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Structure and Function of the Kidney in Multiple Myeloma

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Summary. Morphological examinations of the kidneys of 146 plasmocytoma patients revealed the typical pathological-anatomical picture of myeloma kidney in only a third. In 23%, histological changes characteristic of acute renal failure were present and in a further 17% only evidences of acute renal failure were detected. In 8% the picture was dominated by severe pyelonephritis; nearly a third of all cases showed no morphological peculiarities. When correlated with clinical data it was noted that in renal insufficiency there was pathological evidence in 48% of myeloma kidney, in 36% evidence of acute renal failure. In about a third of all kidneys of plasmocytoma patients with renal insufficiency were there signs of acute renal failure. In only two patients could contracted kidneys be implicated as the cause of renal dysfunction.

In none of the simultaneously-examined seven cases with Waldenström's macroglobulinaemia were changes found corresponding to those of myeloma nephrosis. In three, however the histological picture of acute renal failure was evident. In the discussion of the relationships between renal structure and function, the unusually frequent picture of acute renal failure must be taken into account when considering therapy.

Zusammenfassung. Morphologische Untersuchungen an Nieren von insgesamt 146 Plasmocytompatienten führen zu dem Ergebnis, daß nur in knapp einem Drittel das typische pathologisch-anatomische Bild einer Myelomniere vorliegt, bei 23% gleichzeitig histologische Befunde wie bei akutem Nierenversagen (a.N.) gefunden werden und bei weiteren 17% allein die Zeichen eines a.N. erkennbar sind. In 8% beherrscht eine schwere Pyelonephritis das Bild und nahezu ein Drittel aller Fälle weist keine morphologischen Besonderheiten auf. Aus Vergleichen mit klinischen Daten geht hervor, daß bei einer Niereninsuffizienz zwar in 48% das pathologisch-anatomische Bild einer Myelomniere vorhanden ist, in 36% jedoch gleichzeitig Hinweise auf ein a.N. bestehen. Bei etwa einem Drittel aller Nieren Plasmocytomkranker mit renaler Insuffizienz sind allein die Zeichen eines a.N. zu erkennen, nur zweimal können Schrumpfnieren als Ursache der Nierenfunktionsstörungen angesehen werden. In keinem der gleichzeitig untersuchten 7 Fälle mit Makroglobulinämie Waldenström ist ein der Myelomniere entsprechender Befund vorhanden, dreimal liegt jedoch auch hier das histologische Bild eines a.N. vor. In der Diskussion der Beziehungen von Struktur und Funktion der Nieren wird auch im Hinblick auf therapeutische Konsequenzen auf das ungewöhnlich häufige Bild eines a.N. hingewiesen.

The frequent occurrence of renal insufficiency and the evidence of characteristic morphological renal alterations through multiple myeloma, with in the total conception of "myeloma kidney", lead one to the opinion that the malfunctioning disturbances can always be lead back to particular pathological anatomical conditions. However, there is often a notable discrepancy between terminal uraemia and relatively sparing morphological changes of kidneys, which caused Nonnenbruch as early as 1942, 1949 to recognise this clinical picture as a special form of the "Extra renal Syndrome". Even today it has not yet been possible to correlate

the structure and functional disturbances of the kidneys through this disease in a satisfactory way. Since a further discussion of the functional value of morphological conditions promises little success, as long as we are not in the possession of more precise information about the amount and frequency of the various structural changes, we have set ourselves the exercise of registering over a large number of patients cases, the frequency of the isolated morphological changes in myeloma nephrosis and to compare this information whith available clinical data, in order to establish the morphological basis for experiments to explore renal functional disturbances through plasmocytoma.

Material and Methods

From a total of 162 patients with multiple myelom, the kidneys of 146 cases could be histologically examined. In 139 cases post mortem renal tissue was available and in 7 cases bioptically obtained tissue. 49 of these specimens were obtained through post mortems at the Pathological Institute of Tübingen University, or sent from elsewhere for examination; 93 specimens came from post mortems at the Pathological Institute of Kiel University, or were given us from the collection of Prof. Dr. Lennert. Histological sections from 20 further plasmocytomas were made available to us from the collection of Prof. Dr. Randerath[1].

Firstly, without reference to the clinical data, we noticed in this material the frequency of the single histological features. In the same way, as in earlier studies (Schubert, 1968), the changes signifying the morphological indications of acute renal failure were established. After that we established how many kidneys could be formulated into particular clinical pictures through the use of morphological criteria.

In addition to this, as a comparison, the kidneys of 7 patients were examined, who had died as a result of Macroglobulinaemia Waldenström.

As pathological anatomical factors for "myeloma kidney" we took: (Allen, 1953; Zollinger, 1966).

1. Profuse hyaline or lamellated casts.
2. The syncytium of epithelial cells about the casts.
3. Strong accumulation of hyaline proteindrops in the tubular cells.
4. Severe interstitial fibrosis and tubulus atrophy.
5. Nephrocalcinosis.

A kidney was then classified as a "typical myeloma kidney", when amongst a large number of casts, at least 3 of the 4 other features were apparent.

The picture of acute renal failure was established, when the following histological features were apparent (Randerath and Bohle, 1959; Bohle, Jahnecke and Rauscher, 1964; Bohle, 1965; Schubert, 1968):

1. Wide tubular lumina, particularly of the proximal convolutions without evidence of blocked drainage.
2. Focal tubular necrosis.
3. Localised round cell reactions of the interstitium in the external areas of the medulla, partly with interstitial edema (so-called tubulo interstitial nephritis by Brun, 1954) and/or granuloma—like reactions round localised lesions of distal tubules (as a feature of "lower nephron nephrosis" Lucké, 1946).
4. Chromoprotein casts in distal and collecting tubules (Zollinger, 1952).
5. Large quantities of oxalate crystals, particularly in the distal renal tubular lumina.

The microscopic evaluation ensued on paraffin sections in the following respective stainings: Haematoxylin-Eosin, Goldner Trichrom, Ladewig, van Gieson, PAS, Fibrin-staining and Congo red. In some of the older cases, there were only Haematoxylin-Eosin and PAS stained preparations available. The kidneys of 40 patients could, in addition, be examined under 0.5 μ thick methachrylate embedded Movat silvered semithin sections.

1 Prof. Dr. W. Doerr, Head of the Pathological Institute of Heidelberg University very kindly gave us permission to view the autopsy reports of these 20 cases.

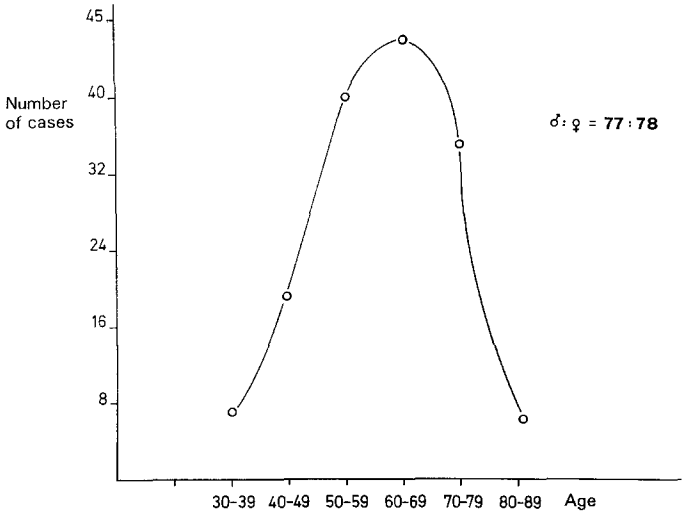


Fig. 1. Age groupings of autopsy obtained multiple myelomas

Finally, in the last section, we compared the results of the morphological examinations with available clinical data. In 65 cases information about the renal function was available to us[2]. Blood pressure examinations were taken into consideration only within the final 14 days and after repeated confirmation, the results of the last day of life were not taken into account. The definition of hypertension was supported by Planz (1969), the definition of hypotonia by Parr (1969). Since the study specimens were obtained from various clinics and gained over a period of 20 years, further more exact clinical data were later only available in a relatively small percent. In addition, due to changes in technique, not all clinical data is readily comparible, which has been illustrated by the methods used to identify the Bence Jones Proteins (BJP).

Results

The age differences in the plasmocytomas which we examined showed a marked climax in the 70's (Fig. 1); the youngest patient was 30, the oldest 87. 77 of the patients of our survey were men, 78 women. Below the sixtieth year, the relationship of patients was slightly in favour of the women. Here, 36 of the patients were women, and 29 men. As shown in Fig. 2, the kidneys were mostly heavier than normal and only in the case of 5 women had contracted kidneys developed.

A breakdown of the recognised histological features typical to myeloma nephrosis showed (Fig. 3) that although casts, with one exception, were apparent in all kidneys, they were, however, in only 30% of the cases predominant in the histological picture. In 66 cases, they were not sufficiently remarkable to attract particular attention and with 37 patients (25.3%) only very seldom did single hyaline casts not differentiate in size and type from those picked at random from autopsy material without recognised renal disease. In kidneys with many casts, these hyaline fine radial striped or lamellated structures are localised in Henle's loops, distal tubules and collecting tubules (Fig. 4a). The more seldom

2 We would like to thank Prof. Dr. A. Bernsmeier, Director of the I. Medical Clinic of the University, Kiel and Prof. Dr. H. E. Bock, Director of the Medical University Clinic, Tübingen for their permission to view the patients records.

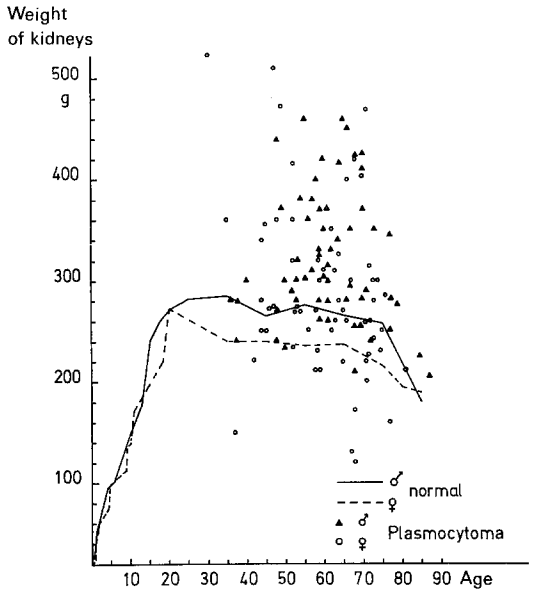


Fig. 2. The weights of kidneys in plasmocytoma. Ordinate: The weight of both kidneys of a patient. For comparison, the normal weight, according to Roessle and Roulet, is shown by a curve

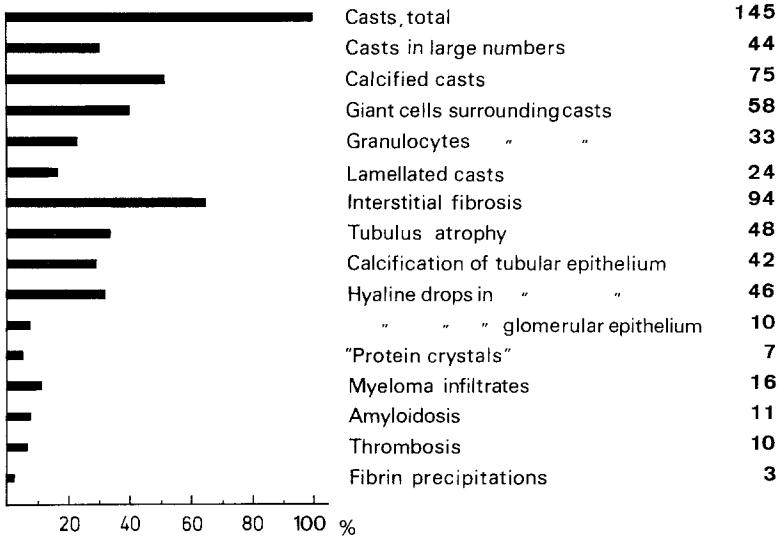
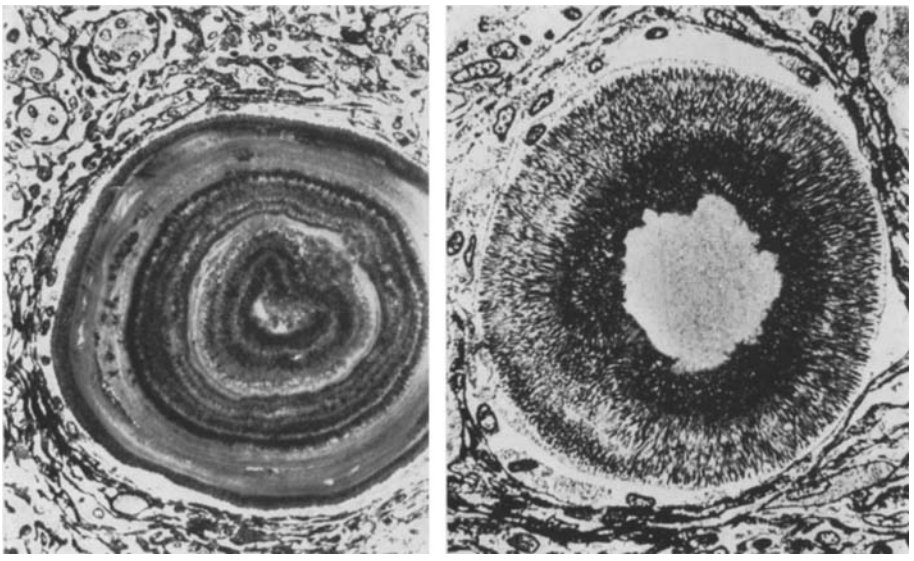


Fig. 3. The number of histological conditions found in kidneys of plasmocytoma patients. Black lines = number percentage; Figures on right edge = exact numbers

pigmented and granulated casts increase to distal parts of the nephron. Concentric layered or lamellated casts with often spinous appearing, sea urchin-like outsides in cross sections (Fig. 4b) were found in 24 kidneys (16.4%). In 21 cases there of



a b

Fig. 4. a T 34/65, 37 years, female. Undifferentiated multiple myeloma with apparently normal serum electrophoresis. History of 4 years severe proteinuria. Concentrated layered tubular cast in the renal cortex with radiar structure of the lamellae. Semithin section, osmium-fixation after formaldehyd fixation. Metychrylate embedding. Movat silver stain, 460:1. b The same case as Fig. 4a. Renal cortex, tubular cast with sea urchin type radiar structure. Semithin section. Treatment same as Fig. 4. 850:1

being organs which exhibited also all the other morphological features of myeloma kidney.

Giant cell type or syncitial cell proliferations can be arranged round casts and their fragments, or grow out into lumina of tubula like precipitations (Fig. 5). They lie mainly in the straight portions of distal tubules in the outer medulla and are in 11.7% of all cases so numerous that they are immediately noticeable and would very probably be found in a needle biopsy. Some casts, in approximately $^1/_5$ of all the kidneys, were surrounded by granulocytes, often in the formation of lacunar edgings. Nephrocalcinosis, which was evident in 75 cases, was more strongly marked in 46 patients and affected mostly the casts, 29 times in the cases of kidneys which otherwise showed no symptoms of myeloma nephrosis. Calcification of tubular epithelium is seldom; out of 42 cases, it was in 27 more strongly marked and in 15 cases less, distributed particularily round calcificated casts in both proximal and distal tubules. In the kidneys of 46 patients was a particular focalised accumulation of hyaline proteindrops in tubular cells notable, out of which in 12 cases only slightly evolved and mostly localised in the proximal tubules. In a few kidneys (10), in which hyaline drops were visible by lightmicroscopy in the glomerular epithelium, these drops were also localised in the proximal parts of the convoluted portion of this nephron.

The generally focalised tubular atrophy is mainly evident in the outer cortex, and although present in a third of all kidneys, only in 10 cases so comprehensive

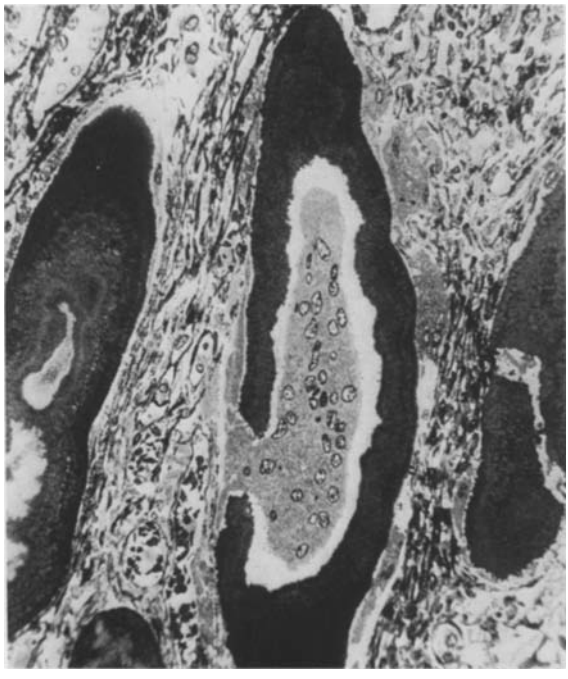


Fig. 5. Same case as Fig. 4. Renal cortex, growth of multinucleated giant cells in pipe formed tubular casts. Semithin section. Treatment same as Fig. 4. 340:1

as to be particularly noticeable; and here the weight of the kidneys, with one exception, was reduced. As with tubular atrophy, interstitial fibrosis is also mostly focalised and particularly localised in the outer cortex and of the 94 positive cases, 69 times particularly clearly (Fig. 6).

Crystals usually characterized as "protein crystals" were apparent in 7 cases, although only once in large quantities. The crystals, only in one case just slightly double refractive, with Azan and Goldner Trichrom luminous red with the Fibrin stain violet demonstrable, lie in the proximal tubules almost completely in strongly swollen tubular epithelium in the form of slender rods and needles, roughly 0.5–2.0 μ wide and up to 80 μ long (Fig. 7a). In addition, most tubular cells also contain numerous rice like crumbs and granules, which show all stages of transition to the described crystal forms and contain the same colourful characteristics. This can, in part, possibly be explained by transverse sections of long crystals. These cells also appear to break down and distribute their contents in the tubular lumen. The same structures with the formation of small crystals can also be identified in the surface epithelium of numerous glomerula of these kidneys. In Henle's loops, distal tubulus and collecting tubules, these crystals are however practically only to be found in the small tubular lumina and are here, as a rule, noticeably bigger, also forming prismatic, rhombic, 4 or more sided structures (Fig. 7b).

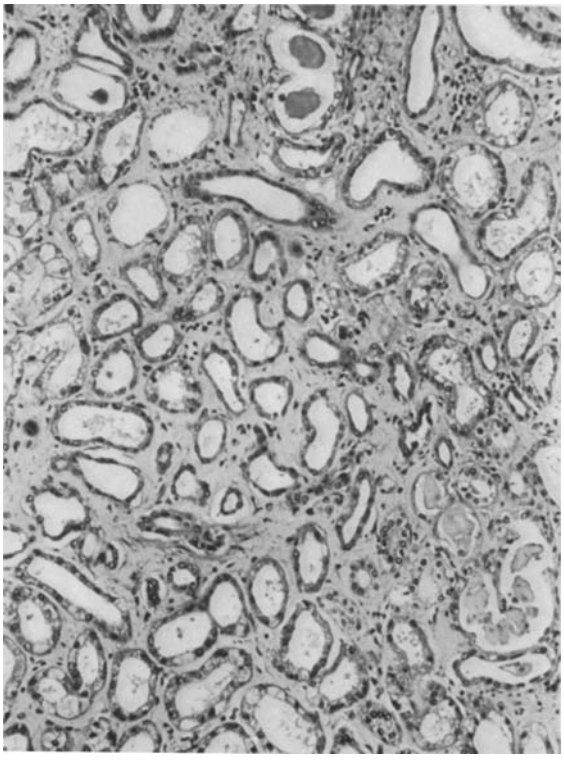
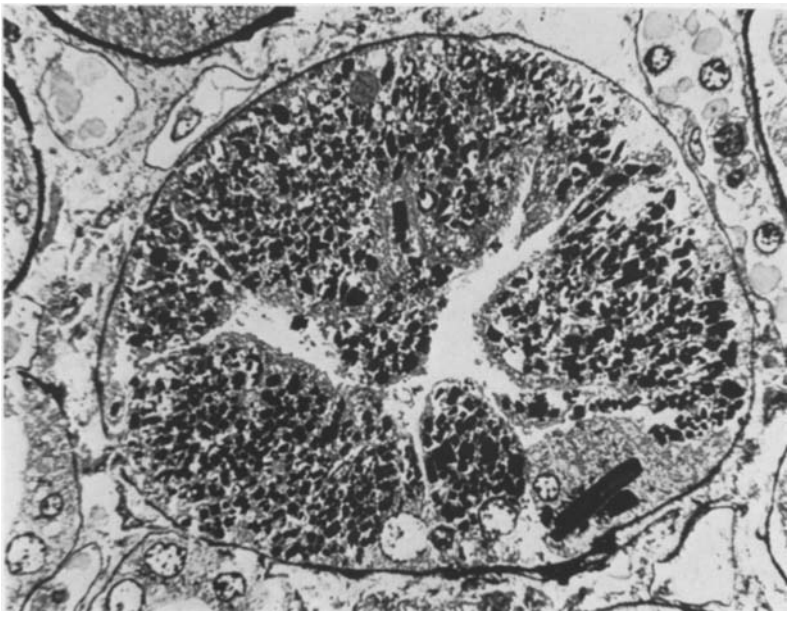


Fig. 6. T 745/68, 74 years, male. Plasmocytoma without paraprotein in the immunelectrophoresis. Death caused by uraemia. (U^+ 585 mg-% creatinine 14,4 mg-%). Renal cortex, diffuse interstitial fibrosis, only isolated casts without surrounding giant cells. Paraffin section. Goldner-Trichrom 135:1

In only one of the 7 cases are the, in the Goldner-staining light grey green coloured, crystals to be found only sparingly in the interstitium of the renal medulla, and are surrounded by foreign body giant cells, which were otherwise only found round intra-tubular localised crystals in one other kidney. In the case of one patient (586/67), crystals of the same size, structure and colour as in the proximal tubular epithelium were observed in the cytoplasm of tumour cells and reticular cells in the tumour area, as well as partly between cells in myeloma groupings of the bone marrow.

A change of the crystal form during the autolysis is not recognised. This was shown by the comparison of within 30 minutes post portum obtained kidneys, with kidneys of the same patients obtained by obduction 13 and 15 hours after death in two cases.

In cases in which amyloid deposits were apparent in kidneys (Figs. 8 and 9), the foregoing recognised features of myeloma nephrosis were not obvious. In only 4 of a total of 11 cases with amyloid deposits in the kidney is presented in a small way the picture of a myeloma kidney. One of these cases (131/67) contained multinuclear giant cells round subcapsular located hyalinised, Congo-red-positive



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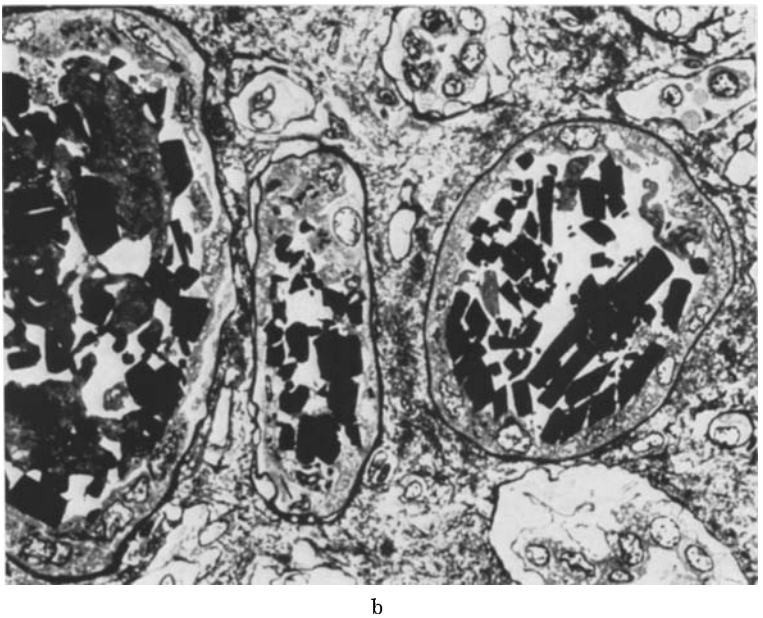

b

Fig. 7. a T 586/67, 61 years, male. Undifferentiated γ-G-plasmocytoma, total protein in the Serum 6.0 g-%, Bence-Jones-Protein positive (Uroparaprotein +) in the urine. Multiple "protein crystals" in the epithelium of proximal tubule, Semithin section, Treatment same as Fig. 4. 900:1. b Same case as Fig. 7a. "Protein crystals" in the lumina of the distal tubule. Treatment as for Fig. 9. 600:1

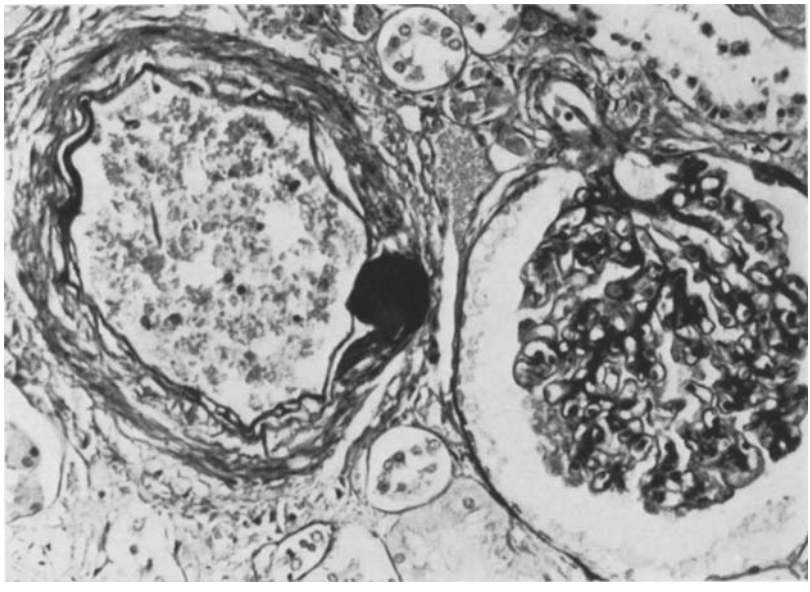

Fig. 8. T 53/63, γ-plasmocytoma. Bulky amyloid deposits in the artery walls. PAS staining. 240:1

glomerula (Fig. 9) and round amyloid deposits in the walls of the arcuatae and radiatae arteries, but not, however, round the in this kidney only seldom apparent hyaline Congo-red-negative casts. Apart from amyloid deposits and occasional hyaline drop like protein projections in the surface epithelium, we cold not light-optically recognise important changes of the glomerula.

The formation of thrombosis in certain intrarenal blood vessels was noticed in the kidneys of 10 patients, occurring 9 times in the venae arcuatae and interlobularies (Fig. 10) and only once in the Aa. arcuatae. In a further case, the Vena renalis on one side was blocked by a thrombosis. Amyloid degeneration of the kidneys was not found in any of these cases. However, there was often a definite spatial relationship between thrombosis forming on the walls in the intrarenal veins and massed hyaline Congo-red-negative deposits, in part covered by a lymphoplasmacellular infiltration in the bordering connective tissue. In one kidney (552/68), this type of hyaline mass was present in the vein lumina and had been covered by platelet clumps (Fig. 11). In one of the 3 patients with fibrin strands or clots in the glomerular and intertubular capillarias, a consumption coagulopathy has been clinically noted.

After we had collected these single histological findings, and after due consideration of the aformentioned morphological criteria, we could establish how often the pathological anatomical picture of typical myeloma kidney and that of acute renal failure occurred in our specimens. As can be seen from Table 1, typical myeloma kidney was apparent in 43 (29.4%) of all cases. In addition to the symptoms of a typical myeloma nephrosis, in 25 of these cases those of acute

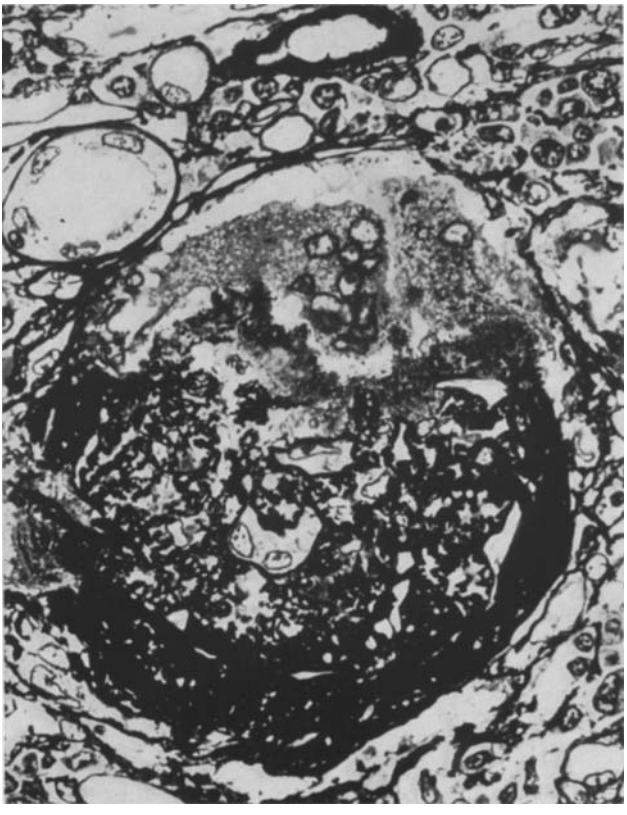

Fig. 9. T 131/67, 67 years, male. Clinically: micro-plasmocytoma. Pathologically anatomically: diffuse plasmocytoma of the bone marrow. Serumelectrophoresis: No certain evidence of paraprotein- Kappa- and Lambda-chains in the Serum. Death caused by uraemia (Serum creatinin 10 mg-%). Amyloidosis of the glomerula. Multinuclear giant cells surrounding hyalinised Congo-red-positive glomerula. Semithin section. Treatment as for Fig. 4 600:1

renal failure were also evident. Only 18 times (12.3%) was myeloma kidney apparent without any further pathological anatomical evidence for acute renal failure. In a further 24 cases, signs of acute renal failure without morphological symptoms of myeloma kidney were obvious (16.5%). As also set out in Table 1, 12 kidneys showed only very slight typical features of myeloma kidney (Low Grade Myeloma Kidney), 9 of these kidneys, however, had very obvious signs of acute renal failure. Thus, the total number of kidneys with dominant signs of acute renal failure amounts to 33 (22.6%).

Due to advanced autolysis in 14 kidneys, acute renal failure due to certain histologica indications (grouped infiltrants on the corticomedullary junction of the type known as tubular interstitial nephritis, oxalate crystals in the tubular lumina, chromoprotein casts, collections of unripe blood cells in the marrow capillaries), could only be estimated. These cases are specially noted in Table 1.

Finally, a heavy purulent, partly abcessed pyelonephritis was apparent in 12 cases, occurring equally in specimens with myeloma kidney and those with indications of acute renal failure.

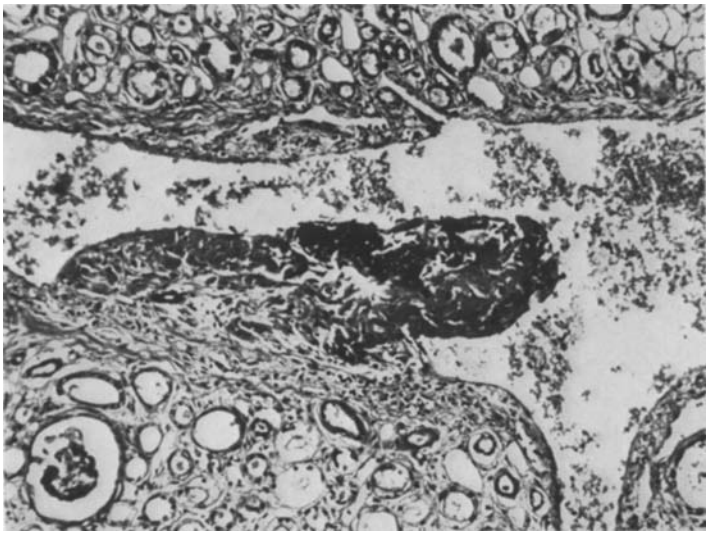

Fig. 10. T 103/67, 68 years, male. γ-G-plasmocytoma. Total protein in the serum 16.2 g-%, death through uraemia (Serumcreatinin 14,1 mg-%, U^+ 630 mg-%). Partly developed thrombus in the region of the described wall lesions of a Vena arcuata. HE-staining. 115:1

Table 1. *Amount of pathologically-anatomically kidney diagnosis with plasmocytoma patients*

Typical myeloma kidney without signs of acute renal failure	18	(12.3%)
Typical myeloma kidney with signs of acute renal failure	25	(17.1%)
"Low grade myeloma kidney"	12	(8.2%)
of which with dominating signs of acute renal failure	9	(6.2%)
Symptoms of acute renal failure without myeloma nephrosis	24	(16.5%)
Questionable acute renal failure (autolysis)	14	(9.6%)
Pyelonephritis	12	(8.2%)
Unremarkable kidneys	41	(28.1%)

Of the 7 Waldenström cases, none exhibited a typical myeloma kidney comparible morphological picture. Here also, the average weight of both kidneys of 334 g (270–410 g) was above the norm. The following morphological findings here can be thus itemised:

Only isolated hyaline casts in all 7 cases, indeed in no kidney in large numbers; calcified casts 3 times, granulocytes round the casts once, multinucleated giant cells were found as seldom as lamellated casts. Interstitial fibrosis occurred twice; tubulus epithelium calcification could not be proved; in 2 cases hyalin proteindrops were noticeable in the epithelium of proximal convolutions we did not find "protein crystals", fibrin precipitations in the peripheral blood vessels or thromboses. In 2 patients, there were tumour infiltrations in the kidneys, and once amyloid deposits were evident.

In three cases out of this clinical complex, the pathological anatomical picture of acute renal failure was also apparent.

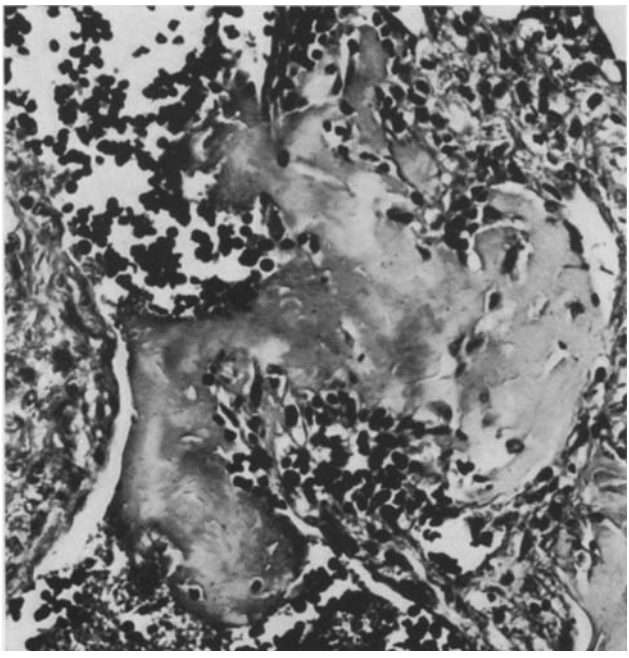

Fig. 11. T 552/68, 61 years, male. γ-G-plasmocytoma. Total protein in serum 15 g-%, amyloidosis. Interruption of knotty amyloid masses from the perivascular connective tissue into a vein lumen of an arcuatabranch. Goldner-Trichrom-staining. 285:1

More exact clinical data concerning the renal function was available to us in 65 of the plasmocytoma cases. As shown in Table 2, only with 9 of these patients (13.9%) was normal renal function registered up till the time of death. In all 9 cases, the kidneys were morphologically unremarkable. With 23 patients (35.4%), uraemia was registered clinically as the main cause of death. In 27 cases with clinically noted renal dysfunction, we found the pathological anatomical picture of myeloma kidney, of which 20 showed simultaneously the signs of acute renal failure (Table 3). With 29 of the 56, that is 51.8% of the patients with renal insufficiency, no typical myeloma kidney was apparent morphologically. Here, we found 16 times the syndrome of acute renal failure; twice an etiologically non-classifiable contracted kidneys, and 8 times a definite morphological identifi-

Table 2. *Clinical data about the renal function shortly before the death of 65 plasmocytoma patients*

Renal function ($n = 65$)		
Normal	9	(13.9%)
Slightly reduced ($U^+ < 100$ mg-%)	12	(18.5%)
Severely reduced ($U^+ > 100$ mg-%)	44	(67.7%)

Table 3. *Pathological anatomical diagnosis of the kidney conditions with plasmocytoma patients with renal dysfunction*

The morphology in renal insufficiency ($n = 56$)		
Myeloma kidney	7	(12.5%)
Myeloma kidney and acute renal failure	20	(35.8%)
Acute renal failure	16	(28.6%)
Amyloidosis	2	(3.6%)
Pyelonephritis	1	(1.8%)
Contracted kidneys	2	(3.6%)
Autolysis, undefinable (not myeloma kidney)	8	(14.3%)

cation was not possible due to advanced autolysis. With one very severe case of myeloma kidney with strong proteinuria and a further "low grade myeloma kidney", no retention of urinary substances occurred clinically until death.

Records of regular examinations for Bence Jones Proteinuria were available to us from 42 patients. 26 times (61.9%) a Bence Jones Proteinuria (BJP) could be diagnosed from the urine; 16 times (38.1%) the tests showed negative.

12 of the 26 positive cases (46.2%) had pathologically anatomically typical myeloma kidneys. A BJP was remarked in 20 patients with renal insufficiency (37.7% of the patients with renal dysfunction); BJP was not however found in the urine of 6 patients with disturbances of excretory functions. On the other hand, 3 out of 9 patients with normal renal functioning (33.3%) eliminated BJP in their urine. In 3 out of the 6 cases with protein crystals in the kidneys BJP was apparent, in two cases of which this protein was not evident in the urine and in the further one case there was no data available to us.

In one collective, more differentiated protein analyses of the urine were carried out (Doz. Dr. Aly, Doz. Dr. Braun, Medical Clinic University of Tübingen). Here, in 18 of the 22 examined cases (81.8%) (in part in very small quantities) BJP could be diagnosed; whereas in another group of mostly older cases only the normal precipitations tests and isolated paper-electrophoresis were carried out. Of the latter group, BJP was only found in the urine of 8 of the 21 patients (38.1%).

Table 4. *Isolated clinical data with plasmocytoma patients*

	n	Normal	Raised	Lowered
Serum calcium	45	9 (4.7–5.5 mval/l)	13	13
Serum calcium with nephrocalcinosis	19	3	8	8
Serum protein (total protein)	41	11 (6.5–8.0 g-%)	19	11
Blood pressure during the last 14 days	23	15	1 (160/95 mmHg)	7 (systol. <105 mmHg)
ESR in the last 14 days (first hour)	34	Ø	15 $>$ 100 mm 9 50–100 mm 10 $<$ 50 mm	Ø

With 12 patients the serum protein concentration exceeded 10 g-%, the highest amount contained 17 g-% (see also Table 4). We could not diagnose a definite relationship between the total protein in the serum and morphological changes in kidneys (Table 5).

Table 5. *Comparison of the pathological anatomical kidney conditions with the serum total protein in the last days before death*

Kidney condition	Hyper-proteinaemia	Hypo-proteinaemia	Normal total serum protein
Normal	10	2	1
Acute renal failure	3	1	5
Myeloma kidney	2	4	2
Myeloma kidney + acute renal failure	3	4	2
Contracted kidneys	1	0	0

As far as can be seen from the few figures, the pathological anatomical picture of myeloma kidney appears to fit in sooner with normal or lower total serum protein. A relationship between the serum calcium-level and the development of nephrocalcinosis was just as little apparent (Table 4) as between the onset or the quantity of a renal insufficiency and the serum calcium-level (Table 6).

Table 6. *Relationship between serum calcium levels and renal function*

	Normo-calcaemia (4.7–5.5 mval/l)	Hyper-calcaemia	Hypo-calcaemia
Strong renal insufficiency	4	5	6
Lower renal insufficiency	3	1	4
Normal renal function	—	1	1

Discussion

In approximately a third of the plasmocytomas which we examined, we observed pathological anatomical changes in the kidneys typical of the morphological picture of myeloma kidney, as it has been classified by, among others, Allen (1951) and by Zollinger (1945, 1966), with many giant cell surrounded renal tubule casts, hyaline drops in tubular cells, marked tubules atrophy, interstitial fibrosis and nephrocalcinosis. However, these symptoms only occur particularily markedly and without any other form of renal disease in 12 % of the examined multiple myelomas. In approximately 23%, histological conditions as in acute renal failure were apparent simultaneously; with a further 16.5%, we only found the characteristic signs of acute renal failure and in 12 cases, a severe pyelonephritis dominated the picture. Nearly a third of all kidneys showed no morphological irregularities, apart from arterial sclerosis type changes in relation to age.

These results concur with those published by Bell (1933) with 32% Glenchur *et al.* (1959) with 29% of autoptically examined plasmocytomas in which typical myeloma kidney was found and also agrees with the percentage of morphlogiocally unremarkable kidneys found by Geschickter and Copeland (1928) of 30%. Also in animal experiments only 40% of the mice with typical myeloma showed signs of morphologically recognisable renal damage (Coleman *et al.*, 1962).

As opposed to some published material (Zollinger, 1958; Michon *et al.*, 1959; Larcan *et al.*, 1962) we found no characteristic lightmicroscopic changes in the kidneys of our Waldenström cases (see also Lennert, 1955; Schrade *et al.*, 1958). There were none of the typical myeloma kidney type symptoms apparent with any of the patients in particular the notable cast formation and giant cells (see also Morel-Maroger *et al.*, 1970). However, we also saw three times here the picture of an acute renal failure.

Isolated statements about histological changes of renal structure in 100% of multiple myeloma (Wallgren, 1932) lead to the question of the value of isolated microscopic phenomenen, which is raised in double form. On the one hand, these findings are of particular interest to pathologists in relation to their diagnostic significance to biopsy and autopsy preparations; and on the other hand, the question is in how far the functional disturbances of the kidneys in multiple myeloma are explainable through histologically recognisable alterations. The first part of this question is relatively easy to answer. If the previously mentioned histological conditions are found together in large quantities, the morphologist can then diagnose plasmocytoma by the renal changes. However, none of these five conditions alone has an absolute diagnostic significance.

Thus, interstitial fibrosis and glomerulum-hyalinisation with tubulus atrophy in the outer renal cortex can in general not be regarded as characteristics of myeloma kidneys, but rather more often as the result of frequent arterial sclerosis in this age group. Further, this type of interstitial fibrosis can also be observed after long standing acute renal failure, and apply here als prognostically unreliable signs (Bohle *et al.*, 1970). Nephrocalcinosis can equally be observed by other destructive bone processes, such as the with multiple myeloma differential diagnostically not always easily definable primary and secondary hyperparathyreoidismus, idiopathic-hypercalcaemia, D-hypervitaminosis, Lightwood-Albright-Syndrome amongst others (Jaccottet, 1959); likewise, hyaline drops in the tubular cells occur in the most varied geneses through proteinuria (Randerath and Bohle, 1959 among others), and in the same way casts also occur in large quantities as a symptom of proteinuria and a insufficient intratubular urine flow by other renal diseases although then seldom lamellated. Indeed even the largely specific multinucleated giant cells round the tubular casts, which we observed in 40% of our kidneys, could occur occassionally in other renal lesions, as for example amyloidosis (Randerath, 1948), round calcium casts from other geneses, round sulphonamide crystals (Allen, 1953). Multinucleated giant cell like epithelial regenerations round the casts, indicate by acute renal failure, that these casts have lain for some days in the tubular lumens (Schubert, 1968), and Allen maintains that giant cell type epithelial groups can also at times be observed in the kidneys of healthy individuals over 40 years of age.

In the same way, the other conditions, observed individually, are not absolutely characteristic and most particularily too seldom to merit special diagnostic significance. The tumour cell infiltrations in the kidneys could here most easily be considered, since from our experience after painstaking searching, these are not quite so seldom; which, all things considered, agrees with observations made by Günter *et al.* (1961) who diagnosed plasmocytoma infiltrations in 12% of the kidneys. Pazmantier and Azar (1969) noticed intrarenal plasmocytoma infiltra-

tion in as many as 10 out of 57 cases (=17.5%, see also Hayes *et al.*, 1953). However, it is exactly this extreme level which illustrates how difficult it can be in isolated cases to estimate the limits of dense mostly plasma-cellular infiltrants of inflammation from a tumour infiltration. Differing subjective opinions about these infiltrants cannot be excluded.

Since by 3–10% of the plasmocytomas amyloid deposits were found in the kidneys (Apitz, 1940; Lichtenstein and Jaffee, 1947; Allen, 1953; Cauchie *et al.*, 1962), a plasmocytoma should be sought after, as, at least from our observations, no syndrome of a typical myeloma kidney was simultaneously apparent in most cases. These deposits classified into the group of "pericollagenic amyloid" by Missmahl (1964), occasionally unusual localised deposits, can be surrounded in the blood vessel walls by foreign body giant cells, indeed even fully hyalinised glomerula were bordered by this type of giant cell in one of our cases.

Particular attention is always be paid to the deposits of paracrystaline structures or "proteincrystals", which are however seldom. Until 1950, 14 observations of this type of crystals in the kidney were reported (Sikl, 1950), twice a Fanconi-Syndrome of adult had simultaneously developed (Constanza and Smoller, 1963). Valachs statement (1957) that crystaline structures were apparent in the kidneys of 22% of myeloma cases has not yet been confirmed from other authors. In only one of our cases were crystals evident in large quantities; but frequently cast fragments simulated crystals forms. As in previous examinations, we were not able to further clarify the nature of these crystals. Cryoglobulinaemia, which should be apparent in 1–2% of the plasmocytomas (Recant and Hartroft, 1959) did not occur in any of our 22 cases examined thereupon. As opposed to other studies (Löhlein, 1921; Sikl, 1950; Randerath and Bohle, 1959), but in confirmation of Allen (1953) and Cauchie *et al.* (1962), we could not prove—with one exception—a double refraction in polarised light in paraffin section. Even combined electronmicroscopic and immunologic studies have as yet given no information as to the make-up of the crystals. Neither H- or L-chains of even polymere of the γ-globulines are clearly identifiable in them (Suzuki and Takahashi, 1969).

If these morphological changes in many cases give us reliable diagnostic information, it is correspondingly much more difficult to find an answer to the question in how far, thereby the disturbances of renal function are explainable, which are observed in 30–80% of the plasmocytoma cases (Bayrd and Heck, 1947; Lichtenstein and Jaffe, 1947; Allen, 1951; Moeller, 1955; Sanchez and Domz, 1960; Harvey *et al.*, 1963; Kaufmann, 1965; Williams *et al.*, 1966; Lamertz *et al.*, 1968; and others). This question shows its importance when it is realised that after pneumonia uraemia, with 21.9% is the second highest cause of death with plasmocytoma (Sanchez and Domz, 1960), and Allen estimates that uraemia as being in 43% the cause of death and indeed, also in our cases, uraemia was clinically dominant with 35.4% of all patients.

There has, however, been no lack of efforts to correlate structure and functional disturbances of the kidneys in plasmocytoma. Particularly in earlier work (Ehrich, 1932 Bell, 1933; Apitz, 1940; Oliver, 1945, on the other hand McKenzie, 1968), renal tubule blockages were considered as a deciding factor in renal insufficiency, leading in part to the morphological changes in the sense of a nephrohydrosis

(Ehrich, 1932), whereas the greater majority of modern authors reject the obstruction theory and stress, that the casts are a result of renal dysfunction and not their cause (Brass, 1943; Randerath, 1948; Armstrong, 1950; Nonnenbruch, 1949; Killmann *et al.*, 1957; Healy, 1963; Zollinger, 1966; Bryan and Healy, 1968; Levi *et al.*, 1968 amongst others). There are also no specific myeloma changes or lesions to be found on the glomerula, through which a renal insufficiency could be explained (Boulet *et al.*, 1962; Hamburger *et al.*, 1966; Kenis *et al.*, 1966; Reubi, 1970). Occasionally described thickenings of the basal membranes are uncharacteristic (Allen, 1951; Kobernick and Whiteside, 1957; Fisher *et al.*, 1964; Abrahams *et al.*, 1966; Rosen *et al.*, 1967) and not definitely definable from paraffin cuts. Exact measurements of Wehner and Feurer (1970) have however confirmed the guesses of other authors (Kobernick and Whiteside, 1957; Kawamura, 1964; Hamburger *et al.*, 1966) that, in opposition to Bell (1933), Fisher *et al.* (1964), Rosen *et al.* (1964) as well as Abrahams *et al.* (1966), no increase in endothelial cells, mesangium cells and overall cells in comparison to the norm by similar glomerular surfaces was apparent; a condition whose functional relevance, particularily in relation to the hardly comprehensible conception of glomerulonephrosis, very critically evalued by Cauchie *et al.* (1962), remains to be evaluated.

Amyloid degeneration of the kidney occurs too seldom amongst these many cases of renal insufficiency to give any weight to the idea that it is a causing factor; in the same way as changes in other regions of the renal vessel system are uncharacteristic and not more frequently occuring as with patients of this age group without multiple myeloma. The earlier impression of a larger thrombosis percentage (Apitz 4 out of 18; Brass 3 out of 13 myeloma cases) was not born out over a larger study.

The tendency to thrombosis should be rather less with myeloma patients (Bricker *et al.*, 1959), and in vitro, the fibrinformation in the blood of patients with multiple myeloma can be so disturbed, that an intrinsic gel and no fibrin strands or corpusclelike coagulations develop, which is possibly the result of a calcium shortage through Ca^{++}-Absorption by atypical serum protein (Craddock *et al.*, 1953; Bricker *et al.*, 1959; Mholer *et al.*, 1967; Scheurlen, 1969).

Accordingly, we only found fibrin precipitations in the glomerulum capillaries of three kidneys. There again, in 8 cases, we noticed developing thrombi in intrarenal veins, which formed on the basis of the described wall lesions in the region of lymphoplasmocellular infiltrations of the vein walls, or by the outbreaks of hyaline, partly amyloidtype masses in the vessel lumina. Here, definite local vessel changes were decisive.

Particulary the discussed disturbances of the microcirculation by sludge phenomena, hyperviscosity-syndrome etc. (E. Smith *et al.*, 1965; Scheurlen, 1969 and others), as a result of dysproteinemia and hyperproteinemia can be as little discovered in slices lightmicroscopically as the hypothetically damaging effect of BJP or other proteins on the tubular epithelium. Since, after more modern examinations of protein metabolism in the kidneys for example by the breakdown of BJP, a greater significance has been attached to this, than was previously the case (Solomon *et al.*, 1963, 1964; Truax *et al.*, 1965; Wochner *et al.*, 1967; Jensen, 1970), the question is thus raised, whether a quantitative or qualitative out of the ordinary load of proteins either severely overload, make vulnerable or damage the tubular cells of the kidneys; amongst which most particularily tubular lesions in proximal and distal tubules are discutable, which cannot simply lightoptically be recognised.

We could not prove a definite relationship between hyperproteinemia and morphological conditions of the kidney. From our experience, hyperproteinemia appeared more likely in cases with a normal kidney picture, whereas myeloma kidney occurred most often with normal or lower total serumprotein (see Table 5).

The frequently observed disproportion between the amount of renal dysfunction and the slight morphological changes were the reason why Nonnenbruch (1949) and Höpker (1948) added myeloma kidney to the group of extra renal syndromes, in which Nonnenbruch particularily classified renal functional disturbances, which we today recognise as acute renal failure. In the last few years, pathological anatomical examinations have established morphological criteria (Lucke, 1946; Brun, 1954; Randerath and Bohle, 1959; Jahnecke, Bohle and Brun, 1963; Bohle, Jahnecke and Rauscher, 1964; Bohle, 1965; Remmele, 1968; Schubert, 1968) which enable us to diagnose through the use of pathological anatomical preparations acute renal failure. Assisted by these specifications, we could prove, in about 23% of all the myeloma patients, as obvious renal lesions the signs of acute renal failure. In addition, 25 of a total of 43 "typical myeloma kidneys" (58%) showed also very clear signs of acute renal failure. In a further 12.1%, some morphological indications also spoke for acute renal failure; here, however, due to advanced autolysis, we regarded the results with reservations. These results concur with statements of Cauchie's *et al.* (1962), who maintained that 27% of uraemia cases are caused not through myeloma kidney, but rather more likely through the extra renal syndrome.

Some authors also maintain that as a rule with plasmocytoma cases a *slowely* increasing chronic renal insuficiency occurs and only seldom an *acute* renal failure (Moeller, 1955, 1968; Fritz *et al.*, 1970); whereas in the last few years, it has repeatedly been proved from the clinical side that acute renal failure is also not so seldom as was previously supposed (Killmann *et al.*, 1957; Kolff, 1955; Jutzler *et al.*, 1961; Healy, 1963), and the tendency to acute renal failure of myeloma patients has been particularily brought forward (Rees and Waugh, 1965). The danger from the i.v. pyelogram is well known (Bartels *et al.*, 1954; Brüdigam and Moeller, 1957; Myhre *et al.*, 1956, 1957; Killmann *et al.*, 1957; Moeschlin, 1958; Perillie and Conn, 1958), whereby principally the associated thirst period, i.e. dehydration, comes to the fore (Addis, 1948; Perillie and Conn, 1958; Rees and Waugh, 1964). The noticeably frequent vomiting of myeloma patients (Armstrong, 1950; Thaysen *et al.*, 1957, amongst others), the regularly appearing anaemia, the tendency to hypotonia (Sapper *et al.*, 1953) and the above mentioned microcirculatory disturbances are further factors, which could favour the rise of kidney damage in the sense of acute renal failure.

Whether nervous conditioned vessel spasms, for instance those brought about through compression fractures of the vertebral bodys, are here of any particular significance, must be proved by further examinations. In this connection, the previously etiologically unexplained spastic epigastrium pains of myeloma patients must also be investigated (Scheurlen, 1969). Repeatedly observed polyuria and frequent isosthenuria with plasmocytoma cases are also to be found in acute renal failure and are allowed as signs of a "tubular insufficiency" (Moeller, 1955, 1968). In this aspect, the hyperplasia of the juxtaglomerular apparatus is also of interest, which we found in all of our therefor examined plasmocytoma cases (Spahn and Schubert, 1971), and which Meyer (1970) was able to prove with acute renal failure after hypovolemia.

We are therefore of the opinion, that with a substantial number of the plasmocytoma patients, renal lesions are in the first place responsible for the disturbances, of renal function, which cannot be differentiated from those of acute renal failure caused by another illness. The slow sinking beginning of renal insufficiency would in certain circumstance therefore be explainable, which with myeloma cases through passing, hardly clinically noticeable changes of the circulatory condition, depressions of the kidney functions occur, as they do with countless other illnesses indeed even in healthy inidviduals under certain stresses, here, however, without any further difficulty reparable but with which, due to plasmocytoma, because of the above mentioned predisposing phenominen particularily the qualitative and quantitative change of the protein elimination in the primary urine, these light, at first latent, conditions remain irreversible and the summation of such precidents causes increasingly severe renal damage. The through giant cell attached casts cannot, for example as opposed to other cases despite polyuria, be so quickly washed out again during a recovery period and induce chronic circumscribed inflammation and interstitial fibrosis which is left as a remnant of "latent acute renal failure" and clearly hinders a functional restoration. The morphological conditions, particularily interstitial fibrosis as with recurring acute renal failure (Bohle *et al.*, 1970) give rise at least to the supposition that the chronic progression of renal insufficiency of multiple myeloma is also at the bottom of processes, which are only gradual and not completely differentiated from those of acute renal failure through other causes. If the intensity of the causing factors is stronger the complete picture of *acute* renal failure arises, which, according to the results of our pathological anatomical study, does not appear to be as seldom as was previously supposed. As a result of the morphological picture we even consider that functional disturbances of the sort as with acute renal failure begin the onset of renal insufficiency in plasmocytoma patients. The changed supply with proteins in these functionally damaged kidneys could add to the damage and cause secondary structural changes (for example casts with giant cells), which overshadow the discrete primary morphological conditions of acute renal failure.

This, in a small percentage of cases, at first sight histological picture of "typical myeloma nephrosis" does not, however, always appear to be a hopeless condition. Even myeloma nephrosis with numerous giant cells round many casts is clearly reversible if there is no prognostically unfavourable stronger interstitial fibrosis, as continued studies by Bryan and Healy (1968) have shown. Since pathologically anatomically only the picture of acute renal failure appears or dominates, one could from this draw therapeutic consequences, and as recent observations show (Zollinger, 1970), "myeloma kidney" only seldom occurs where particularily careful control of the circulatory function and of the fluid and electrolyte balance and where timely therapy for renal functional disturbances has been practised.

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