephrosclerosis’ as a consequence of malignant hypertension [9–11]. We feel that primary and secondary malignant nephrosclerosis can be distinguished in that in primary malignant nephrosclerosis all preglomerular vascular lesions are of similar age, whereas in secondary malignant nephrosclerosis the lesions are of different ages (Figure 4). It has meanwhile become apparent that primary malignant nephrosclerosis is the morphological counterpart of the haemolytic–uraemic syndrome. It is more frequent in females (particularly after hormonal contraception) in contrast to secondary malignant hypertension, which is more frequent in males [12].

What have we learned from the above?

Clinicopathological analysis of the vascular lesions has forced us to change the paradigms to explain the
aetiology and the pathogenesis of benign nephrosclerosis. We have also come to learn that in malignant nephrosclerosis the same morphological lesion may be caused by two entirely different aetiologies.

The role of glomerular lesions in progression

Classical opinion held that in glomerular diseases renal failure develops when the primary glomerular lesions have substantially reduced the filtration surface and thus led to a reduction of glomerular filtration rate. As a result, histological studies of the diseased kidney focused almost exclusively on the alterations of the glomerulus [13–18]. Morphometric analysis of the kidneys in diabetic nephropathy by Mauer et al.[19] and Osterby et al. [20,21] reported a tight correlation between the filtering surface on the one hand and GFR on the other.

Very early on [22–24] we were struck by the paradoxical observation that even severe glomerular lesions in glomerular diseases such as endocapillary glomerulonephritis, membranoproliferative glomerulonephritis, diabetic glomerulosclerosis, and perireticular renal amyloidosis, were not consistently accompanied by an elevation of serum creatinine if the postglomerular capillary bed was not compromised [23] (Figure 5). Such glomerulopathies were associated with progressive renal failure only when the postglomerular capillaries were obliterated by interstitial fibrosis, thus presumably interfering with postglomerular blood flow. A highly significant inverse correlation was noted between the relative capillary surface of the renal cortex on the one hand and serum creatinine concentration on the other. We wish to illustrate this diabetic glomerulosclerosis (Figure 6) and perireticular renal amyloidosis (Figure 7).

Do these observations of ours [22,23,25,26] and of others authors [27,28] force us to change past paradigms to explain chronic progressive loss of renal function in glomerular disease? I think yes. In contrast to many statements in literature I do not feel that glomerular lesions by themselves are sufficient to explain impaired renal function in the majority of cases. To take an extreme case: rapidly progressive extracapillary glomerulonephritis with renal failure. I do not feel that renal failure is explained by obliteration of Bowman’s space by crescents [22]. Crescents consist not of visceral epithelial cells [29,30] (which are postmitotic and cannot proliferate) [31–33], but of pluripotent blood-derived mononuclear cells (Figure 8) [34] which are trapped and accumulate in Bowman’s space. Even in its initial stage extracapillary glomerulonephritis may be accompanied by acute renal failure [22]. Our belief is strengthened by the observation that glomerular reserve capacity is so enormous that even advanced reduction of the filtration surface, as documented by light and electron microscopy, does not necessarily lead to an increase in serum creatinine [24]. The Achilles’ heel for renal function is not the glomerulus, but the postglomerular capillary. If this tenet is
correct, it is the lesion of the postglomerular vessel that leads to renal failure (Figure 9).

This concept raises the issue of which process damages the postglomerular capillaries. Obviously an interplay between altered tubular epithelial cells and interstitial cells leads to interstitial fibrosis [35,36]. Several hypotheses on the genesis of interstitial fibrosis have been proposed, e.g. exposure of the luminal surface of tubular epithelial cells to serum proteins as a result of glomerular leakage [37,38]. Several factors may be involved and we proposed one further hypothesis. According to Hawkins and Cochran [39] and to McCluskey [40] lesioned glomeruli release an autoantigen into Bowman’s space. We presume that the site of origin of this autoantigen is the glomerular epithelial cell [41], which desquamates and releases GBM material from the basal membrane (Figure 10). Such material, which is normally sequestered and cannot be recognized by the immune system, may become accessible to the immune system after processing by tubular epithelial cells and by lymphocytes in intertubular location (Figure 11). This hypothesis requires confirmation; if it is correct, it would imply that interstitial fibrosis is the result of an autoaggression process.

Conclusions

What have we learned from a life-time of work on glomerular pathomorphology?

It is obvious that intellectual economy requires working hypotheses to handle the data provided by observational or interventional studies. The above examples illustrate, however, that we have to keep an open mind and have to be prepared for the possibility that our concepts and paradigms may be wrong and may have to be modified in the light of new data (or new interpretations). I feel that the example of nephrosclerosis and primary glomerulopathies is illustrative and serves to make investigators humble. The change of paradigms, according to Kuhn, is a painful process and may explain why such new concepts often cause controversy and are met by fierce opposition.

Acknowledgements. This article is dedicated to Professor Ernst Jünger, a great poet, philosopher, and morphologist on the occasion of his 103rd birthday. The text is the written version of the Farewell Lecture at the Eberhard Karl University, Tübingen on 16 February 1990.

References