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# Renal Pathology in Biopsy

## Light, Electron and Immunofluorescent Microscopy and Clinical Aspects

With the Collaboration of
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Translated by E. Castagnoli

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# Preface

Vor die Therapie setzten die Götter die Diagnose.
Otto Nägeli

Renal biopsy has decisively enriched renal diagnostics. Kidney diseases may be monitored during their entire course, and new techniques—such as immunofluorescence and electron microscopy—may be systematically applied, resulting in novel insights into the morphogenesis, pathogenesis, and etiology of kidney lesions. These insights, in turn, have served as new starting points, in the spirit of the quotation above, for the institution of causal therapy by the clinician.

This work presents our findings based on 20 years of experience in evaluating renal biopsies. As of the end of 1974, our computer-supported, systematic clinical, morphologic, and follow-up evaluation of case material consisted of over 2000 biopsies, including 679 examined by electron microscopy and 400 by immunofluorescence microscopy. The subsequent 500 biopsies (400 studied by electron microscopy and 300 by immunofluorescence) were considered qualitatively only. In order to enhance qualitative findings with quantitative data, it was necessary to devise new methods for quantifying electron-microscopic findings. Additionally, we attempted to correlate cytologic and immunofluorescent observations to integrate the isolated findings of electron microscopy into a vital cytologic pattern of reactions. We also attempted to evaluate the almost overwhelming flood of publications, especially those appearing within the last 10 years.

The idea for this book was conceived a decade ago. At that time, however, our own experience in renal biopsy diagnostics seemed insufficient to support such a major undertaking. In the following years, renal biopsy diagnostics developed so rapidly that evaluation of case material very quickly became out of date. Even though progress is still being made, it now appears, that by and large, the purely descriptive histopathologic evaluation of renal biopsy for the more important lesions, e.g., glomerulonephritis, transplants, and familial diseases, has matured. This is reflected by the increased attention in the literature to the pathogenesis and etiology of kidney diseases. We believe, therefore, that the time is ripe for the present work. Our objectives are:

1. To present the current status of knowledge of the bioptically determinable aspects of kidney diseases. In order to fulfill this goal, we have considered as many of the findings in the latest literature as possible (about 2000 references) mindful of the difficulties this poses to the reader.
2. To set up a frame of reference for the use of on-going work of renal pathologists for whom the section on general pathology is chiefly intended.
3. To enable the nonspecialized pathologist to arrive at a correct diagnosis and to recognize which cases merit the attention of specialists. The section

on special pathology is included especially for this purpose and accordingly, light-microscopic findings have been used as the main basis for disease classification. We feel that this nosologic approach is justified since we are convinced that the majority of renal biopsies can be evaluated appropriately and reliably with light microscopy only. However, both routine immunofluorescent and electron-microscopic examinations are indispensable for the specialist.

4. To further the histopathologic interest of clinicians involved in nephrology and thus to promote the often diagnostically significant role of renal biopsy.

Our collaborators helped us in the fields of immunology (F. Gudat), electronmicroscopy of the blood vessels (U. Riede), clinical findings and basic knowledge of transplantation (G. Thiel) and pathology of tubules (J. Torhorst).

We would very much appreciate the help of our readers in calling our attention to omissions and errors which may occur in this book. We thank you in advance for your courteous cooperation.

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We wish to express our appreciation to Dr. P. Schmid (Zurich) in charge of the Department of Medical Statistics of the Basle University for his invaluable advice on statistical problems.
Without the unstinting and engaged work of our technical assistants who, with much care and love, prepared our electron micrographs—Mrs. B. Amsler, Miss B. Baumgartner, Mrs. I. Bremer, Miss C. Nyffeler, Miss G. Haberkorn, Mrs. S. Bowald, Miss M. Wacker and Miss G. Krey—the present work would hardly have been possible, and we thank them all. The same gratitude is due to Miss M. Nebiker and Mr. H. R. Zysset for their outstanding skill in preparing schematic drawings and photographs. The above-instanced colleagues and fellow workers are only a pars pro toto of the many people who have contributed to this book. We do not wish to omit extending our acknowledgement to all the archivists who spared no effort in providing us with findings from case histories, some of which were decades old. Similar appreciation is due to all of the practicing physicians and hospital physicians in Switzerland, Germany, and Italy who were considerate enough to provide us with follow-up data on many of our patients. In this connection, we wish to express our whole-hearted gratitude to the directors of the registration offices and death registers in Germany and Switzerland who, by using "detective" methods, were able to trace many of our patients who, subsequent to our contact with them, became scattered throughout the world.
Our very special thanks are due to our publisher, Dr. h.c. H. Goetze, and his coworkers for his and their understanding help and generous cooperation in assuring publication of the great number of figures presented in this book.
Last but not least, we wish to express our great appreciation to the Swiss National Science Foundation (Grant 3.013.73) whose idealized encouragement and financial support over the years has, in the final analysis, made this work possible.

# Table of Contents

# General Abbreviations

| | |
|---|---|
| LM | Lightmicroscopy, lightmicroscopical |
| EM | Electronmicroscopy, electronmicroscopical |
| IF | Immunofluorescence, immunohistology |
| GN | Glomerulonephritis |
| FGN | Focally accentuated glomerulonephritis, segmental-focal glomerulonephritis |
| non-GN | Non-glomerulonephritic nephropathies |
| SLE | Systemic lupus erythematosus |
| AG | Antigen |
| AB | Antibody |
| BM | Basement membrane |
| C1, C2, etc. | Complement components |
| Ig | Immunoglobulin |
| EvG | Elastin (Weigert's resorcin)-van Gieson stain |
| Z | Data of the authors summarized for the present publication |
| Frequency in: | If not otherwise specified, |
| autopsy | the overall autopsy series comprises 25,000 autopsies, |
| biopsy | the overall biopsy series comprises 2080 biopsies |
| $a > b$ | a more than b |
| $a < b$ | a less than b |

Part I

# Technique and General Pathology

# 1. Clinical and Procedural Aspects

Although a few scattered reports on surgical biopsy and needle biopsy go back quite some time, it was the pioneering serial examinations of Castleman and Smithwick (1943) on renal material obtained during surgery and those of Alwall (1952) and Iverson and Brun (1951) on tissue obtained by renal needle puncture which opened the way for bioptic kidney evaluation [195].

## Clinical Aspects

### Value of Biopsy

Histopathologic diagnosis is indispensable if the accuracy of clinical (pre-bioptic) diagnosis is to be assured. The validity of the above statement is clearly illustrated in Table 1.1 which compares and contrasts clinical and histopathologic diagnosis from our own case material. Consideration of this table shows that the percentage of cases correctly diagnosed clinically ranged from 40–90%. Renal biopsy, accordingly, was required for correct diagnosis in 10–60% of all cases within a given diagnosis.

### Indications and Contraindications

Following thorough assessment of a patient's medical problems, the clinician must decide whether or not the case requires renal biopsy. Although the listings of absolute and relative indications and contraindications vary slightly in extent and emphasis from author to author, they do reveal good general agreement with respect to the major ones included. These consensuses are given in Table 1.2 [517, 705, 1325, 1449].

## Procedural Aspects

### Biopsy Technique

Two principal procedures have been developed to obtain kidney tissue:

1. Needle biopsy which may be done:
   a) Blindly by percutaneous puncture
   b) Percutaneous puncture under direct radiologic control after visualization of the kidney with radiopaque media
   c) Openly, under direct visual control by means of a small transmural incision.

Table 1.1. Clinicopathological index of diagnostic agreement in our material (material obtained by both needle and surgical biopsy)

| Histopathological diagnosis | Clinical diagnosis | | | | | | |
|---|---|---|---|---|---|---|---|
| | Glomerulonephritis ($n=716$) | Pyelonephritis ($n=329$) | Acute int. nephritis ($n=25$) | Benign/malignant nephrosclerosis ($n=70$) | Diabetic glomerulosclerosis ($n=10$) | Amyloidosis ($n=19$) | Other diagnoses ($n=89$) |
| Glomerulonephritis | 645=90% | 30 | 3 | 13 | 5 | 1 | 40 |
| Pyelonephritis | 20 | 248=75% | 3 | 15 | – | 1 | 18 |
| Acute interstitial nephritis | 4 | 5 | 10=40% | – | – | – | – |
| Benign/malignant nephrosclerosis | 10 | 12 | – | 42=60% | 1 | – | 31 |
| Diabetic glomerulosclerosis | – | 3 | – | – | 4=40% | – | – |
| Amyloidosis | 4 | – | – | – | – | 16=84% | – |
| Other diagnosis | 33 | 36 | 9 | – | – | 1 | Not examined |

2. Surgical biopsy, which calls for full-scale surgical intervention. In order to prevent artifacts due to squeezing and pressing, we recommend that tissue be removed with a biopsy needle even when the kidney is exposed. Wedge excisions with the scalpel are, nevertheless, useful when special indications are present. Forceps should not be used for biopsy since they cause squeeze and pressure artifacts and, moreover, do not reach into the medulla.

Table 1.2. Absolute and relative indications and contraindications for renal biopsy (includes our own experience)[a]

| Indications | Contraindications |
|---|---|
| *Absolute* | |
| For diagnosis and differential diagnosis of | |
| 1. Diabetic glomerulosclerosis, Amyloidosis | 1. Presence or suspicion of kidney abscess or tuberculosis |
| 2. Gout, Nephrocalcinosis (in absence of radiologically demonstrable calcification) | 2. Pyonephrosis |
| 3. Unclarified, persistent proteinuria or nephrotic syndrome | 3. Perinephritis |
| 4. Unclarified, persistent renal hematuria | 4. Polycystic disease of the kidneys |
| 5. Differentiation between pyelonephritis and glomerulonephritis | 5. Kidney tumors |
| 6. Systemic disease with renal involvement | 6. Bilaterally contracted kidneys and advanced renal insufficiency |
| 7. Acute renal failure of unknown etiology | 7. Anatomical or functional presence of only one kidney (except kidney transplant) |
| 8. Familial nephropathies | 8. Malignant, intractable hypertension |
| 9. Hypertension of unknown etiology | 9. Hemorrhagic disorders |
| | 10. Patient unwillingness |
| | 11. High risk patient for operation, i.e., should biopsy complication require surgery |
| *Relative* | |
| 1. Monitoring of disease progression | 1. Pregnancy |
| 2. Monitoring treatment response (follow-up) | 2. Inadequate patient cooperativeness as in neurologic and psychiatric disorders and debility |
| 3. Need to determine prognosis | 3. Senescence |
| 4. Appropriate and justifiable scientific purposes | |

[a] For kidney transplants see page 565.

Table 1.3. Advantages and disadvantages of needle and surgical biopsy procedures

| Biopsy technique | Advantages | Disadvantages |
|---|---|---|
| Percutaneous (blind) needle biopsy [1449] | 1. Realization in local anesthesia<br>2. Simplification of effort for serial biopsy programs<br>3. Minimal demands on patient and medical personnel | 1. Little control over biopsy site<br>2. Lack of direct hemostatic control<br>3. Limited tissue yield<br>4. Relatively high risk of complications |
| Percutaneous needle biopsy with radiologic control [67, 413, 639, 807] | 1. Good control over biopsy site (especially lower kidney pole)<br>2. Low bleeding complication due to lack of major blood vessels<br>3. In case of massive bleeding only pole resection is necessary<br>4. Realization in local anesthesia<br>5. Simplification of effort for serial biopsy programs | 1. Lack of direct hemostatic control<br>2. Greater demands on patient and medical personnel<br>3. Limited tissue yield |
| Open (visual) needle biopsy [654] | 1. Control over biopsy site<br>2. Hemostatic control<br>3. Increased time for procedure<br>4. Relatively low risk of complications | 1. Requires general anesthesia<br>2. Greater demands on patient and medical personnel<br>3. Limited tissue yield |
| Surgical biopsy | 1. Absolute control over biopsy site<br>2. Assured hemostatic control<br>3. Assured adequate tissue yield<br>4. Direct visualization of kidney and renal vessels<br>5. Low risk of complications | 1. Requires general anesthesia<br>2. More demanding on patient and medical personnel<br>3. Use dependent on patient operability |

Table 1.3 (continued)

| Biopsy technique | Advantages | Disadvantages |
|---|---|---|
| Surgical biopsy | 6. Possible in patients when other techniques are not allowed: e.g. obesity, danger of bleeding | |
| | 7. If no experience with other techniques | |

## Tissue Yield

The term 'tissue yield' refers to the actual amount of cortical renal tissue—assessed by the number of glomeruli present—obtained by biopsy (Fig. 1.1 + 1.2).
For most renal lesions, at least five glomeruli must be present in the biopsy material for its proper evaluation, diagnosis and classification. For purely diagnostic purposes, in severe, diffuse lesions such as amyloidosis and epimembranous glomerulonephritis, only one glomerulus may prove sufficient.

***Percutaneous (Blind) Needle Biopsy.*** The amount of renal material obtained by this procedure depends, to a great extent, on the skill and experience of the operator. A summarization of results from the literature on 8081 closed needle biopsies shows that renal tissue was obtained in 93.5% of biopsies on patients under 14 years of age and 89.8% on older patients ([1450]; 91%: [806]; 94.9%: [370]; but 29%: [764]).
In 500 biopsies examined only by light microscopy (LM) which came to our attention for study between 1950 and 1967, 11% contained no glomeruli and 7.2% less than 5, i.e. in 18.2% of the biopsies evaluation was either impossible or was severely handicapped. There was an average of 13 glomeruli in those needle biopsies containing more than 5, and the best yield, of 105, was obtained in the biopsy from a 3-year-old child. Since 1967, we have noticed that the tissue yields in the needle biopsies we have studied have improved such that 92% of them contain more than 5 glomeruli.

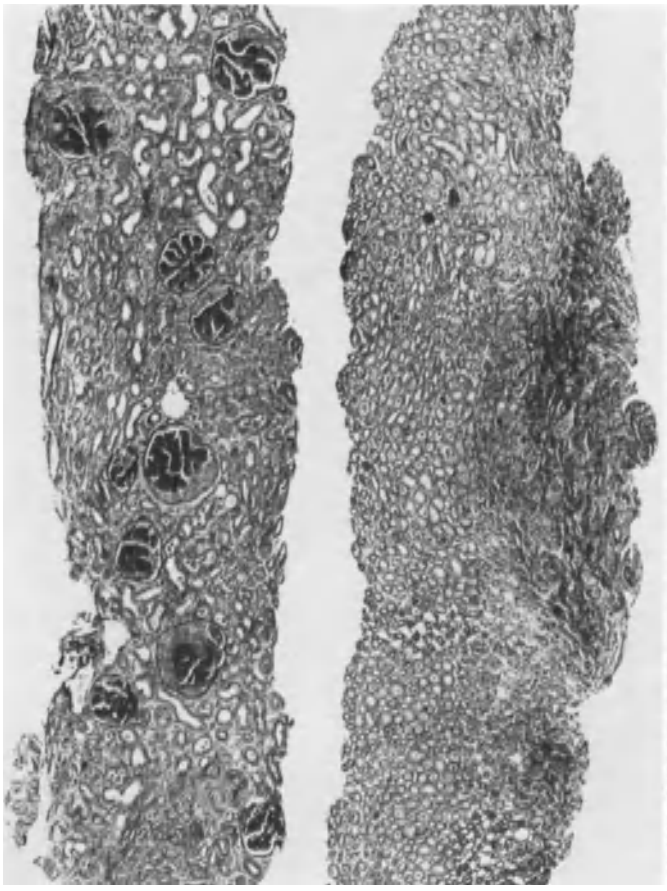


**Fig. 1.1.** Very well preserved needle biopsy of diffuse membranoproliferative GN; left, cortical tissue; right, medullary tissue. Female: 10 years. PAS (× 50)

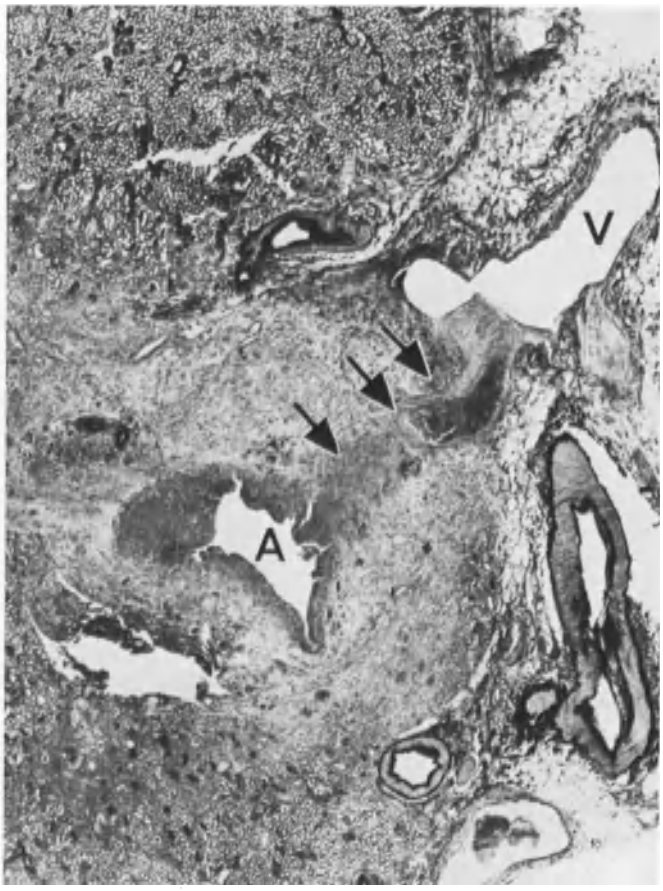



**Fig. 1.2.** Arteriovenous aneurysm following open needle puncture. Artery (*A*), vein (*V*), aneurysmal canal (→). EvG (× 10)

***Open (Visual) Needle and Surgical Biopsy.*** These practically always supply a sufficient amount of renal tissue. As every experienced pathologist knows, however, even these procedures are not foolproof and, on rare occasions, the investigator may find himself confronting scar tissue instead of renal parenchyma.

### Diagnostic Reliability of Minimal Tissue Yield

The reliability of diagnoses based on needle biopsy material (containing a minimum of five glomeruli) depends, of course, on the nature of the disease process. Thus, needle biopsy diagnosis on a series of patients suffering from diffuse renal disease such as glomerulonephritis (GN) showed an 84–100% agreement with diagnoses from autopsy material of the same patients [821]. This correspondence is sharply curtailed in the case of focal lesions such as pyelonephritis which, for example, only amounted to 51–86% in a similar comparison with patients presenting with this disease [821]. Open surgical biopsy should assure 100% diagnostic accuracy for such focal lesions.

### Complications

The constant improvement in the quality of biopsy technique has been paralleled by a steady decline in the number of complications. The procedure itself is well tolerated by the kidney as evidenced by animal experimentation, which has shown that the tissue defect caused by biopsy heals uneventfully and rapidly [375].

The principal danger associated with renal biopsy is bleeding which can become serious; this is especially true for hypertensive patients and those having a tendeny to bleed as well as chronic renal insufficiency [370, 375]. The overall frequency of fatal complications is about 0.1% (i.e., 0.07%: [806]; 0.1%: [519]; [370]; 0.09%: Z).

Our own experience has shown us that bioptic penetration at the corticomedullary junction is especially prone to cause dangerous hemorrhage since the arcuate arteries at this region are very vulnerable to injury. We have observed two deaths due to postbioptic hemorrhage as well as two incidents of perirenal hematoma of such magnitude as to require nephrectomy. In one further case from this series, open biopsy led to massive perirenal hematoma, the management of which required numerous blood transfusions and, finally, operative correction.

In addition to acute or subacute hemorrhage, needle puncture of an artery may result in arterial or arteriovenous aneurysm [359a], which becomes less frequent if Travenol instead of Vim-Silvermann needles are used. In our own two cases requiring nephrectomy mentioned above, one kidney, removed on the ninth postbiopsy day, had a thrombosed arterial aneurysm and the other kidney, removed on the twelfth postbiopsy day following surgical biopsy, had a ruptured arterial aneurysm (Fig. 1.2, see also review in [1199]).

An analysis of the literature relating to complications arising from needle biopsy [375] on 15,135 cases is given below in Table 1.4 (see also for rate of complications: 8.1%: [370]; [519]).

Table 1.4. Complications from needle renal biopsy [375] in 15,135 cases

| Complication | Incidence (%) |
|---|---|
| 1. Macrohematuria | 3.40 |
| 2. Perirenal hematoma | 0.56 |
| 3. Oliguria/anuria | 0.08 |
| 4. Circulatory shock | 0.11 |

A few cases with sepsis or bleeding leading to vascular obstruction from coagula have been reported [505, 1407].

Finally, it should be noted that a biopsy procedure aimed at obtaining renal tissue may completely miss its intended target and end up with gastric mucosa or tissue from the spleen, liver (as in three of our own cases without complications), pancreas or a suprarenal gland [1449].

We have personally received one pretended kidney biopsy containing only intestinal mucosa. On the other hand, 0.14% of our biopsies to date contained kidney tissue which was obtained during liver biopsy.

# 2. Clinician's Role in Renal Biopsy Management and Processing

## Biopsy Planning

### Clinicopathologic Cooperation

Coordinated prebiopsy planning between clinician and pathologist significantly contributes to the success of biopsy in a given case. Before carrying out renal biopsy, a clinician should, accordingly, consult the responsible pathologist and inform him of the diagnostic and procedural aspects of the case in question so that they can choose the appropriate biopsy technique.

### Microscopy Method Priorities

Priority decision-making by the pathologist with respect to type and sequence of techniques of microscopy—EM, IF, LM—to be used is largely dictated by the prebiopsy diagnosis. For example, with disease states such as Goodpasture's syndrome and SLE. IF is given priority over EM. On the other hand, for the diagnosis of suspected familial renal disease such as Alport's syndrome, EM takes precedence over IF. With rare diseases, such as Bartter's syndrome, LM (requiring Helly's fixative solution) is the initial choice for examination.

example, is only possible when two tissue cylinders are present.

A suggested priority allocation of tissue for EM, IF and LM study with reference to the tissue amount present is given in Figure 2.1.

*Cylinder 1*

If cylinder 1 contains tissue > 1 cm long
then allocate some pieces → EM.

(Place biopsy on filter paper moistened with NaCl and keep in covered Petri dish.)

*Cylinder 2*

If cylinder 2 contains:

| No tissue | Tissue < 1 cm long | Tissue > 1 cm long |
|---|---|---|
| then allocate rest of cylinder 1 → LM | then allocate rest of cylinder 1 → IF or LM; cylinder 2 → LM or EM (allocation choice depends on the diagnostic problem) | then allocate parts of cylinder 2 immediately → EM; cylinder 1 → LM; cylinder 2 remnant → IF |

**Fig. 2.1.** Allocation of renal tissue for LM, EM and IF

## Tissue Processing by Clinicians

### Guidelines[1]

Once the renal tissue has been obtained, the proper equipment and solutions for its further processing must be readily available.

The type of tissue processing chosen will chiefly depend on the amount of tissue obtained which will more or less dictate the type and sequence of microscopy investigations that can be undertaken. IF examination, for example, is only possible when two tissue cylinders are present.

Examination of this table indicates the advantages which are obtained when two tissue cylinders (referred to in Fig. 2.1 as cylinders 1 and 2) are obtained on routine biopsy.

### EM Processing

*Preparation*

1. A stock solution of glutaraldehyde[1] (25% strength and stabilized with amberlyst) should be readily available.

[1] Although this discussion has been formulated with needle biopsy in mind, its tenets are broadly applicable to tissue obtained with open biopsy.

[1] In Europe, glutaraldehyde may be obtained from Serva Feinbiochemica, Heidelberg, Merck (No. 4239), Darmstadt (both West Germany); and Brunschwig Chemie, Basel, Switzerland.

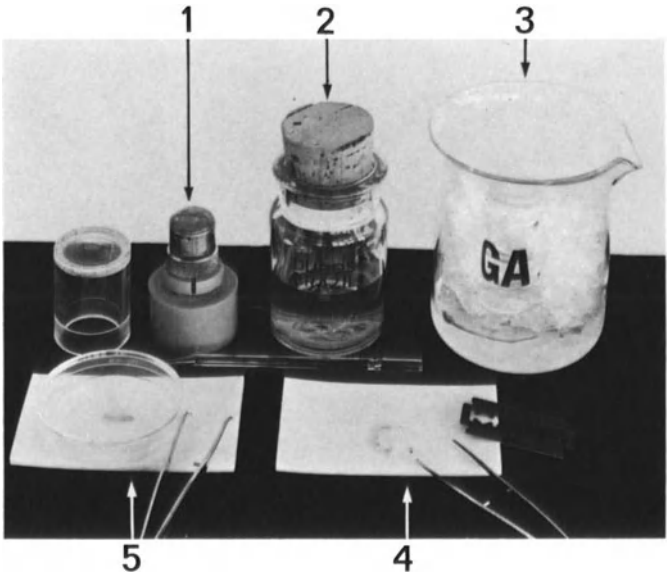



**Fig. 2.2.** Complete set for preservation of kidney biopsy material:
1. Block-holder with cover and depot of a supporting substance, e.g., tragant for IF material
2. Dubosq-Brazil or other fixative solution for LM
3. Glutaraldehyde solution in ice for EM
4. Teflon plate with drop of glutaraldehyde containing tissue pieces for EM
5. Separate set of teflon plate and pincers for trimming and storing material in moist chambers

2. Shortly before needed, prepare sufficient standard solution (for biopsy use) by adding 5 ml of sodium phosphate buffer solution (pH 7.2) to each 0.45 ml of the 25% glutaraldehyde stock solution used; the standard glutaraldehyde solution is now 2%.
3. Prior to biopsy, pour 5 ml of the 2% standard glutaraldehyde solution into an appropriate glass container for subsequent tissue delivery.
4. Immediately before biopsy cool down enough 2% standard glutaraldehyde solution with ice and pour onto a wax or teflon plate to a depth of 0.5 ml.

*Procedure*

Within seconds after biopsy completion, place tissue intended for EM on the wax or teflon plate layered with glutaraldehyde and with a razor blade using cutting strokes (do not crush tissue!), cut the tissue into the smallest possible pieces ($< 1$ mm).
Then, very gently transfer the cut pieces using fine pincers or, even better, a Pasteur pipette, into the delivery glass containing 2% standard glutaraldehyde solution.
This glass must then be kept for at least 4–6 h (at the most 3–4 days) in a refrigerator at $+4°$ C prior to delivery, and may be sent by express mail along with LM material. No special cooling is required.

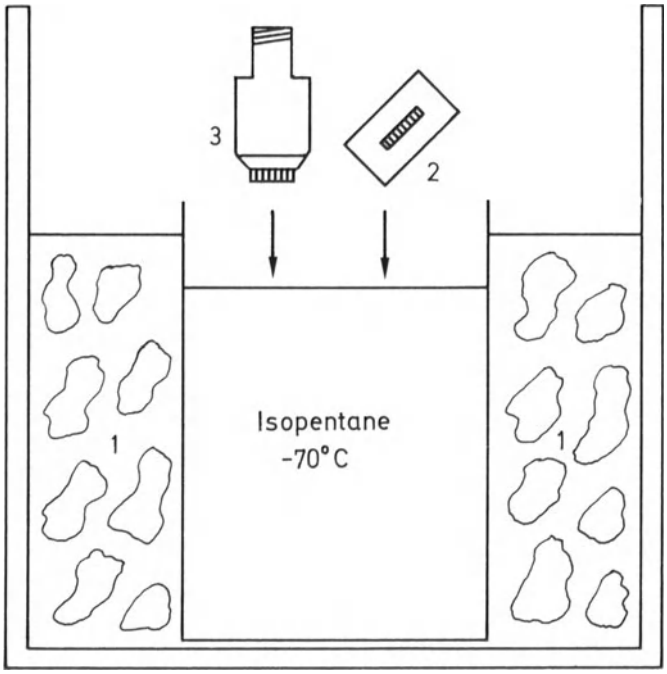



**Fig. 2.3.** Cooling of IF material:
1. Cooling fluid ($CO_2$ + acetone or liquid nitrogen)
2. Filter paper with tissue fragment
3. Block-holder with tissue fragment in situ

**IF Processing**

*Preparation*

Fill a tall 50 ml open-mouthed glass flask with isopentane[1] (2-methylbutane) and cool to $-70°$ C with either an acetone-dry ice mixture or with liquid nitrogen.

*Procedure*

Unlike EM processing, a 10–15-min interval after biopsy is tolerated for IF tissue before further processing if the tissue is kept cool during this period.
1. The biopsy tissue (resting on NaCl-moistened filter paper) may be put directly onto a block holder (Fig. 2.2). The tissue should be placed there on a supporting substance (such as tissue tec or tragant both treated with physiological NaCl solution) to permit its proper positioning to assure cutting of plane parallel sections on the cryostat later.
2. After support is assured, immerse the tissue in the pre-cooled ($-70°$ C) isopentane for 5–30 min (Fig. 2.3).

[1] Available at Fluka AG, (No. 59080) Buchs, Switzerland; and Merck (No. 6056), Darmstadt, West Germany.

3. Remove the frozen specimen which now may be:
   a) Sectioned on the cryostat immediately
   b) Stored in an air-tight jacket at −30° C in a deep-freeze or
   c) Delivered quickly elsewhere for further investigation in an airtight jacket surrounding dry ice.

We have found freezing in a jet of $CO_2$ gives less favorable results than in isopentane. Slow freezing in deep-freezing devices leads to tissue destruction which is due to ice crystal formation.

**LM Processing**

Fixation is a well-known process and is achieved in 4% or 10% neutral formalin, Dubosq Brazil or in various other special media (p. 8).

We have found it very helpful to provide those clinical centers dependent on us for their pathology work with an instruction leaflet summarizing the steps to be taken—as indicated in this chapter—for handling renal biopsies prior to their arrival at our institute. When resident pathologists are available, they should personally secure tissue immediately following biopsy.

# 3. Renal Biopsy Management and Processing by the Pathologist

## Light and Electron Microscopic Procedures

### Light Microscopy Procedures

#### Fixation and Embedding

Table 3.1 details our suggestions regarding renal biopsy fixation and embedding. We prefer nonresident suppliers to use formalin for fixation since it is more stable and durable than Dubosq-Brazil. Embedding in paraplast has the advantage of permitting sections to be cut at a uniform thickness of 2 μm.

We put 2–5 sections on each slide. It is recommended that:

1. The slides of a given series be numbered sequentially to permit tracking of an individual glomerulus throughout the series.
2. The section thickness be indicated on the slides in the event of subsequent histometric and semiquantitative work-up of the tissue being desired.

If no glomeruli are found by routine processing of a renal biopsy cylinder, the material must be prepared again in serial sections. In 16 such cases of our own, we encountered glomeruli in 8 (more than five glomeruli in two needle biopsies and less than five in six).

*Rapid Embedding*

We are frequently requested by centers engaged in kidney transplantation to perform frozen section diagnosis on needle biopsies obtained from acutely deteriorating transplanted kidneys. Our experience has shown the frozen section technique to be inadequate for this purpose. Therefore, we use—and recommend—the rapid embedding procedure given in Table 3.1 which allows completion of sections stained with HE, EvG, and PAS within 4 h.

The methyl metacrylate (MMA) embedding procedure given in Table 3.1 is not suited and too expensive for routine use. Its use is best restricted to centers which do histometric work regularly or for preparation of material for educational purposes.

It should be noted that MMA with LM is no substitute for EM. If smaller institutes are confronted with the choice of either introducing the MMA procedure or acquiring the apparatus essential for IF work, we recommend the latter alternative.

***Fixatives.*** A brief profile of the fixation media mentioned in this text is given below.

1. Neutral formalin (4 or 10%).
2. Dubosq-Brazil (required for Masson's trichrome stain)

| | |
|---|---|
| 80% alcohol | 150 ml |
| Periodic acid | 1 g |
| Formalin (40%) | 60 ml |
| Glacial acetic acid | 15 ml |

Durability of use: about 1 week.

3. Helly's solution (only necessary for Bowie's stain):
   Müller's solution: Formalin sublimate = 10:1
   Müller's solution:

| | |
|---|---|
| Potassium bichromate | 25 g |
| Sodium sulfate | 10 g |
| Aqua bidest | 1000 ml |

   Formalin sublimate:

| | |
|---|---|
| Sublimate | 20 g |
| Formalin (40%) | 10 ml. |

#### Staining

The most important staining procedures are given below.

**PAS Stain** (Periodic Acid + Schiff's Reagent)

*Solution*

1. Periodic acid as 0.5% aqueous solution.
2. Schiff's reagent: preparation:
   a) Pour 200 ml of boiling aqua dest. over 1 g of pulverized parafuchsin; shake for about 5 min and cool to 50° C, then filter.
   b) Add 20 ml of 2n sulfuric acid and cool to 25° C by irrigation (water coat).
   c) Add 2 g of water-free potassium metabisulfite.
   d) Let stand at room temperature for 24 h (until solution devoid of color).
   e) Store well covered in the dark. The solution cannot be used if it starts to turn red; in this case, add 2 g of charcoal and filter to clear solution.

Table 3.1. Fixation and embedding procedures for light microscopy

| Supplier | Resident supplier | | Resident supplier | Nonresident supplier |
|---|---|---|---|---|
| Embedding procedure | Routine embedding | | Rapid embedding | Routine embedding |
| Fixative | Dubosq-Brazil | | Neutral formalin 10% | Neutral formalin 4% |
| Duration of fixation | 6–24 h: Room temperature<br>Needle biopsy < 12 h<br>Open biopsy > 12 h | | 15 min at 37° C<br>(needle biopsy only) | Unlimited at room temperature |
| Past fixation | 4% neutral formalin<br>6–24 h: Room temperature<br>Needle biopsy < 12 h<br>Open biopsy > 12 h | | – | Dubosq-Brazil<br>6–24 h: Room temperature<br>Needle biopsy < 12 h<br>Open biopsy > 12 h |
| Embedding | Paraplast | MMA<br>(methyl metacrylate) | Paraplast | Paraplast |
| Dehydration | | | | |
| Alcohol 70% | 30 min | 2 h | 10 min | See paraplast embedding procedure for resident supplier |
| Alcohol 70% | 30 min | 12 h | 10 min | |
| Alcohol 96% | 20 min | 1 h | 10 min | |
| Alcohol 96% | 20 min | 1 h | 10 min | |
| Alcohol 100% | 20 min | 1 h | 10 min | |
| Alcohol 100% | 20 min | 1–12 h | 10 min | |
| Xylol | 20 min | – | 10 min | |
| 100% Alcohol: Chloroform (3:1) | – | 1 h | – | |
| Chloroform | – | 3 h | – | |
| Embedding media | [a]Paraplast: 30 min, change to fresh paraplast: 60 min | [b]MMA 1 h using pill glass with plastic cover<br>MMA 2 h<br>MMA + [c]BPO: 6–12 h covered[e]<br>MMA + BPO + [d]P-N, 3–4 days at 40° C[f] | Paraplast: 30 min change to fresh paraplast: 30 min | |
| | Rotating Minot microtome | Jung microtome 1130 | As paraplast, routine embedding | |
| Cutting | C-profile knife | D-knife | | |
| Section thickness | Constant 2 µm | 0.5–1 µm | | |
| Stain (after drying) | Routine (HE, EvG, PAS, PASM, Masson's trichrome/ AFOG) | HE, PASM, CAB | HE, EvG, PAS | |
| Duration of processing | About 24–36 h | 1 week | About 4 h | |

[a] Paraplast obtainable at Sherwood Medical Industries Inc. 1831 Olive St., St. Louis 63163, MI/USA.
[b] Methyl metacrylate (MMA) obtainable at Bender and Hobein, Zürich, Switzerland.
[c] Benzoyl peroxide (BPO) obtainable at Bender and Hobein, Zürich, Switzerland.
[d] Plastoid-N (P-N) obtainable at Roehm and Haas, Pharma GmbH, Darmstadt, West Germany.
[e] MMA + BPO: 10 ml MMA + 0.2 g BPO.
[f] MMA + BPO + P-N: 10 ml MMA + 0.4 g BPO + 25 ml P-N.

3. Sulfur dioxide-containing water:
   Mix 10 ml of a 10% solution of water-free sodium bisulfite (furosum) and 10 ml of the 2n sulfuric acid with 200 ml of tap water.

*Staining Procedure*

1. Periodic acid for 5 min.
2. Wash with aqua dest.
3. Schiff's reagent for 20 min.
4. $SO_2$-containing water three times for 2 min each.
5. Place in water for 15–30 min.
6. Hemalum for 1 min (nuclear stain).
7. Wash, then place in an alcohol series of increasing concentrations.
8. Clear in xylol and mount.

*Result:* PAS-positive substances (basement membranes, mesangial matrix): intense red-violet; nuclei: blue.

## **PASM Stain** (Periodic Acid + Silver Methenamine)

*Solution*

1. Silver solution
   Silver nitrate (5%) 5 ml
   Borax (2%) 5 ml
   Hexamethylentetramine (3%) 40 ml (store in refrigerator).
2. Periodic acid (1%).
3. Sodium thiosulfate (3%).
4. Gold chloride (0.25%).

*Note:* 1. Prepare all solutions with aqua bidest. 2. Prepare silver solutions shortly before use.

*Staining Procedure*

1. Immerse in chloroform for 15 min, then in the alcohol series of decreasing concentrations, then in aqua bidest.
2. Periodic acid (1%) for 10 min.
3. Flush in aqua bidest for several seconds.
4. Silver solution for $1^1/_2$–2 h at 60° C.

*Note:* Before proceding, by microscopic control, the glomeruli should be deep black.

4. Flush in aqua bidest for several seconds.
5. Gold chloride (0.25%) for up to 30 s.

*Note:* Slide now blue-grey.

6. Flush in aqua bidest for several seconds.
7. Sodium thiosulfate (3%) for 2 min.
8. Wash in tap water 2 min.
9. Series of increasing concentration of alcohol as above.
10. Clear in xylol and mount as above.

*Result:* Basement membrane and mesangial matrix black; immune deposits: usually slightly brown.

## **Masson's Trichrome Stain**
(Fixation is Dubosq-Brazil solution, see p. 8)

*Solution*

Preparation of light-green stain:
Light-green 1 g
Distilled water 50 ml
Acetid acid 0.5 ml

*Staining Procedure*

1. Pass section through increasing alcohol series to 96%.
2. Refix in Bouin solutin at 60° C for at least 1 h.
3. Wash away yellow color with water.
4. Stain nuclei in Weigert's iron hematoxylin for 10 min.
5. Wash in tap water.
6. Flush with aqua dest.
7. Stain with Biebricht scarlet red and fuchsin acid[1] in the ratio and times as follows:

| Biebricht scarlet red: Fuchsin acid | Duration |
|---|---|
| 7:3 | 1 min |
| 1:1 | 3 min |
| 1:9 | 15 min |

8. Flush briefly with aqua dest.
9. Stain with phosphotungstic acid (5%) for 15 min.
10. Pour Masson's light-green stain directly on slide and mix with phosphotungstic acid for 15 min.

*Note:* microscopy control at this point reveals connective tissue stained green.

11. Flush briefly in water.
12. Flush briefly in 1% acetic acid.
13. Immerse in 96% alcohol, then absolute alcohol and then clear in xylol, and mount.

*Result:* Nuclei: black; cytoplasm, collagen fibers, mucus: blue-green; protein (immune) deposits (fibrinoid): orange-red (if results unsatisfactory, use longer dried sections, 24 h).

## **AFOG Stain** (Acid Fuchsin Orange G)

*Solution*

Anilin blue[2] – 1 g. Boil in 200 ml of distilled water then cool. Add orange G[3] – 2 g and acid fuchsin[4] – 3 g. Adjust the pH with HCl to pH 1.09.

[1] Fuchsin acid available at Chroma (No. 10765) Stuttgart, West Germany.
[2] Chroma-Gesellschaft, Stuttgart, West Germany (Chroma No. 1B501).
[3] Chroma No. 1B221.
[4] Chroma No. 1B525.

*Staining Procedure*

1. Fix with formalin or Dubosq-Brazil.
2. Deparaffinize.
3. Refix in Bouin for 24 h, the first 2 h at 60° C.
4. Water (until slide white).
5. Nuclear stain with Weigert iron hematoxylin for 1 min.
6. Differentiate in 1% HCl-alcohol.
7. Blue, then place in warm alkali tap water.
8. Phosphoromolybdic acid (1%) for 5 min.
9. Rinse with distilled water.
10. AFOG solution for 5 min.
11. Rinse briefly in water.
12. Alcohol series, twice 96%, twice absolute alcohol, xylol.

*Results:* Protein droplet: lively red; BM and connective tissue: blue; erythrocytes: yellow–yellowish green.

## Bowie's Stain

(For staining the granula of the juxtaglomerular apparatus)

*Fixation Procedure*

1. Fix in Helly's solution for 48 h.
2. Wash in running water for 24 h.
3. Embed in paraplast.

*Solution*

1. Dissolve 1 g of Biebricht scarlet red in 250 ml of distilled water (solution 1).
2. Filter (filtrate 1).
3. Dissolve 2 g of ethyl violet in 500 ml of distilled water (solution 2).
4. With constant stirring, filter solution 2 into filtrate 1 until neutralization of solution 3 is achieved (when a little of the solution dripped on filter paper shows no color except for the precipitate itself).
5. Filter solution 3 once more and dry the precipitate.
6. The stock solution is then prepared by dissolving 0.2 g of the precipitate from solution 3 in 20 ml of 96% alcohol.

*Preparation of Bowie's Solution for Use*

Place 15–20 drops of Bowie's stock solution in 100 ml of 20% ethyl alcohol.

*Staining Procedure*

1. Dehydrate as usual.
2. Fix section in Helly's solution (if not done primarily).
3. Resublimate (determine time required in advance).
4. Place in running water for 5 min.
5. Place in potassium chromate solution (2.5%) and keep at about 40° C overnight.
6. Flush in distilled water.
7. Place in Bowie's solution for use for 24 h.
8. Blot the slide dry.
9. Immerse quickly two or three times in fresh clear acetone until excessive color is washed away.
10. Differentiate in xylol-carnation oil mixture (1:1) until the section appears red to reddish purple.
11. Clear twice with fresh xylol and twice with fresh benzol, mount.

*Result:* Renal parenchyme: red; elastic fibers and juxtaglomerular granules: purple-blue; red blood cells: amber.

## Cresyl Violet Stain for Bacteria

*Staining Procedure*

1. Color the sections in a 1% solution of cresyl violet for 20 min.
2. Differentiate in 70% alcohol until no more color is given off. In case of strong overcoloring, differentiate in acetic acid (1:500 or 1:100) until only the nuclei remain colored.
3. Quickly dehydrate in absolute alcohol, clear with xylol, cover.

*Result:* Bacteria and all nuclei: deep violet; fibrin: greenish.

## Lepehne's Peroxidase Reaction for Hemoglobin

Fix in formalin (not too long!); use thick sections $>5\,\mu m$.

*Staining Procedure*

1. Add a mixture of 0.5 ml of Perhydrol[1] and 4.5 ml of 70% alcohol to 2 ml of a 0.6% solution of benzidine in 96% alcohol. Let it work for 10 min on section.
2. Place section in 50% alcohol, then water.
3. Stain with hemalum for 30 s.

*Result:* hemoglobin: dark brown.

## Thioflavin T Stain for Amyloid

[1656] for phlorwhite BBU see: [1817]

*Solution*

Add 0.5 g of a 0.5% Thioflavin T solution[2] to 100 ml aqua bidest.
Stir, warm to 50 60° C, let cool, then filter.

[1] Merck, Darmstadt, West Germany.
[2] Thioflavin T available at Fluka (No. 88630) Buchs, Switzerland.

*Procedure*

1. Stain nuclei with hemalum or Weigert's hematoxylin for 8 min, flush with distilled water and blue with tap water, then again flush with distilled water.
2. Stain section with freshly prepared Thioflavin T solution for 7 min.
3. Wash off briefly with water.
4. Differentiate in a 1% aqueous hydrochloric acid solution (20 ml 1 n HCl + 52 ml distilled water) for 15 min.
5. Wash in water.
6. Carefully blot up the water with filter paper (sections should be as dry as possible).
7. Dehydrate twice, both for 30 s; then, 1 min in absolute alcohol. Clear in xylol, cover with eukitt.
8. Read slides with blue or UV fluorescence.

*Result:* Amyloid: under blue fluorescence: bright yellow to green; under UV fluorescence: dark green to blue green with whitish undertone.

## Special Technique for Methyl Metacrylate Embedded Tissue

(see Table 3.1)

*Stretch Method With Butyl Glycol*

1. Place sections directly from the microtome in a mixture of 10 parts of absolute alcohol to 2 parts alcoholic butyl glycol and boil for 5–10 min.
2. Transfer to distilled water (avoid tension!).
3. Before stretching, place sections in alcoholic butyl glycol for about 1 min (section will become soft).
4. Lay sections on slide with pincers.
5. Moisten a small soft brush with alcoholic butyl glycol and gently stretch out and press section onto slide.
6. Dry with two or three pieces of soft tissue paper by pressing gently.
7. Dry directly in chloroform and stain.

## Staining of Methyl Metacrylate Embedded Tissue

### *Hemalum – Eosin Stain*

*Staining Procedure*

1. Remove methyl metacrylate from sections in chloroform for 20 min and then place in series of decreasing alcohol concentrations.
2. Stain with hemalum for 15 min.
3. Blue in tap water.
4. 1% erythrosin stain for about 2 min (stronger stain than eosin).
5. Place sections in series of increasing concentrations of alcohol; clear in xylol.

### *PAS Stain* (Periodic Acid + Schiff's Reagent)

*Staining Procedure*

1. Remove methyl metacrylate from sections in chloroform for 20 min and then place in a series of decreasing alcohol concentrations.
2. Place sections in 1% periodic acid for 2 h.
3. Flush well in distilled water.
4. Stain in Schiff's reagent (see p. 8) for 3 h.
5. Wash for 15 min in running water.
6. Stain with hemalum for 1 min.
7. Blue in tap water, then series of increasing alcohol concentrations, then xylol.

### *PASM* [PAS – methenamine Silver Stain (after Movat)]

*Staining Procedure*

1. Remove methyl metacrylate, place sections in a series of decreasing concentration of alcohol, then aqua bidest.
2. Stain with 1% periodic acid for 10 min.
3. Flush in aqua bidest.
4. Stain with silver solution (see p. 10) at 60° C for $1^1/_2$–2 h until glomeruli deep black.
5. Flush in aqua bidest.
6. Place sections in 3% sodium thiosulfate solution for 2 min.
7. Flush in water, then place sections in a series of increasing alcohol concentrations, then clear in xylol.

# Electron Microscopy Procedures

## Fixation and Embedding

*Fixation* (see p. 5)

2% glutaraldehyde in sodium phosphate buffer.

*Preparation of Sodium Phosphate Buffer*

| Solution A | Solution B |
|---|---|
| 0.2 mol $NaH_2PO_4H_2O$ = | 0.2 mol $Na_2HPO_4 \cdot 12\,H_2O$ = |
| 6.9 g in 250 ml aqua dest. | 71.6 g in 1000 ml aqua dest. |

*Buffer Mixture*

Mix 103.5 ml solution A, 346.5 ml solution B and 465.0 ml of aqua bidest. together. Then, with constant shaking add 5 ml of 7% solution of $CaCl_2$ dropwise. The pH should now be 7.4. Correction to this value may be done with 0.2 mol NaOH or HCl.
Osmolarity ca 360 mosm.
Store at 4° C; viable for 2 months.
Shortly before use, add 0.45 ml of a 25% solution of glutaraldehyde (see p. 5) to 5 ml of the sodium phosphate buffer.

The tissue should be fixed at 4° C at least for 4 h especially if mail delivery is foreseen. The maximal duration for fixation is about 7 days.

*Wash Buffer*

Following fixation, place tissue in the sodium phosphate buffer for $^1/_2$ h to several days at 4° C. Change the buffer during this time at least twice.

*Osmium Fixation*

Work with osmium must be carried out under a flue. The osmium solution is made by dissolving 1 g $OsO_4$ in 50 ml aqua bidest (=2% solution). Let this solution stand in a brown flask, which should be closed with a polished-down stopper for at least 24 h at room temperature or until the $OsO_4$ is dissolved. Shake well before use.

*S-Collidin Buffer*[1]

Preparation:

| | |
|---|---|
| S-collidin | 2.67 ml |
| Aqua bidest | 50 ml |
| HCl, 1 n | 9 ml |

Dilute to 100 ml with aqua bidest. (pH 7.4–7.45, osmolarity: 220–240 mosm).

Fixation Solution:

2 ml of 2% $OsO_4$
1 ml of 0.2 mol s-collidin buffer
Final $OsO_4$ concentration: 1.33% = 67 mosm.
Fix tissue in above solution for 1 h at room temperature.

*Wash Solution*

Wash tissue in S-collidin buffer for 15–30 min during which the buffer should be changed twice.

*Dehydration and Embedding in Epon*

Preparation of Epon

| Stock solution A | Stock solution B |
|---|---|
| Epikote[a] 812: 72 ml | Epikote 812: 100 ml |
| DDSA (dodecenyl succinate anhydrate)[b]: 100 ml | NMA (nadic methyl anhydride)[b]: 76.5 ml |
| Stir for $^1/_2$ h | Stir for $^1/_2$ h |

[a] Shell, Zürich, Switzerland (Art. No. 1300).
[b] Acima, Buchs, Switzerland.

[1] Obtainable at Fluka AG, Buchs, Switzerland, as S-Collidin puriss. No. 27690/A 52379.

At 4° C, the stock solutions can be kept for several months. Before preparation of the final solution, the stock solutions must be brought to room temperature.

*Preparation of Final Solution*

Mix four parts of solution A and six parts of solution B and stir thoroughly with a glass rod for at least 5 min.
A 2% solution of DMP-30[1] can be used for acceleration and catalyzation (DMP-2,4,6-dimethylamino phenol, caution: light sensitive!).
Dehydrate the tissue as follows:
Increasing alcohol series for 15 min each (70%→95%→100% alcohol); in 100% alcohol, two immersions of 15 min each. Then twice in propylenoxide[2] for 20 min each then handle tissue as follows:

1. Propylenoxide–Epon final solution (1:1) for 1–3 h.
2. Propylenoxide–Epon final solution (1:3) overnight.
3. Put 2 drops of the Epon final solution in a gelatin capsule and then put in tissue.
4. Place gelatin capsule in incubator at 37° C for 2 h, if kept overnight, at 45° C (in the presence of high humidity, add an exsicant).
5. Then warm to 60° C for 3 days.
6. On the fifth day, completely fill gelatin capsule with Epon and keep at 60° C for 48 h for hardening.

## Cutting and Staining

A. Semi-Thin Sections
Prepare 1 µm sections on the ultra microtome. Fix onto slide by laying on a hot plate at 60° C for 2–3 h.
B. Azure Methylene Blue Stain (for other status: [1818])
Preparation
A = 1% Azur II[3] in aqua dest.
B = 1% methylene blue[4] in a 1% borax solution
Mix equal parts of A and B together.
Staining procedure: Drop the stain onto the slide, then draw the slide quickly through an open flame until the stain begins to evaporate. Wash off with water.
C. Ultra-Thin Sections
Prepare sections on ultra microtome with interference colors in the silver spectrum.
D. Contrasting: uranyl acetate and lead citrate.

*Uranyl acetate:* Dissolve 0.8 g of uranyl acetate in 20 ml of 50% alcohol, shake well and then filter and contrast in dark room for 15 min. Wash with 50% alcohol and aqua bidest.

*Lead citrate:* Dissolve 0.03 g of lead citrate in 10 ml of freshly prepared aqua bidest. Add 0.1 ml of a 10 n NaOH solution dropwise and centrifuge at 2000 RPM for 5 min.
Contrast for 5 min, wash with aqua bidest and dry thoroughly with filter paper.

[1] Christ AG, Aesch, Switzerland.
[2] Merck, Darmstadt, West Germany (Art. No. 12492).
[3] Merck, Darmstadt, West Germany (Art No. 9211).
[4] Fluka, Buchs, Switzerland (Art No. 66720).

## Immunohistologic Procedures, Morphometry and Clinically Related Topics

### Topics in Immunohistology

Immunohistology permits localization of numerous substances with antigenic (AG) sites in tissue preparations. This is achieved by means of specific antibodies (AB) provided with tracer substances which can be rendered visible at the AG-AB tissue binding site.

Of chief importance for renal biopsy diagnosis is the demonstration of immunoglobulins, complement components, fibrin and other serum proteins which—mainly but not exclusively—can be part of pathogenetic immunocomplexes. Other components which can be demonstrated in these complexes may be endogenous, e.g., DNA, or exogenous, e.g., bacteria, viruses, drugs. The latter-mentioned components may also act directly to cause injury i.e., independent of AG-AB reactions.

The following discussion is primarily restricted to a presentation of practical guidelines for the utilization of FITC (fluorscein-iso-thiocyanate) which is the most popular tracer currently in use for immunofluorescent work. For individual, ad hoc preparation of specific antisera and/or fractionating and labeling methods, the reader is referred to appropriate, specialized texts [580, 1180, 1714, 1735].

Finally, a short discussion of the immunoperoxidase method (IP) which used chemically stably bound active enzymes instead of fluorochrome as tracer is given; it is used mainly as an alternative to the FITC method.

#### Tissue Processing

Two factors determine the successful outcome of immunofluorescence:

1. The quality of the antisera
2. The efficiency of AG preservation. This assumes that the tissue preparation be done as quickly and carefully as possible.

It is noted that autopsy material obtained later than 12 h after death will not, in general, yield satisfactory results (for contrary experimental evidcnce, see [1477]).

##### *Fixation*

Chemical fixation is mainly suitable for bacteria, viruses and protozoa unless their antigenic properties after fixation have been individually confirmed; it is less suitable for soluble proteins ([580]; for IF after formalin fixation

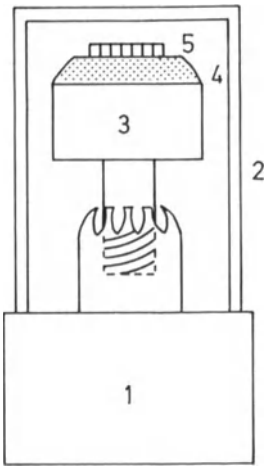



**Fig. 3.1.** Device for storing IF material in the deep freezer:

1. Socle
2. Airtight cover
3. Block-holder with
4. Supporting mass, e.g., tissue tec
5. Tissue fragment

of kidneys, see [365a, 722a]). In general practice it is advisable to use unfixed and frozen material, especially if antigens of different quality are to be studied at the same time. For freezing and delivery of biopsy material (see p. 6).

##### *Storage*

Frozen material, when placed in airtight containers at −30° C to −70° C, can be kept safely for months (with long storage, however, the quality of IF suffers). A rational method for storing deep-frozen material is given in Figure 3.1. An absolute requirement for optimal IF examination is that the tissue cylinder never be warmed above −30° C. Damage ascribable to tissue warming is manifested as fragile sections, extensive loss of structural preservation and excessive background staining.

Alternatively, cryostat sections may be stored with a dessicant (e.g., $CaCl_2$, Drierite) in airtight containers placed in a deep freezer.

In order to avoid formation of condensed water on warming the tissue, the containers should only be opened when they are at room temperature. Tissue treated in this way can also be used for delivery.

##### *Cryostat Sections*

Two slides, each provided with 4–6 serial sections should be prepared for each AG to be demonstrated. This means that an optimal IF program will require 10–20 slides and at least 40 serial sections. It is recommended that an occasional section be taken randomly during the cutting to determine if—and how many—glomeruli are present.

## Immunohistologic Incubation

### *Methods*

Two methods, direct and indirect, are principally available (Figs. 3.2, 3.3).

*1. Direct Method*

Single step-antigen demonstration with specific, FITC-labeled antiserum.
Advantages:
1. Requires less effort
2. Is less prone to give problems.

Disadvantages:
1. Less sensitive
2. More expensive since each antigen requires its specific antiserum labeled with FITC.

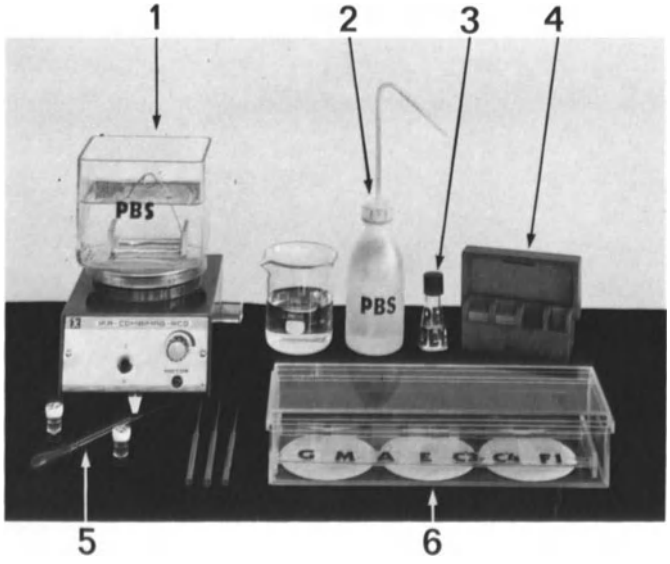



**Fig. 3.2.** Complete set for IF incubation:
1. Magnetic stirrer with "wash buffer" (PBS)
2. Wash buffer and reservoir for rinsing slides
3. Glycerine-PBS mixture (embedding medium)
4. Cover glasses
5. Pasteur pipettes and cups containing antisera to be used
6. Moist chamber for incubation of slides

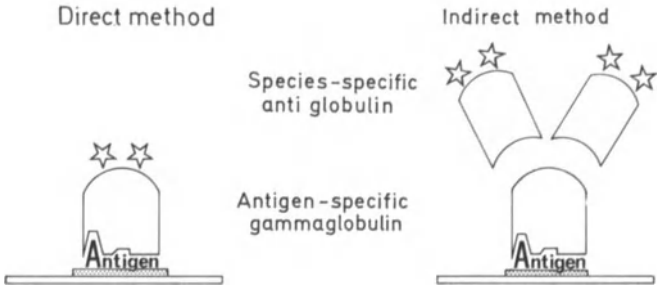



**Fig. 3.3.** Schematic comparison between direct and indirect IF methods. Note multiplier effect for fluorescence in the indirect method by increase of labeled antibody per antigen. FITC (☆ ☆)

*2. Indirect Method* (Sandwich Method, Antiglobulin Method)

The tissue section is covered with nonlabeled antiserum (e.g., of rabbit) which is specific for the AG in question.
This specifically bound, heterologous gamma globulin is rendered visible in a second step by a labeled, species-specific antiglobulin (e.g., goat antirabbit gamma globulin).
Advantages:
1. Greater sensitivity through amplification of binding sites
2. More economical since one single-labeled, species-specific antiserum can be combined with as many antisera of the corresponding animal species as desired.

Disadvantages:
1. Requires more time
2. Is more susceptible to nonspecific fluorescence since undesired binding in the first step will be amplified by the final incubation.

Because of its greater sensitivity, the indirect method is indicated whenever possible.

### *Antisera*

The following firms, among others, have relevant labeled and unlabeled antisera commercially available:

| Firm | Address |
|---|---|
| 1. Hoechst-Behring AG | Marburg, West Germany. |
| 2. Cappel | Downington, Pennsylvania, USA |
| 3. Hyland | Costa Mesa, California, USA |
| 4. Meloy | Springfield, Virginia, USA |
| 5. Miles-Seravac | Kankakee, Illinois, USA |
| 6. Nordic | Tilburg, Holland. |

*The selection* of antisera is based upon:
1. The incubation method chosen (direct or indirect)
2. The spectrum of the investigation envisaged.

Antisera should be monospecific and evidence a high precipitation titer (hyperimmune sera). For FITC-labeled sera an optimal molar FITC: protein ratio of 1.5–4.0 should be achieved.
*Antisera for Testing in Renal Biopsy Examination.*
The following antisera are recommended:

| Antiserum | Specific for |
|---|---|
| 1. Anti-IgG | gamma chains |
| 2. Anti-IgM | μ chains |
| 3. Anti-IgA | alpha chains |
| 4. Anti-IgE | epsilon chains |
| 5. Anti-C3 (=beta-1C/beta-1A) | |
| 6. Anti-C4 | |
| 7. Anti-Clq | |
| 8. Antifibrin(ogen) | |

The identification of complement components C4 and/or Clq renders additional evidence for complement activa-

tion via the classical AG-AB-mediated pathway, whereas the demonstration of C3 alone may be the result of activation via the alternative pathway as well.
Optimally, the following specificities may also be tested:
1. Anti-D
2. Anti-Australian antigen (anti-HBs Ag) and other antiviral and antibacterial antisera
3. Anti-DNA: for the demonstration of nuclear factors in SLE, the FITC-labeled gamma globulin fraction of human lupus sera with anti-DNA activity may be used.

*Sera Testing.* Before histologic testing, the antisera are tested against the specific AG and against possible cross-reacting AG by means of immunodiffusion (Ouchterlony test) or, preferably, through immunoelectrophoresis in order to confirm their monospecificity. Then, the immunohistologic specificity and the optimal dilution on known positive test tissue is determined for the antisera. Subsequently, a dilution series (1:10, 1:20 ... 1:100) is set up and that dilution is sought which, with a negative background, results in an undiminished, brilliant fluorescence (usually 1:30, 1:40 or 1:50). Both the labeled and unlabeled sera are diluted stepwise for use in the indirect method. In a checkerboard titration assay, each dilution of the unlabeled serum is set up against the conjugate in a dilution range which, by itself, does not give background staining of the test tissue. Portions of the serum of 0.3–0.5 ml are frozen at the selected dilution, stored in a deep freezer and thawed for immediate testing.

*Incubation.* The following setup is required for incubation (Fig. 3.2):
1. Moist chamber
2. Phosphate buffered physiological NaCl solution (PBS)
3. Pasteur pipettes
4. Magnetic stirrer.

The stock solution for PBS is

| | |
|---|---|
| $Na_2HPO_4 \cdot 2H_2O$ | 29,25 g |
| $KH_2PO_4$ | 4,90 g |
| NaCl | 160,00 g |
| Aqua bidest. | 1000,00 ml |

Before use, dilute the PBS stock solution with aqua bidest. in the ratio of 1:20.
Figure 3.4 presents the procedure and Figure 3.5 control possibilities for immunohistologic incubation. All incubations take place at room temperature and in a moist chamber. The sections are covered with diluted antisera (ca 0.3–0.5 ml). Following each incubation, the antisera are carefully flushed off with PBS and washed twice in a fresh bath of PBS, most profitably on a magnetic stirrer. The sections must not be allowed to dry out (intensified background staining).

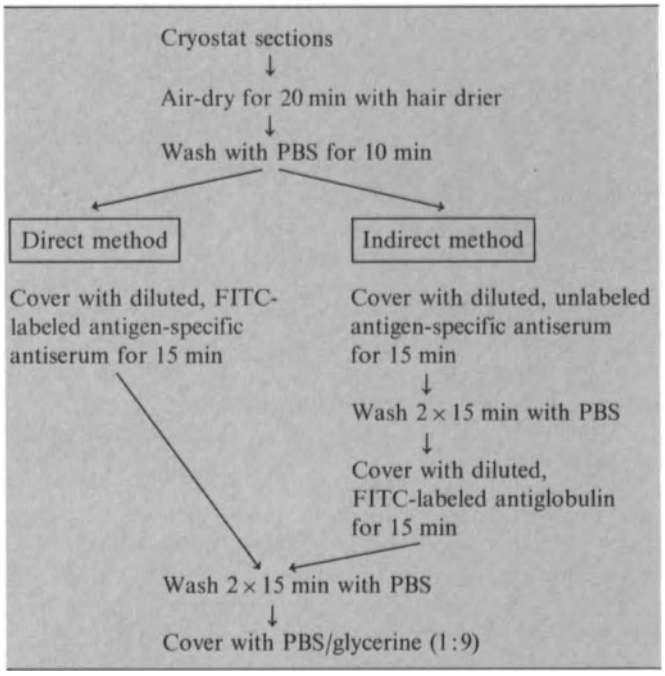



**Fig. 3.4.** IF-incubation scheme (all steps at room temperature)

| *Direct method* | *Indirect method* |
|---|---|
| 1. Incubation with FITC-labeled nonspecific antiserum (excludes non-specific tissue affinity) | 1. Replacement of the first layer through a) PBS and b) nonspecific serum of the same species (excludes non-specific binding of the sera and cross-reactions of the conjugate with tissue components) |
| 2. Absorption of the antigen-specific antiserum with desired antigen (loss of fluorescence) | |
| 3. Blockage of the desired antigen in the section by preincubation with antigen-specific antiserum of other animal species (loss of fluorescence). | |

**Fig. 3.5.** Control possibilities for specificity

The preparations are finally covered with a PBS/glycerine mixture (1:9 at pH 7.4–8.0). Drying out may be prevented by sealing on the cover-slips with a layer of nail polish or wax. We believe that storage of the sections—at 4° C—should not exceed 2–3 days.
Therefore, photographic documentation of the characteristic findings should be done as quickly as possible.

## FITC-Immunofluorescence

***Microscopy Equipment.*** A fluorescent microscope provided with an appropriate light source (high pressure mercury lamp or the considerably cheaper halogen

lamps) and special filters are necessary for FITC-immunofluorescence.

Incident lighting, which achieves illumination and focusing of the exciting light through the objective lens from above, is a decided improvement over conventional built-in lamps for bright or dark field illumination. Incident illumination assures optimal excitation of the fluorochrome and greater resolution especially under high power magnification.

Since FITC is unstable, permanent preparations cannot be made. Therefore the preparations require immediate photographic documentation which represents a significant disadvantage of FITC-immunofluorescence. This disadvantage is counterbalanced by the great specificity and sensitivity which characterizes immunofluorescence (e.g., in experimental GN, a concentration of 0.25 ml of bovine serum albumin per gram kidney tissue was found to be the sensitivity threshold [1746]). Additionally, IF is a multifaceted, economical and relativity rapid method which may lead to quick results i.e. on the same day as biopsy.

***Photography.*** For black and white photos, we use Ilford HP4, an exposure time of 30–60 s and fine-grain developer with about a 30% increase in developing time. For color photos, we use Kodak High-Speed-Ektachrome 22 DIN with intensified developing.

***Undesired Fluorescence.*** Table 3.2 gives suggestions for the recognition and abolition of fluorescence which is in no way related to the antigen under study (undesired fluorescence). Such fluorescence can be caused by specific AG-AB reactions as a consequence of cross-reactions of the specific antiserum with other AG or as

Table 3.2. Errors in fluorescence, their source and remedial action (compare also [580, 1180])

| Error | Source | Control | Remedial action |
|---|---|---|---|
| Diffuse background staining | 1. Free FITC in conjugate | 1. Dialysis against PBS chromatography with Stephadex G-25 | |
| | 2. Overlabeling of the conjugate | 2. Determination of FITC: protein ratio | 2. DEAE cellulose chromatography |
| | 3. Insufficient serum dilution | 3. Test out higher dilution stages | |
| | 4. Electrostatic binding on negatively charged tissue | 4. Control No. 1 in Fig. 3.5 | 4. None |
| | 5. Electrostatic binding on negatively charged AB | 5. Absorption with DEAE cellulose | |
| Patchy background staining on the cylinder surface | 1. Tissue contact with glutaraldehyde or other fixative during preparation | – | 1. Use of pincers reserved exclusively for IF work |
| | 2. Crushing of tissue | | |
| False positive fluorescence | 1. Antiserum monospecific, but cross-reacting with other antigens | 1. Identity reaction by immunodiffusion with cross-reacting antigen | 1. None. Try antiserum from other species |
| | 2. Antiserum polyvalent (not monospecific) | 2. Immunodiffusion Immuno-electrophoresis Control Nos. 2 and 3 in Fig. 3.5 | 2. Absorption with nondesired antigen |
| | 3. Cross-reaction of the labeled AG | 3. Immunodiffusion Immuno-electrophoresis Control Nos. 2 and 3 in Fig. 3.5 | 3. Absorption with antigen, possibly kidney tissue, insolubilized human serum |
| Insufficiently positive or false negative fluorescence | 1. Antiserum overdiluted | 1. Test sections | 1. Concentrate antiserum |
| | 2. Precipitation titer too low | 2. Determine titer | 2. None: discard serum |
| | 3. Poor technique | 3. – | 3. Repeat incubation |
| | 4. Underlabeling of the conjugate | 4. Determine FITC: protein ratio (not lower than 1.5) | 4. DEAE cellulose chromatography |

a consequence of the presence of other AB in the serum used which lead to false positive reactions.
Therefore, it is recommended that several antisera of the same specificity be compared if there is any question of the correctness of interpretation of results (also in cases of probable false negative results). It should also be borne in mind that fluorescence can occur by nonimmunologically related, i.e., nonspecific, fluorescence of the tissue itself. If this is ascribable to the conjugate (overlabeling, nonbound FITC), chromatographic fractionation of the conjugate [580], absorption with powdered tissue (lyophilized mouse liver) or with normal homogenized and washed tissue for correction may be tried. If tissue is used, 1 volumetric unit of tissue is mixed with 2 units of serum for 30–60 min at room temperature; then the serum is recovered by high speed centrifugation.
These absorption methods do cause losses of AB, however, these may be avoided by using higher dilution of antisera which give the same results.

### Immunoperoxidase (IP) Technique

The range of use for IP-sera is similar to that of FITC-labeled sera in IF. The difference is that an enzymohistochemic demonstration of the coupled peroxidase follows the incubation with the immune sera. In general, the results with IF- and IP-methods are analogous [348]. However, both methods have advantages and disadvantages which must be taken into consideration (for a review see [1566]).
Several methods for chemical coupling between peroxidase and immunoglobulins are described in the literature [58, 290, 1182, 1183].
Peroxidase labeled sera have also recently become commercially available (e.g., Cappel Laboratoires, Downington, Pennsylvania, USA). The coupling procedure with difluoro-dinitrophenyl sulfone [1183], which entails roughly equivalent expenditure as FITC labeling, yields peroxidase-labeled sera which can be used with good results in cryostat sections for LM (Fig. 3.6).
Reliable demonstration of peroxidase can be made with diamino-benzidine [589]. Stain-contrast can be enhanced through additional treatment with osmium.
Stain-intensity with IP, in contrast to IF, is determined not only by the amount of antigen and titer of the immune sera but also by the kinetic properties of the enzyme and the concentration of the enzyme substrate. Therefore, the IP-method is easily controlled, even if an optimum between intensity and resolution of the

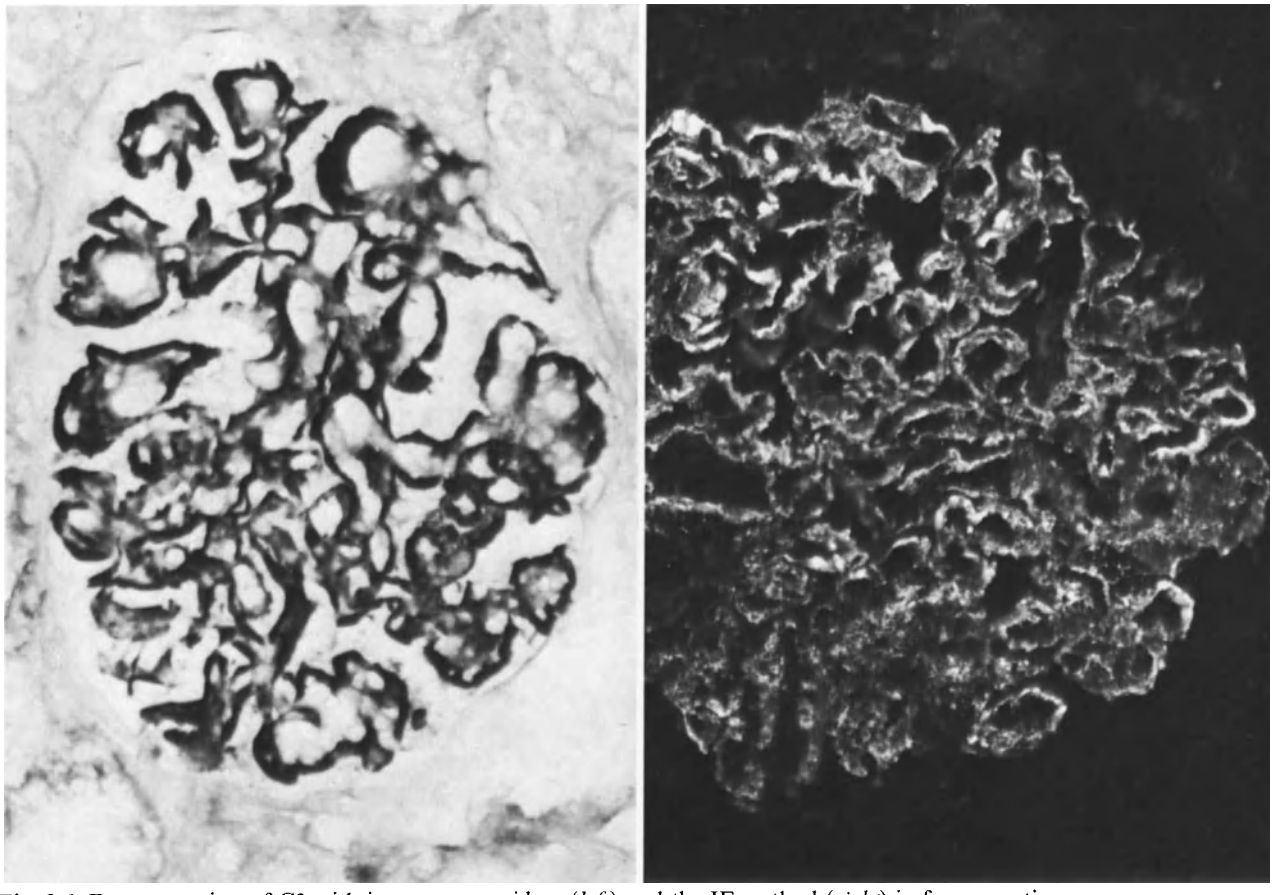


**Fig. 3.6.** Demonstration of C3 with immune peroxidase (*left*) and the IF method (*right*) in frozen sections

staining must be found. The sections stained by the IP-method, especially after osmium treatment, provide a permanent record. Furthermore, they can be studied with a standard light microscope.

The disadvantage of the IP-method in LM is that more incubation steps are needed than in IF. In principle, IP-methods can also be used for electron microscopic demonstration of antigens, since the reaction product of diamino-benzidine is osmiophilic [1482]. Here, the main technical problem is poor tissue penetration of the coupled sera which may be overcome by using lower molecular weight fragments of immunoglobulins and enzymes or by pretreatment of the tissue [882, 901, 945].

The incubations with immune sera and peroxidase-labeled sera are analogous to IF-methods. The following procedure for the IP-technique after incubation with the peroxidase-labeled sera has given reliable results:

1. Wash 2 × 15 min in PBS.
2. Cover with diamino-benzidine solution and incubate for 10–20 min in the dark.
   Preparation of Diamino-Benzidine Solution
   Dissolve 5 mg 3,3′-diamino-benzidine tetrahydrochloride (Sigma Chemical Co. St. Louis, Missouri, USA) in 10 ml of 0.05 mol Tris-HCl buffer (pH 7.4) and add 0.1 ml of a 1% $H_2O_2$ solution.
3. Wash for 15 min in PBS.
4. Layer with an aqueous 1% $OsO_4$ solution and incubate for 30–45 min.
5. Wash 15 min in PBS.
6. Wash briefly with aqua dest., dehydrate in the alcohol series, clear briefly in xylol and mount.
   (The usual immunologic and histochemical control incubations must be carried out regularly. See also Table 3.2.

## Morphometry Technique

A great deal of effort has been expended to find reproducible objective methods which can correlate changes in individual renal elements (glomeruli, tubules, etc.) and their structures (mesangium, BM etc.) with clinical symptomatology and functional parameters [450, 1274, 1579].

Results obtained with the + grading scale (0–4) are modest in comparison to the effort involved; its use requires very extensive experience. Easily reproducible results are obtained with morphometry, a technique rigorously limited to purely scientific investigation [404, 1624, 1705]. Nevertheless, morphometric methods can be used for renal biopsy evaluations when 7–10 glomeruli are present. Semiquantitative data agree well, in general, with those obtained quantitatively.

The following conditions must be fulfilled for morphometric examination:

1. Absolutely standardized preparation of material from fixation to embedding
2. Uniform section thickness (inscription of section thickness on slides desirable)
3. Evaluation on identically stained sections (PAS/PASM).

## Clinically Related Topics

### Normal Laboratory Values

[367, 538]

The clinically most important laboratory values [367, 538] are listed below. Some of the values are age-related, (for correlation to age, please refer to references given).

*Normal Blood (B) and Serum (S) Values*

| | |
|---|---|
| Potassium (S) | 3.4–5.2 mEq/l |
| Sodium (S) | 138–151 mEq/l |
| Calcium (S) | 4.7–5.5 mEq/l |
| Chloride (S) | 101–111 mEq/l |
| Phosphate (S) | 2.5–4.1 mEq/l |
| Glucose (B) | 50–100 mg/100 ml |
| Cholesterine (S) | 120–250 mg/100 ml |
| Triglyceride (S) | 123 ± 49 mg/100 ml |
| Beta-lipoprotein (S) | 210–400 mg/100 ml |
| Urea (S) | 10–40 mg/100 ml |
| Creatinine (S) | 0.8–129 mg/100 ml |
| Uric acid (S) | 2.9–6.9 mg/100 ml |
| Inulin clearance (Cin) | |
| ♀ | 109 ± 13.5 ml/min/1.73 m² } body |
| ♂ | 124 ± 25.8 ml/min/1.73 m² } surface |
| PAH clearance ($C_{PAH}$) | |
| ♀ | 592 ± 153 ml/min/1.73 m² } body |
| ♂ | 654 ± 163 ml/min/1.73 m² } surface |
| Creatinine clearance ($C_{CR}$) | > 80–90 ml |
| Protein (S) | |
| Total | 6.6–7.9 g/100 ml |
| Albumin | 3.7–4.5 g/100 ml |
| Globulin (total) | 2.5–3.6 g/100 ml |
| Alpha$_1$-globulin | 0.25–0.46 g/100 ml |
| Alpha$_2$-globulin | 0.60–0.81 g/100 ml |
| Beta-globulin | 0.76–0.97 g/100 ml |
| Gamma-globulin | 1.2–1.42 g/100 ml |
| IgG | 1143 ± 235 mg/100 ml |
| IgA | 204 ± 85 mg/100 ml |
| IgM | 72 ± 23 mg/100 ml |
| Fibrinogen | 440 ± 150 mg/100 ml |
| Complement Fractions [1397] | |
| C1q | 19 mg/100 ml |
| C2 | 3 mg/100 ml |
| C3 | 130 mg/100 ml |
| C4 | 43 mg/100 ml |

*Normal Blood (B) and Serum (S) Values*

*Normal Urine Values*

| | |
|---|---|
| Volume | 500–2000 ml/24 h |
| Osmolarity | 33–1300 mosm/kg/water |
| Specific gravity | 1005–1035 |
| Protein (Biuret/Kjeldahl method) | 250 mg/24 h |
| Blood cells (visualfield [VF] using 40 × objective) | |
| Erythrocytes | 100–2000/min (≦2 per VF) |
| Leukocytes | 500–4000/min (≦4 per VF) |
| Casts: | |
| hyaline casts | No pathologic significance, also found in healthy individuals |
| granular, wax and cell casts | pathologic, disease of renal parenchyma |
| Bacteria | 0 (< 100,000/ml = contamination possible, > 100,000/ml, pathologic; attention with female patients as spontaneous urine contamination possible) |

All values obtained from laboratories should be accompanied by the laboratories' normal values which tend to vary from laboratory to laboratory [655, 1325].

**Collecting, Summarizing and Processing of Data** [101, 1381]

To assure optimal scientific evaluation as well as maximally accurate diagnosis, the most comprehensive anamnestic, clinical and laboratory biopsy information should be available to the pathologist. For data collection, we use appropriate coding sheets developed from extensive system analysis which allow registration of 170 anamnestic, clinical and laboratory items which can be used for preparing the corresponding punch cards for ultimate electronic data processing.

Appropriate coding sheets are also available for pathologic and follow-up data (90 parameters for LM, 110 for EM, 200 for IF and 50 for therapy and follow-up). These procedures guarantee complete coverage of a case, i.e., from the familial history to pathological findings to follow-up of the patient.

# 4. Histology of Normal Kidney Tissue

[1575]

***Definition.*** Normal kidney tissue consists of unchanged nephrons (glomeruli and tubules), vessels and interstitium, reveals unchanged BM and mesangium upon examination with EM and is IF-negative.

Since the trajectory of a needle biopsy is not exactly parallel to the renal segments, cylinders of kidney tissue often contain elements of the medullary rays and collecting ducts in addition to cortical structures (glomeruli, proximal and distal, convoluted tubules) (Fig. 4.1, [317]).

## Glomerulus

(Figs. 4.2, 4.3, 4.13)

Upon entering Bowman's capsule, the vas afferens divides into two to five (rarely more) branches which form a network of anastomizing capillary loops which are arranged in lobuli. The mesangium is a supporting structure for the capillary loops and is spread out between them (Figs. 4.5, 4.6). The loops are covered externally by flat podocytes (visceral epithelium). The podocytes of infants and small children are cubic (Fig. 4.4).

The convolute of capillary loops is enveloped by Bowman's capsule which consists of a thick BM and a parietal (capsular) epithelium. In male children, the epithelium of the proximal convoluted tubules often projects into the capsular space (fetal glomerular development: [1662]).

### Capillary Loop Content

Normally, only a few erythrocytes are found in the capillary loops since glomeruli generally loose their blood during needle biopsy. No more than six leukocytes per glomerulus are encountered in thin sections (2 μm) of normal kidney tissue. Under EM, we have observed fibrin fibers in the loops of one normal biopsy obtained by surgery.

### Basement Membrane

The BM is morphologically the most important element of the glomerulus. It is chiefly studied with the PAS or PASM stain (Figs. 4.2, 4.13). In tangential sections only, the BM appears to completely envelop the loop lumens. Actually, the lumen of each loop borders in the region of the glomerular stalk on a mesangial cell which is covered by endothelium (Fig. 4.2). In some instances, mesangial matrix bars may be interposed between the endothelium and mesangial cell which, however, do not become entirely separated by the bars.

The mesangial cell is covered externally by the BM itself which procedes to the next loop. In the region of contact between mesangium and BM, the BM is irregular (Fig. 4.7) and the lamina rara interna merges gradually with the mesangial matrix (the basement membrane-like substance of the mesangium), while the lamina densa and lamina rara externa remain intact [926].

The BM appears five times wider in LM than in EM. This means that LM stains cause staining of cytoplasmic elements of endothelial and epithelial cells, a fact which would explain the BM thickness observed under LM [1508]. Fusion of podocyte foot processes does not lead to discernable BM thickening under LM. As viewed with EM, the total thickness of the vertically cut BM amounts to about 1100 Å (0.11 μm) for children and 2700–3500 Å (0.27–0.35 μm) for adults [341, 1108, 1154, 1536].

The electron opaque lamina densa (Figs. 4.7, 4.8) is bordered subendothelially by the neutral polysaccharide-rich lamina rara interna, (ca. 300 Å) and subepithelially by the predominantly acid mucopolysaccharide-containing lamina rara externa (ca. 600 Å) [1119]. The lamina rara interna along the mesangium is usually loosened (Fig. 4.11). Chemically, the BM consists of 90% protein (58% collagenous and 42% noncollagenous protein); the amino acid composition of BM protein is strikingly similar in various animal species. BM collagen differs from tendon collagen in its high content of hydroxylysine, in the presence of cystine which is absent in tendon collagen and in its lower content of glycine [1575]. The other constituents of BM are carbohydrates (8%) and lipids (2%) [132, 204, 925, 1108, 1376, 1575].

From the physico-chemical point of view, the BM represents a thixotropic gel, a state allowing cell passage through the BM and its subsequent immediate closure. A crystalloid structure of the lamina densa has been postulated but not proven [1658].

Changes in chemical structure of the BM in GN have been shown but the relevant reports have not been

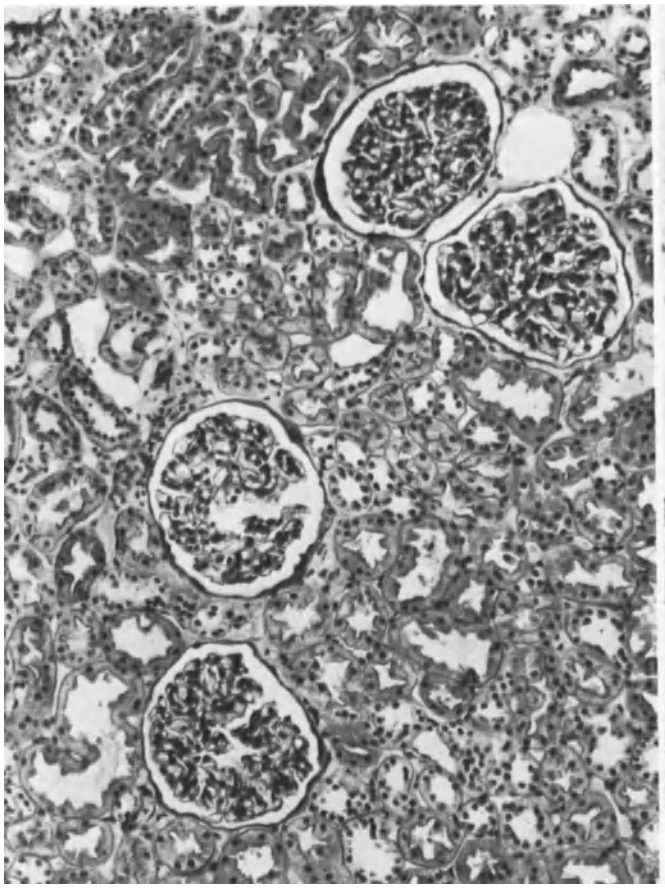


**Fig. 4.1.** Normal renal cortical tissue. Male, 62 years. PAS (×146)

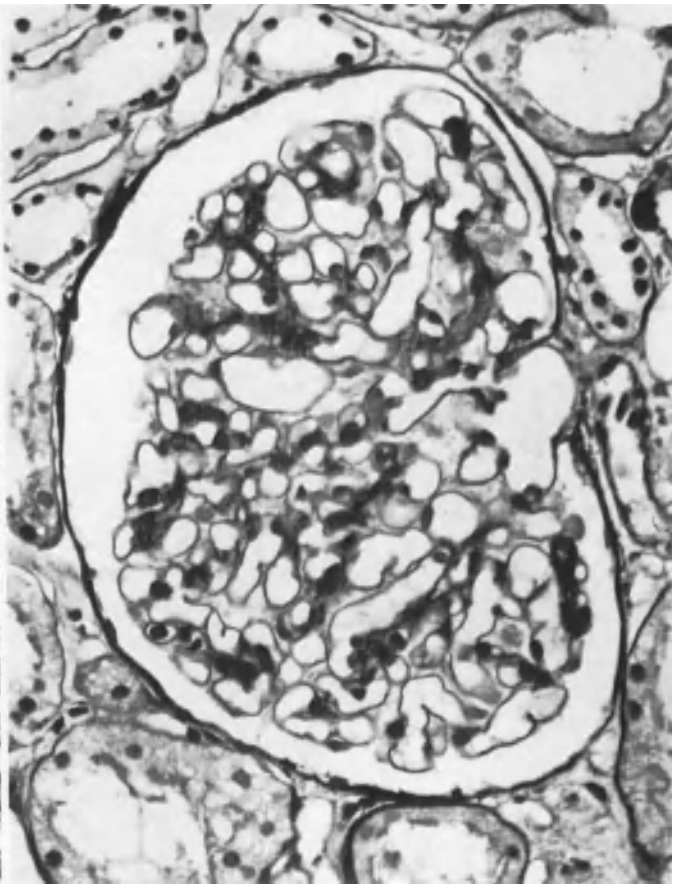


**Fig. 4.2.** Normal glomerulus obtained at liver biopsy. Male, 62 years. PAS (×440)

uniform [996, 1108]. They especially involve the collagen and lipid constituents. In chronic GN, a decrease in the disaccharide content of BM has also been reported [996].

Within a week after transplantation, the BM evidences a considerable increase in lipids and a slight change in carbohydrates. No changes in BM chemical structure have so far been detected in diabetes mellitus [1108].

In fetal life, both the podocyte and endothelium appear to participate in formation of the BM [154] while in later life it is chiefly the podocyte [1108, 1680, 1681], although minor components may be formed by the endothelium at this time too [1681]. A participation in BM formation by the mesangium is probable [1577] especially in the presence of inflammatory reactions [1226]. The endothelium clearly participates in the formation of the BM in pathologic processes [154, 1108, 1109, 1805].

The turnover of the BM in adulthood is unknown. It is reported to be 60 days for the rat [1382] and longer than 145 days for the mouse BM [212]; these values cannot be adopted for man. Mesangial cells, endothelium and epithelium probably participate in a permanent breakdown of BM [1681].

***Function.*** The BM is an essential component of the glomerular filter. It has been possible to show with different tracer techniques (dextrans of various molecular weights, ferritin, peroxidase etc.) that low-weight molecules (<60,000 Daltons) pass unimpeded through the BM. Permeability decreases with increasing molecular weight. The BM filtering process may be due either to rigid pores of various sizes or to a fibrillar network embedded in a gel (pore equivalents of 20–80 Å: [259, 459a, 1320, 1442, 1575]).

## Podocytes

The podocytes (visceral epithelium, Figs. 4.6, 4.9, 4.10) appear as cells with multiple pseudopod-like processes under EM; their nuclei are larger than those of the endothelium and their chromatin structure is looser [1065]. In thin LM sections, the foot processes so clearly seen with EM are just discernable. The interdigitating foot processes appear very prominently with scanning EM (Figs. 4.9, 4.10). The spaces between two foot processes measure about 550 Å (filtrating slit pores:

[1633]). These are covered by a 50 Å-thick slit membrane [1536]. The fine granular cytoplasm contains moderate amounts of endoplasmatic reticulum, a well-developed Golgi apparatus, few mitochondria and occassionally lysosomes, microtubuli and pinocytic vacuoles. Further, bundles of fibrils with a diameter of 50–80 Å are found diffusely distributed under the cytoplasmic membrane (the so-called osmiophilic substance). These bundles are usually accumulated in the foot processes (Fig. 4.8) and are especially prominent in cellular edema. They are reminiscent of myofibrils [925, 1633, 1777] and are, perhaps, the morphological substrate of cellular motility, a notion supported by the demonstration of spontaneous glomerular contraction in vitro [137]. The possibility of podocytic contraction acting as a fluid pump has also been advanced [454]. The fibrils (osmophilic substance) of the podocytes near the BM are strongly increased in proliferative processes (possible increased BM formation: [1109]).

In the cysterns of the endoplasmatic reticulum, PAS positive condensates have been demonstrated and have been interpreted as condensation products and precursors of BM substance [1610, 1231].

Rarely, podocytes also contain cylindrical structures (max. $4.5 \times 0.5$ µm) which consist of up to 20 parallel lamella. Their significance is not known [1664].

***Function.*** Podocytes are responsible for the synthesis and possibly partly for the catabolism of peripheral BM (see p. 22). By incorporation of $H^3$-labeled proline in cell cultures, they have been shown to form extracellular basal lamellae within 24 h. They are also thought to be involved in the reabsorption of macromolecular material [259]. Podocytes are considered to act as a barrier to passage of molecules of 160,000–180,000 Daltons; they are easily permeable to molecules of 40,000 Daltons [1575]. Smaller molecular compounds are supposed to pass through the foot processes [1536]. The slit pores appear to partially restrain passage of smaller molecules and immunocomplexes [809, 819, 1628]. The role of the glycocalix (glycoprotein layer over the slit pore) in this process is unknown [1481].

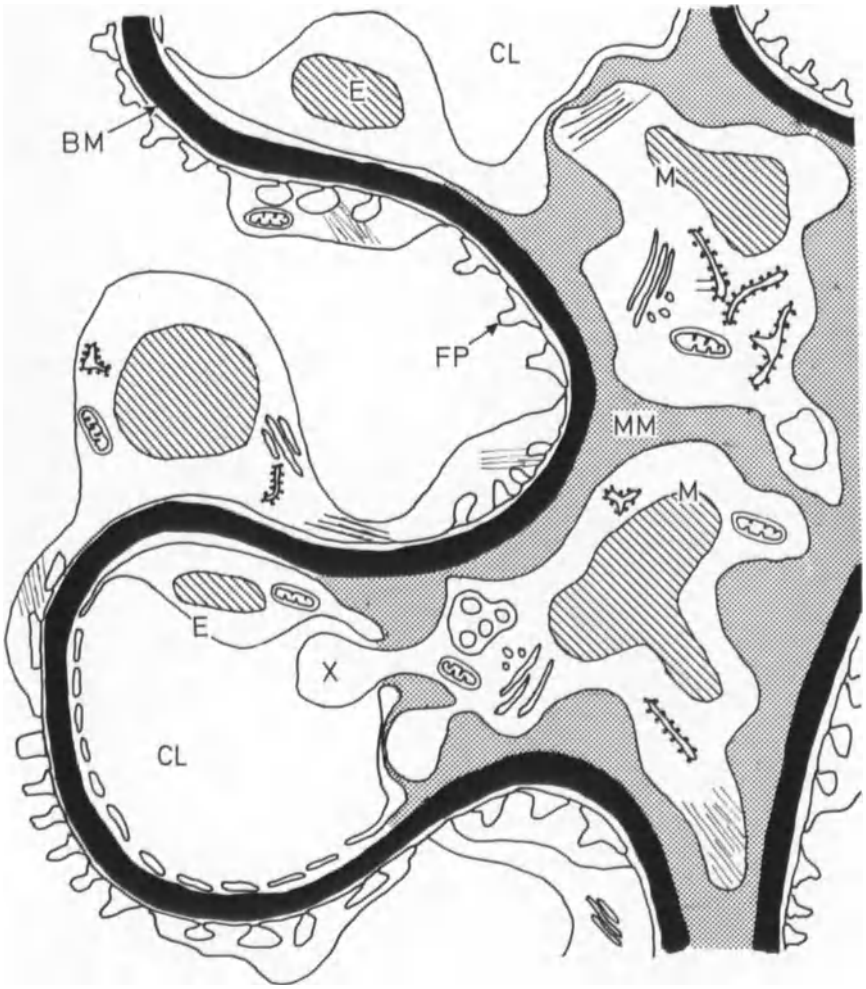
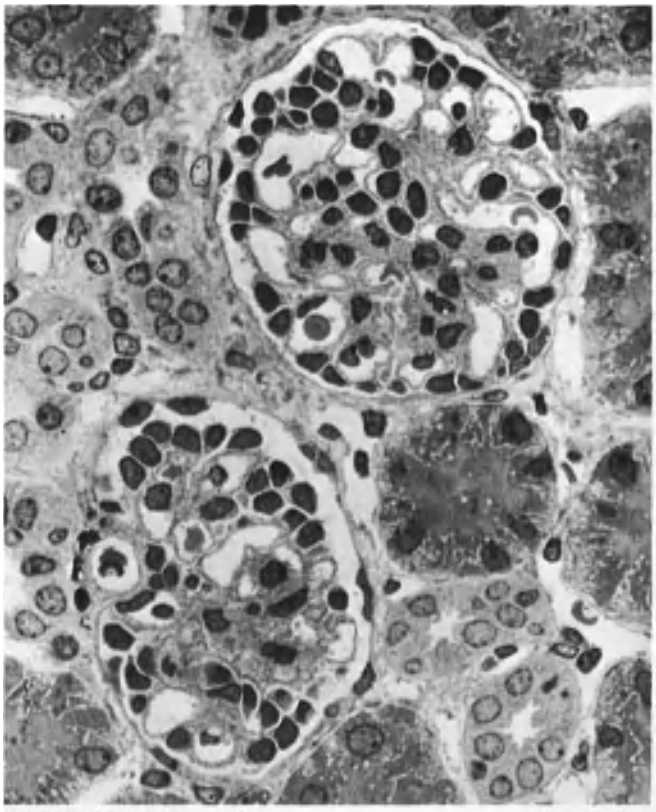
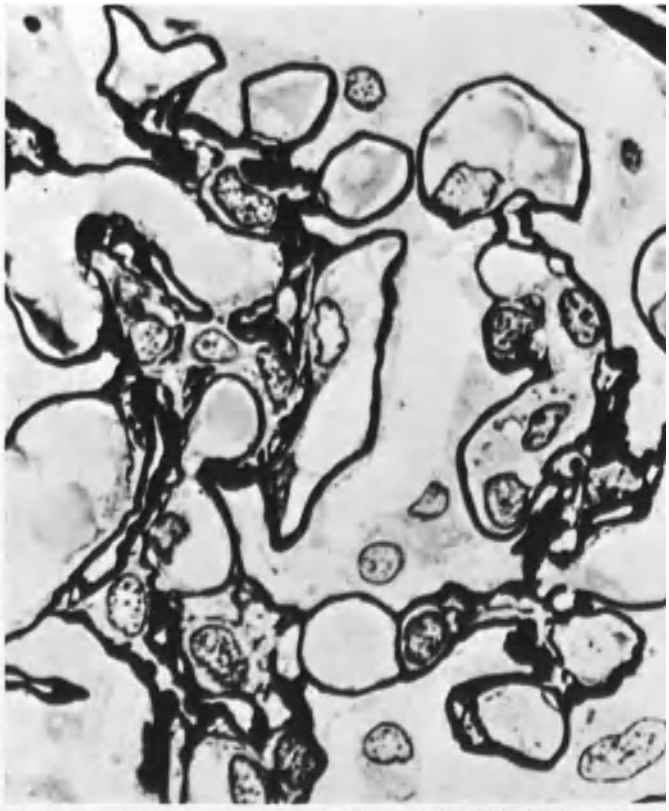
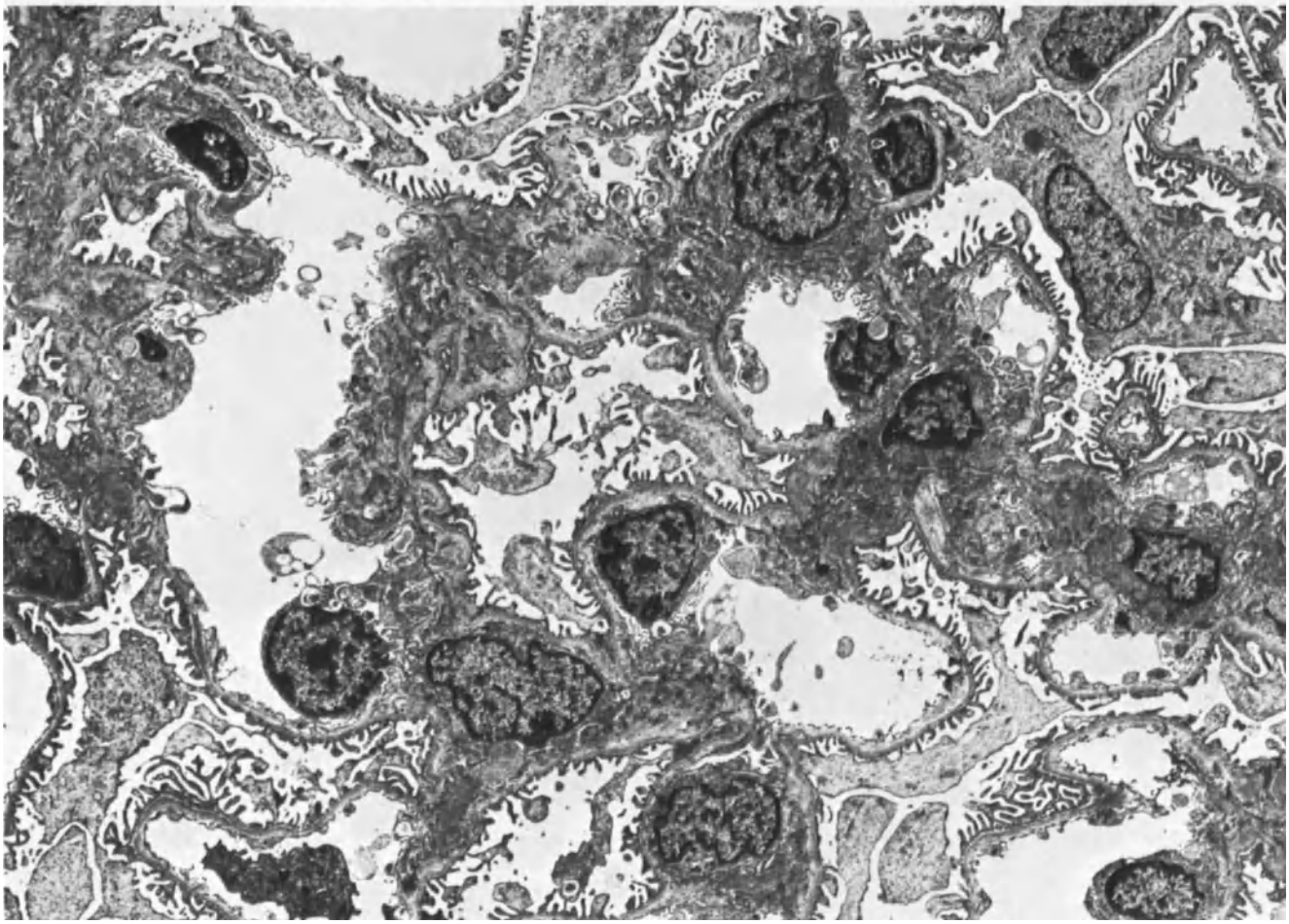



**Fig. 4.3.** Schematic representation of a glomerular capillary loop and adjacent mesangium. Mesangial cell (*M*), endothelium (*E*) podocyte with foot processes (*FP*), capillary lumen (*CL*) capillary protuberance (*X*), mesangial matrix (*MM*), basement membrane (*BM*)





4.4
4.5



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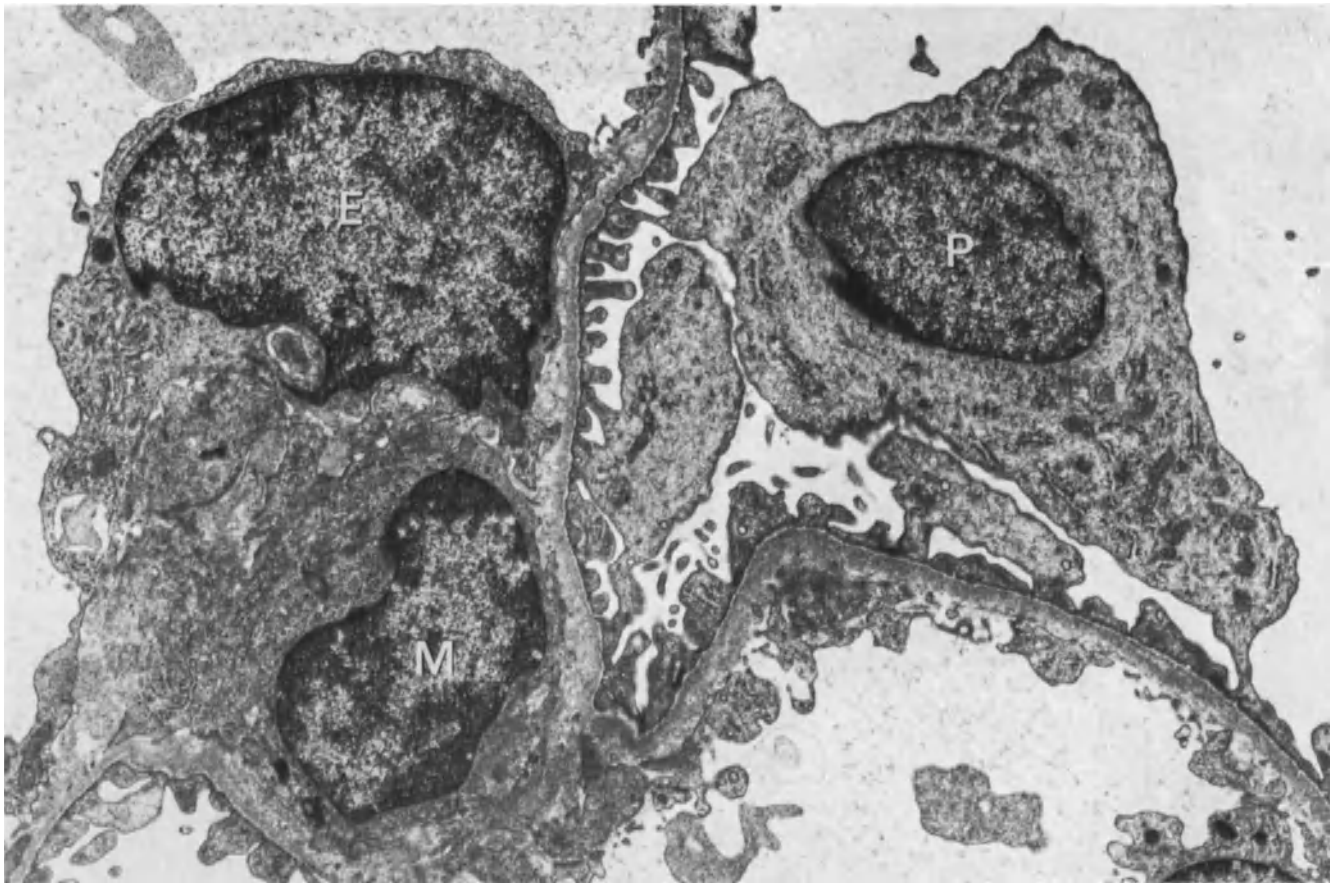



**Fig. 4.7.** The three glomerular cell types: Endothelial cell (*E*), mesangial cell (*M*) separated from endothelium by BM-like material, and podocyte (*P*) with foot processes. Female, 16 years. EM (×9000)

## Endothelium

Endothelial cells (Figs. 4.6, 4.7; see also p. 30) are about as numerous as the podocytes [745]. They cover the inner aspect of capillary loops by a flat cytoplasmic, often fenestrated layer (diameter of fenestrae: 1000 Å). The cytoplasm contains only a few organelles and a very scanty endoplasmatic reticulum; the nuclei are a little smaller and more compact than those of the podocytes.

◁ **Fig. 4.4.** Normal glomerulus with characteristic cubic podocytes of 1-year-old boy. Semi-thin section, toluidine blue (×300)

**Fig. 4.5.** Mesangium and capillary loops of a normal glomerulus. Note very scanty amount of argyrophilic matrix in mesangium. Semi-thin section. Male, 25 years. PASM (×1200)

**Fig. 4.6.** Part of a normal glomerulus with almost empty capillary loops. Endothelium (*E*) and mesangial cells (*M*) are not hypertrophied. Podocytes (*P*) are not swollen and the foot processes are very well preserved. Female, 20 years. EM (×2700)

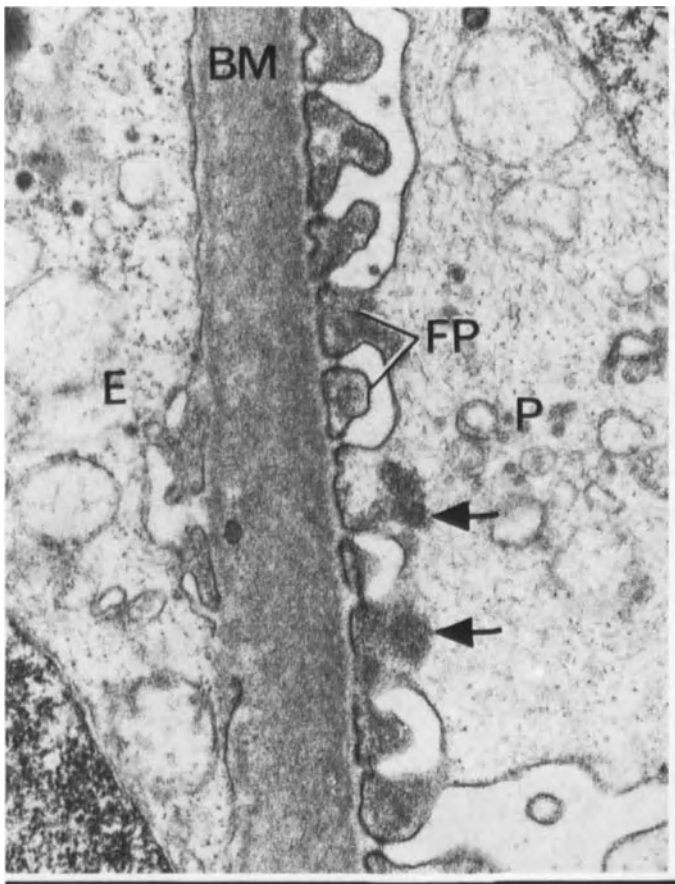
***Function.*** The endothelial cells form a barrier to other cells and large-sized particles [1575].

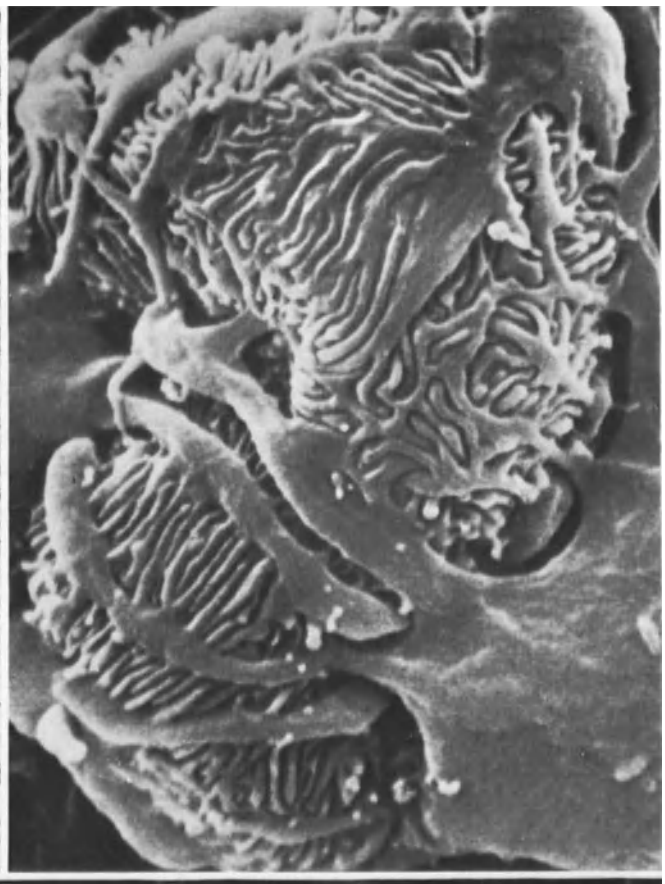
Large molecules can reach the BM cytopemtically through the endothelial cells [1077]. The significance of the protective role of the endothelium in preventing direct contact between thrombocytes and BM—and thus hindering thrombus formation—is controversial. Some authors accept the concept [723] and others reject it [723].

Endothelial cells are also important for fibrinolysis [1690] as attested by the extensive reduction of fibrinolysis and formation of fibrin deposits in the presence of endothelial injury. For additional details see p. 502.

## Mesangium

The significance of the fourth structural element of the glomerulus, the mesangium [1476], is still the least understood (Figs. 4.6, 4.7). It consists of stellate cells (stalk cells, intercapillary cells [1665]) and of a net of matrix formed by them (Fig. 4.11). The matrix is a BM-like substance and, according to others, also contains acto-



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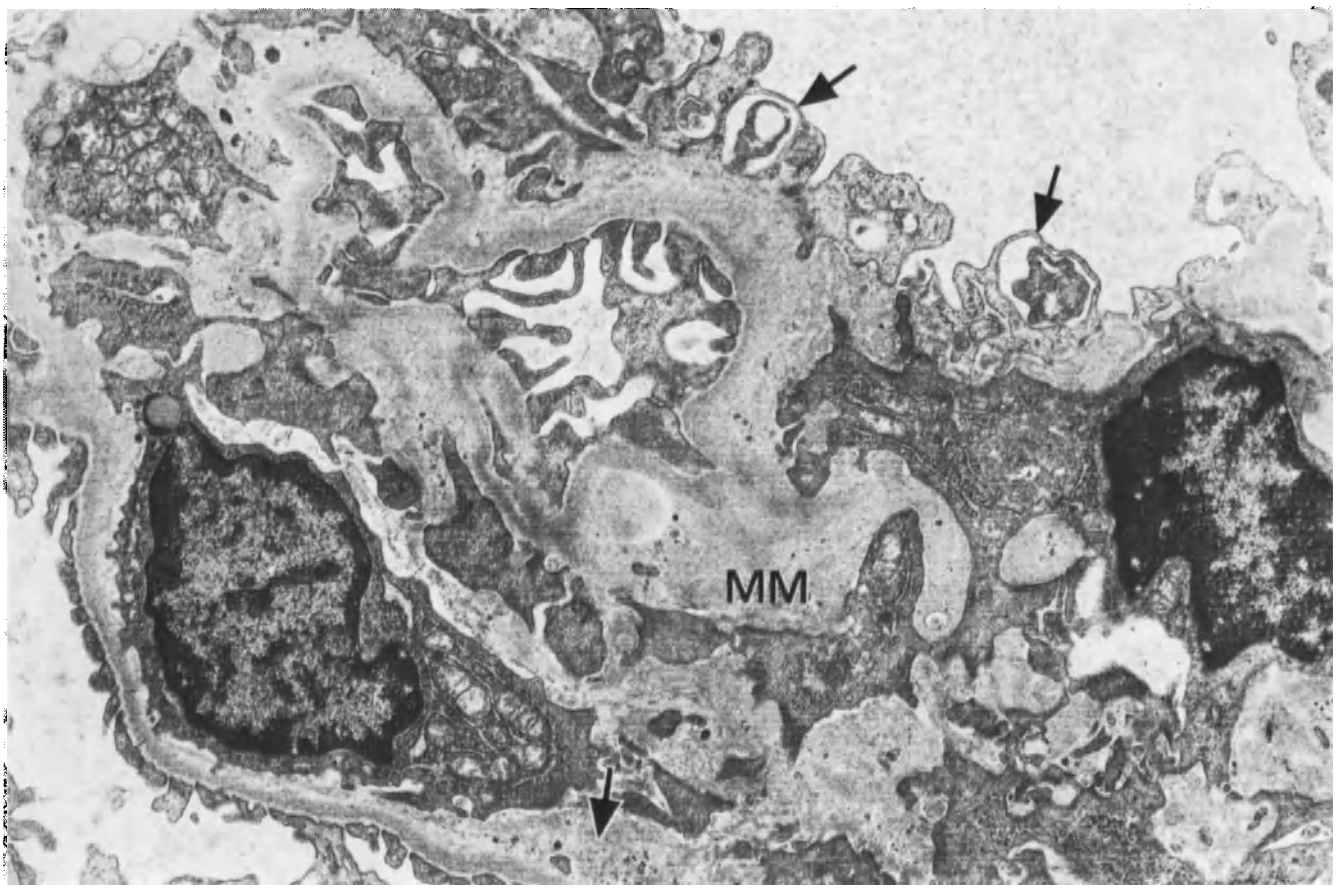



**Fig. 4.11.** Normal glomerulus with capillary protuberance (→) projecting into capillary lumen. Mesangial matrix (*MM*) and BM along mesangium (→*at bottom*) are loosened, and the mesangial matrix evidences scattered degenerative granules. Male, 38 years. EM (×10,800)

◁ **Fig. 4.8.** Part of normal peripheral glomerular loop. Endothelium (*E*), podocyte (*P*), foot processes (*FP*) of a podocyte with moderately rich fibrillar osmiophilic substance (→). The three layers of the BM are clearly discernible: narrow subendothelial lamina rara interna, wide osmiophilic lamina densa, and narrow lamina rara externa immediately under foot processes. Slit-membrane is evident between the foot processes. Male, 8 years. EM (×28,000)

**Fig. 4.9.** Compare Figure 4.10; podocytes with interdigitating foot processes of different order. Scanning EM (×9150)

**Fig. 4.10.** Scanning EM micrograph of glomerulus with clearly recognizable loops covered with podocytes and their foot processes of different order (×2400). We are indebted to Dr. Spinelli, Basle, for this photograph

myosin [1434]. Mesangial cells constitute $^1/_4$–$^1/_3$ of all glomerular cells (see p. 28 and [745]).

As observed in LM, the mesangial cells are enveloped with PAS- and PASM-stainable matrix and BM except in the region of the capillary protuberances where they lay directly on the endothelium or even project into the capillary lumen (Figs. 4.6, 4.11). Their darker cytoplasm sets them off from endothelial cells.

Under EM, microfilaments are distinguishable both in the perinuclear cytoplasm and cell processes of the mesangial cells. These microfilaments are thought to consist of actomyosin [104], other cellular microtubuli, and a large amount of ribosomes [1093]. The endoplasmatic reticulum is considerably more developed than that of the endothelial cells. Unfortunately, however, this feature hardly simplifies the problem of differentiating the two cell types in the presence of proliferative reactions in which all differences can disappear.

The Golgi apparatus is also well developed, but lysosomes are scarce. A few of the pseudopod-like cell processes can extend as far as into the loop lumen (Fig. 4.11). Capillary protuberances are possibly osmoreceptors (see also [1080, 1093].

The mesangial nuclei are slightly notched. We feel that significant notching of the nuclei indicates activation (see also [213, 1284, 1620]).
The mesangial matrix can be rendered visible for LM work with the PAS and PASM stain. The total surface of the mesangium (i.e., of the cells and matrix) is a very important diagnostic parameter and it can only be reliably evaluated on tissue embedded in paraplast or synthetics impregnated with PASM and sectioned to 2–3 μm. In evaluating total surface, it is important to bear in mind that the mesangium becomes substantially wider with increasing age. Thus, even in the small glomeruli of the newborn, the total mesangial surface amounts to 6.2% of glomerular sectional area and to 10.4% in the elderly [1702], (for an opposing view, see [404]; see also Table 4.2, p. 22). The mesangial matrix makes up 48% of the total mesangial surface area [1230]. In evaluating the mesangium, it is important to acertain that the wall of the ampulla glomeruli (infundibulum), which is located at the point of entrance of the vas afferens into the glomerulus, is wider than the mesangium usually is at the periphery.
Another important mesangial diagnostic parameter has proven to be the number of mesangial cells per mesangial area. We have found with LM that not more than 10% of the glomeruli have more than three mesangial cells per mesangial area.

***Function.*** In addition to the purely supportive role of the mesangium (cells and matrix), the clearance of filtration residues is of great functional importance [259]. Mesangial cells are viewed by many workers as macrophages since they can contain phagolysosomes [1093] and it is a well-documented fact that isolated lipid and protein droplets are found in the mesangium of 'normal' kidneys in individuals over 30 years of age [111].
The matrix is also characterized as a "mesangial space" [1476] communicating with the subendothelial space and especially so in the region not covered by BM. Large molecular substances, e.g., ferritin [461], thorotrast [926] and small molecular substances, e.g., horseradish-peroxidase [589], aggregated gamma globulin [1027, 1028], dextranes [259], proteins [1077] and immunocomplexes can, following their experimental administration, pass within a few minutes into the mesangium where they are either passed on through intercellular channels or phagocytized by mesangial cells.
A transmitter function (possibly via pressure or electrolyte concentration) between the capillary lumen and the juxtaglomerular apparatus has also been ascribed to the mesangium [1089].
Interpretation of intracellular fibrils as myofibrils [101] and the occurrence of glomerular contraction in vitro [1575] has led some workers to regard mesangial cells as myogenous elements [1434a].
Finally, the mesangial cells form the BM continguous with them (Fig. 4.11) as well as the surrounding matrix which, due to its chemical structure [1575] and antigenicity [1476], seem to differ from the matrix of the peripheral glomerular BM.

**Bowman's Capsule**

Capsular epithelium (parietal epithelium) is normally single layered. Capsular epithelial cells are rich in organelles. The tubular epithelium can extend into the capsule especially so in young males under 15 years of age (♂:♀ = 2.5:1). Capsular BM of normal kidneys is not infrequently unevenly thick and occasionally split (4 out of 12:Z). Additionally, BM thickness increases with age [341]. We have rarely observed deposits in the capsular BM of normal kidneys.

## Obsolescent Glomeruli

A few scattered obsolescent (hyaline) glomeruli with associated atrophy of their tubules, interstitial fibrosis and sporadic lymphocytic infiltrates are present in almost every kidney, especially in those of small children and the aged [341] (Table 4.1). Obsolescent glomeruli are more frequently found in the subcapsular areas than in the juxtamedullary (contra: [802]). The percentage of incidence varies between 3.6% and 0.35%.
Except in infants below 2 years of age, we did not find more than two obsolescent glomeruli per visual field containing 10 glomeruli each in the normal kidney. Anything exceeding this in individuals $>2$, $<70$ years of age must be considered pathologic [802]. It is reasonable to assume, therefore, that glomeruli which become obsolescent during childhood ultimately disappear.
The reason for such obsolescence is obscure; it may be attributable to physiologic involution or to the result of summated minimal injuries incurred during life [508].

## Glomerular Morphometry

Average values obtained by morphometric study of the glomerulus in homogenous material [1624] are given in Table 4.2. These values were obtained on 1–2 μm thick sections of autopsy material; they are comparable to thin (3 μm) paraplast sections obtained from biopsy material.
Values for the glomerular diameter slightly different from those given in Table 4.2 have been reported by other investigators: e.g. a glomerular diameter of

Table 4.1. Frequency of obsolescent glomeruli in the normal kidney

| Age group (years) | <2 | 3–10 | 20–30 | 60–70 |
|---|---|---|---|---|
| Number of cases investigated | 4 | 4 | 4 | 4 |
| Number of glomeruli per case ($\bar{x}$, SD) | 622±118 | 731±144 | 422±151 | 291±82 |
| Total number of glomeruli | 2489 | 2927 | 1521 | 1164 |
| Obsolescent glomeruli in % of total glomeruli/case ($\bar{x}$, SD) | 3.6±6.8 | 0.35±0.24 | 0.92±0.63 | 3.57±2.88 |
| Number of glomeruli per visual field ($\bar{x}$, SD) | 10.5±2.2 | 9.5±1.7 | 10.8±2.5 | 7.7±1.6 |
| % visual fields with obsolescent glomeruli | | | | |
| Subcapsular | 23[a] | 4.5[b] | 7.9[b] | 31.9[a] |
| Juxtamedullary | 9.4 | 0.7 | 11.3 | 13.6 |
| % visual fields without obsolescent glomeruli | 82.4 | 97.2 | 90.5 | 77.0 |
| % visual fields with: | | | | |
| One obsolescent glomerulus | 9.2 | 2.1 | 7.8 | 21.6 |
| Two obsolescent glomeruli | 4.6 | 0.7 | 1.7 | 1.4 |
| Three or more obsolescent glomeruli | 3.8 | – | – | – |
| Number of glomeruli per visual field with three or more obsolescent glomeruli | ~10 | >65 | >65 | >15 |

VF = visual field.
[a] Indicates significant difference between subcapsular and juxtamedullary zone ($\chi^2$-Test).
[b] Not significant.

Table 4.2. Average values for morphometric parameters determined on human kidneys [140, 675, 1624]

| | Autopsy material<br>Methyl metacrylate. Section thickness: 1–2 µm<br>Fixation in 4% formalin. CAB[a]/PASM stains | | | Biopsy material<br>Paraplast. Section thickness: 2–3 µm.<br>Fixation in 4% formalin. PAS stain | | |
|---|---|---|---|---|---|---|
| Age (years) | Children 5–10 ($n$=5) | Adults 20–30 ($n$=5) | Adults 65–80 ($n$=5) | Children 3–9 ($n$=5) | Adults 17–30 ($n$=5) | Adults 51–55 ($n$=3) |
| Number of glomerular sections per mm² of renal cortex | 6.6 | 2.6 | 2.5 | – | – | – |
| Glomerular diameter in µm (in three dimensions) | 161 SD 22 | 217 SD 17 | 218 SD 30 | – | – | – |
| Mesangial area per glomerular unit area in % | 13 | 16 | 15 | 13 | 14 | 16 |
| Number of nuclei per glomerular section area (diameter 150 µm) | 80 | 48 | 44 | 147 | 102 | 107 |
| Glomerular capillary lenght for kidney (km) | 8.7 | 14.4 | 9.9 | – | – | – |
| Glomerular basement membrane surface area for one kidney (m²) | 0.46 | 0.64 | 0.43 | – | – | – |
| Capillary area per glomerular unit surface area (%) | 33 | 36 | 33 | | | |

[a] Chromotrope anilin blue stain.

205–255 µm for adults and 150 µm for children [1494] and 160 µm for adults and 116 µm for children [738]. These relatively slight differences are ascribable to the considerable variation in glomerular size in the various age groups [418, 1624].

Capillary length of all glomeruli in a kidney shows a very high degree of variation which is a direct function of age (Table 4.2). The surface area of glomerular BM amounts to 0.43–0.64 m² per kidney (see also [404]). Podocytes account for 36–43% of glomerular cells, endothe-

lial cells for 32–34% and mesangial cells for 25–30% [745, 1494, 1533]. For different values: [1705], children: [1341], note that differentiation between endothelial and mesangial cells is problematic and, in the presence of pathologic processes, scarcely possible.

## Juxtaglomerular Apparatus
[1217, 1616]

The juxtaglomerular apparatus (JGA, Figs. 4.12, 4.13, 4.14, 4.15, 4.16) is the structure of contact between the vessels and tubules. It plays an essential role in the regulation of hemodynamics.
The histologic elements of the JGA are vas afferens, vas efferens, Goormaghtigh's cell group and macula densa. Capillaries are regularly found in close proximity of these JGA elements [448, 1089, 1383].

### Vas Afferens

The vas afferens demonstrates epitheloid cells = modified smooth muscle cells (Fig. 4.16) – as well as smooth muscle cells themselves. The epitheloid cells are larger, polymorphic, and possess larger nuclei than the other myocytes of the arteriolar tunica media. They are characterized by cytoplasmic granules (Fig. 4.16) in which renin activity has been demonstrated [305, 1437]. The cytoplasm is richly endowed with cellular organelles, which is characteristic of active secretory cells i.e. rough endoplasmatic reticulum and Golgi complexes with protosecretion granules and specific secretion granules which often display crystalline structure. Additionally, lipofuscin granules – due to their irregular form and inhomogenous contents – are clearly differentiable ultrastructurally from secretion granules (Fig. 4.16). Transitional forms between the two have been described [1383]. Using special LM staining techniques, granules containing renin cannot be differentiated with certainty from lipofuscin. Immunohistologic procedures are also problematical since highly purified renin preparations for antibody production are not available. Because of this problem, most workers use cell number or surface size of the JGA as parameters for evaluating diseased tissue (for literature on morphometry of the JGA see [1089]).

### Vas Efferens

The vas efferens usually has a wider lumen and thinner wall than the vas afferens. In addition to smooth muscle cells, an occasional epitheloid cell is encountered in its wall.

### Goormaghtigh's Cell Group

Goormaghtigh's cell group is found in the wedge between the vas afferens, vas efferens, and the macula densa. This structure consists of small cells with extensively branching cytoplasmic processes which are embedded in a BM-like substance (Fig. 4.13). The cytoplasm contains the same organelles encountered in epithelioid cells; secretion granules, however, are rarely found. The cell group merges imperceptibly with the glomerular mesangium. As in the wall of the vas afferens, unmyelinated nerve fibers are regularly observed.

### Macula Densa

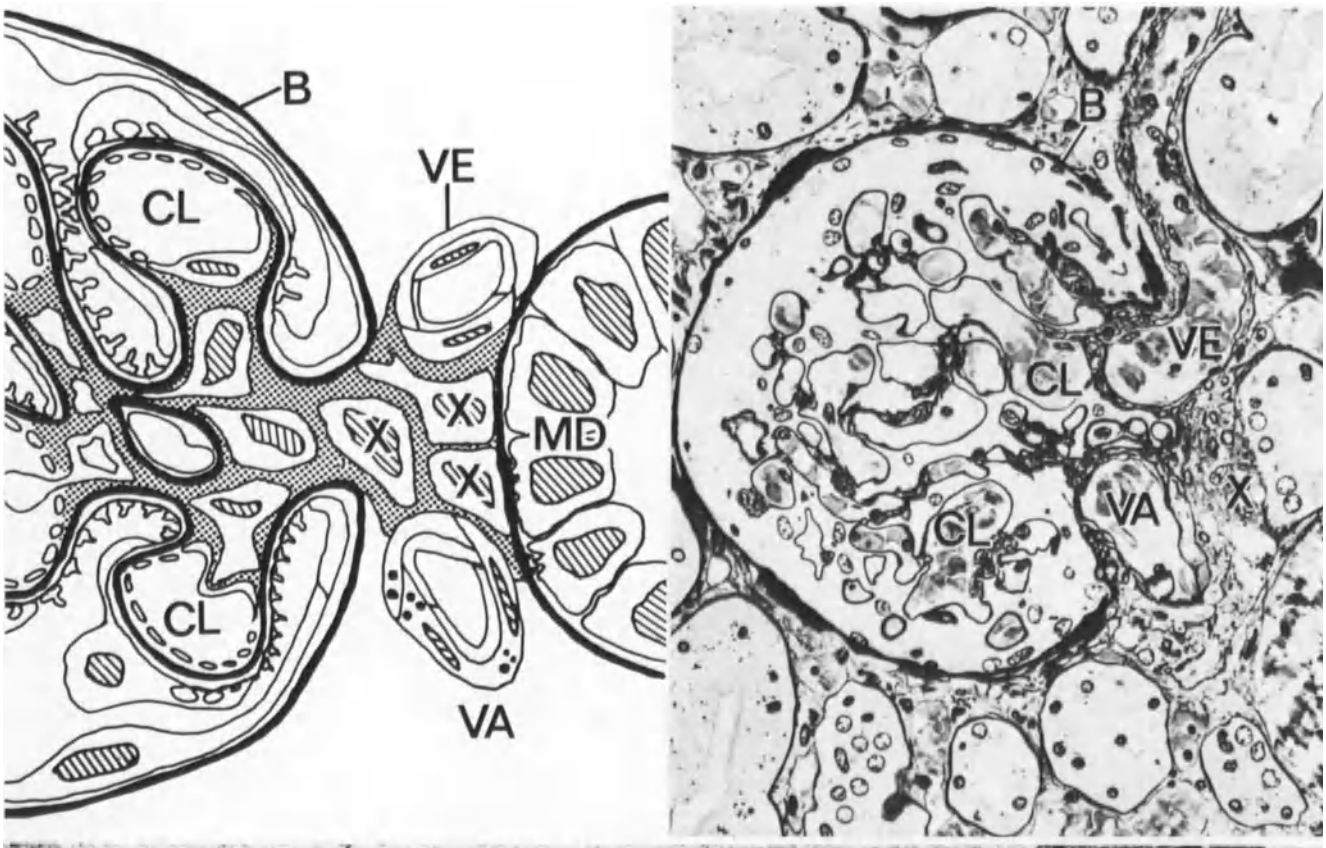
The macula densa is a specialized structure of the distal tubule. It is in (contiguous) contact with the vas afferens, Goormaghtigh's cell group and vas efferens. At this point of contact, the tubular BM merges with the BM-like substance which forms the common interstitium for both vessels and for the Goormaghtigh cell group (Figs. 4.13, 4.14). Here and there, basal tubular epithelial processes come into direct contact with Goormaghtigh's cells.
The cells of the macula densa differ from neighboring cells of the distal tubule in having less cytoplasm, a less pronouncedly developed basal labyrinth, and smaller and less regularly arranged mitochondria. Other cell organelles do not have any special characteristics. The size of the nuclei is equal to that of neighboring tubular cells.

Despite very extensive research devoted to discovering the immediate stimulus which activates the JGA, the problem has remained unsolved. Pressure, volume and ionic composition of the blood in the vas afferens and the ionic composition in the cells of the macula densa have been proposed as triggering mechanisms for JGA activation [170, 368, 1089, 1616].

**Fig. 4.12.** Schematic presentation of juxtaglomerular apparatus. ▷ Macula densa (*MD*), vas afferens (*VA*) with granulated myoepithelial cells, vas efferens (*VE*), Goormaghtigh cell group (*X*), capillary loop lumen (*CL*), Bowman's capsule (*B*) with BM and capsular epithelium

**Fig. 4.13.** Juxtaglomerular apparatus of normal kidney. For abbreviations see Figure 4.12. Male, 21 years. Semi-thin section, PASM (×330)

**Fig. 4.14.** Part of juxtaglomerular apparatus of a normal kidney: macula densa (*MD*), Goormaghtigh cells (*X*) and myoepithelial cells (*MY*) with lipofuscin granules. Female, 29 years. EM (×5100)

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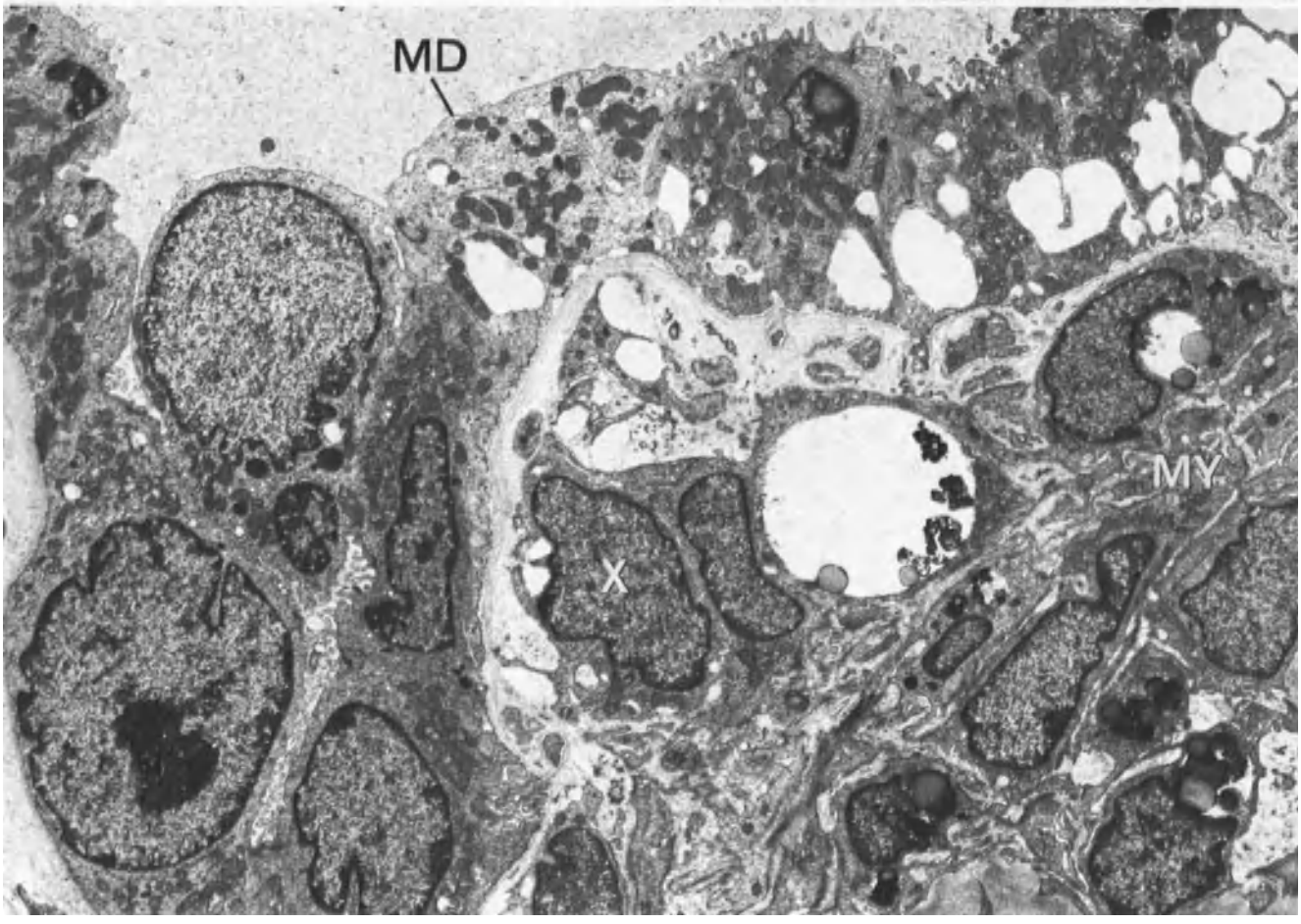


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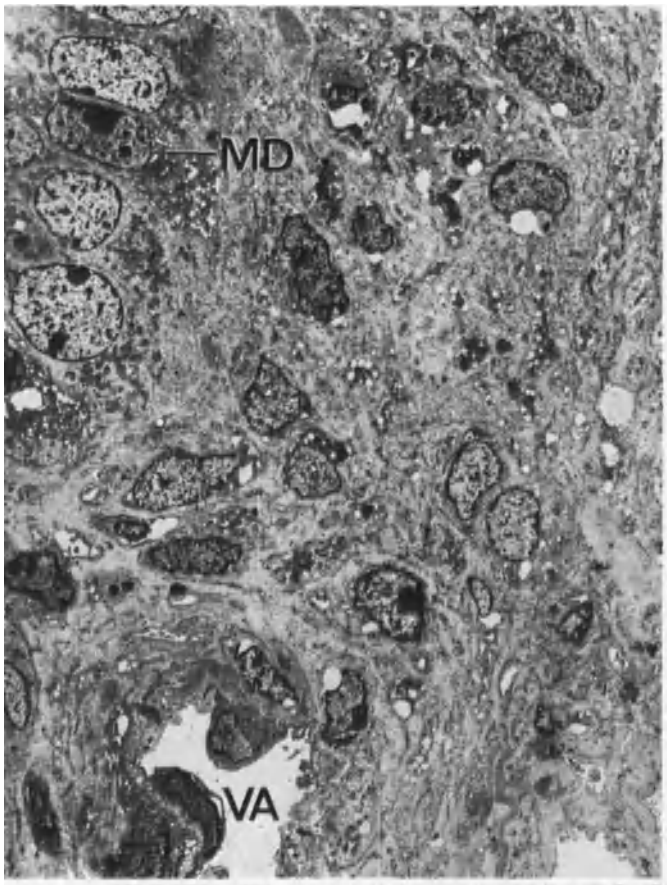


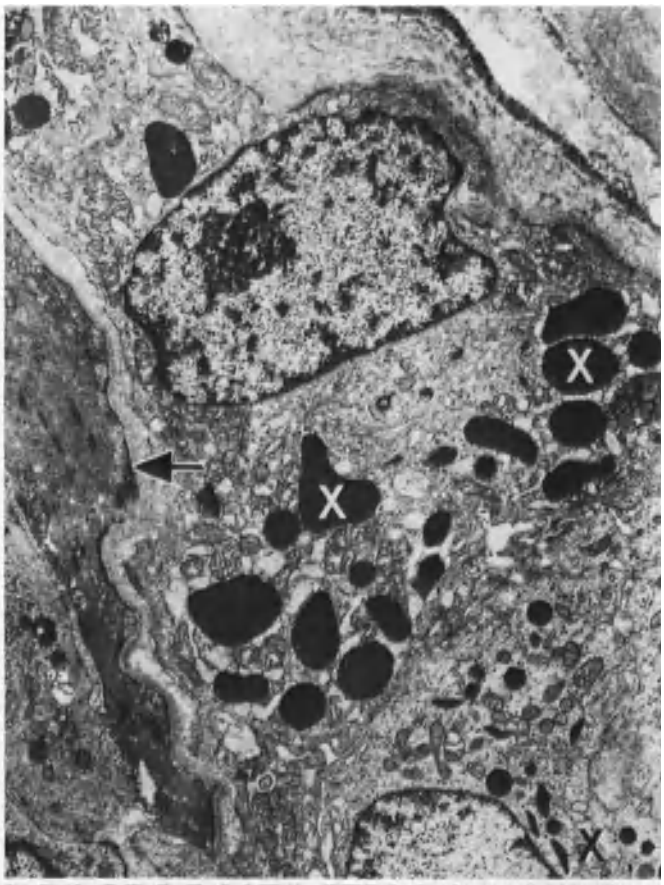


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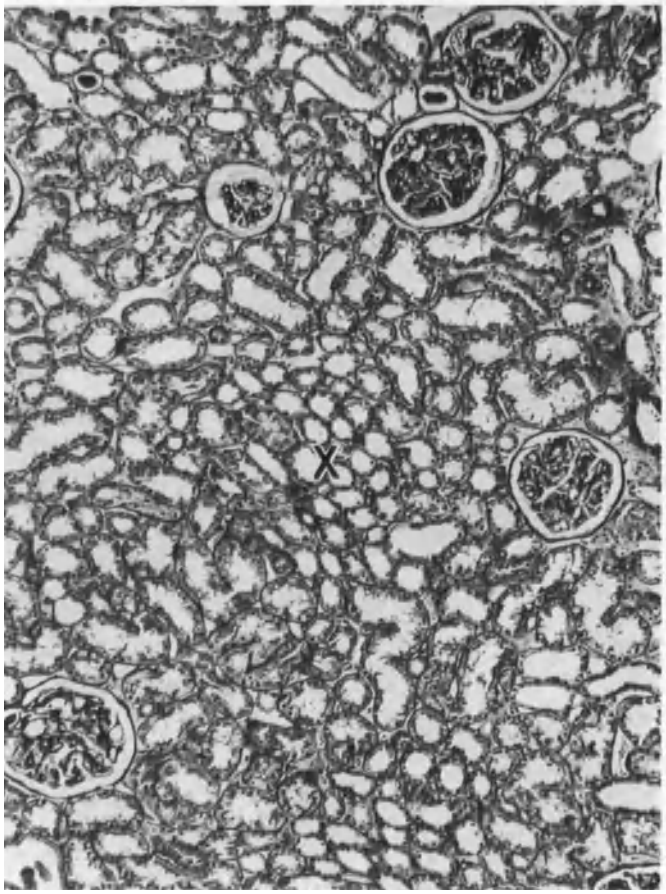


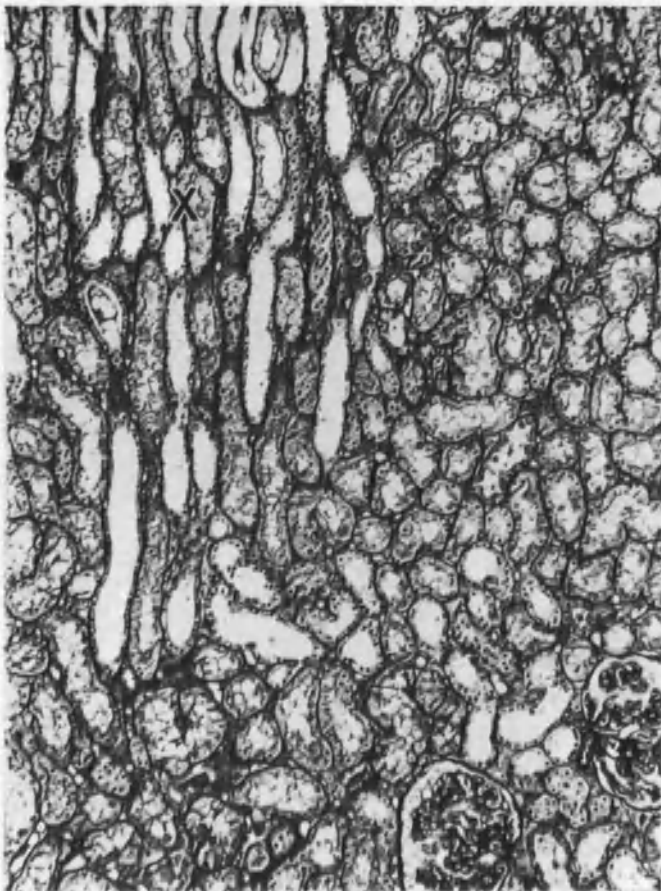


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## Renal Tubules[1]

Cortical tissue with glomeruli and proximal and distal convoluted tubules are found in general in a kidney biopsy (Fig. 4.1). The cortical tissue is arranged mantle-like about the medullary rays (Figs. 4.17, 4.18). In this latter region the straight parts of proximal and distal tubules as well as collecting ducts of the juxtamedullary glomeruli are found. Henle's loops and collecting ducts are found in the outer zone of the medulla and collecting ducts and Henle's loops of the juxtamedullary nephrons in the inner zone (papilla).

The juxtamedullary nephrons, which constitute about 10–20% of all nephrons, have long loops of Henle which extend as far as the papilla. Henle's loops of the other nephrons are shorter and extend only to the outer zone of the medulla. Functionally, the two nephron populations are different in that the juxtamedullary population is more susceptible to disease than the subcapsular [544, 763].

### Proximal Tubules

The brush border, the most important characteristic for identifying the proximal tubules, is clearly visible with the PAS stain.

Mitochondria can be seen at the cell base in the proximal convoluted tubules in thin paraplast embedded sections and semi-thin (epon-embedded) sections. The mitochondria are arranged vertically to the BM in the folds of the basal labyrinth (Fig. 4.28). Since the basal labyrinth is nearly absent in the straight proximal tubule, the mitochondria are not arranged very regularly. Optically, empty resorption vacuoles are often seen under the brush border. The nuclei of the entire proximal tubule are located basally. Identification of other cytoplasmic organelles with LM requires special procedures.

***Proximal Tubule, Convoluted Part.*** The cell membrane of the proximal convoluted tubules (Figs. 4.19a, 4.20a) facing the lumen consists of densely packed microvilli (brush border). On the base of the brush border, the cell membrane forms tubular infoldings (plicae) which are partially coated with moderately electron-opaque material (glycocalyx). Under these tubular infoldings, larger usually optically empty resorption vacuoles are found (Figs. 4.21, 4.24, 4.27). The basal labyrinth is formed by interdigitating neighboring cells. The infoldings of the basal labyrinth extend to the apical third of the cell. The cigar-shaped mitochondria are arranged in rays parallel to the cell membrane of basal labyrinth infoldings which are perpendicular to BM. Following glutaraldehyde immersion fixation, the mitochondria evidence an electron-opaque matrix so that the cristae mitochondriales are not always clearly recognizable.

Further cellular organelles reguarly encountered are:

1. Various types of lysosomes:
   a) Phagosomes and phagolysosomes (heterolysosomes) with partially electron-opaque, inhomogeneous contents (hyaline-protein-droplets: Fig. 8.22, p. 128).
   b) Cytosomes and cytolysosomes (autolysosomes) which surround and degrade cytoplasmic particles (Fig. 4.22).
   c) Telolysosomes (lipofuscin residual bodies) which contain indigestible material (Fig. 4.23).
2. Multivesicular bodies, consisting of several vesicles of about the same size surrounded by a membrane, are probably lysosomal cell organelles (Fig. 6.74, p. 93).
3. Microbodies with homogeneous, moderately electron-opaque matrices frequently exhibit crystal-like condensations under the membrane (possibly nucleoid equivalents Fig. 4.25).
4. Smooth endoplasmic reticulum, which is often in close spacial contact with microbodies. The paramembranous tubular system along the lateral cell membrane is a special form of the smooth endoplasmic reticulum (Fig. 4.24).
5. Rough endoplasmic reticulum.
6. Golgi fields (Fig. 4.26).

***Proximal Tubule, Straight Part.*** The basal labyrinth is mostly absent in the straight proximal tubules (Figs. 4.20, 4.24). Accordingly, the mitochondria in this region are not regularly arranged and cigar-shaped forms are only rarely observed. In the straight part, there are fewer lysosomes but more microbodies and smooth endoplasmic reticulum than in the convoluted part. Fibrils

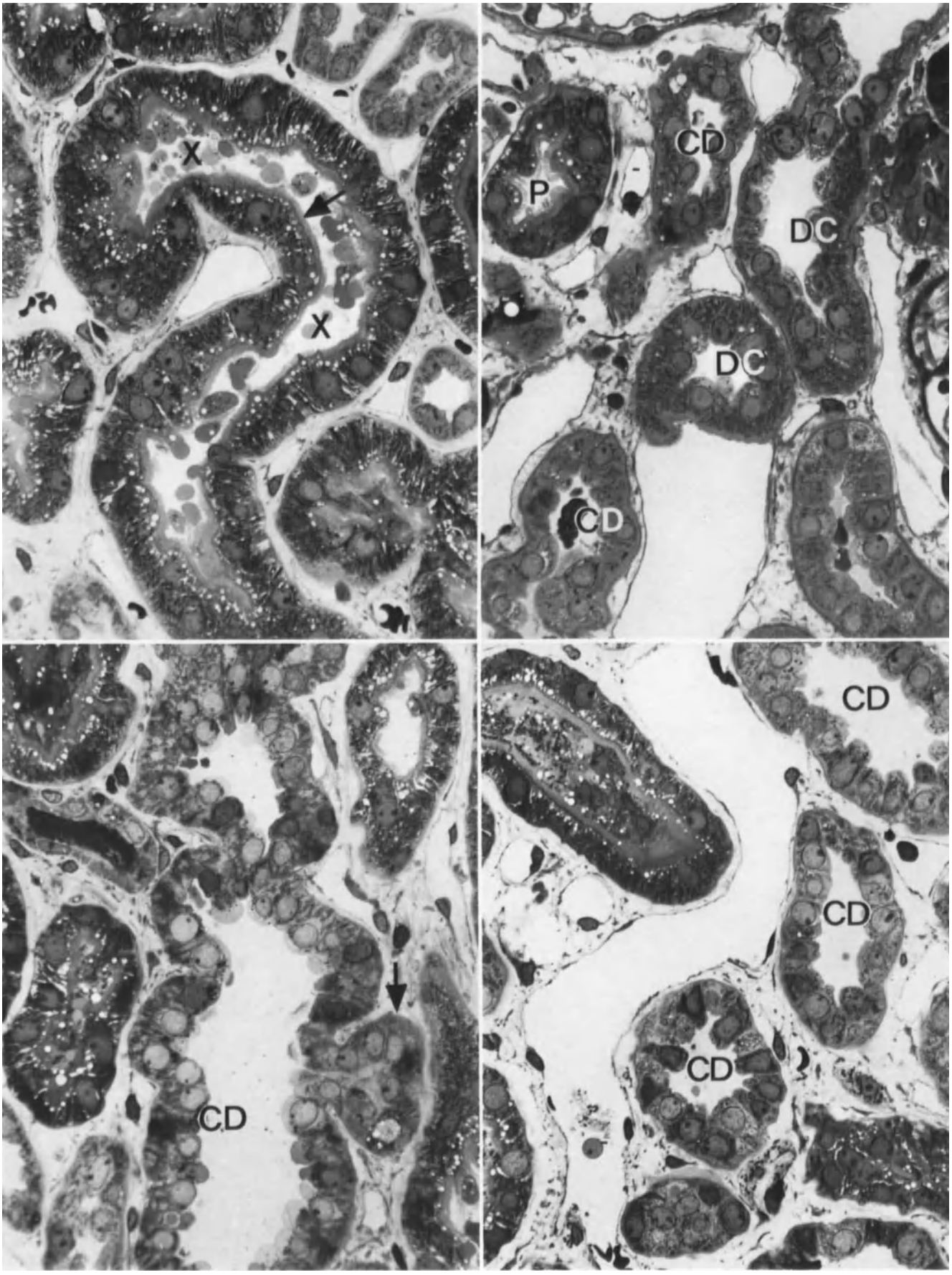
[1] Morphology: [214, 218, 927, 1172, 1382, 1617, 1618, 1624]; physiology: [180, 1134, 1220, 1439, 1488, 1581, 1752].

◁ **Fig. 4.15.** Juxtaglomerular apparatus of the contra lateral kidney in early childhood pyelonephritis from a 27-year-old hypertensive woman. Between vas afferens (*VA*) and macula densa (*MD*), Goormaghtigh and myoepithelial cells can be seen. EM (×1900)

**Fig. 4.16.** Myoepithelial cells with numerous renin granules (*X*) which occasionally evidence a rhomboid crystalloid form. Myocyte (→). Male, 38 years. EM (×7200)

**Fig. 4.17.** Normal renal cortical tissue: Transversely sectioned medullary ray (*X*) between the proximal tubules. PAS (×100)

**Fig. 4.18.** Longitudinal section of medullary ray (*X*) from normal kidney. PAS (×100)

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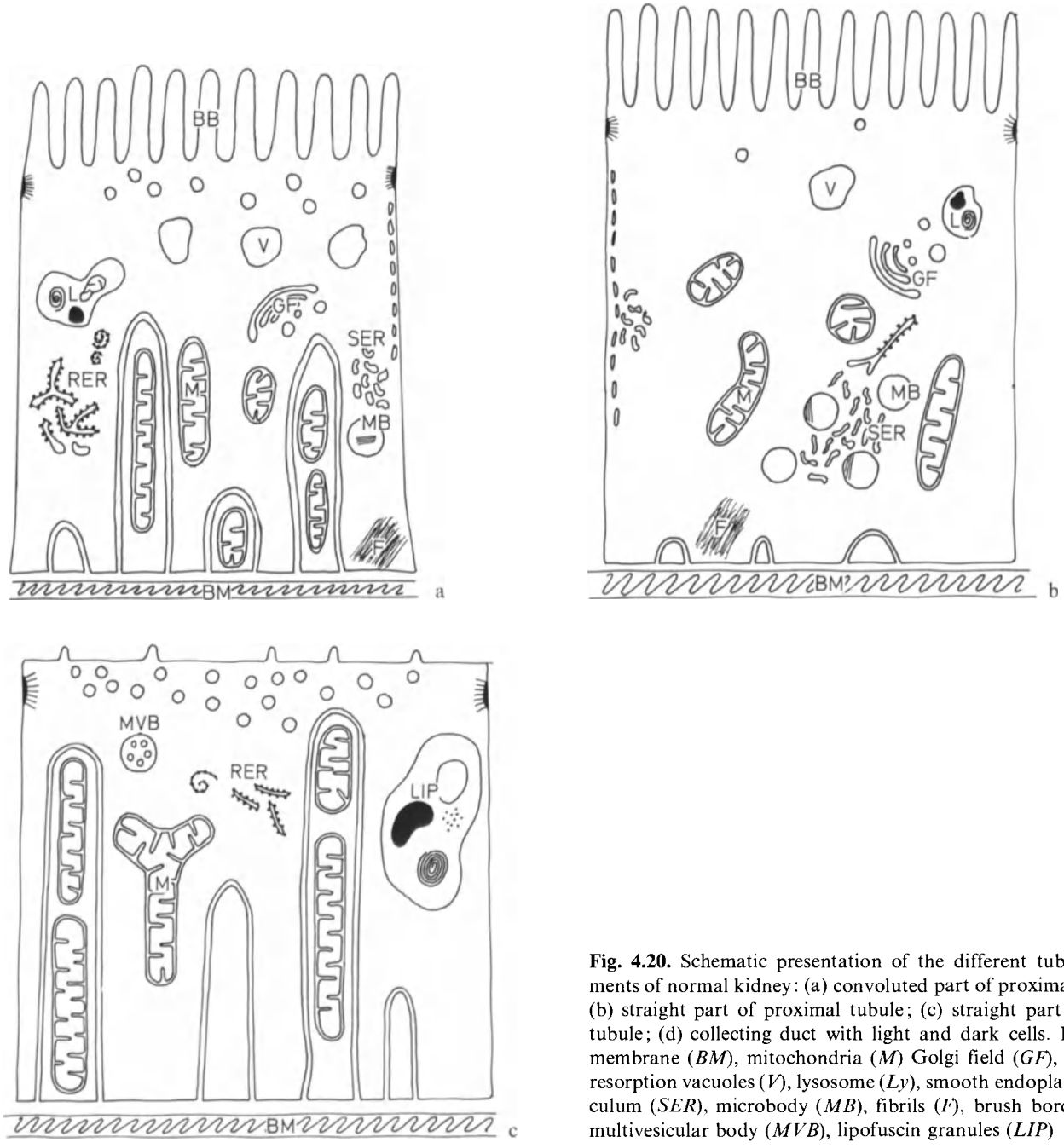
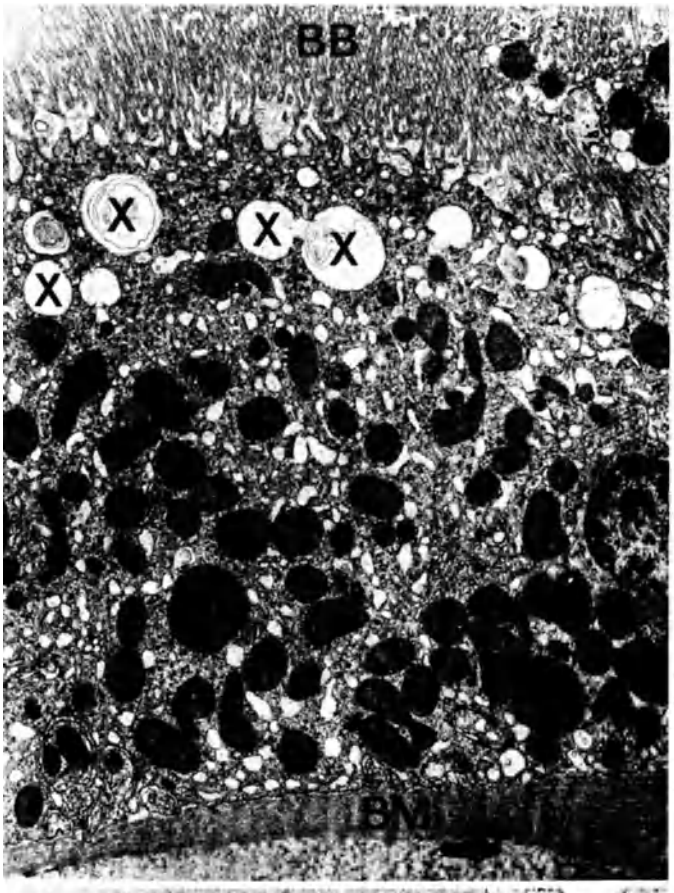
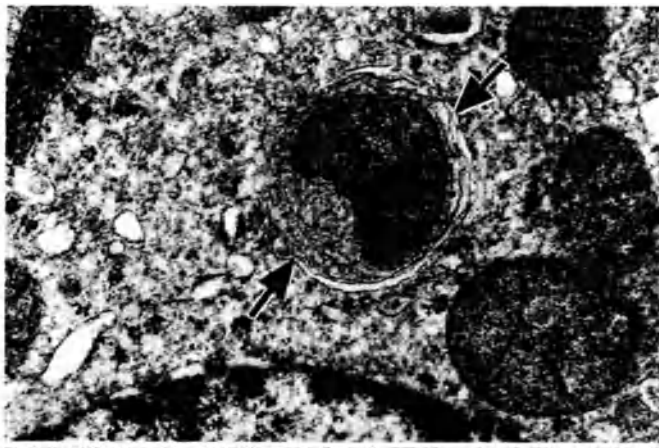
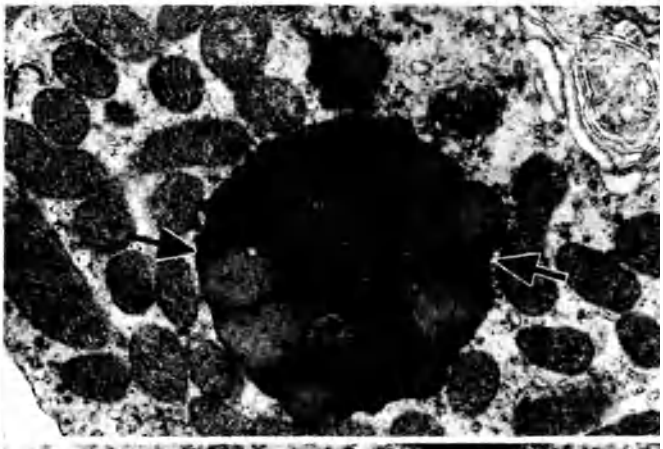



**Fig. 4.20.** Schematic presentation of the different tubular segments of normal kidney: (a) convoluted part of proximal tubule; (b) straight part of proximal tubule; (c) straight part of distal tubule; (d) collecting duct with light and dark cells. Basement membrane (*BM*), mitochondria (*M*) Golgi field (*GF*), cilia (*C*), resorption vacuoles (*V*), lysosome (*Ly*), smooth endoplasmic reticulum (*SER*), microbody (*MB*), fibrils (*F*), brush border (*BB*), multivesicular body (*MVB*), lipofuscin granules (*LIP*)

◁ **Fig. 4.19.** Different tubular segments of a normal kidney:
(a) proximal convoluted tubules with potocytosis (*X*); brush border is distinctly recognizable as a thin, grey border (→)
(b) proximal convoluted tubules (*P*), collecting ducts (*CD*)
(c) distal convoluted tubules (*DC*) with diverticulum (→)
(d) collecting ducts (*CD*) with light and dark cells. Semi-thin section, toluidine blue (×400)





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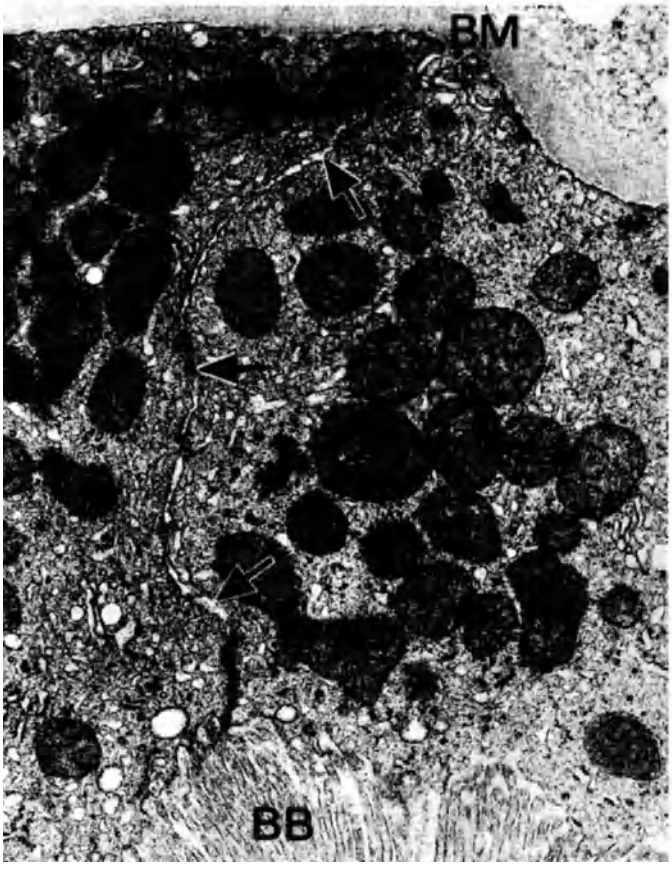


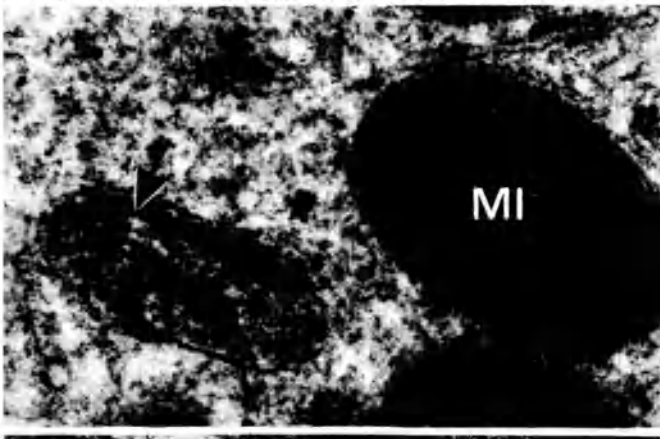


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arranged in bundles lie on the cell bases of the proximal and distal tubules. The fibrils probably contain actomyosin and are thus indicative of a contractile system [663, 1776].

### Thin Limb of Henle's Loop

The epithelial cells of the thin limb of the descending and ascending loop of Henle are considerably lower than those of the proximal tubule. The scanty cytoplasm of the epithelial cells is bulged towards the lumen by the nuclei. The diameter of the thin limb of Henle is about $^1/_2$–$^2/_3$ of that of the proximal tubule. No other identifying characteristics can be observed by LM (Fig. 4.20b).

The low cells contain few organelles, and the apical membrane has only isolated microvilli. The mitochondria are essentially smaller than those of the proximal tubules and there are no microbodies.

### Distal Tubule

The distal tubule has no brush border. The straight parts of the distal tubule shown in Figs. 4.19b, 4.20c (ascending, thick limb of Henle's loop) is characterized by parallelly arranged mitochondria which, in the compartments of the basal labyrinth, stand perpendicularly on the BM (Fig. 4.28), an arrangement which is less pronounced in the convoluted part. Lipofuscin granules are regularly observed in the straight part.

◁ **Fig. 4.21.** Straight part of proximal tubule with brush border (*BB*) and apical resorption vacuoles (*X*). Tubular basement membrane (*BM*). Male, 53 years. EM (×7480)

**Fig. 4.22.** Cytolysosome (autolysosome) (→) in proximal tubular cell. A mitochondrium with cristae can be seen within the cytolysosome. Female, 22 years. EM (×24,500)

**Fig. 4.23.** Telolysosome (→) in a proximal tubular cell. Male, 33 years. EM (×7330)

**Fig. 4.24.** Perimembranous tubular system between two cells of the proximal tubule. Brush border (*BB*), tubular basement membrane (*BM*). Cell border (→) with tight jonction at apical cell border. EM (×11,220)

**Fig. 4.25.** Microbody with marginal crystalloid (→) condensation (possibly nucleoid equivalent) in a proximal tubular cell. Mitochondrium (*MI*). Fanconi's syndrome without cystinosis. Male, 2.5 years. EM (×70,000)

**Fig. 4.26.** Golgi apparatus (→) in a cell of the straight part of the proximal tubule. Long stretched mitochondrium (*MI*). Female, 17 years. EM (×13,000)

Nuclei are situated apically in both straight and convoluted parts. By micro-dissection techniques, diverticula (Fig. 4.20c) can be regularly demonstrated in the convoluted parts—especially in the aged [341].

In contrast to the proximal tubule, no brush border covers the apical cell membrane of the distal tubule which demonstrates only a few stunted microvilli. The concentration of small vesicles in apical cell regions is striking. The distal tubule is devoid of microbodies as opposed to the proximal tubule. Phagosomes, phagolysosomes, multivesicular bodies, smooth endoplasmatic reticulum as well as Golgi fields are, however, always encountered. Rough endoplasmatic reticulum and lipofuscin granules are abundant.

The basal labyrinth is as markedly developed in the straight parts of the distal tubule as it is in the proximal convoluted tubule (Fig. 4.28). Cigar-shaped mitochondrial sections, due to the arrangement of the basal labyrinth, are present, but the basal labyrinth is less developed in the distal convoluted tubules than in their straight parts and the mitochondria are often oval.

The macula densa (see p. 30) is a part of the distal tubule which touches the vascular pole of the glomerulus. Its cells have little cytoplasm and their nuclei, therefore, lie very densely next to each other. The same organelles occur in the scanty cytoplasm as are found in the neighboring distal tubular cells. There is no basal labyrinth.

### Collecting Ducts

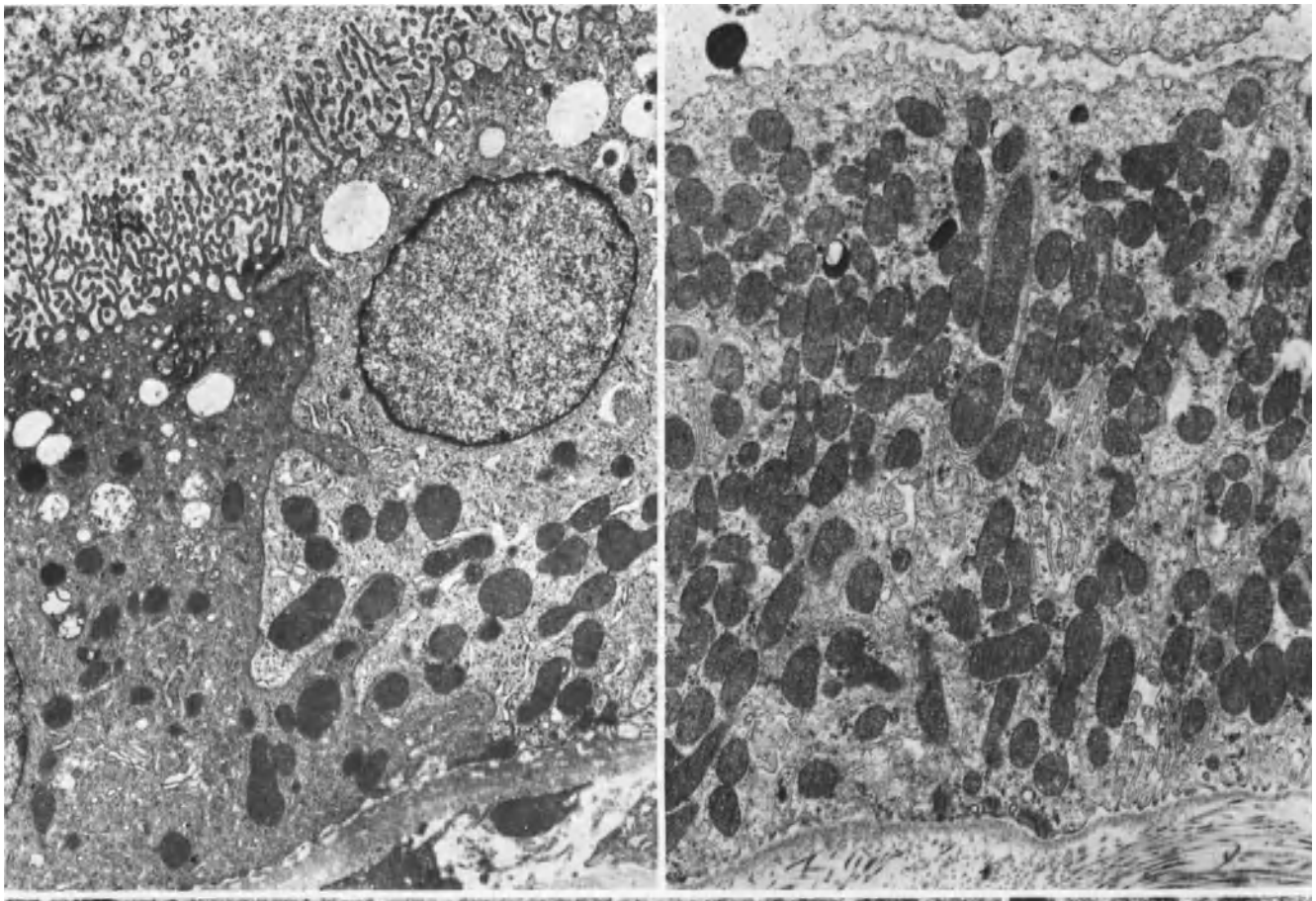
Two cell types (Figs. 4.19c, d; 4.20d) can be identified by LM or EM in the collecting ducts (Fig. 4.29):

1. Light cells with loose cytoplasmic ground substance and few cell organelles are frequently observed.
2. Dark cells with opaque cytoplasmic ground substance and densely concentrated cell organelles are occasionally encountered (Fig. 4.19d, 4.29). They are more frequent in the proximal part of collecting ducts [1172].

Stunted microvilli are present in the apical cell membrane. Cilia are uniformly present and short infoldings of the plasma membrane are seen at the cell bases. The mitochondria are generally oval or irregularly shaped and somewhat smaller as those of the proximal renal tubules. Phagosomes, phagolysosomes, multivesicular bodies, rough endoplasmatic reticulum and lipofuscin granules are also present.

### Tubular Basement Membrane

The thickness of the BM (Fig. 4.30) varies considerably in the different sections of the tubules (distal tubule > proximal tubule > collecting duct). The BM thickness increases with age [341]. Thin BM usually have a homo-



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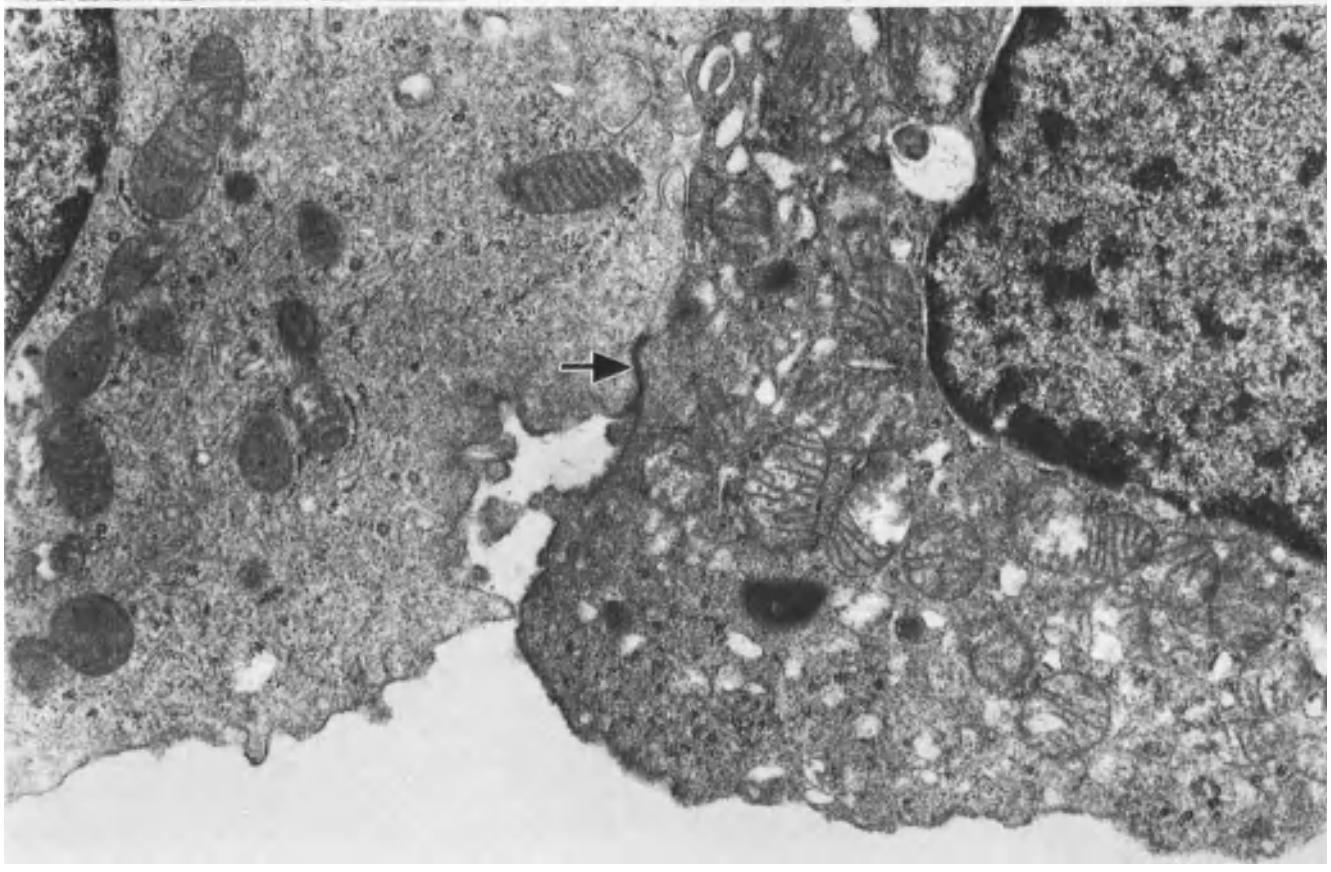

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geneous structure while the thicker ones are lamellated and contain granular and/or vesicular inclusions (Fig. 4.31). Upon chemical analysis, little difference is noted between tubular and glomerular BM [999]. Tubular BM is said to contain less glucose, galactose, hydroxyproline and glycine. The amino acid content of tubular BM is more similar to that of collagen, the corresponding content of glomerular BM. There is still disagreement as to which cells form tubular BM: tubular epithelium [1268] or interstitial fibroblasts [1663].

## Blood Vessels
[1382]

The renal vessels consist of endothelium, smooth muscle cells (myocytes) and connective tissue. All of these structures—or a combination thereof—are arranged in a certain sequence to form the tunica intima, media and adventitia.

### Middle-Sized Arteries

Middle-sized renal arteries (e.g., arcuate) have an intima consisting of endothelial cells and a BM bordering on a lamina elastica interna. Between the endothelial BM and l. elastica interna normally a cell-free layer—designated as the subendothelial space [1311a]—is found.
The media is formed by at least three to five layers of myocytes which are embedded in a framework of elastic and collagen fibers. A l. elastica externa separates the media from the adventitia which consists chiefly of fibroblasts with scattered myocytes.

◁ **Fig. 4.27.** Straight part of a proximal tubule showing two neighboring tubular cells with varyingly numerous resorption vacuoles (heterolysosomes). Due to glutaraldehyde fixation, mitochondria appear homogeneous and dark. Brush border is clearly evident, but almost no basal labyrinth is recognizable. Male, 22 years. EM (×11,500)

**Fig. 4.28.** Tubular cells of straight part of distal tubule without brush border. Basal labyrinth is evident. There is parallel arrangement of the mitochondria. Female, 32 years. EM (×10,000)

**Fig. 4.29.** Clear and dark cell of collecting duct. Note the abundance of organelles in the dark cell. Desmosome (tight junction) (→). Female, 32 years. EM (×16,000)

### Small Arteries

The small renal arteries, e.g., the interlobular arteries, have an outer diameter of $60 \pm 9.9$ µm [1133]. The media consists more or less of three layers of myocytes and elastic as well as collagen fibers. There is no l. elastica externa. The adventitia consists of a few fibroblasts.
With increasing age the BM and l. elastica interna of the small arteries—as is true for the entire vascular system—undergo splitting and lamellation which is accompanied by broadening and fibrosis of the intima [341].

### Arterioles

The arterioles (vas afferens and vas efferens) have a diameter of $29.8 \pm 2.8$ µm [1133]. The l. elastica interna is usually absent so that the endothelial cells and their BM border directly on the media which generally consists of one layer—rarely two—of myocytes. Nevertheless, lumpy aggregates of elastic fiber material do occur between the myocytes. No adventitia is present, and surrounding fibrocytes are a part of the interstitial connective tissue (Fig. 4.32).

### Intertubular Capillaries

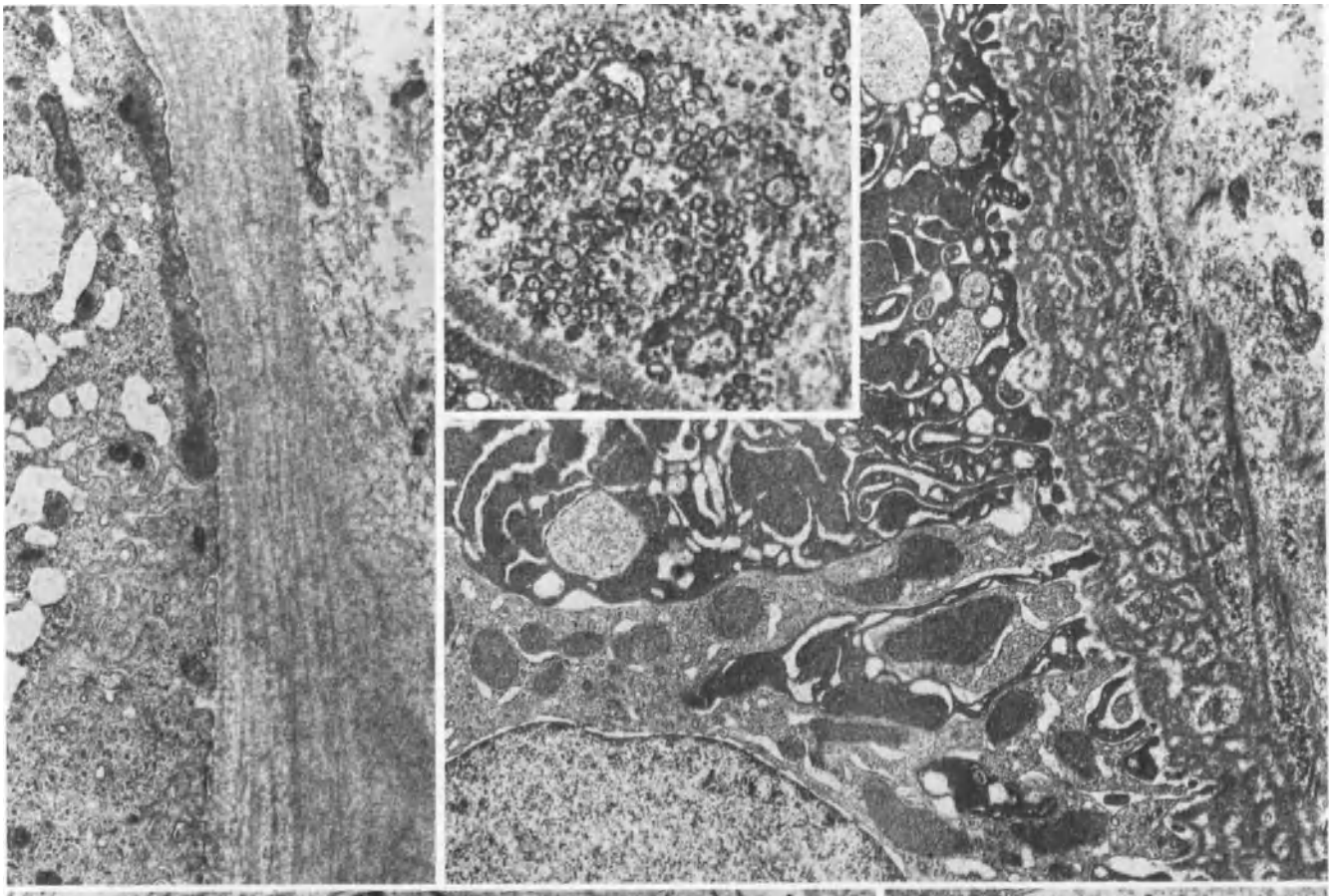
The intertubular capillaries demonstrate a continuous BM and an endothelium provided with pores (Fig. 4.33). Cytoplasmic processes of pericytes entwine the endothelial tube.

### Renal Veins

The morphology of the renal veins corresponds to that of the arteries. Grossly, the lumen of veins is larger than that of corresponding arteries.
Microscopically, the wall of the small veins consists of an endothelium and its BM and a single—seldom two—layered media. Rich accumulations of elastic and collagen fiber material are found in the relatively large subendothelial space. Collagen fibers and fibrocytes are arranged externally on the myocytes of the media.

### EM of Components of the Vascular Wall

***Endothelium.*** The endothelial cells of the larger renal vessels form a poreless coating [1311a]. Towards the vessel lumen, scattered villus-like cytoplasmic protusions are often observed.
The quantity of endothelial cells is age dependent: more in the young and the old and less in the middle-aged [545a].



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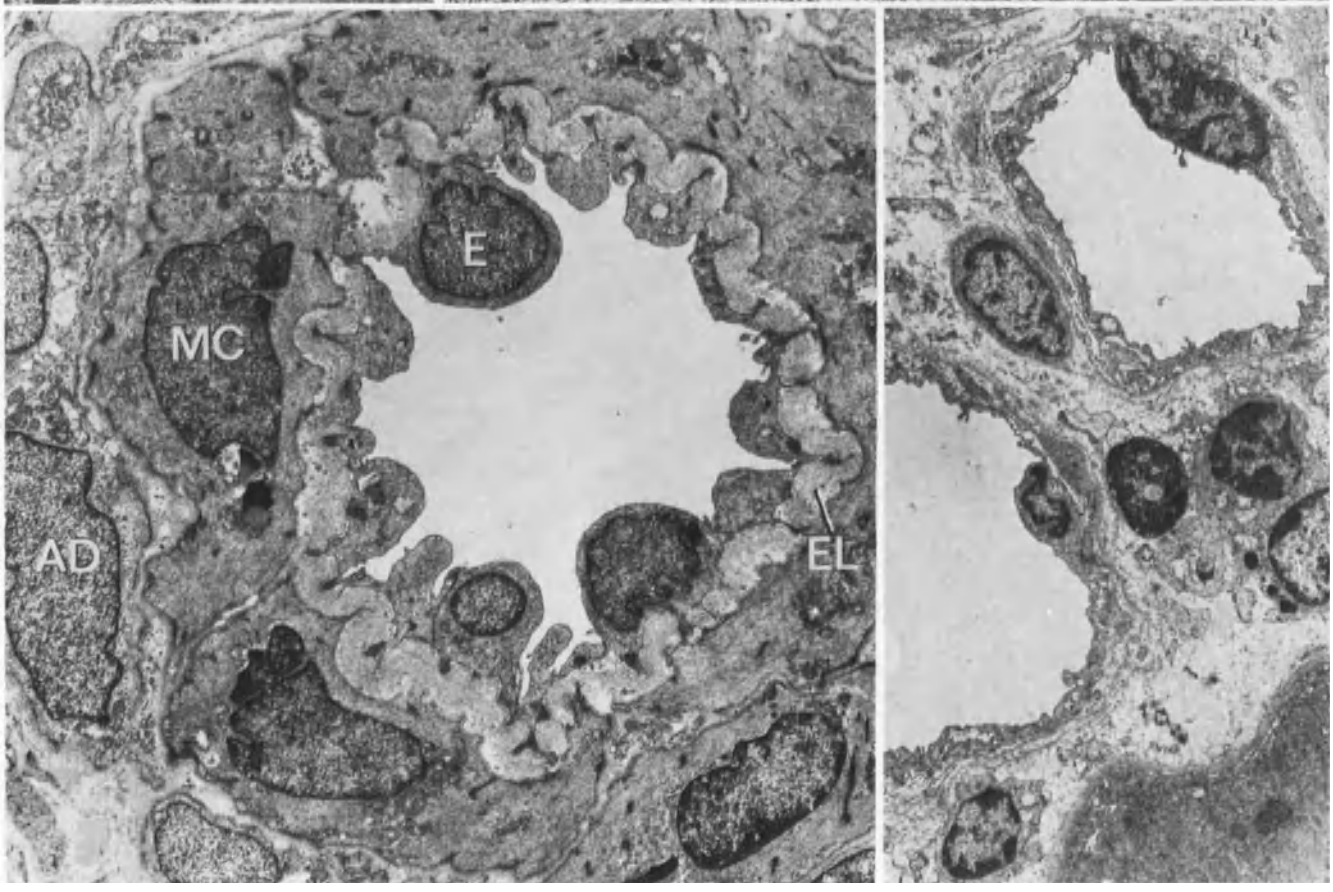


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In addition to cytoplasmic microfibrils (myofibrils) the endothelial cells also contain lysosomes as well as tubular dense bodies [1713a] which are in structural contact with the Golgi apparatus.

The BM consists of a microfibrillar network as well as of acid and neutral glycosamino glycanes. The cytoplasm of the endothelial cells is condensed by accumulation of basal microfilaments (Fig. 4.34). These condensations represent areas of anchoring with the microfibrillar network of the BM [1638a]. The thickness of the BM increases with age and often appears fibrous following glutaraldehyde fixation.

***Elastic and Collagen Elements.*** The multiplicity of elastic structures (fibrils, membranes) is explicable by their morphogenesis. The initial structural units of elastic tissue are the granules which subsequently coalesce to form microfibrils. The microfibrils go on to form a dense network which, with progressing maturation, becomes invested by an amorphous ground substance (=proteoglycanes) such that the fibrillar pattern is no longer recognizable. Continual maturation of the fibrils leads to homogeneous elastin structures in the form of fibers which are ultimately transformed into membranes [791a, 791b].

With decreasing caliber of the blood vessels, the continuity of the l. elastica interna gradually disappears. In the arterioles only lumpy aggregates of microfibrils are observed.

The collagen fibrils in the vascular wall typically exhibit axial periodicity (cross-striation). Arteriolar walls have a few delicate collagen fibrils while those of the arteries are broader and those of the adventitia are very abundant.

◁ **Fig. 4.30.** Tubular basement membrane with slight lamellation. Male, 38 years. EM (×8800)

**Fig. 4.31.** Reticulation of tubular BM with nests of granular and vesicular degradation particles (inset). Male, 38 years. EM (×8800; inset ×24,750)

**Fig. 4.32.** Normal arteriole with one myocyte layer only from a 16-year-old boy. Endothelial cell (*E*), elastic lamella (*EL*), myocyte (*MC*), adventitial cell (*AD*). External elastic membrane is absent. EM (×5790)

**Fig. 4.33.** Normal intertubular capillaries. Isolated phagocytes and small lymphocytes are seen in interstitium. Male, 45 years. EM (×3450)

The subendothelial space is bordered by the endothelial BM above and the plasma membrane of the media myocytes below. It is absent in the arterioles in childhood and is only narrowly developed in the small arteries. It is more spacious in adulthood and filled with granulovesicular cell debris [545a].

***Myocytes.*** The myocytes of the media are spindle-shaped cells with numerous cytoplasmic processes forming an arcade-like cell surface.

The myocytes are covered by BM-like substance which, together with the cytoplasmic membrane, forms the sarcolemma.

Numerous micropinocytotic vesicles are found on the myocyte surface. The smaller the vessel and the younger the individual, the closer together the myocytes are concentrated.

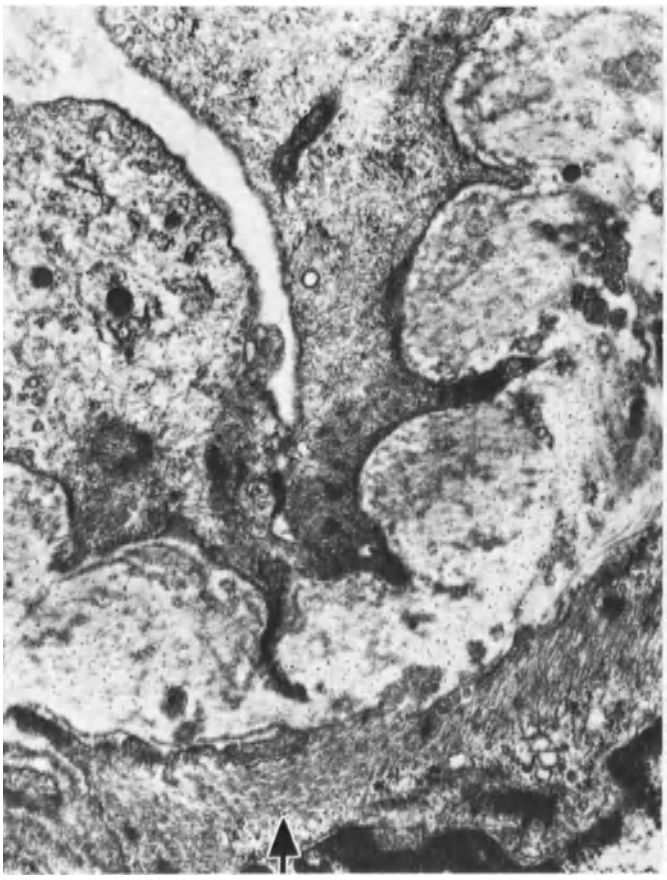
The myocyte nucleus, depending on the state of contraction, is either spindle- or wave-shaped. The cell organelles, numerous free ribosomes, scanty rough endoplasmatic reticulum, mitochondria and a small Golgi apparatus are located at both nuclear poles. With increasing age, large lipid-containing vacuoles of various opacities (lipofuscin) are found in the polar cell regions.

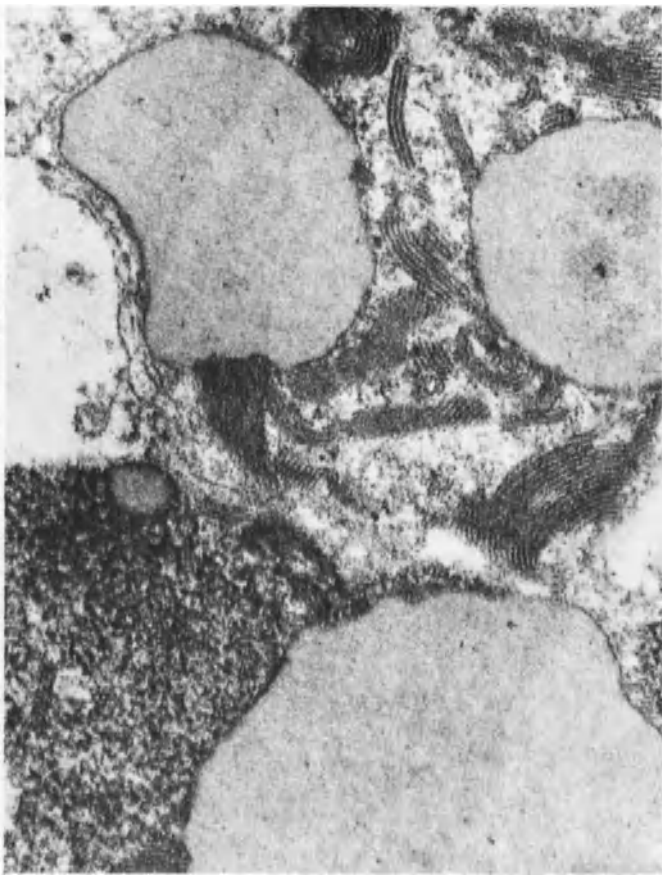
Myofibrils make up the main volume of the myocytes. They insert on the cell membrane and are arranged longitudinally in the myocytes. Patch-like focal condensations in the sarcoplasma—usually encountered at the cell periphery—are considered to be anchoring sites for myofibrils [1311a].

There are so-called cytoplasmic granules—other than those mentioned above—in the myocytes (Fig. 4.35) termed telolysosomes, which differ from lipofuscin granules of other cell types by the presence of crystalloid inclusion of lipoprotein material [149a]. Telolysosomes occur sporadically also in renal vessels under normal conditions but they increase with age, following kidney transplantation, and in hypertension and diabetes mellitus [149a]. It has been proposed that telolysosomes originate from plasma proteins filtered through the blood vessel or from phagocytized immunocomplexes [149a].

***The Adventitia.*** Fibrocytes of the adventitia of the larger vessels (Fig. 4.36) are spindle-shaped and exhibit numerous cytoplasmic processes. Additional constant structural characteristics are the presence of a well-developed rough endoplasmatic reticulum, a prominent Golgi field and mitochondria. The fibrillar elements of the adventitia consist of collagen fibrils of various sizes, some of which demonstrate 640 Å periodicity.

***Function of the Vascular Cell Elements.*** The endothelial cells (see also p. 25) form a barrier against the bloodstream. They are very active in the uptake of both solid (phagocytosis) and fluid (pinocytosis) elements from the bloodstream [704b, 1564a, 1568c, 1568b].





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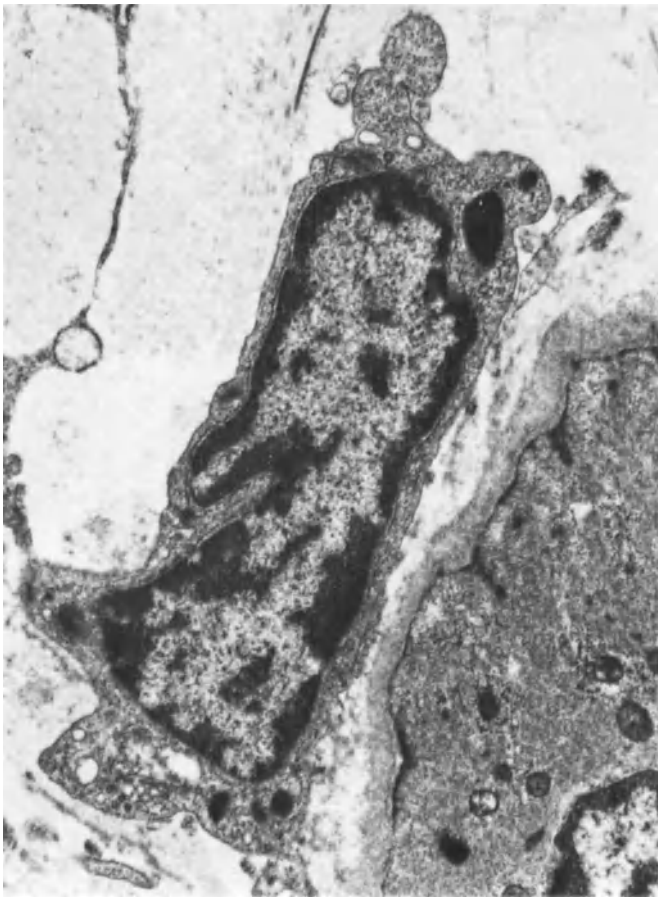


**Fig. 4.34.** Anchoring zone of an endothelial cell on internal elastic membrane. Note increased number of microfibrils (→) in the myocytes. Male, 7 years. EM (×20,000)

**Fig. 4.35.** Fingerprint-like (possibly) lipoprotein inclusions beside large vacuoles in a myocyte of a middle-sized artery. Male, 37 years. EM (×72,000)

**Fig. 4.36.** Adventitial fibrocyte from a normal middle-sized renal artery of a 7.5-year-old boy. EM (×15,000)
◁

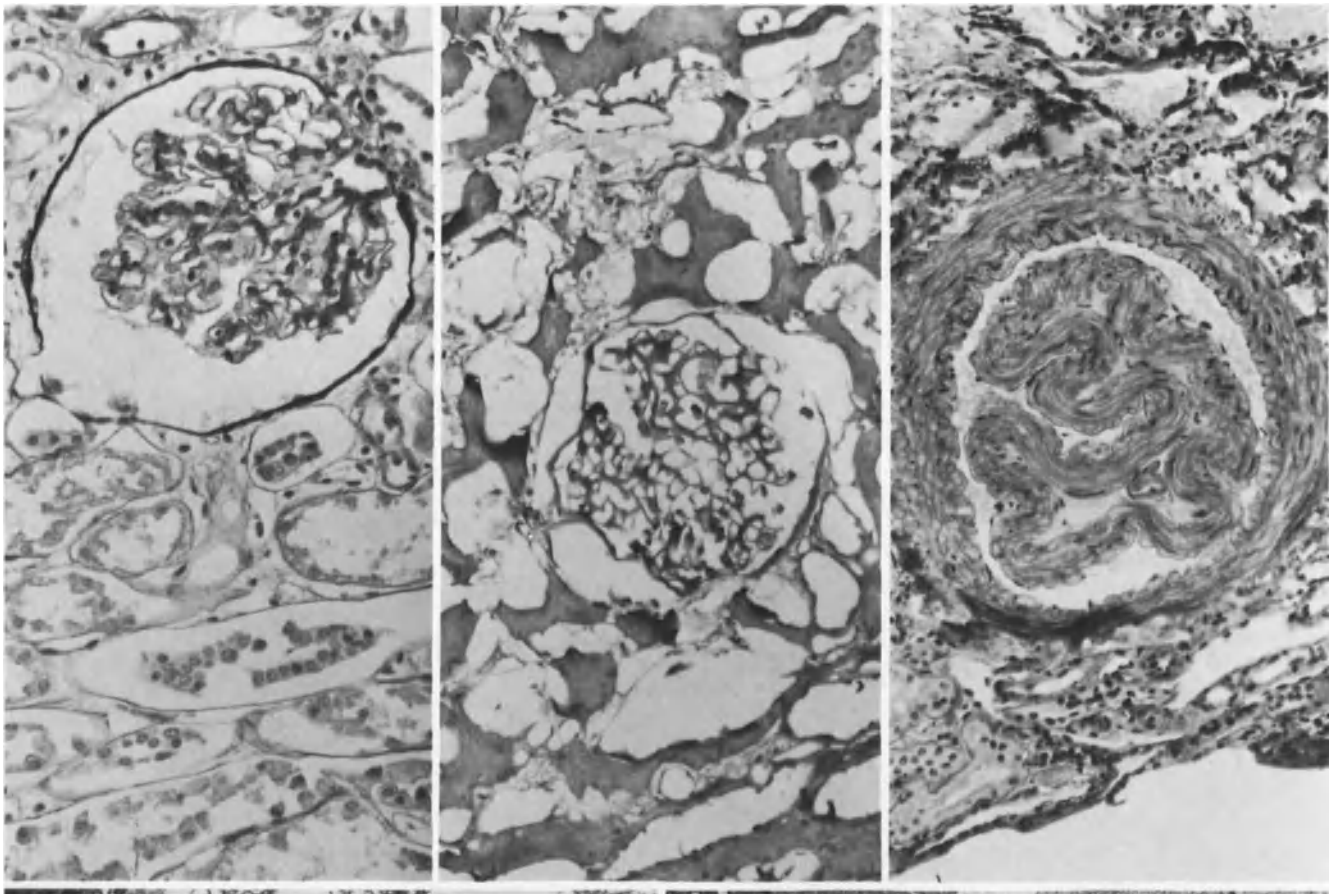
**Fig. 4.37.** Obvious autolysis of the proximal tubules following ▷ maintenance of tissue for 24 h in a NaCl solution in contrast to the fairly well preserved glomeruli. PAS (×220)

**Fig. 4.38.** Freeze artifact from maintenance of biopsy material in a refrigerator. PAS (×150)

**Fig. 4.39.** Artifical invagination of the media of a middle-sized artery. PAS (×100)

**Fig. 4.40.** Fixation artifact in normal renal tissue consisting of dissolution of mitochondrial matrix (*X*). EM (×10,000)

**Fig. 4.41.** Fixation artifact in form of severe potocytosis (evagination) of cytoplasmic material into the lumen (*X*). EM (×2900)



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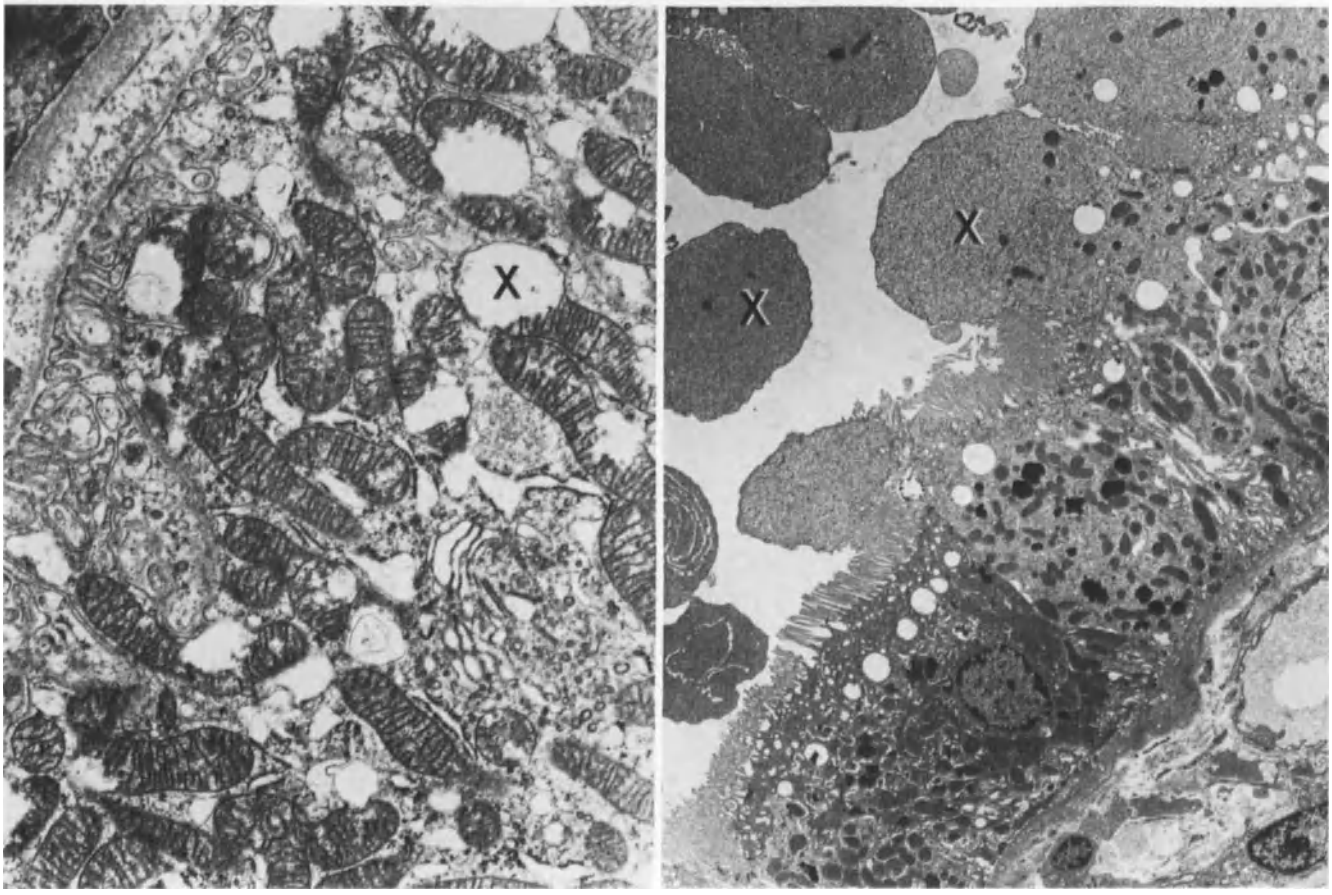


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They synthesize—at least to some extent—the subendothelial BM [1311a, 1675a]. They contain actomyosin [101] and are contractile which permits loosening of the endothelial cover at cell boundaries, with resulting increase in permeability of the vessels [788a]. It is noted that endothelial cells demonstrate considerable powers of regeneration [1565a].
Myocytes assure active contractibility of the vascular wall and passive elasticity through synthesis of elastic and collagenous fibers as well as of BM-like ground substance [861a, 1336]. Endothelial repair is in part accomplished by the myocytes of the media [666a]. The myocytes are also the source of the cellular elements observed in the subendothelial space of the larger vessels [704b].
The fibrocytes and fibroblasts of the adventitita produce and also phagocytize elements of the connective tissue ground substance [1602a]. They also possess—to a slight extent—a contractile apparatus which corresponds to that of the myocytes [520a].

## Interstitium: Connective Tissue, Lymph Vessels and Nerves
[739, 914, 1169, 1382]

Initially, the ***interstitial tissue*** of the normal renal cortex is extremely delicate but with increasing age does undergo progressive fibrosis extending as far as the papilla [341]. The tissue is composed of a few collagen fibers—especially in the region of the vessels and glomeruli—and of reticulin fibers which merge with the BM of the tubules and glomerular capsule.
Fibrocytes are extremely scanty. Some scattered lymphocytes and histiocytes are nearly always encountered. A small number of lymphocytes commute back and forth in the tubule reaching the inter-epithelial spaces by traversing the tubular BM [162].
Interstitial fibers, which are argyrophilic, have a diameter of about 200 Å which is less than that for collagen ("reticular microfibrils": [914]). The cortical fibers are arranged in a network while the somewhat thicker medullary fibers run parallel to the tubules and vessels. Unique to the medulla are stellate cells found adhering to both tubules and vessels [571]. As viewed with EM, these cells are seen to have a strongly developed Golgi apparatus and numerous osmiophilic droplets [1232] which are probably involved with the formation of prostaglandin (medullin) and/or other vasodepressive lipoid substances [694, 960a, 1191].
***Lymph vessels*** are also found in the interstitium where they are hard to recognize with LM. The larger vessels run parallel with the blood vessels, especially with the arcuate and interlobular arteries. The smaller branches and the lymph capillaries are chiefly found in the periglomerular area and again perivascularly.
In the medulla, they occur in close contact with the blood capillaries as viewed in EM. Under LM they cannot be demonstrated unless contrast media are used [739] (contra: [107a]; no lymphatics in the medulla or the periglomerular area [885]).
Interstitial lymph vessels can be differentiated from blood vessels by the absence of the following elements [1354]: continuous BM, erythrocytes in their lumens, pericytes, fenestration of the endothelium.
Functionally [1219] the lymph vessels play an essential role in regulating the appropriate intrarenal osmotic and hydrodynamic pressure and appear to serve as a sort of safety-valve [815]. In cases such as ureter ligation, hydronephrosis and venous congestion, a considerable increase in the cortical lymph flow develops. Ligation of the larger lymph vessels leads to swelling of the kidney and impairment of sodium transport resulting in severe polyuria [1219].
***Renal nerves*** [1169, 1382] are predominantly unmyelinated. They arise form the coeliac, mesenteric and aortic-renal plexuses. Within the kidney, they accompany the renal arteries and veins and terminate in the juxtaglomerular apparatus, in the cortical interstitium [80] and in Bowman's capsule [1465] respectively.

## Histological Artifacts

Artificial influences on histologic findings must be considered in all post-mortem biopsies. The most important artifacts result from inadequate fixation, freezing, drying out, and squeezing.
The proximal renal tubule is the most sensitive element (Fig. 4.37) as is clearly indicated by investigation of freshly infarcted renal tissue. Typical histologic changes include:
1. Detachment of proximal tubular cells from each other and from the BM
2. Increased eosinophilia of the cytoplasm
3. Nuclear pycnosis and, later
4. Poor nuclear staining.

In such biopsy material, masses of protein are always found in tubular lumens and capsular spaces [371]. It is important to note that intravital changes such as necrosis always include inflammatory and regenerative responses. In inadequately fixed tissue, bacterial colonies may develop; these are easily identified as artifacts by the complete lack of inflammatory response.
In larger completely normal blood vessels, the lumen may be occluded by bars of smooth muscle (Fig. 4.39). Serial sections demonstrate that this condition is ascribable to invagination of the vascular wall arising from extreme vasoconstriction.

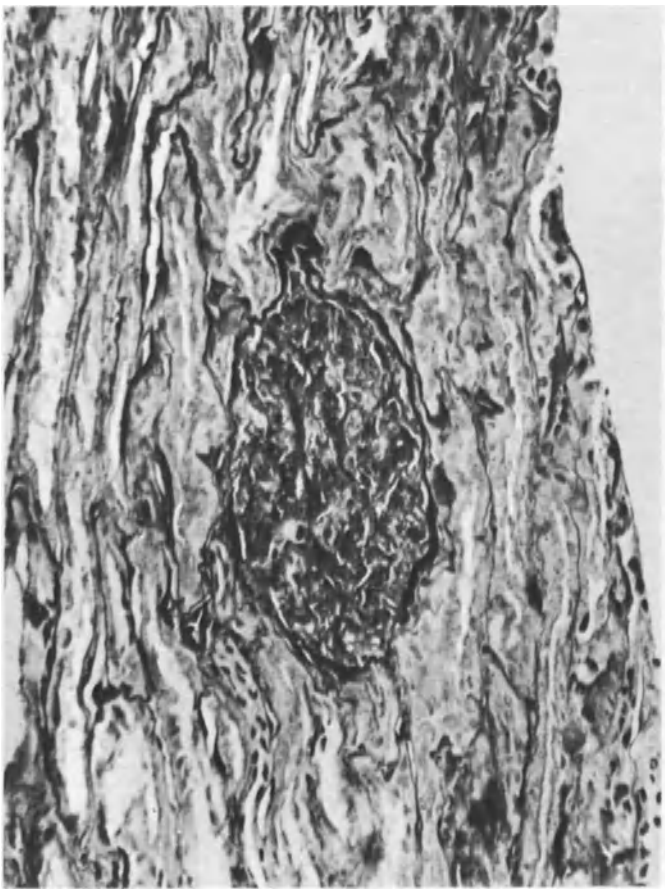


**Fig. 4.42.** Desiccation artifacts of renal tissue evidenced by shrinkage of glomeruli and tubules and by poor nuclear staining. PAS (×200)

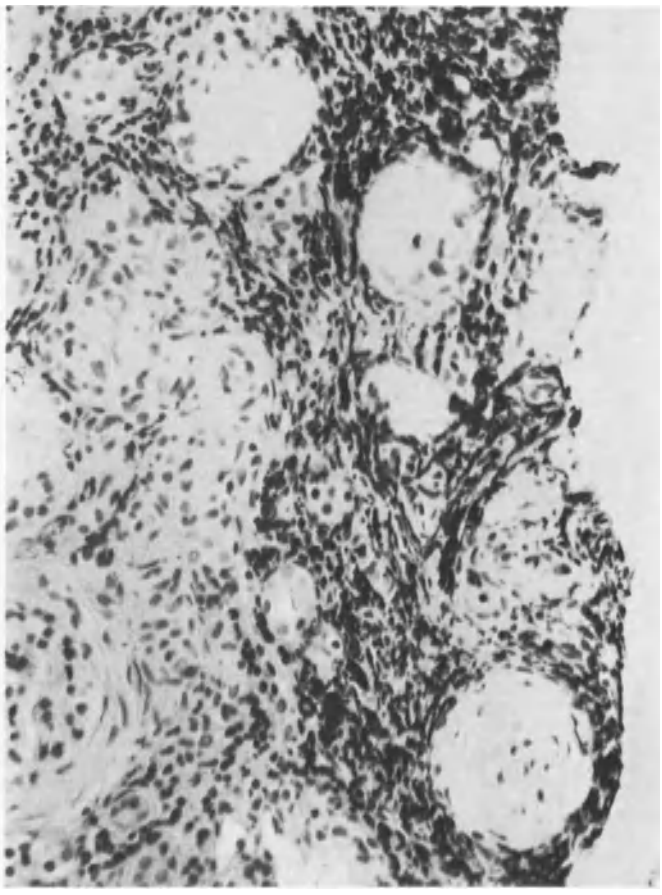


**Fig. 4.43.** Bruise effect in biopsy tissue (especially prominent in the interstitium). Spindly deformation of nuclei and condensation of the chromatin. Glomeruli and vessels are little affected. HE (×200)

We have observed a peculiar gross vacuolar or vesicular transformation of the entire kidney tissue (Fig. 4.38), when placed in refrigerators while in fixatives or when delivered in dry ice along with IF material [1791].
Consequences of inadequate immersion fixation, specially noted under EM [1029] may be:

1. Tubular luminal collapse caused by epithelial swelling [762]
2. Protrusion of apical cytoplasmic material into the lumen with loss of the brush border, i.e., potocytosis (Fig. 4.41)
3. Cell membrane rupture
4. Mitochondrial swelling
5. Lysis of matrix (Fig. 4.40)
6. Interstitial edema.

Effects of drying, which occur with extraordinary rapidity in warm operating rooms, are recognizable by the high degree of cytoplasmic shrinkage and by the loss of nuclear staining (Fig. 4.42).
The effects from tissue squeezing and crushing, which usually occur at the edges of the biopsy specimen especially in open knife or forceps biopsies, are evidenced by spindle shape transformation and over-staining of nuclei (found almost exclusively in interstitial cells, Fig. 4.43).
For details on artifacts with IF, see p. 17.

# 5. Introduction to Renal Histopathology

## Guidelines for Evaluation of Renal Biopsy

Prior to the actual study of a biopsy, it is absolutely essential that the pathologist has detailed knowledge of the patient's personal particulars (age, sex etc.), case history, clinical symtomatology and hitherto administered therapy. Comprehensive clinical information can considerably facilitate biopsy examination provided that the pathologist is sufficiently versed in clinical medicine.

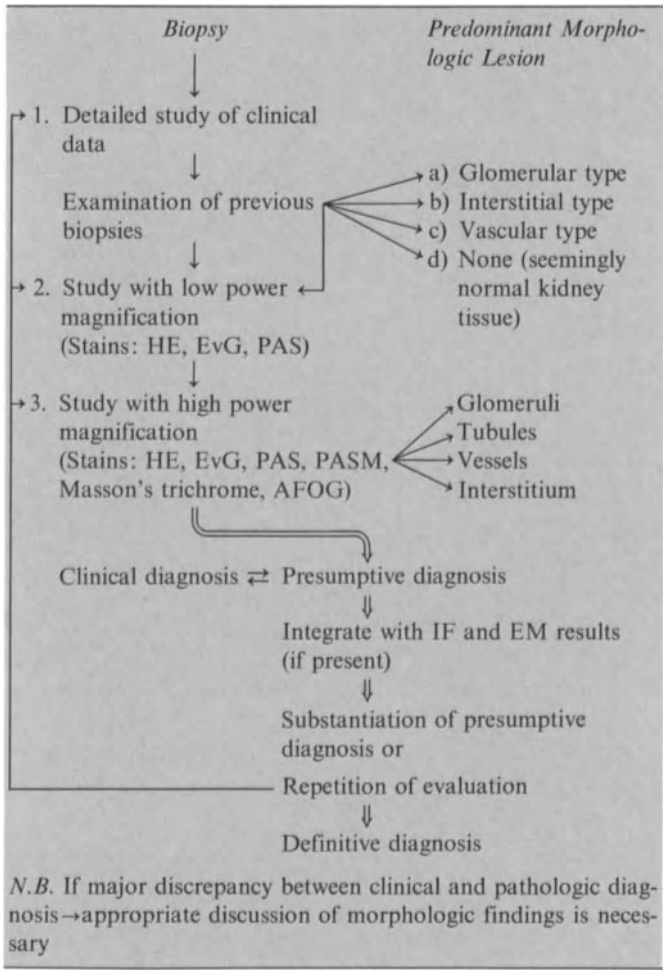



**Fig. 5.1.** Stepwise evaluation of kidney biopsy

The pathologist is also responsible for assuring that any discrepancy present between the clinical diagnosis and morphologic findings be appropriately resolved (coordinated reexamination of both clinical and pathologic findings and their interpretation). To facilitate pathoclinical cooperation and understanding we use standardized reply forms requesting relevant information from clinicians of mutually pertinent data.

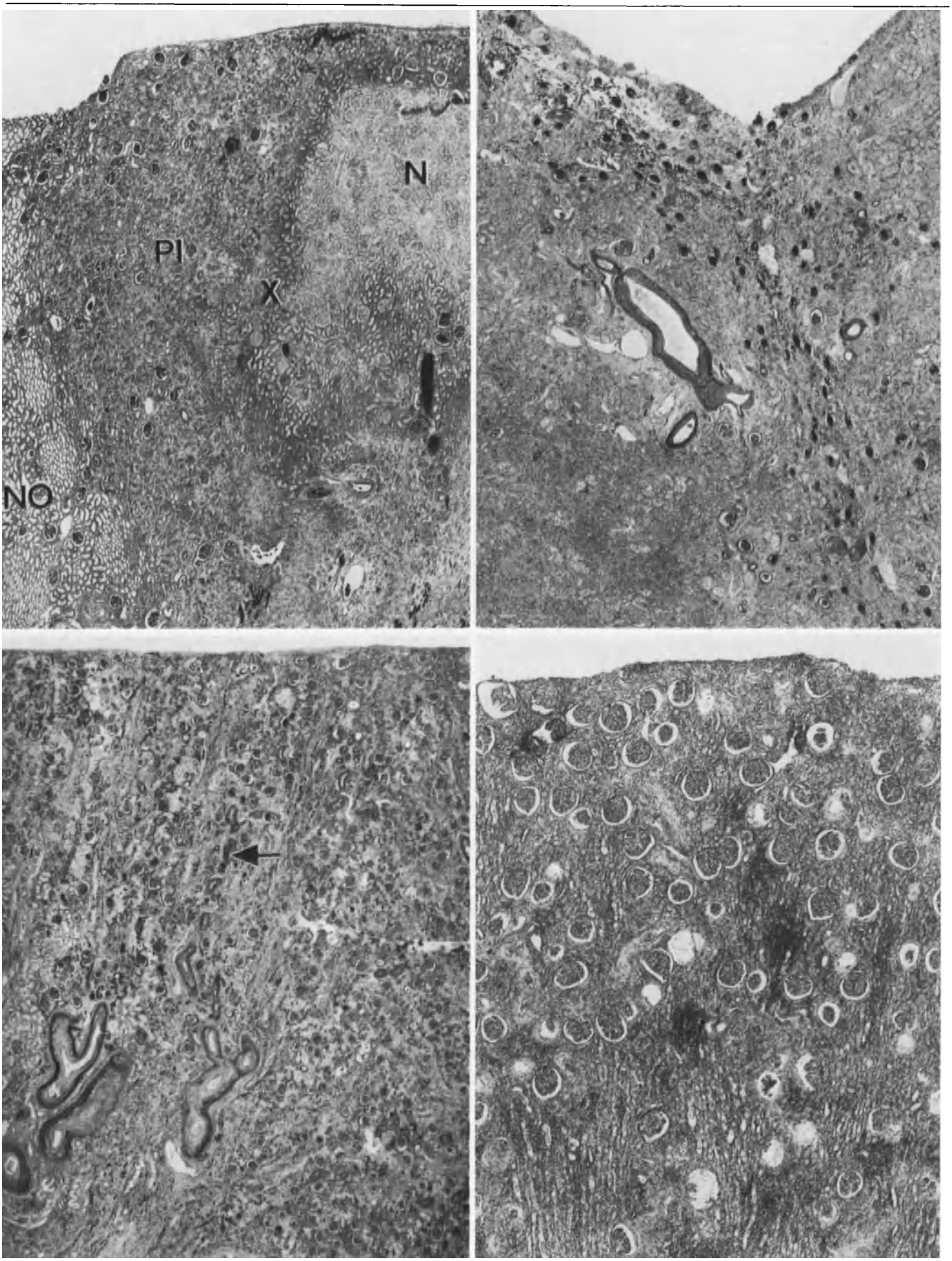
The investigation of biopsy preparations is initiated with study of the material under low-power magnification. This approach is especially rewarding for open biopsy material since it provides sufficient tissue for examination which occasionally permits formulation of a presumptive diagnosis, especially in the presence of focal processes. The evaluation process leading from biopsy to diagnosis is given schematically in Figure 5.1.

**Fig. 5.2.** Acute anemic renal cortical infarct occurring 4 days ▷ after surgery. Necrosis (*N*), dark zone caused by accumulation of leucocytes (*X*), perifocal ischemic zone (*PI*), normal kidney tissue with slight dilatation of tubular lumens (*NO*). Female, 26 years. HE (×12)

**Fig. 5.3.** Infarct scar with retraction of the surface. Glomeruli transformed into solid spheres. Heart surgery 4 years previously with intravasal coagulation. Female, 64 years. PAS (×18)

**Fig. 5.4.** Subinfarct in malignant nephrosclerosis. Glomeruli are relatively well preserved but are densely packed next to each other. Width of cortex is markedly reduced. Large arteries demonstrate severe adaptive intimal fibrosis. Arteriolosclerosis (→). Male, 45 years. PAS (×13)

**Fig. 5.5.** "Central arterial contracted kidney" (due to stenosis of renal artery), weight: 60 g. Glomeruli are well preserved but extremely densely packed. Tubules are severely atrophic, and interstitium exhibits isolated inflammatory infiltrates. Nephrectomy because of hypertension. Male, 51 years. HE (×40)

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## Definitions

**Diffuse:** A pathologic change exhibited by more than 80% of all glomeruli.
**Focal:** A pathologic change exhibited by less than 80% of all glomeruli.
**Global:** A pathologic change of an entire glomerular capillary convolute.
**Segmental:** A pathologic change restricted to one segment (lobule) of the glomerulus.
**Hypercellularity:** Accumulation of white blood cells (leukocytes, monocytes) and/or proliferation of in situ tissue cells.
**Exudation:** Leukocytosis of the capillary loops along with escape of plasma and possibly of leukocytes and erythrocytes into the capsular space.
**Proliferation:** Multiplication of in situ tissue cells (for the mesangium, in relation to the total mesangial surface).
**Mesangial/glomerular sclerosis:** Increase in the amount of BM-like substance = mesangial matrix without demonstrable collagen fibrils.
**Mesangial glomerular fibrosis:** Demonstrable collagen fibrils.
**Fibrinoid and hyalin** are two entirely descriptive terms used in LM. In renal histopathology, they are often used indescriminably and lead, accordingly, to frequent misunderstanding. Neither term permits conclusions regarding the chemical nature of the substances or of their origin (Table 5.1). Since the terms are purely descriptive and their use strongly entrenched in the literature, they cannot usually be avoided. We advocate that they be rigorously defined according to their response to stains and EM and IF as noted in Table 5.1. It would be even better to describe hyalin and fibrinoid substances respectively by their true chemical term, i.e., instead of fibrinoid/hyalin droplets in tubules = protein droplets etc. Please note that according to our definition, both hyalin casts and tubular droplets are fibrinoid.

Table 5.1. LM, EM and IF characteristics of hyalin and fibrinoid

| Method | Reaction | |
|---|---|---|
| *LM stains* | *Fibrinoid* | *Hyalin* |
| v.G. | Yellow-orange | Lively red |
| HE | Lively red | Lively red |
| PAS | Carmine red | Pale blue (variable) |
| Masson trichrome | Bright red | Greenish (variable) |
| OFOG | Bright red | Blue |
| PASM | Negative | Brownish (variable) |
| IF | Plasma proteins often immunoglobulins | Negative (practically without exception) |
| EM | Osmiophilic and finely granular | Variable |

## Typical Renal Lesions Under Low Power Magnification

### Infarct

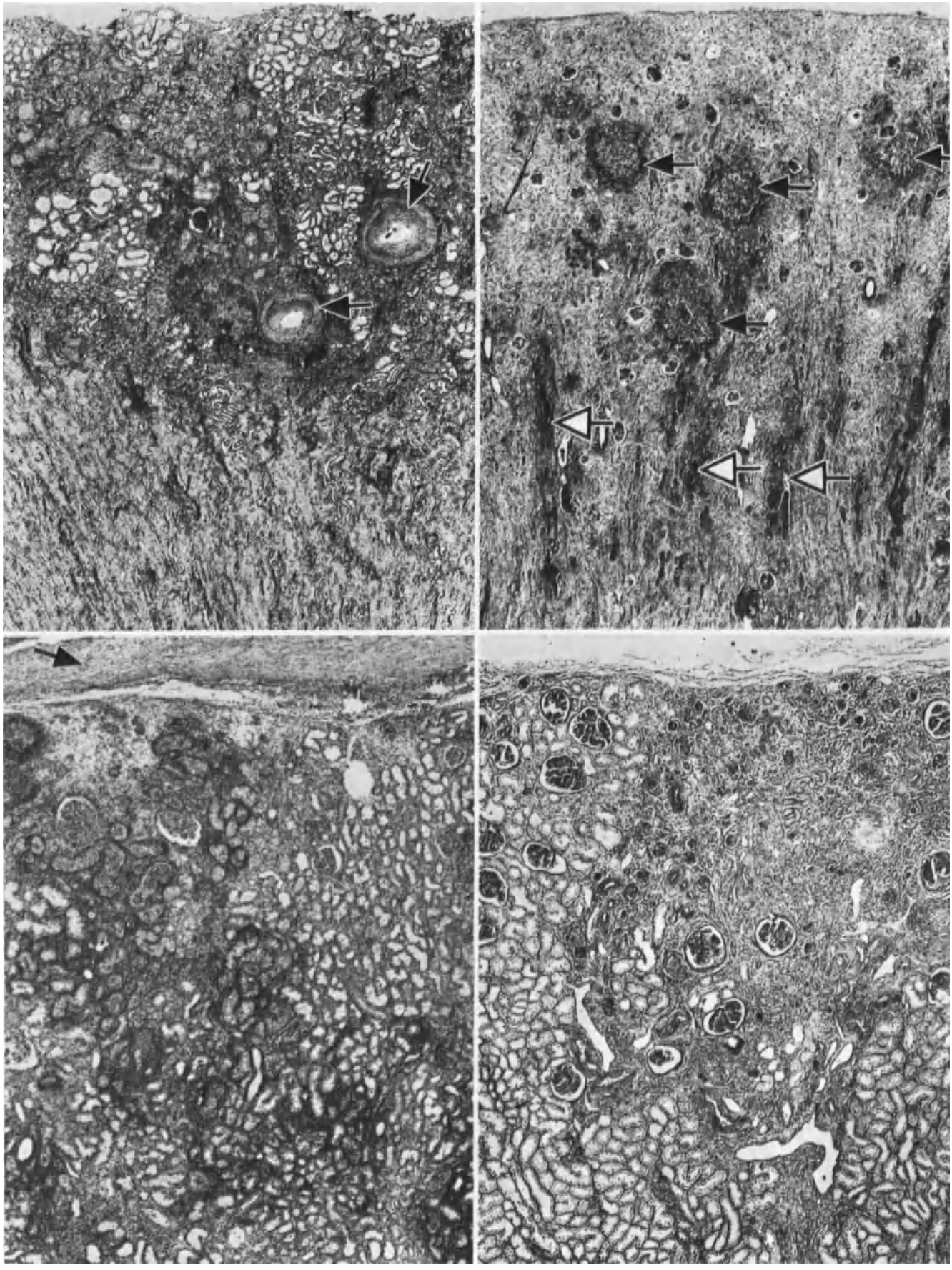
Acute infarcts present no diagnostic difficulties since tubular necrosis of noninfarct origin is never so clearly demarcated and always exhibits some change in neighboring elements (Fig. 5.2). So, the close proximity of freshly necrotic, regenerating and unchanged tubuli to each other is never observed in infarcts. A striking feature of infarcts, on the other hand, is the presence of a clearly defined bordering zone of reactive hyperemia and inflammation (Fig. 5.2).
Old renal infarcts are charcterized for months by the presence of necrotic glomeruli and tubules whose architecture is preserved (Fig. 5.3). Even in very old infarct scars, completely collapsed and 'hyalinized' tubuli can be identified.
Traumatic lacerations of parenchyma exhibit the features of infarcts along the edge of the tears. The cleft defect of the tear is initially filled in with fibrin and blood, then organizing tissue ultimately form a scar which can be differentiated from that of an infarct by the absence of identifiable parenchymal elements.

**Fig. 5.6.** Radiate scars of the renal cortex in arteriolosclerosis and severe arteriosclerosis (→). Female, 39 years. Van Gieson (×27) ▷

**Fig. 5.7.** Metastatic, embolic purulent focal nephritis in *Candida albicans* septicemia. Multiple glomerular abscesses (→) and so-called medullary excretory foci (↠) Male, 69 years. PAS (×16)

**Fig. 5.8.** Acute purulent pyelonephritis in stone obstruction of ureter: dark areas representing polymorphonuclear leukocytic infiltrates. Fibrous kidney capsule (→). Male, 54 years. HE (×31)

**Fig. 5.9.** Cortical focus in chronic pyelonephritis due to stenosis of ureteral ostium: wedge-shaped destruction of tubules accompanied by interstitial infiltration. Glomeruli are partly preserved. Male, 4 years. PAS (×28)



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### Massive Subinfarct

The massive subinfarct (incomplete infarct, vascular scar) is recognizable by the increased number of glomeruli per surface unit which is due to atrophy of the tubules (Figs. 5.4, 5.5; [1808], see also p. 508). A focal, interstitial inflammatory reaction can be present (Fig. 5.5). The smaller the subinfarct, the better the chance of finding the occluded vessel.

### Small Subinfarct

The small subinfarct is the substrate for the so-called arteriosclerotic scars of the renal cortex due to lesions of small and middle-sized arteries. Even smaller subinfarcts are found in association with lesions of the arterioles as occurs in arteriolosclerosis, arteriolonecrosis and nodular glomerulosclerosis (Fig. 5.6).

### Acute Purulent Pyelonephritis

This form of pyelonephritis cannot be differentiated from medullary and cortical nephritis due to purulent embolism (Fig. 5.7, see p. 426). The predominantly vascular character (glomerular/intertubular capillaries) of the disease disappears quickly and a severe inflammatory infiltration of the parenchyma is found which still retains its focal character and consists mainly of polynuclear neutrophilic leukocytes (Fig. 5.8).

### Chronic Pyelonephritis
So-Called Destructive Interstitial Nephritis

This renal change can be readily differentiated from vascular scars by the presence of focal inflammation of the interstitium and by tubular destruction (Fig. 5.9). A striking feature of the lesion is the relatively good preservation of the glomeruli (Figs. 5.9, 5.10). Although in cases of coalescence of foci the differential diagnosis under low-power magnification is difficult, it can usually be resolved under higher power.
The occurrence of so-called thyroid-like foci in scarred areas (Fig. 5.11, see p. 437) is highly characteristic for pyelonephritis; they usually do not occur in vascular or glomerular processes nor—with the exception of kidney tuberculosis (Fig. 5.12)—in other interstitial lesions. A typical feature of early childhood PN is the poverty of intact glomeruli and the difficulty in recognizing obsolescent glomeruli. Dysplastic foci, which are never wedge-shaped and which usually evidence large and small cysts, are easily differentiable (Fig. 5.13, see p. 51).

### Nondestructive Interstitial Nephritis

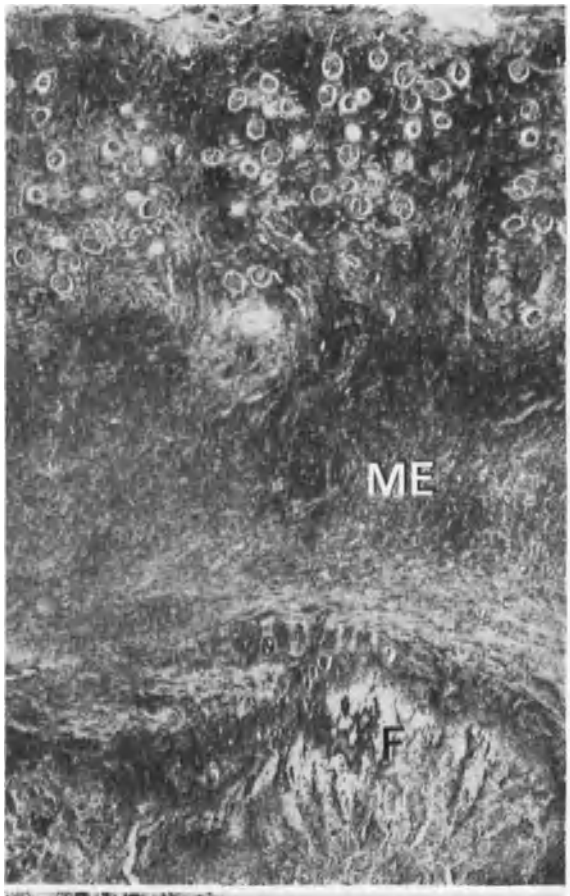
Acute nondestructive interstitial nephritis (see p. 407) is characterized in the acute phase by the hypercellularity of the interstitium and its broadening by edema, both especially marked at the corticomedullary junction. The parenchymal architecture is, on the whole, preserved, i.e., there is no actual destruction of the renal elements.
The very rare chronic form is characterized by the uniformity of the tissue as viewed under low-power magnification (Fig. 5.14). One encounters the diffuse but now sclerotic/fibrotic broadening of the interstitium and the prominence of papillary necrosis. Many glomeruli are ultimately obsolescent, and the tubuli are always severely atrophic. Here too, the fundamental renal structure is preserved. Differential diagnosis with respect to nephronophthisis is done by identification of cysts situated at the corticomedullary junction Fig. 5.15) which are mostly present in nephronophthisis. Such identification is only possible on slides with a complete kidney or large sections thereof.

**Fig. 5.10.** Xanthomatous pyelonephritis associated with nephrolithiasis: Massive inflammatory infiltration in the cortex and, above all, in the medulla (*ME*). Renal pelvis has been replaced by granulation tissue with numerous foam cells (*F*). Glomeruli in inflamed cortex are fairly well preserved, but densely packed. Female, 34 years. HE (×23) ▷

**Fig. 5.11.** So-called thyroid-like focus, i.e., widened tubules with atrophic epithelium and compact colloid-like contents in hydrocalicosis. Focal, marked narrowing of the cortex (→). Surgical biopsy. Female, 84 years. PAS (×62)

**Fig. 5.12.** Tuberculous putty kidney with thyroid-like transformation of overlying parenchyma. Caseous focus encapsulated by connective tissue (*X*). HE (×10)

**Fig. 5.13.** Dysplastic focus in the renal cortex: numerous thin-walled cysts surrounded by fibrous tissue. Male, 68 years. HE (×14)

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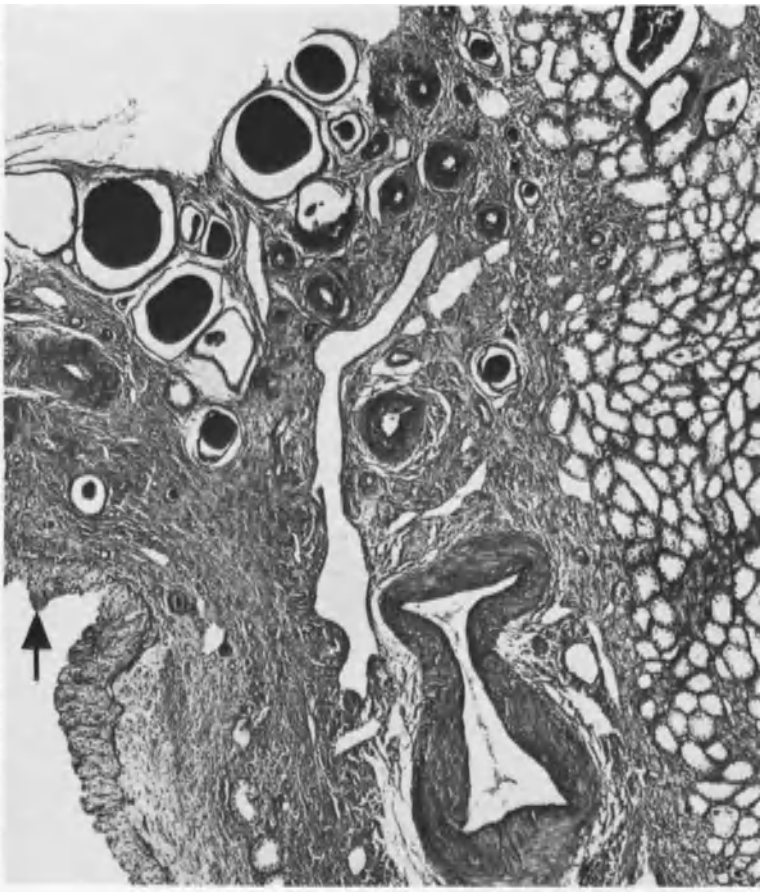

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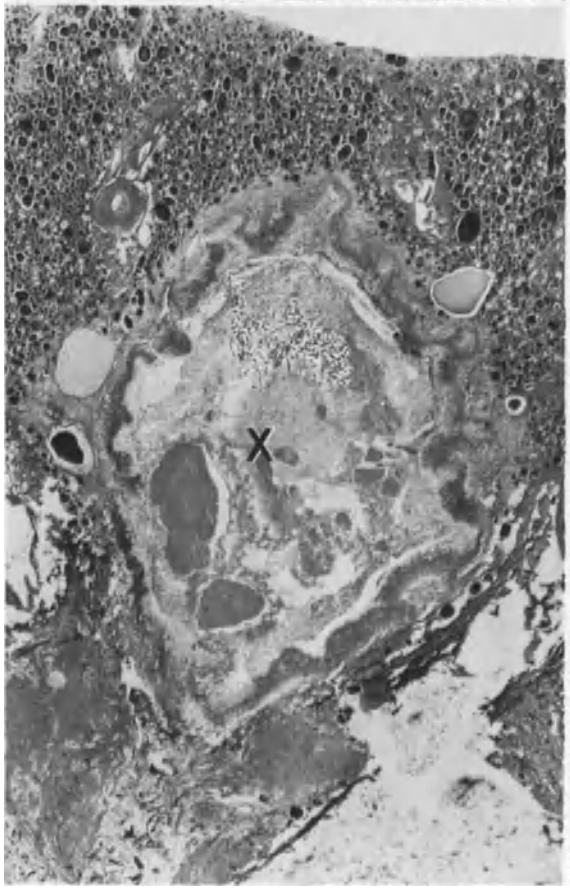


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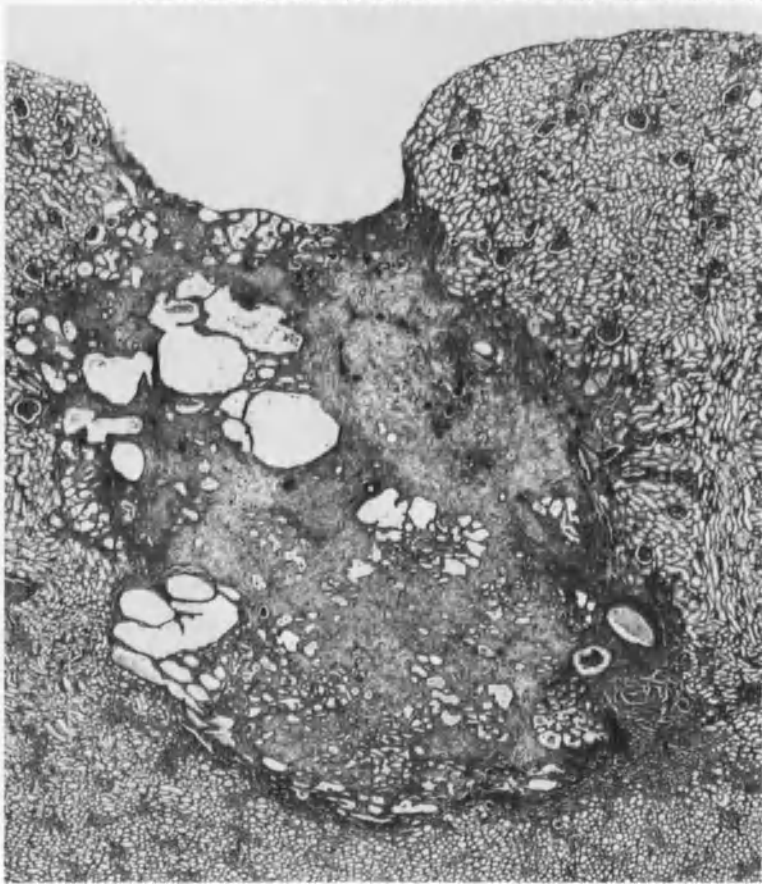

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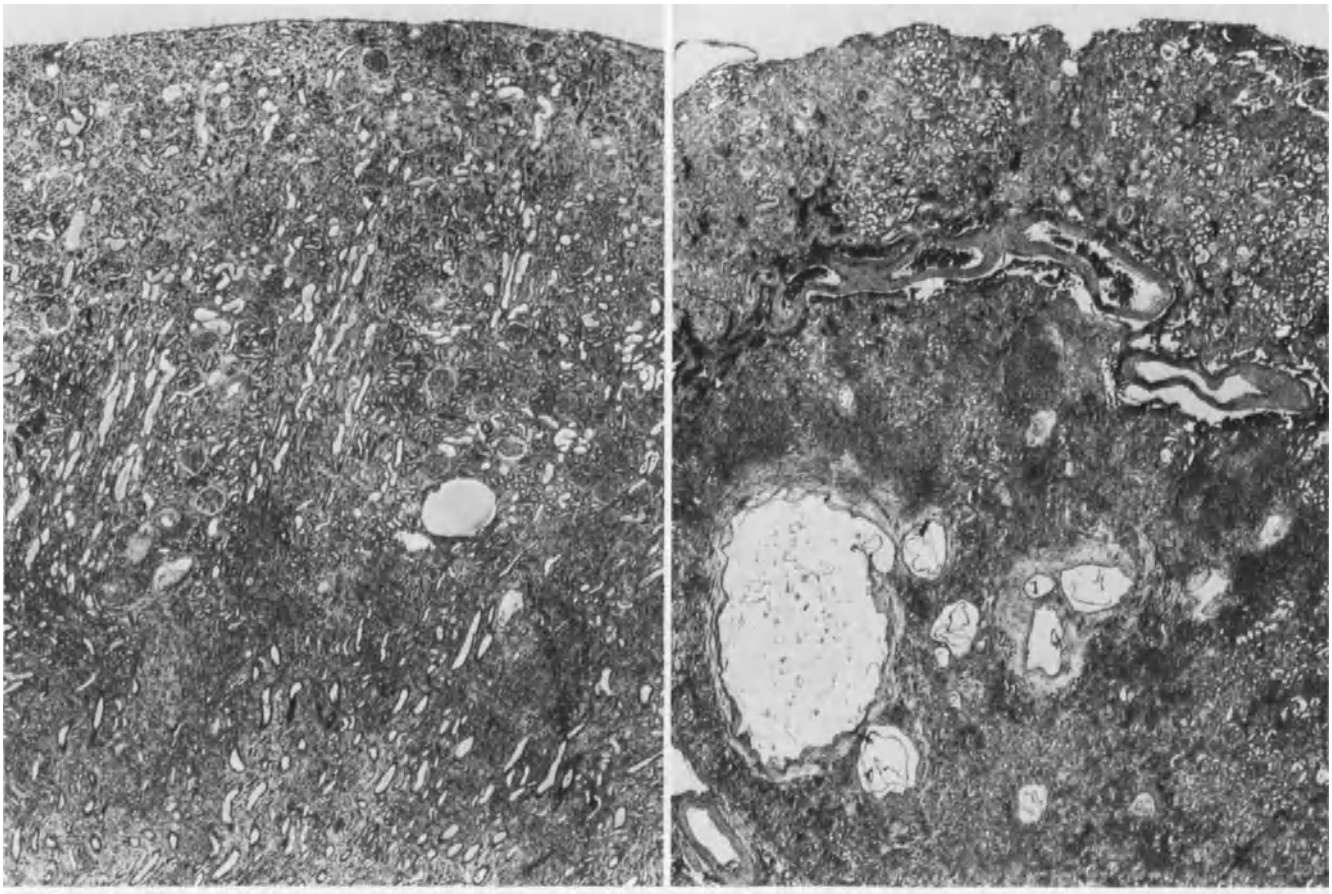

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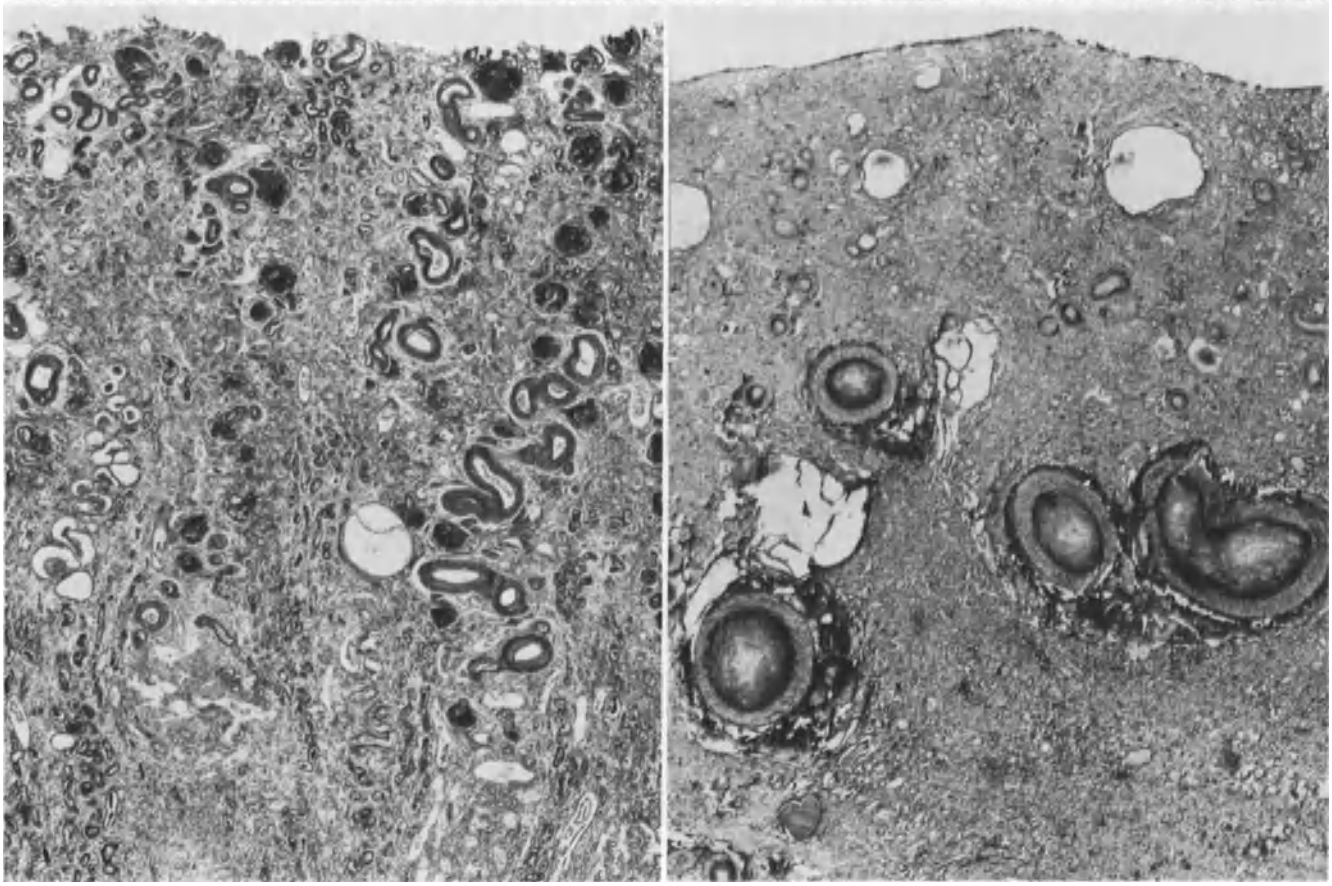

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### Diffuse Glomerulonephritis

Diffuse glomerulonephritis is not difficult to identify under low-power magnification. It is typically characterized by involvement of almost all glomeruli and the absence of destructive foci. Changes in the blood vessels cannot be differentiated from those found in other diseases (Fig. 5.16).

### Contracted Kidney (End Stage Kidney)

The actual contracted kidney often eludes further etiologic classification (Fig. 5.17); this is especially true after prolonged hemodialysis. Thus, all arteries evidence severe adaptive intimal fibrosis (Fig. 5.17), which is most pronounced today subsequent to prolonged dialysis or to kidney transplantation.

◁ **Fig. 5.14.** Chronic interstitial nondestructive nephritis. Overall renal structure is preserved. Surface is smooth. Glomeruli and tubules are intact; interstitium is widened and inflammatorily infiltrated. Male, 60 years. HE (×23)

**Fig. 5.15.** Nephronophthisis: Near the corticomedullary junction numerous small cysts and dark areas indicating inflammatory infiltrates are present. Cortex is severely atrophic, vessels are unchanged. Surface is humpy. Male, 12 years. HE (×9.5)

**Fig. 5.16.** Glomerulonephritic contracted kidney: Cortical tissue is very atrophic. Glomeruli are mostly obsolescent. Tubules are atrophic and, in rare cases, show cystoid widening. Surface is finely humpy. Male, 37 years. PAS (×31)

**Fig. 5.17.** End-stage kidney. Scattered secondary cortical cysts and intense adaptive intimal fibrosis of arcuate arteries and their branches. Male, 44 years. Van Gieson elastin (×18)

# 6. Histopathology of the Glomerulus Under High Power Magnification

Following low-power study, the next step involves the determination under high power LM and EM of the structural element(s) most intensely—and, presumably primarily—affected. Conventionally, the study sequence of structures in this process is glomeruli→tubules→vessels→interstitium.

If one is dealing with material obtained by open, surgical biopsy, portions for microscopic study are best suited from edges of pathologic lesions (if the lesion is not diffuse). This manner of evaluation generally yields satisfactory results, but is not so rewarding in advanced processes, especially in contracted kidneys.

In glomerular minimal change, the predominant feature is often that of lipoid nephrosis—lipid deposition in tubular epithelium and interstitial cells—instead of glomerular changes (see p. 367).

A very frequent error in this stage of biopsy evaluation is the misinterpretation of the very obvious adaptive intimal change of the arteries (Fig. 5.17) as a primary vascular disease, an error which can be avoided (study with relatively high-power magnification) by rigorous analysis of the individual structural elements.

For purposes of coherence, LM and EM findings are presented together. In agreement with the sequence of study used by histopathologists, the glomerular parameters will be discussed in the following order:

1. Glomerular size
2. Hypercellularity
3. Changes in the capillary loop lumens
4. Capillary loop necrosis
5. Pathological capillary loop contents
6. Changes of the capillary loop wall.
7. Changes of other glomerular capillary wall constituents
8. Changes of the mesangium
9. Changes of the glomerular capsule
10. Glomerular obsolescence.

## Glomerular Size

Glomerular size varies considerably from individual to individual (see p. 28). Therefore, a table of normal values (see p. 29) must be consulted before a pathologically relevant deviation in size can be diagnosed.

Abnormally large glomeruli are found in association with chronic hypoxemia such as occurs in congenital cyanotic cardiovascular malformations, primary pulmonary hypertension, Indians living in the Andes [1164, 1175, 1542], polycythemia vera [314], and in chronic alcoholism [928], early infantile uretral obstruction [1164], different forms of GN [738], as well as in so-called oligomeganephronias [1394]. An especially pronounced enlargement is observed in the intact glomeruli of contracted kidneys of all etiologies and represents hypertrophy due to excessive load (Fig. 15.39; p. 306; [738]).

We are not aware of any disease in which abnormally small gomeruli occur. Even the fetal glomeruli occurring with the Alport syndrome (Fig. 6.1) do not constitute a special order of size [521].

Fetal glomeruli are, normally, encountered only in children under 6 months of age. However, they do occur in Alport's syndrome and cystinosis beyond this age (36) as well as in congenital nephrotic synchrome see p. 357.

## Hypercellularity

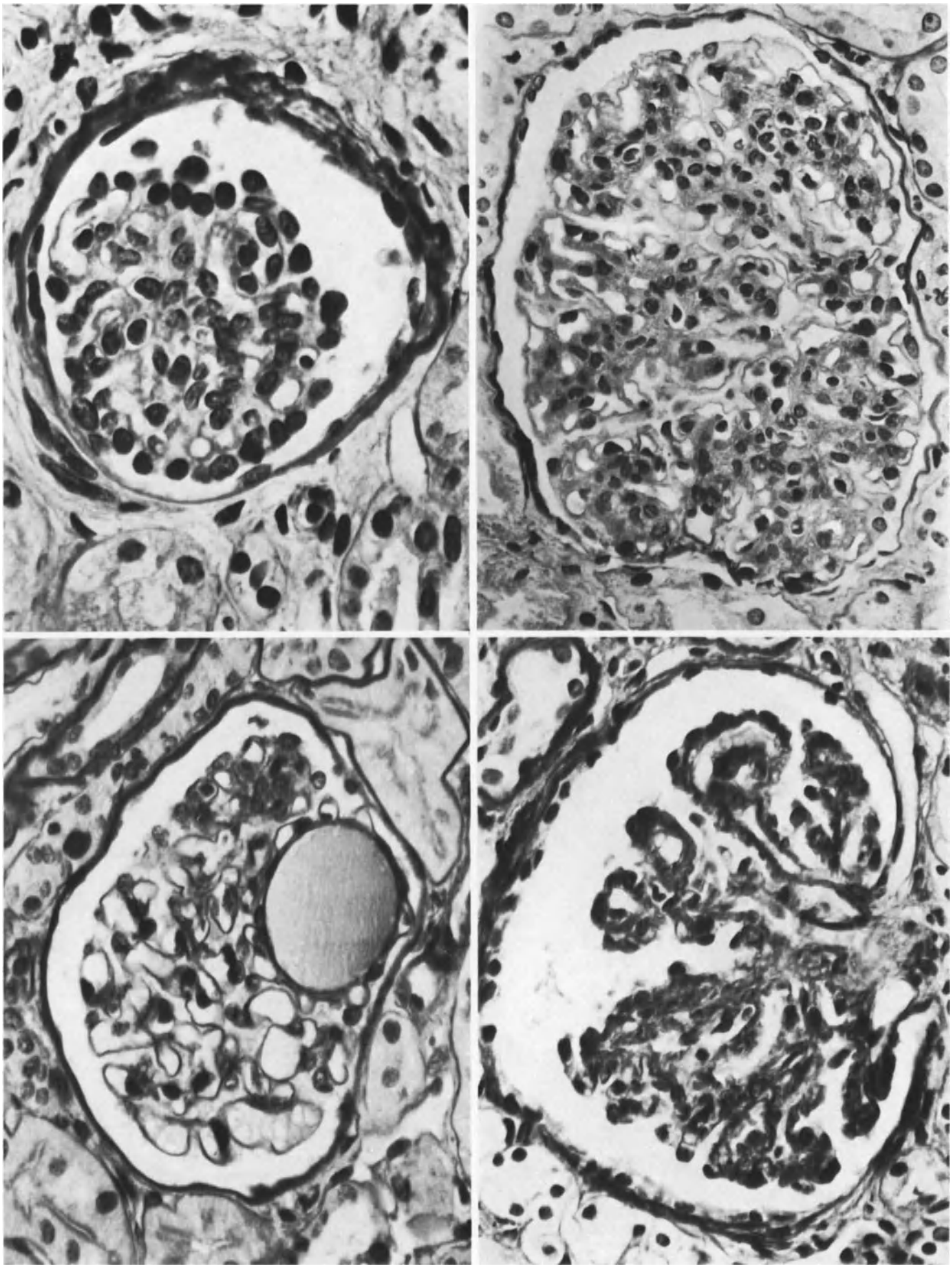
Glomerular hypercellularity is present when, in a thin paraffin section, the normal number of nuclei in a glomerulus (children 80, adults: 44–48) is considerably exceeded (Fig. 6.2).

**Fig. 6.1.** Abnormally small fetal—like glomerulus with cubic podocytes in Alport's syndrome. Capsular BM is partially thickened. Male, 3.5 years. PAS (×750) ▷

**Fig. 6.2.** Mesangial hypercellularity in endotheliomesangial glomerulonephritis, proliferative phase. Male, 15 years. PAS (×500)

**Fig. 6.3.** Capillary loop aneurysm in diabetic glomerulosclerosis. Male, 14 years. PAS (×700)

**Fig. 6.4.** Collapse glomerulus in malignant nephrosclerosis. Very severe wrinkling of capillary loop BM and loop collapse are present. Capsular space is widened. Female, 35 years. PAS (×600)



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It will be scarcely possible during daily kidney biopsy study to count nuclei on glomeruli sectioned equatorially. Day-to-day work depends much more on a practical estimate of the number of nuclei as judged by comparison to normal renal tissue. Slides for such comparison must be of equal thickness (2–3 μm).

If hypercellularity is encountered, the nature of the cells—local = structural, intravasal, or both—must be established. This differentiation is often only possible under oil immersion, for which the PAS stain, which clearly presents the BM, is indispensible.

Increase in intravasal cells may be due to an exudative phase of GN, leukemia or to severe systemic leukocytosis. Cases of structural hypercellularity are generally attributable to glomerulonephritic reactions.

## Changes in Capillary Loop Lumens

***Aneurysms of the Capillary Loops,*** i.e., widening of the entire peripheral glomerular capillary walls, are observed after radiation therapy (Fig. 27.2; p. 545), with diabetes mellitus (Fig. 6.3) and with nephropathies of pregnancy [1494].

Pseudoneurysms with very marked widening of the very translucent l. rara interna occur with transplantation glomerulopathy. In these cases, the l. rara interna can contain a few extruded red blood cells as well as fibrin fibers, the presence of which can very easily lead to the false diagnosis of true loop aneurysms (Figs. 30.47, 30.55; p. 590, 594). The original lumen is severely narrowed in this situation and is easily overlooked.

A further condition which may give rise to incorrect diagnosis of loop aneurysm is the severe loop dilatation found in blood stasis, e.g., in fresh renal infarct and in the intact area adjacent to an old infarct. In both situations, however, all cross-sections of the loops are widened and filled with sludged poorly stained erythrocytes (Figs. 24.29, 30.28; [1068]). Such dilated capillary loops are observed more rarely with chronic right heart insufficiency, renal vein thrombosis and GN.

***Narrowing of Capillary Loops*** may be the result of capillary loop collapse or proliferation, e.g., ingrowth of local cells. Capillary loop collapse is easily recognizable in the PAS/PASM stain by the extensive wrinkling of the BM (Figs. 6.4, 6.9). With EM, it is especially frequently observed in vascular nephropathies or those with vascular involvement, e.g., pyelonephritis (22.9%). We have observed collapse less frequently in transplanted kidneys (12.6%) and in GN (1.6%). As noted in EM, 42.4% of all cases of GN, narrowing of the capillary lumen is predominantly caused by proliferation of in situ structural cells (mesangial and endothelial cells). In pyelonephritic diseases and in arteriolosclerosis (Figs. 6.5, 6.9) we noted proliferative capillary loop narrowing in only 15% of our cases and in 11.5% in transplanted kidneys. We have only once observed the occurrence of collagen fibers in completely obsolescent capillary loops.

## Capillary Loop Necrosis

These necroses (Fig. 6.6) which are often accompanied by so-called hyaline thrombi (better fibrinoid) occur above all in SLE, extracapillary accentuated GN, ischemic states and, with greater frequency, in malignant nephrosclerosis. Partly, they may be caused by increased intracapillary pressure [1090]. Loop necroses are also encountered in some forms of focally accentuated GN, e.g., GN in subacute bacterial endocarditis, Goodpasture syndrome, Wegener syndrome.

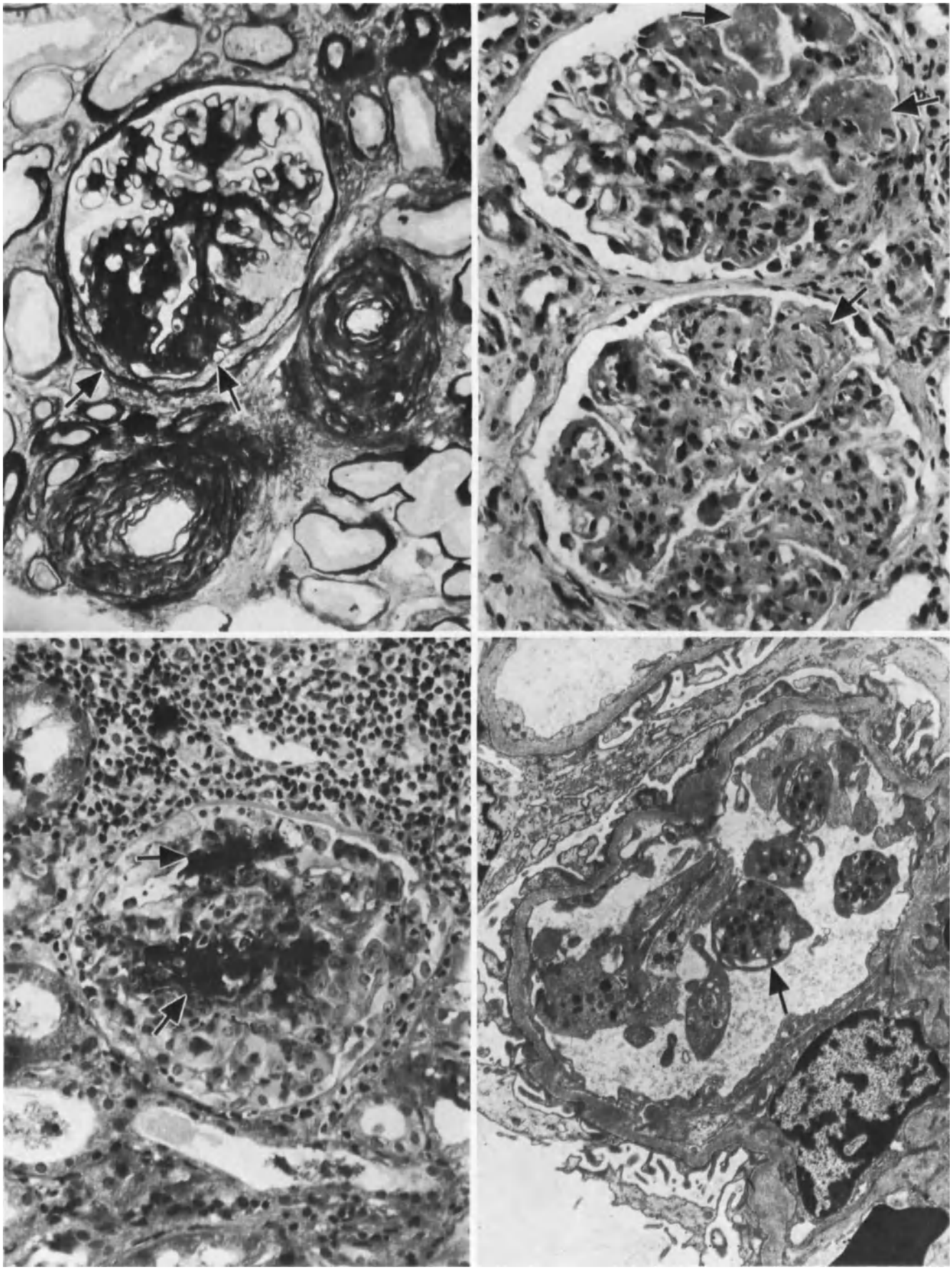
Since necrotic material and thrombi stain yellow with the van Gieson stain, they are usually termed fibrinoid. Fibrin can occassionally be clearly demonstrated with fibrin stains (Fig. 6.7). However, wall necroses can be secondarily impregnated with fibrin/fibrinogen. Strong dimming with the light microscope helps in recognizing the fibrillar structure of fibrin in thrombi. Loop necroses are often accompanied by inflammatory glomerular reactions.

**Fig. 6.5.** Severe arteriolosclerosis in diabetes mellitus with obsolescent glomerular loop segments (→). Male, 59 years. PASM (×310) ▷

**Fig. 6.6.** Capillary loop necroses (→) in membranoproliferative GN associated with SLE. Female, 27 years. HE (×350)

**Fig. 6.7.** Extracapillary accentuated GN with extensive fibrin (→) deposits between glomerular capillary loops. Interstitial inflammation is severe. Male, 46 years. Picro-Mallory (×275)

**Fig. 6.8.** Thrombocytes (→) in glomerular capillary loop (chance finding in latent diabetes mellitus and laxative abuse). Female, 41 years. EM (×650)



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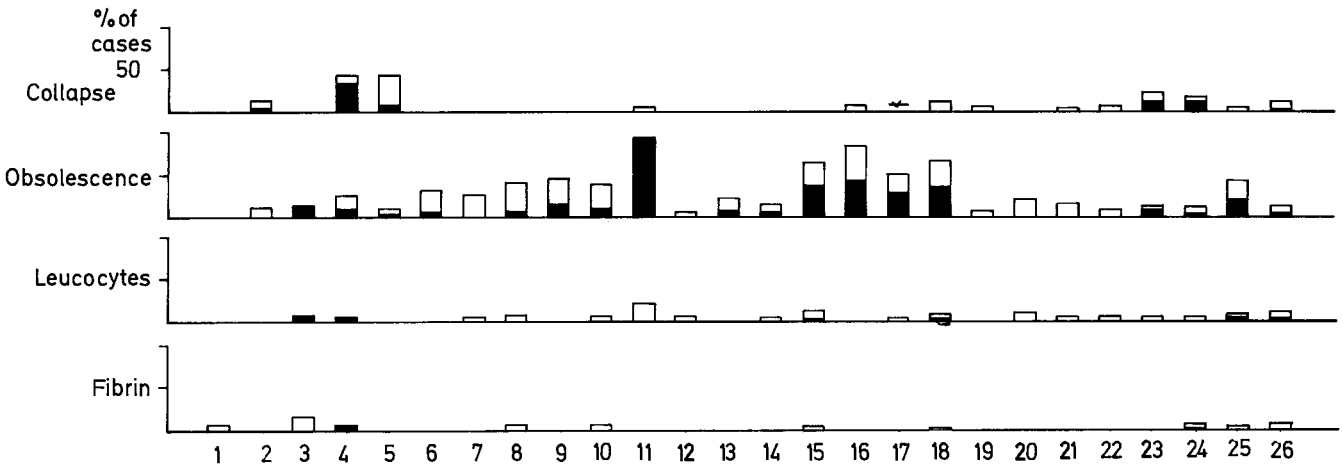



**Fig. 6.9.** Histogram: Change in glomerular capillary loops and their contents. (*n*: number of cases/total number of glomeruli investigated)

1. Normal kidney (17/26)
2. Glomerulonephrosis/glomerulosclerosis (28/48)
3. Acute interstitial nephritis (14/26)
4. Chronic pyelonephritis (26/57)
5. Arteriolosclerosis (21/36)
6. Alport's syndrome (17/35)
7. Proliferative endotheliomesangial GN (18/33)
8. Proliferative sclerosing endotheliomesangial GN (48/94)
9. Proliferative sclerosing endotheliomesangial GN with < 50% crescents (13/24)
10. Total cases of endotheliomesangial GN (87/168)
11. Membranoproliferative GN (19/42)
12. Epimembranous GN stage I and II (15/31)
13. Epimembranous GN stage III and IV (13/24)
14. Total cases of epimembranous GN (28/55)
15. Proliferative FGN without crescents (40/78)
16. Proliferative FGN with < 50% crescents (14/29)
17. Sclerosing FGN (20/39)
18. Total cases of FGN (74/146)
19. Glomerular minimal change IF-negative (17/33)
20. Glomerular minimal change IF-positive (24/40)
21. Total cases of glomerular minimal change (96/177)
22. Transplant glomerulopathy degree 0 and 1 (41/73)
23. Transplant glomerulopathy degree 2 and 3 (21/46)
24. Total cases of non-GN diseases ($n=140$)
25. Total cases of GN ($n=363$, including glomerular minimal changes)
26. Total cases of kidney transplants ($n=95$)

Total height of column represents percentage of positive cases, and black part that of cases with moderately severe to severe findings. Obsolescence refers to glomerular capillary loop occlusion due to proliferation only.

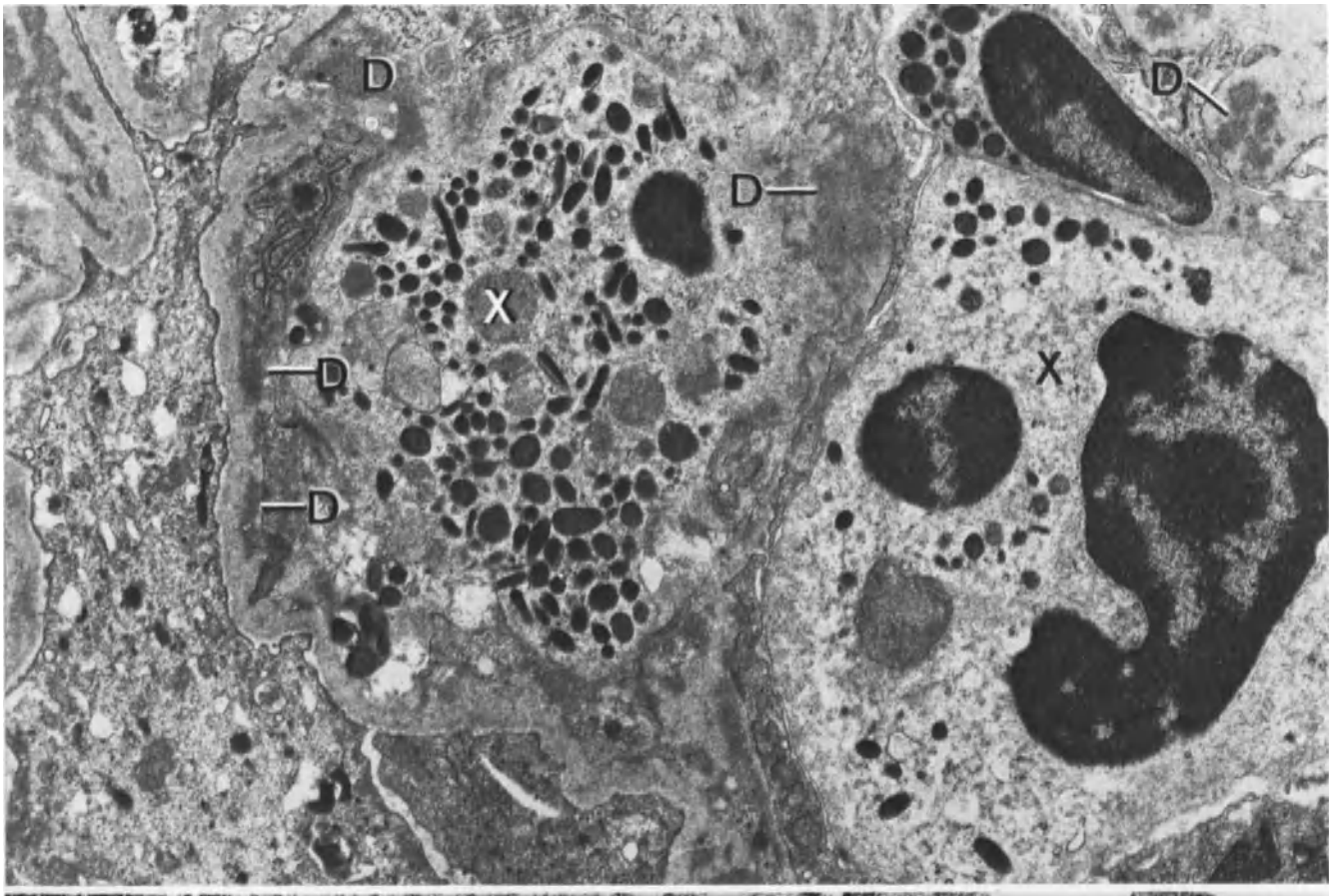
## Pathological Capillary Loop Contents
(see Fig. 6.9)

### Erythrocytes

A moderate number of erythrocytes is found in the capillary loops in practically all biopsies. Massive glomerular hyperemia is observed in chronic right heart insufficiency, in the region of infarcts, in the early stage of vascular transplant rejection and of GN as well as in renal vein thrombosis. Rarely do all glomeruli evidence the same degree of hyperemia.

**Fig. 6.10.** Extracapillary accentuated GN. In the glomerular capillary loops two polymorphonuclear leukocytes can be seen (X), note subendothelial, osmiophilic deposits (*D*). Female, 40 years. EM (× 10,000) ▷

**Fig. 6.11.** Endotheliomesangial GN, proliferative phase. Severe ballon formation (X) and pronounced foot process fusion (→). Male, 48 years. EM (× 26,000)

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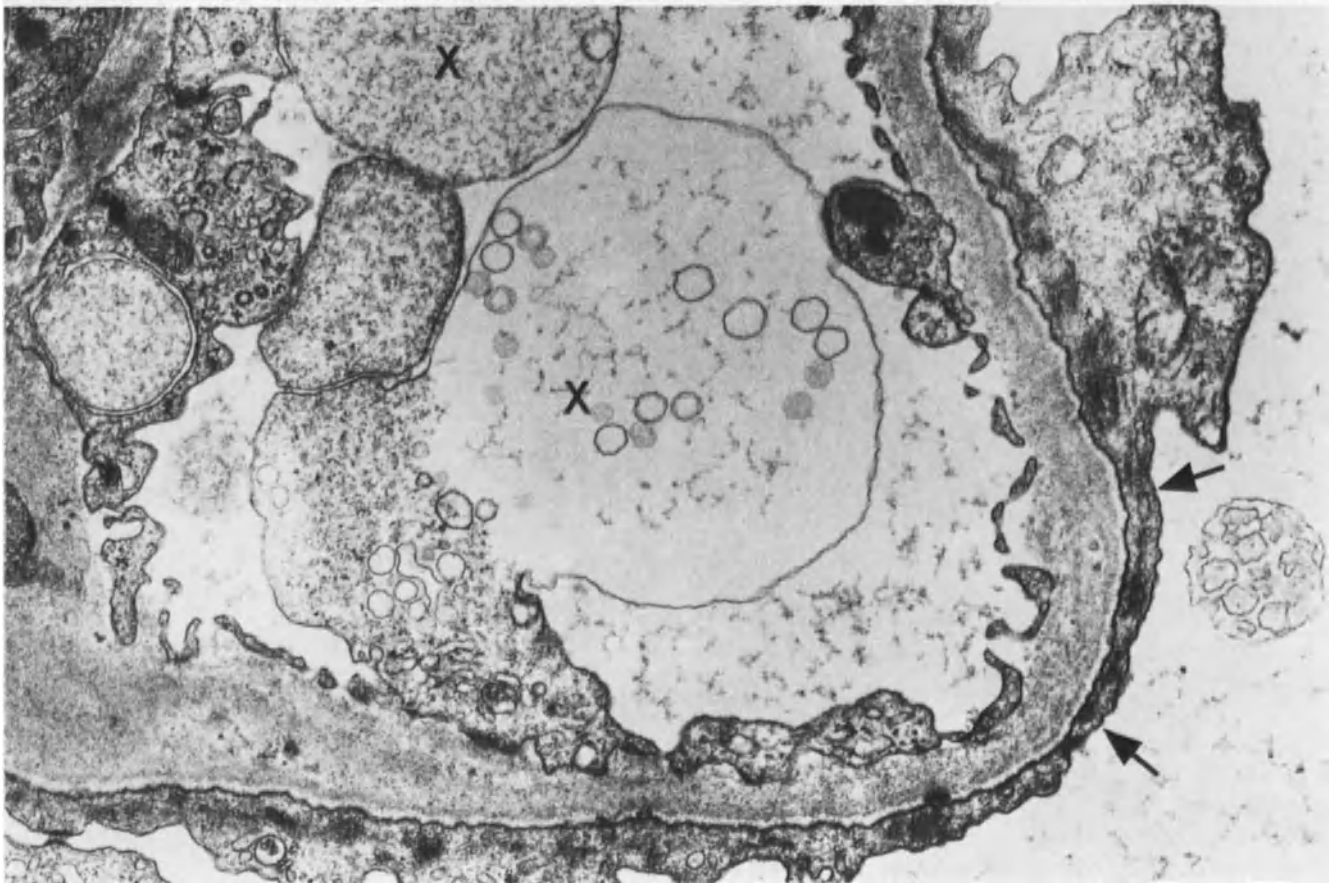


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### Polynuclear Leukocytes

Glomeruli in biopsies normally contain less than 6 leukocytes (in EM, rarely more than 2). More than 20 leukocytes per glomerulus (postmortal more than 12) are certainly pathologic (Figs. 6.10, 14.4; p. 197). An increase in the glomerular leukocytes leads to the picture of hypercellularity (see p. 54). Differentiation between hypercellularity due to increased numbers of leukocytes or to proliferation of structural cells can readily be realized with frozen sections with the perioxidase reaction or, as previously indicated, by study under oil immersion. A glomerular increase in leukocytes occurs in severe systemic leukocytosis, leukemia, acute pyelonephritis and during the exudative stage of GN.
In GN, the increase in glomerular leukocytes is due to the release of leukotaxic substances, especially of complement factors [229].
In our EM material, we found an increase of leukocytes in 7.1% of our GN cases, in 8.6% of kidney transplants and only in 1.4% of other renal diseases.

### Monocytes

Although a few scattered glomerular polymorphonuclear leukocytes need not be the expression of a pathologic condition, accumulations of monocytic elements with their large, spongy nuclei in the glomerulus are always a sign of a pathologic process [875] (Fig. 14.20; p. 204). To be sure, they are rarely observed and are very difficult to differentiate from endothelial or mesangial cells. We found monocytes in 0.9% of GN cases and in 7.6% of our transplants but never in other renal lesions.

### Thrombocytes

A few glomerular thrombocytes do not necessarily indicate disease [1508]. Thus, we found in 1 out of 17 of our so-called normal kidneys a few isolated, intact thrombocytes (Fig. 6.8). However, the simultaneous occurrence of thrombocytes and fibrin is always indicative of a pathologic process. Thrombocytes can only rarely be identified since, following their degranulation, it is very difficult—or even impossible—to differentiate them from so-called "balloons" (Fig. 6.11). We have observed thrombocytes in 4.3% of our transplant cases as well as in intravasal coagulation, but not in other renal lesions (Fig. 6.9).

### Balloons

As viewed with EM, capillary loops often contain large blebs (called balloons) which are free from organelles and are surrounded by membrane (Fig. 6.11). Balloons can arise by evagination of endothelial cells [1470] or mesangial cells [1760], and their formation—which can be induced by any type of noxious agent and especially under hypoxia—probably occurs rapidly [1508].
Presence of balloons in the capillary lumen along with free cell organelles and cell fragments indicates an artifact [1508].

### Fibrin

Isolated strands of fibrin without accompanying leucocytes, thrombocytes or monocytes have occassionally been observed even in so-called normal kidneys (1 out of 17 of our cases, see Figures 6.9, 6.12). In these cases, material was usually from open, surgical biopsies which were taken following clamping of renal vessels.
In general, however, fibrin is an indication of a pathologic process. We have, in EM, observed fibrin in 5.4% of our transplant cases (especially in the acute rejection stage), in 1.3% of our GN cases, and in 2.9% of our cases of other renal diseases, especially pyelonephritis and acute interstitial nephritis (Fig. 6.9).

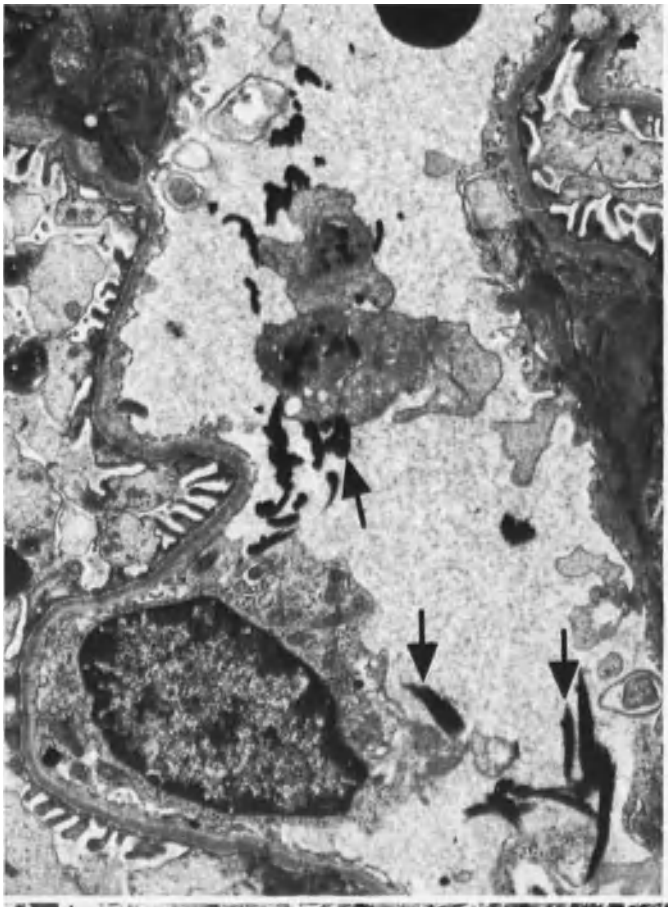
### Thrombi

In general, fibrin-thrombi are easily recognizable in HE stain by their oval or sausage-like form as well as by their fibrillar structure. Loop thrombi are characteristic of general intravasal coagulation and of GN in subacute bacterial endocarditis which is accompanied by a glomerular inflammatory reaction. They are infrequently observed in severe, diffuse GN (Figs. 6.7, 6.13, 6.14).

**Fig. 6.12.** Chance finding of fibrin strands (→) and thrombocytes in needle biopsy of an otherwise normal kidney in the presence of an adrenal cortical tumor. Female, 20 years. EM (×6000) ▷

**Fig. 6.13.** Multiple glomerular capillary loop thrombi (→) in exudative and severely necrotizing extracapillary accentuated GN. Male, 5 years. PAS (×150)

**Fig. 6.14.** Extensive glomerular capillary loop necroses with secondary fibrin thrombi in extracapillary accentuated GN. Female, 46 years. EM (×4000)



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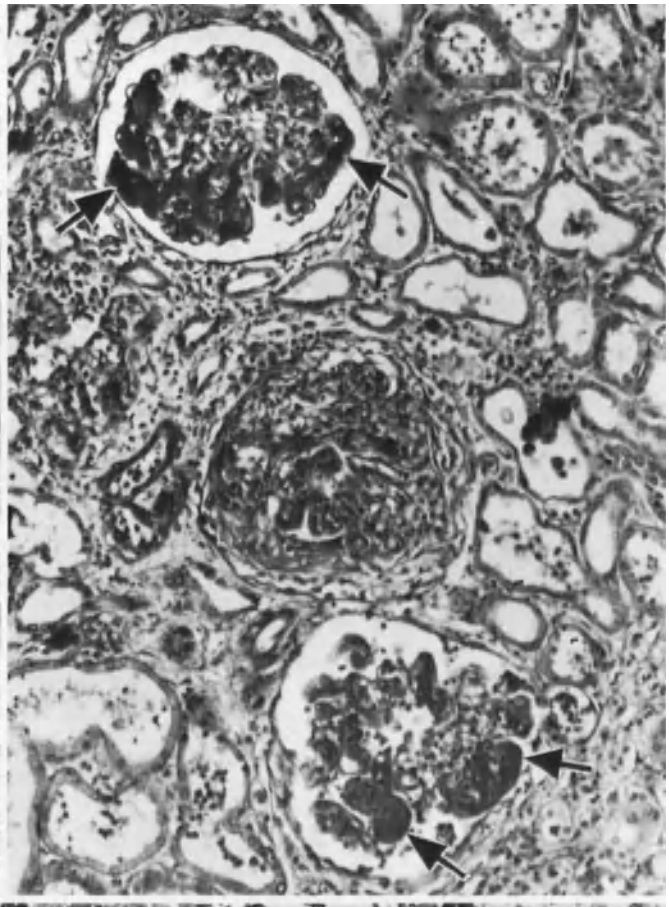

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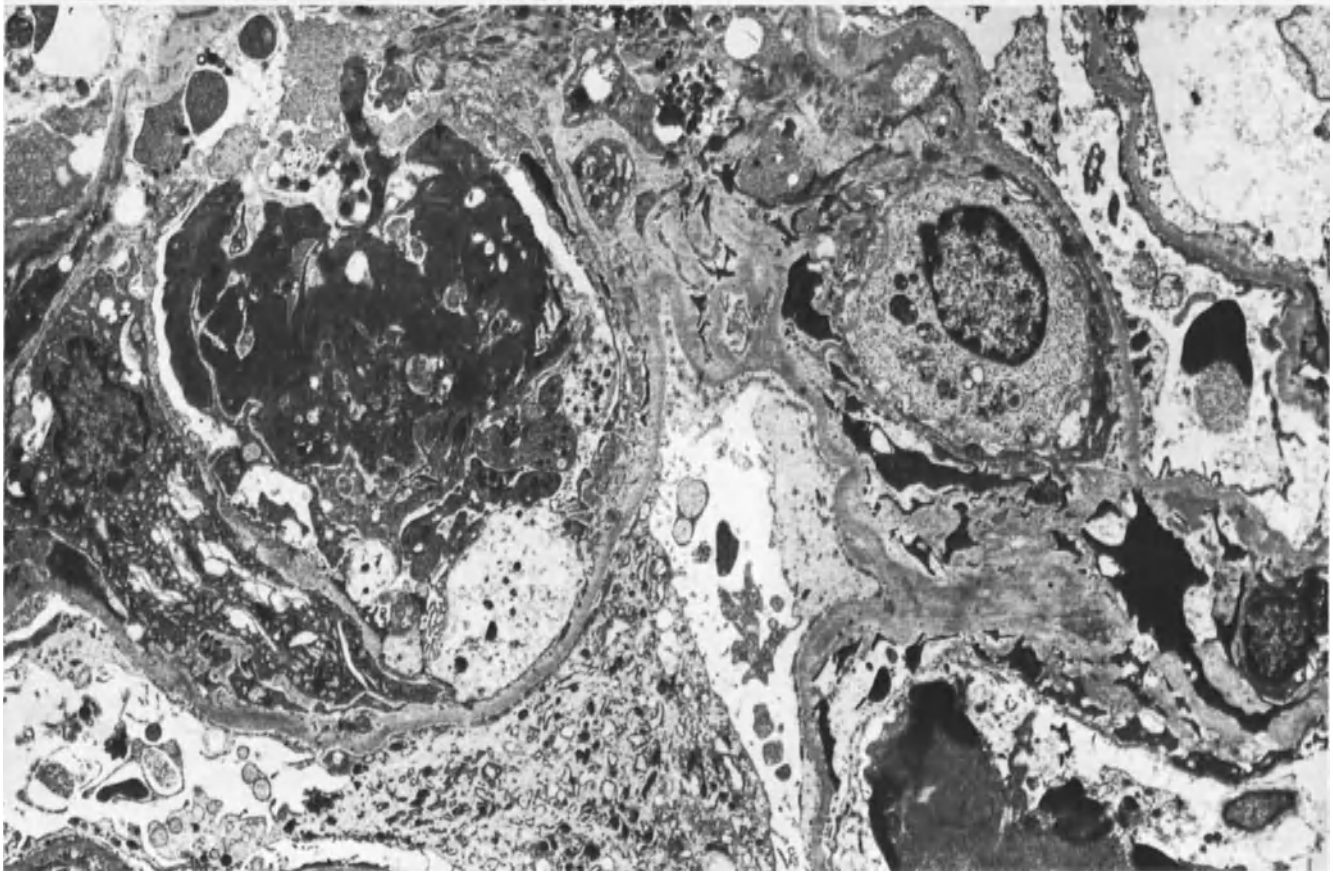

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### Giant Deposits

Loop thrombi must be differentiated from giant deposits (Fig. 6.15) which can fill up the entire capillary loop. These deposits are especially found in SLE (Fig. 17.21, p. 330) [280, 454], in macroglobulinemias [1136], cryoglobulinemias (Figs. 11.22, 11.23; see p. 169) [1138; 1075, 1291], as well as in partially or completely obsolescent glomeruli, e.g., in sclerosing FGN. The fibrinoid loop caps of diabetic glomerulosclerosis of Kimmelstiel-Wilson belong to this category (Fig. 6.19). In HE stains, the deposits appear homogeneous, shining and bright red, while in PAS stains they appear uniformly violet, and in v. Gieson stain yellow. Under LM, they always appear to lie extracellularly but under EM, they can be demonstrated in cryoglobulinemia to lie intracellularly (Fig. 11.22, p. 171).

### Other Findings

As observed under LM, completely empty strikingly oval or sausage-like spaces in dilated capillary loops point to fat embolism (Fig. 24.4).
Bacteria, fungi and tumor cells are rarely found in capillary loops.
Megakaryocytes are found in post-mortem biopsy tissue and especially in patients succumbing to prolonged shock. Interpretation of the presence of free mitochondria and stereocilia (Figs. 6.16, 6.17) is clouded with uncertainty; these findings are probably artifacts.

## Changes of the Capillary Loop Wall

### Wall Thickening Due to BM Changes

Thickening of the glomerular capillary loop wall is also referred to as 'membranous change' [1068] a designation which appears to us unfortunate. For judging the capillary loop wall only loops in the periphery of the glomerular tuft are suitable since in the center of the convolute, small segments of the mesangium can lead to incorrect interpretations. Fundamentally, there are three causes for wall thickening of which each is usually clearly identifiable under LM with the PAS/PASM and Masson trichrome/AFOG stains.

*1. Homogeneous Thickening of the BM.* The homogeneous form of BM thickening is observed in most cases of GN, in transplanted kidneys, Alport's syndrome, diabetes mellitus and in collapsed glomeruli. It is often difficult to diagnose in LM where it may be assumed present when the BM appears as a completely uniformly thickened membrane without any nodularity or splitting.

*2. Doubling of the BM.* A doubled membrane (tram-track picture, Fig. 6.18) is clearly recognizable with PAS and PASM stains. It is due to formation of a new BM either by interposition of mesangial cells or, much more rarely, to BM formation by endothelial cells or podocytes.

*3. Appositional Thickening of the BM.* This thickening occurs by deposition of fibrinoid material on the outer or inner surface of the BM or within the BM (Fig. 6.19) as well as by the deposition of amyloid (Fig. 19.13) under the endothelium and/or epithelium. When using PAS and PASM stains, swelling of cells alone (endothelial cells, podocytes and even fusion of foot processes) will not lead to its misinterpretation as BM thickening.
These three basic phenomena of BM thickening as observed under LM can be resolved into a wide spectrum of individual changes with EM. These changes are presented schematically in Figures 6.21 and their quantitative distribution is indicated in Figures 6.22, 6.23.
The three types of BM widening will now be discussed in greater detail.

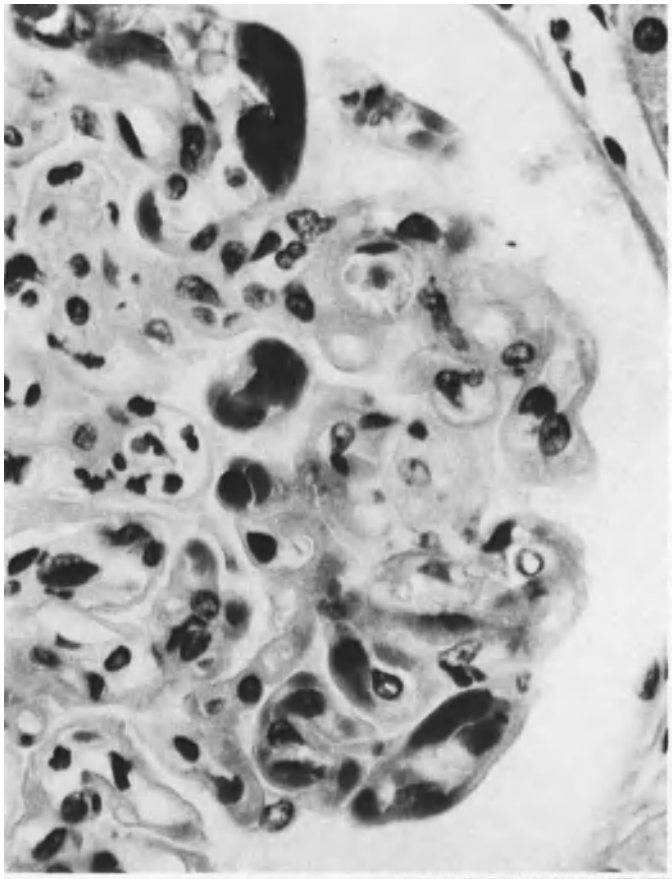
### 1. Homogeneous Thickening of the BM

***Thickening of the Total Peripheral Glomerular Lamina (l.) Densa of the BM.*** This type of thickening is very frequently observed (Fig. 6.20). It is limited partially to a more or less nodular form occuring in short segments in the neighbourhood of the mesangium but, in other cases, the change may encompass the entire circumference of the BM. This mode of BM thickening is frequently encountered in GN [275, 454]; (Fig. 6.22) and is frequently observed in diseases associated with pathologic disturbances of metabolism, e.g., diabetes mellitus (Fig. 19.24) and in ischemia ([1154, 1675]; Fig. 6.22).

**Fig. 6.15.** Extensive fibrinoid giant deposits in severe membranoproliferative GN (exudative stage) which are reminiscent of glomerular capillary loop necroses. Male, 64 years. Masson's trichrome (× 1000) ▷

**Fig. 6.16.** Numerous stereocilia and scattered mitochondria (*MI*) in a glomerular capillary loop in GN. Male, 24 years. EM (× 16,700)

**Fig. 6.17.** Glomerular minimal change: Free mitochondria (*MI*), phago-(hetero-)lysosomes, i.e., protein droplets (*PD*), stereocilia (→), endothelium (*E*). Female, 24 years. EM (× 10,000)



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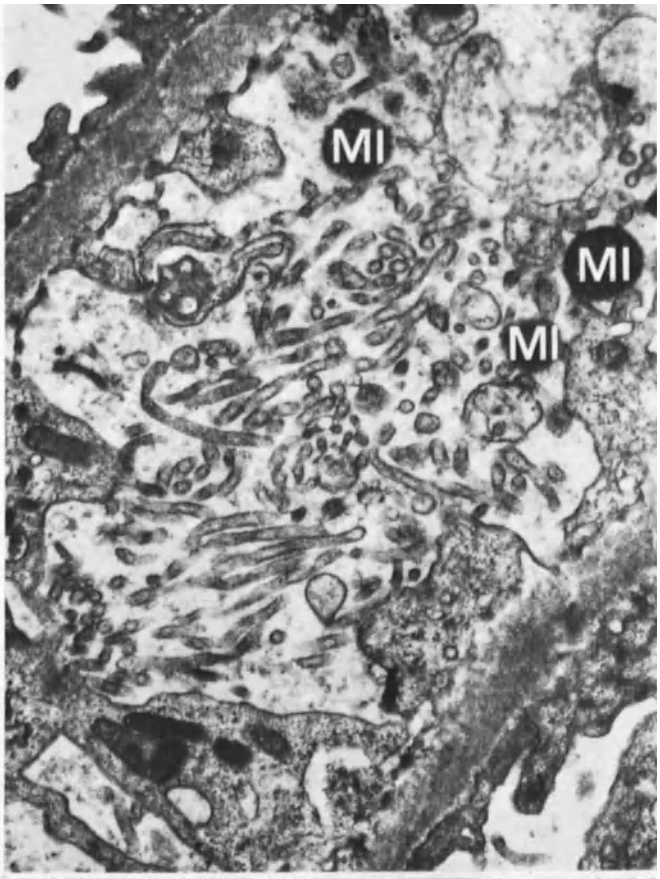


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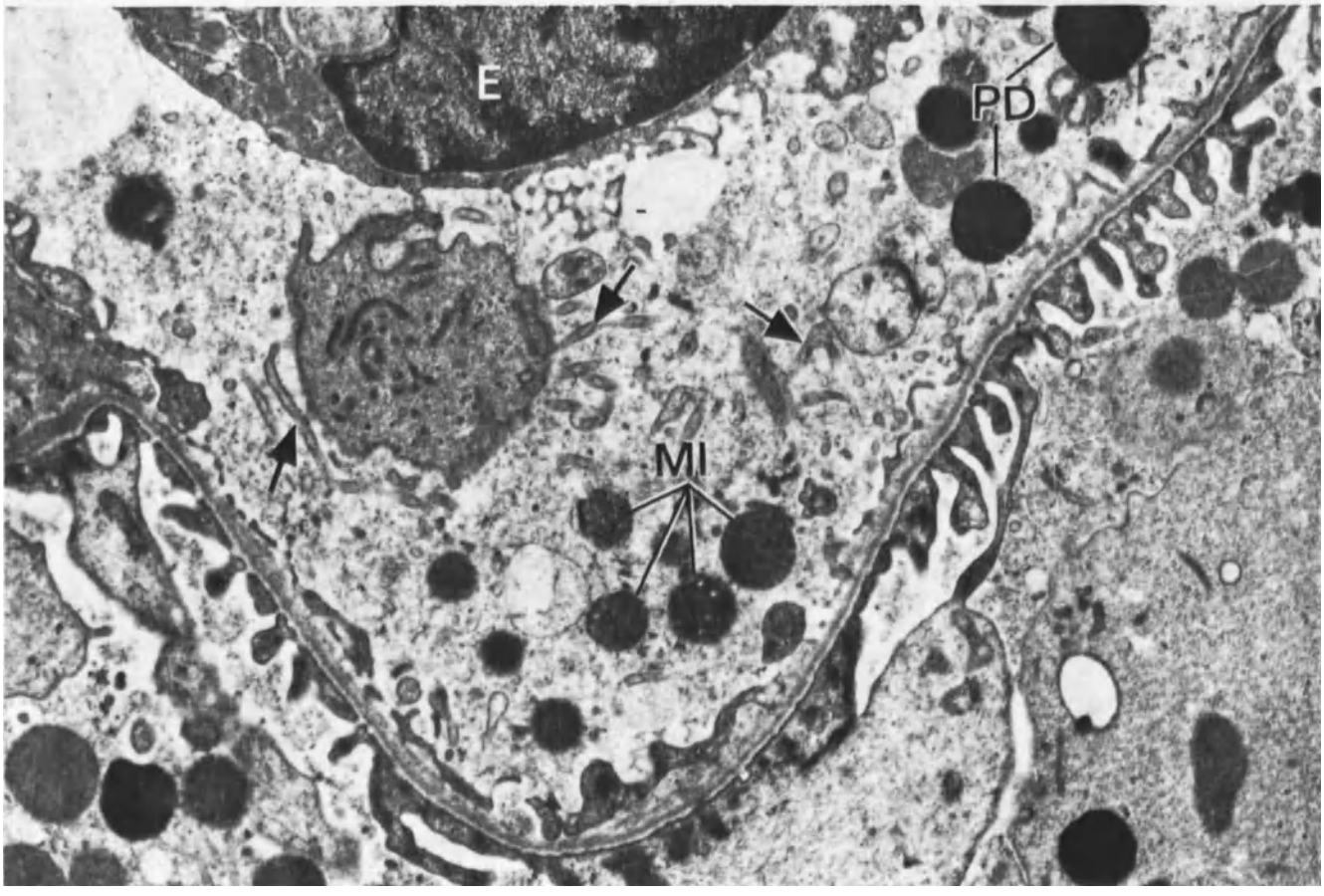


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In ischemia, the usually present simultaneous loop collapse with severe wrinkling of the BM (Fig. 6.20) facilitates the diagnosis. Under EM, one must be careful to avoid false interpretations of tangential sections.

***Lamellation of the Lamina Densa.*** One special form of BM thickening is accompanied by splitting or, rather, lamellation of the l. densa (Figs. 6.21, 6.24). Together with fragmentation and reticulation, it is found regularly in Alport's disease and can, accordingly, be considered pathognomonic for this entity (see Fig. 6.22 and p. 469).
Focal splitting of the l. densa—with some reticulation but without fragmentation—has been found in 14.9% of our GN cases and in 6.5% of our kidney transplants but in only 0.7% of other nephropathies (Figs. 6.22, 6.25).

***Thickening of the Lamina Rara Interna.*** This form occurs very frequently but, except for extremely severe disease, is only demonstrable under EM (Figs. 6.21, 6.22, 6.23, 6.26). The widening of the l. rara interna has been incorrectly referred to as "translucent deposits" [842]. The thickening of the l. rara usually does not exceed the thickness of the l. densa itself and is often limited to BM segments in the neighbourhood of the mesangium.
We have found this change in 50% of all GN (Fig. 6.22) and transplants and in 30% of all nonglomerulonephritic renal diseases. In glomerular minimal change it is rarely missed (Fig. 6.22). We encountered an especially severe form in scleroderma (Fig. 6.27). The occurrence of pad-like widening of the l. rara interna in Weil's disease [1800] as well as its frequent presence in kidney transplants [1805] indicates a pathogenetically primary endothelial lesion (see also [1675]).
When the l. rara interna is much widened—especially in transplants—a very thin newly formed subendothelial densa lamella is formed (Figs. 6.21, 6.22, 6.23, 6.26). The suggestion that this change occurs regularly upon permeation of the l. rara interna with plasma proteins and fibrinogen [841, 1654] appears questionable to us since EM osmiophilic deposits and fibrin are usually absent (no correlation with deposits: Fig. 6.23). The change seems to disappear following restitution of the endothelial lesion (contra, see [1081]).

***Thickening of the Lamina Rara Externa.*** Irregular widening (Fig. 6.21) is, in contradistinction to that of the l. interna, rarely seen, and never under LM. We have observed it only eight times, and exclusively in GN and kidney transplants (Fig. 6.22).

**2. Doubling of the BM**

We always consider a doubling of the BM (tram-track picture) to be present if we find newly formed densa lamellae separated from the original l. densa (Fig. 6.21). Accordingly, two basic forms of BM doubling can be distinguished:

1. BM doubling without cellular interposition in which one or more newly formed l. densa lamellae are separated from the original l. densa by l. rara-like material,
2. BM-doubling in which newly formed l. densa lamellae are separated by mesangial interposition from the original l. densa.

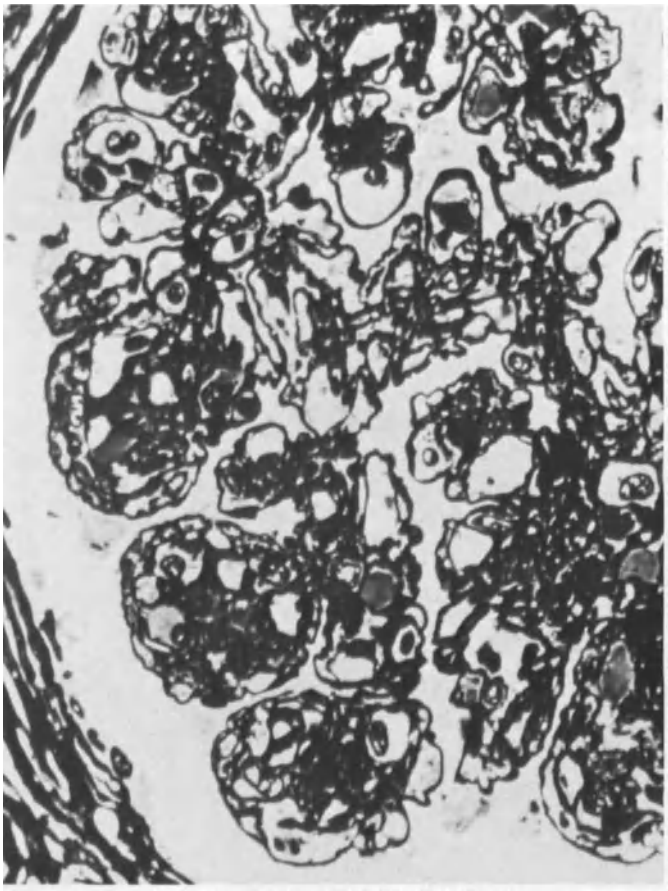
***BM Doubling Without Cellular Interposition.*** In the overwhelming majority of cases, this form of BM doubling cannot be perceived under LM, since the newly formed l. densa lamellae are extremely thin and hardly separated from the original l. densa.

***a) Subendothelial BM Doubling.*** In our material, we have encountered subendothelial formation of l. densa material without mesangial interposition (see p. 595; Figs. 6.21, 6.26) in 16.4% of our GN cases, in 5% of non-GN cases and in 25.9% of our kidney transplant cases (Fig. 6.22). This form is more characteristic for transplants than for GN (see Fig. 6.23). The new formation of l. densa is not necessarily associated with the concomitant presence of peripheral BM deposits (see Figs. 6.23, 6.39) since—under EM—such deposits, in the region of peripheral glomerular BM, are present in only one in three of transplant and non-GN cases but absent in one out of five of the GN cases.
So new formation of l. densa material may depend chiefly on the duration and extent of endothelial injury for which deposits might be one of the instigating factors. This form of BM doubling thus correlates in IF with the presence of glomerular IgG, C3 and fibrin(-ogen) (see Fig. 6.23).

**Fig. 6.18.** Typical 'tram-track' picture consisting of doubling of the peripheral BM with partial transverse connections as seen in a case of membranoproliferative GN. Semi-thin section. Male, 76 years. PASM (×770) ▷

**Fig. 6.19.** Extensive fibrinoid deposits (→) in glomerular capillary loops in diabetes mellitus with arteriolosclerosis. Male, 59 years. PAS (×400)

**Fig. 6.20.** Severe wrinkling of glomerular capillary loop BM in collapse as occurring in malignant nephrosclerosis. Male, 43 years. EM (×7100)



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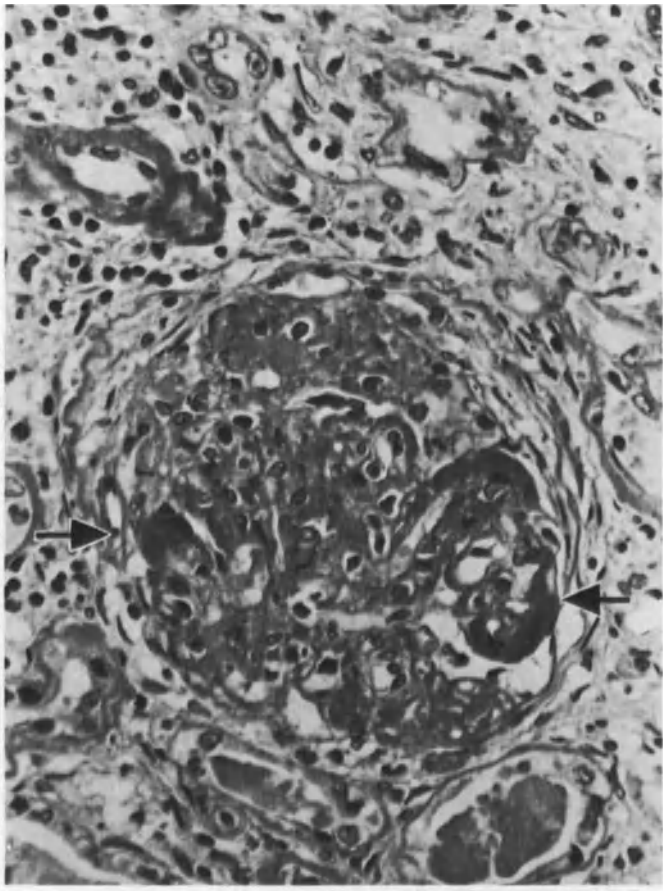

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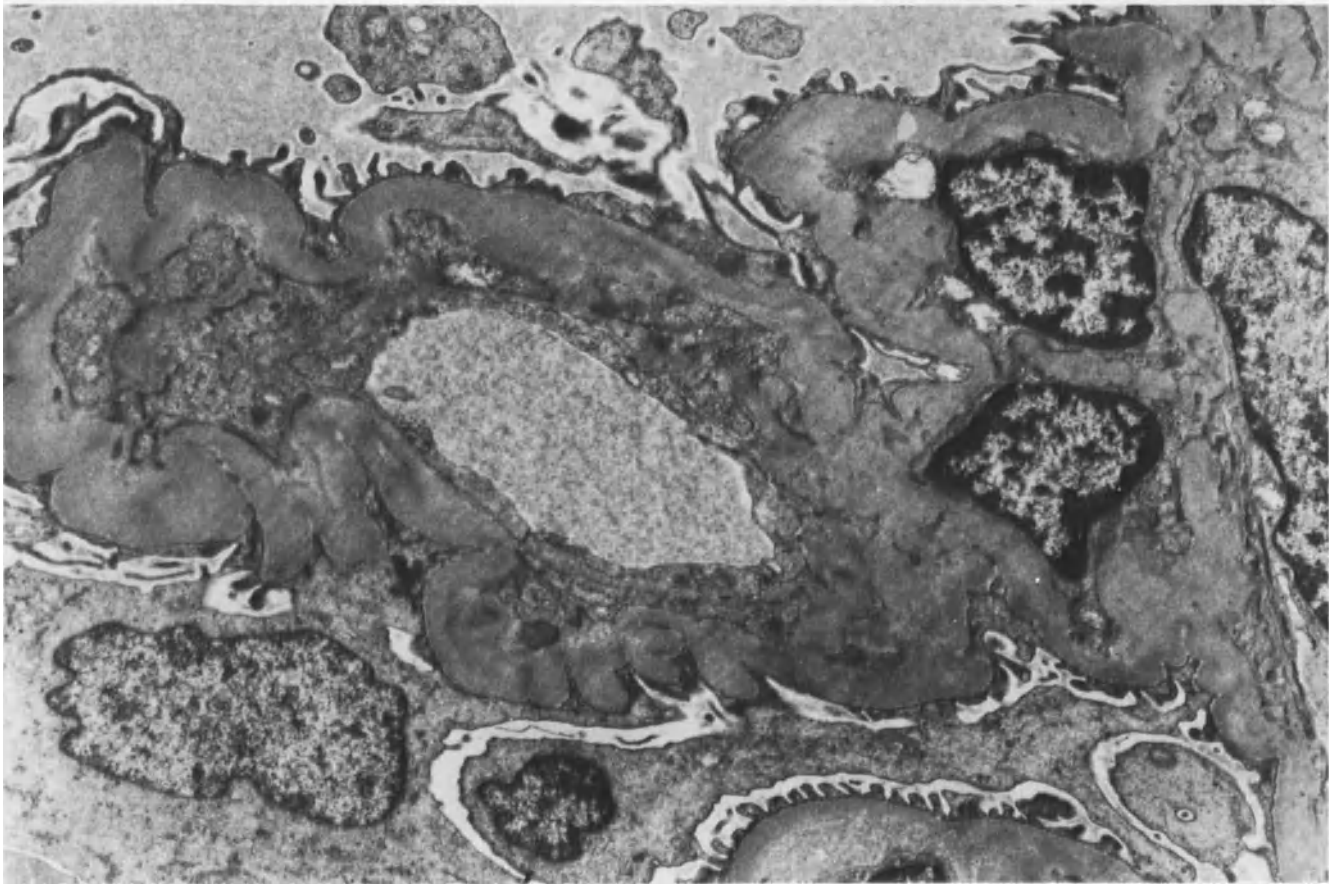

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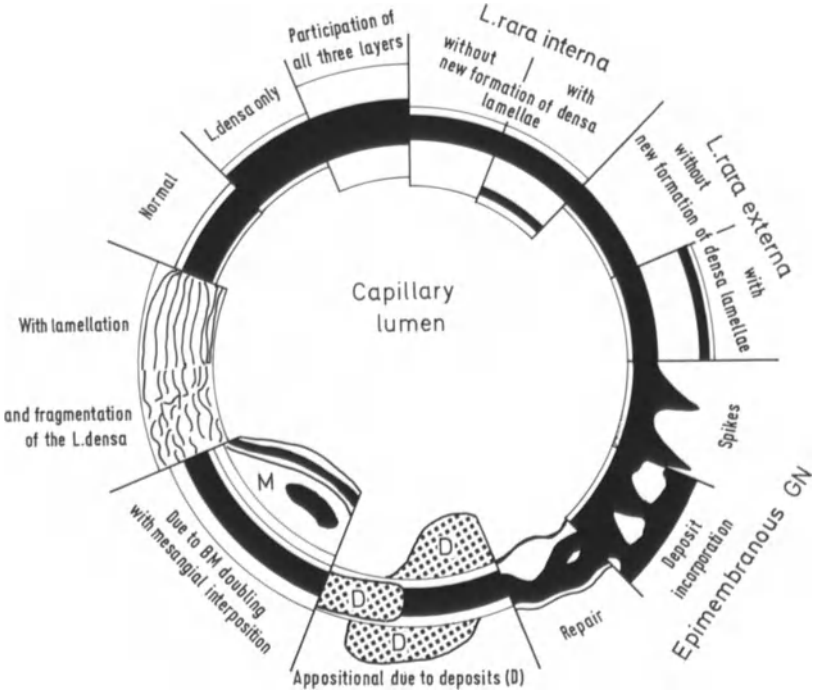
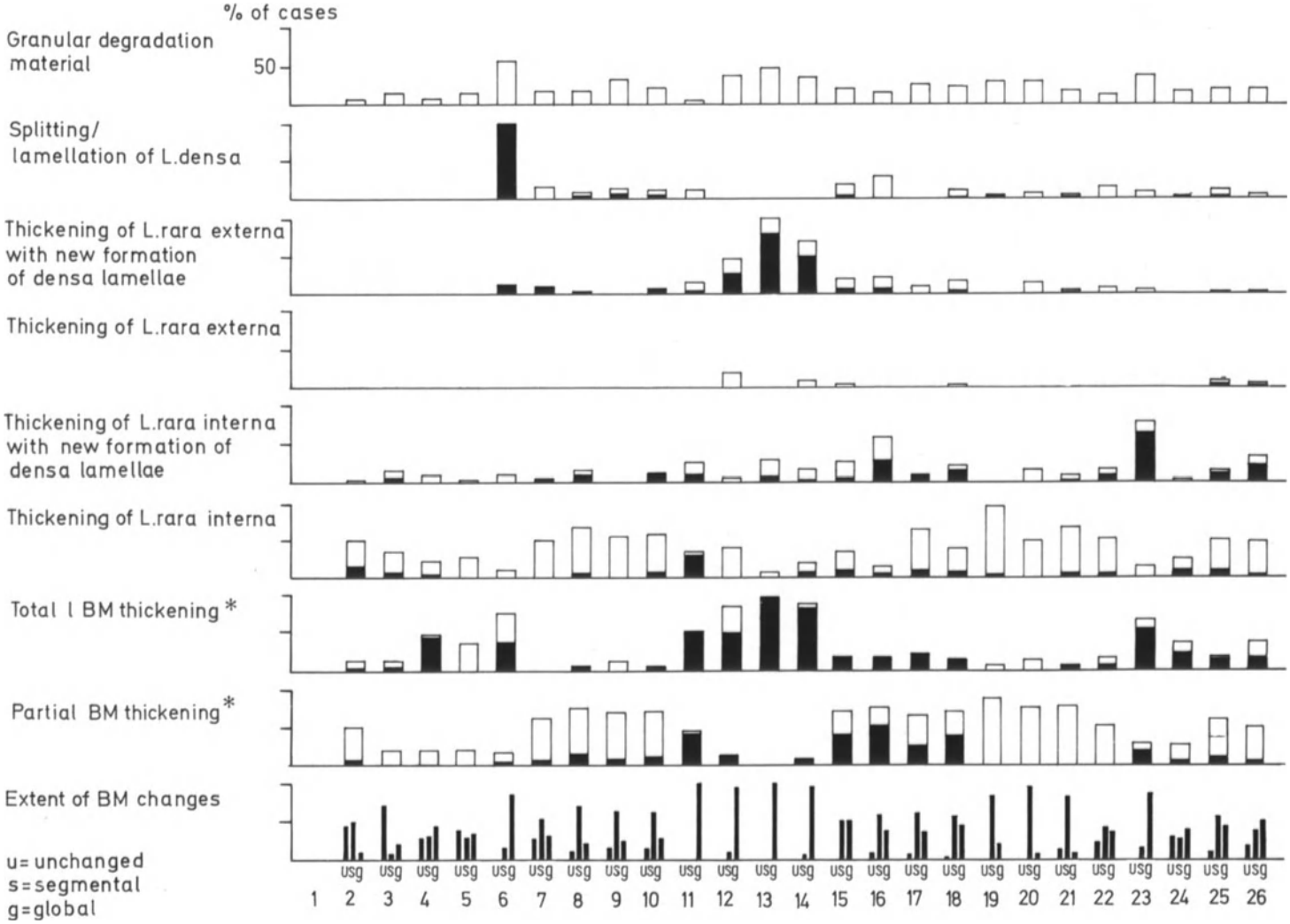



**Fig. 6.21.** Schematic representation of various forms of BM thickening. Mesangial cell (*M*), deposit (*D*). For further details see text

**Fig. 6.22.** Histogram: Glomerular BM changes. For detailed legend see Figure 6.9. No degrees of severity were distinguished for granular degradation material. Partial/total BM thickening (*) refers to lamina densa participation in the single capillary loop. Extent of BM changes refers to the whole glomerulus. For mesangial interposition see Figure 6.34



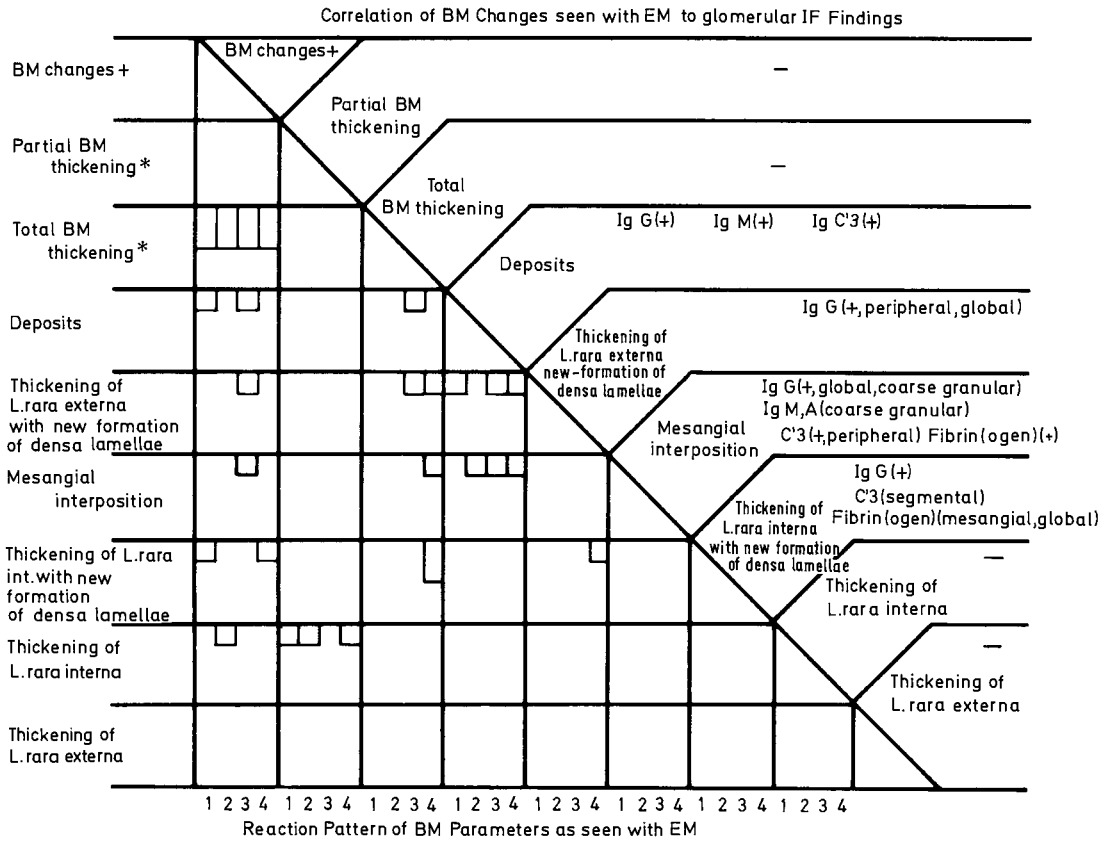



**Fig. 6.23.** Reaction pattern of BM parameters as seen with EM, and its correlation to glomerular IF findings. Based on correlation coefficient ($r > +0.25$). Size of columns in EM reaction pattern give a relative index for strength of relationship.
(+) presence of immunoglobulin independent of further specification

1. All nephropathies (EM $n=663$, IF $n=410$)
2. Non-GN diseases (EM $n=159$, IF $n=84$)
3. GN (EM $n=399$, IF $n=229$)
4. Transplants (EM $n=105$, IF $n=97$)

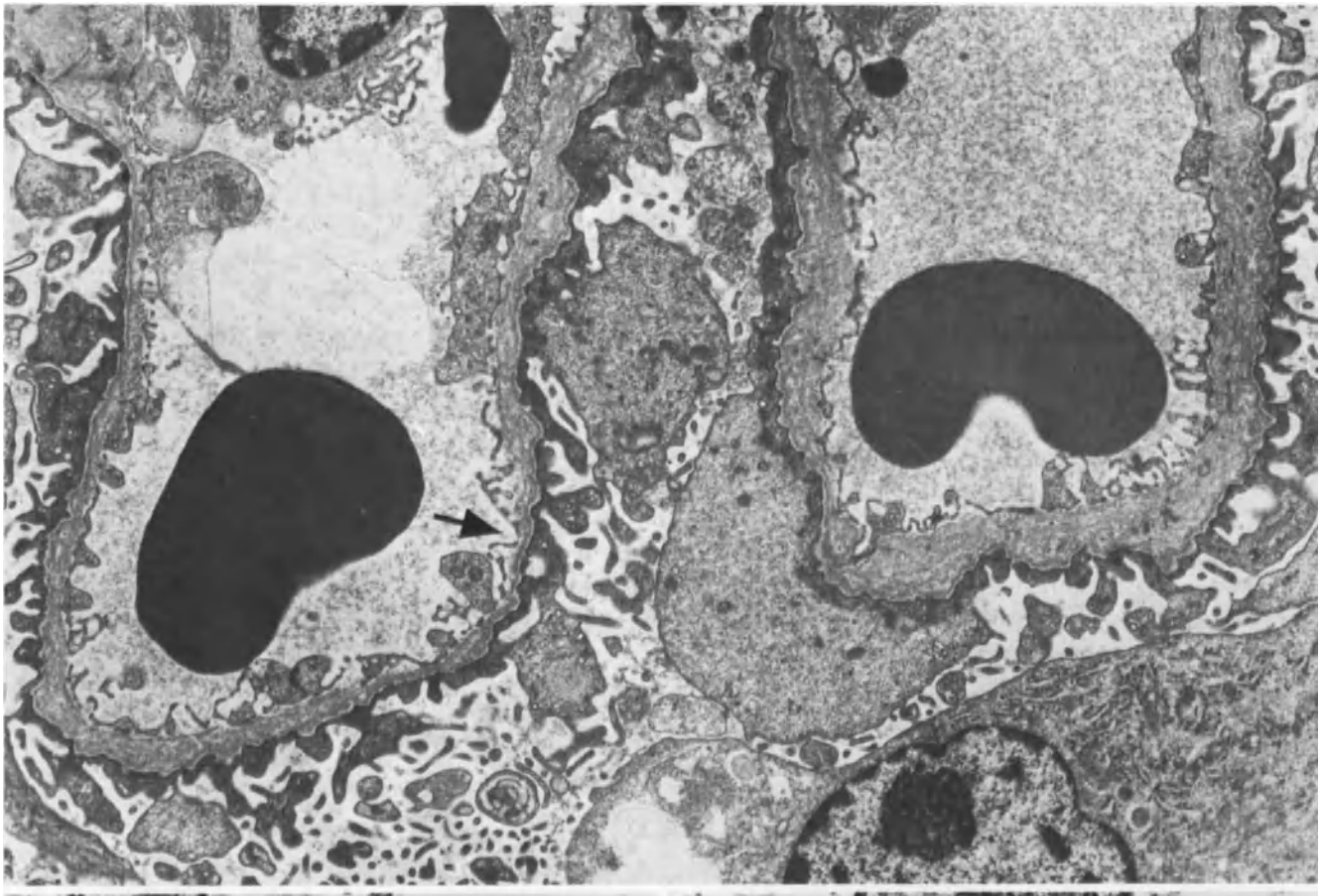
An analogous BM doubling has been described as characteristic for "accelerated obsolescence" in arteriolonecrosis [783]. We have not been able to confirm this finding.

***b) Subepithelial BM Doubling.*** Two forms by which densa material is newly generated subepithelially can be distinguished: (a) lamellar new formation which corresponds to the subendothelial form, and (b) new formation concomitant with epimembranous GN.

*Lamellar New Formation.* This form (p. 322, Figs. 6.21, 6.28) occurs exclusively in GN (14.7% of our cases) with increased frequency in Schönlein-Henoch's syndrome, and in kidney transplants (6.5% of our cases) (Fig. 6.22).
A further noteworthy finding is the occurrence of virus-like particles (see p. 92) in 37.8% of glomerulonephritic cases with subepithelial new densa formation and in only 5.8% in the rest of the GN cases. It appears reasonable to conclude from these findings that pathogenetically, subepithelial new densa formation can be viewed as a reaction to deposits (Fig. 6.23) which may be relatively frequently associated with viral glomerular lesions.

*Concomitant New Formation in Epimembranous GN.* This begins in stage II of epimembranous GN (Figs. 6.21, 6.30). Characteristic spikes appear between subepithelial deposits, which become completely walled-off in stage III (Fig. 6.21) to finally dissolve away in stage IV (Fig. 6.31).
A terminal stage—after a long duration of illness—is characterized by a very pronounced thickening of the BM (Fig. 6.32) with irregular thread-or whorl-like structures occasionally arranged concentrically with cross striations (see p. 71).

***BM Doubling With Mesangial Interposition.*** This form of BM doubling (Figs. 6.21, 6.33) which is also referred



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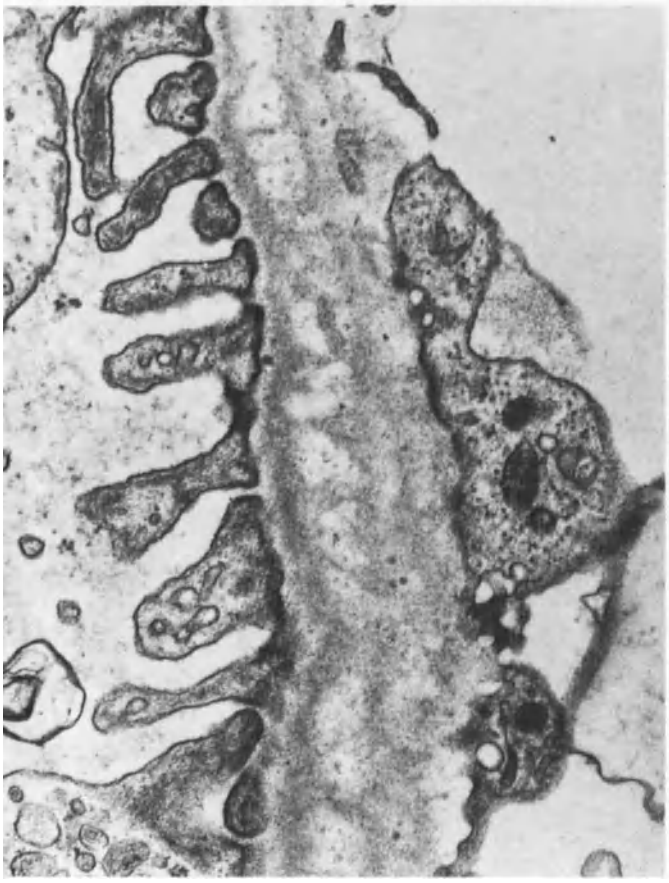

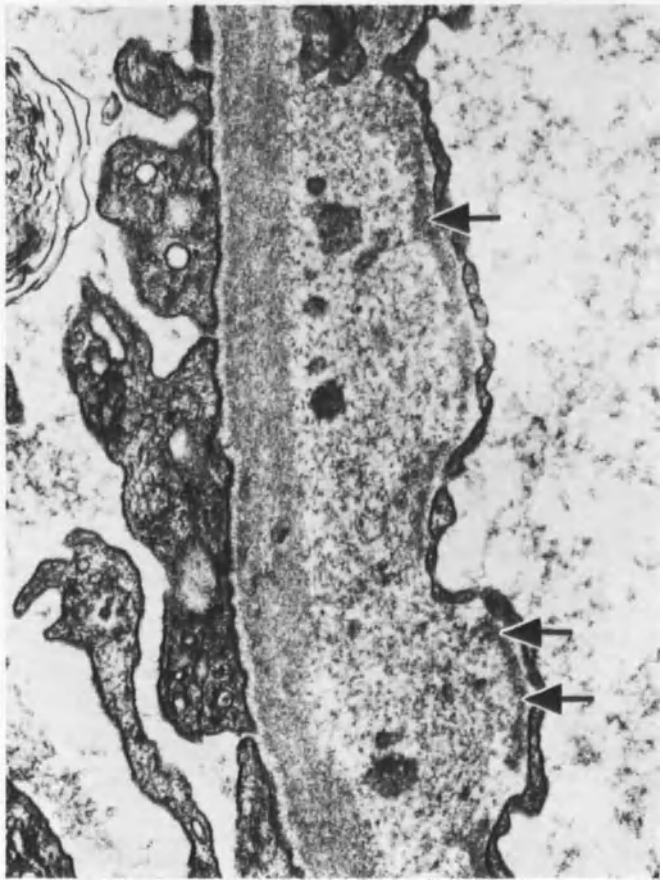

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to as circumferential interposition or intussusception [40, 275, 454] is clearly recognizable with the PAS, or even better, the PASM stain because of the typical presence of the tram-track picture. Mesangial cells which have wandered out to the periphery form a new BM between the endothelium and their own cell bodies. The new BM, which consists mainly of l. densa material, can encompass the entire circumference of the peripheral glomerular capillary loop or only a part of it; this state often leads to obsolescence of the affected glomerular capillary loops (Fig. 6.39).

Subendothelial deposits consisting of C3, fibrin(-ogen), and the main immunoglobulins (IgG, A; Fig. 6.39)—in addition to mesangial cell elements (Fig. 6.39)—are frequently found between the original, somewhat collapsed and wrinkled BM and the new BM irrespective of the underlying disease (see Figs. 6.23, 6.34, 6.39). Although there is a close correlation between subendothelial deposits and mesangial interposition (Fig. 6.39), these deposits were absent in 29.7% of 91 cases where mesangial interposition was demonstrated.

BM doubling with mesangial interposition correlates best with GN (see Fig. 6.23) where it was found in 21.5% of our cases but only in 5.7% in non-GN and in 8.6% of kidney transplants (Fig. 6.22). The doubling is characteristic for membranoproliferative GN but it is also encountered frequently in proliferative and sclerosing FGN (Fig. 6.34).

Pathogenetically, it can be assumed that mesangial interposition represents an attempt to break down large immunocomplexes which have not permeated the BM and which cannot rapidly be removed by and via the mesangium.

◁ **Fig. 6.24.** Severe lamellation and reticulation of peripheral glomerular BM in Alport's disease. Note isolated thinning of BM (→) and severe foot process fusion. Male, 6 years. EM (×11,500)

**Fig. 6.25.** Coarse splitting and suggestive ladder form of lamina densa of glomerular capillary loop BM without deposits in endotheliomesangial GN (proliferative sclerosing stage). Subsequent clinical study excluded Alport's syndrome. Eight months before the present biopsy, a purely proliferative stage was present. Male, 9.5 years. EM (×23,1000)

**Fig. 6.26.** Loosening and severe thickening of lamina rara interna with slight new formation of a narrow subendothelial lamina densa (→). Residual changes 5 years after membranoproliferative GN. Male, 45 years. EM (×27,000)

## 3. Appositional BM Thickening

Protein, usually as immunoglobulin deposits in the region of the BM—designated as fibrinoid in LM and as osmiophilic deposits in EM—are a significant feature of numerous glomerular lesions. Their demonstration requires appropriate microscopic and staining techniques.

The deposits are usually poorly identifiable with LM. Silver impregnation of semi-thin sections is of little help since the deposits are not impregnable. They can, however, (except dense deposits in intramembranous GN after overstaining) be suspected in severe cases of epimembranous GN by the presence of negative spaces between the impregnated spikes. If the deposits are sufficiently large, they can be rendered visible with the following stains:

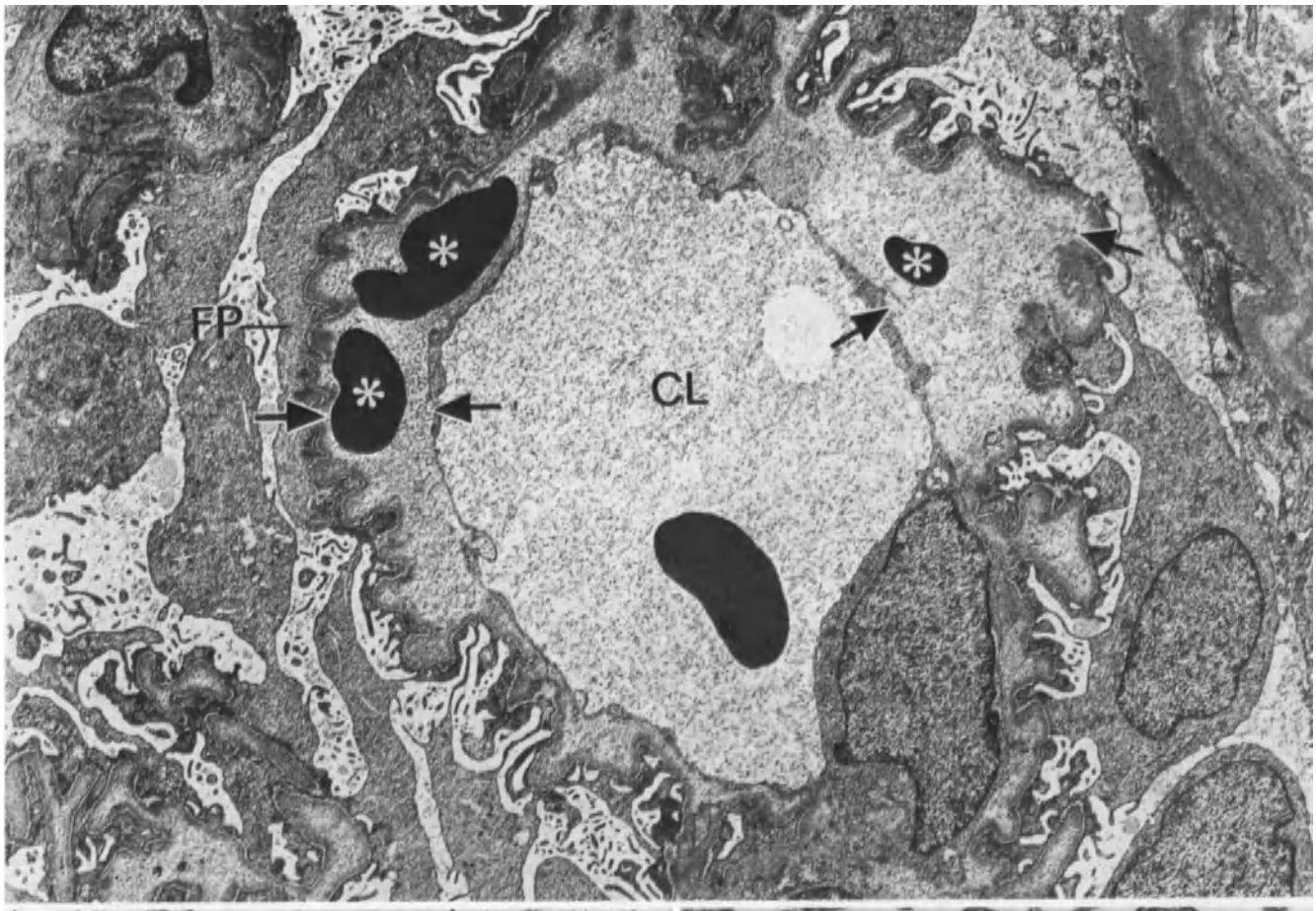
| Stain | Color of deposits |
|---|---|
| Masson's trichrome/AFOG | Orange-red |
| HE | Lively red |
| van Gieson | Yellow-orange |
| PAS | Reddish violet |

We wish to caution, however, that Masson's trichrome/AFOG and similar staining methods render some—but by no means all—of the deposits visible and as such, in contrast to IF, do not permit conclusions relating to the amount and occurrence of deposits. Nevertheless, Masson's trichrome/AFOG stain is the procedure of choice for initial orientation and especially so for those workers who do not have EM or IF at their disposal. Thus, assured recognition of deposits is only guaranteed with EM and IF.

With EM, the deposits are osmiophilic, very electron-dense and all finely granular. They are not sharply delineated, while the cytoplasmic processes of the mesangial cells (also frequently electron-opaque) are very sharply circumscribed. The deposits are not fibrillar as those of amyloid and fibrin.

Deposits consist of immunoglobulins (IgG, IgM, IgA, IgE, IgD), complement, and, on occasion, other serum proteins such as lipoprotein and albumin. Fibrin(-ogen) is not uncommonly demonstrable with IF (17.5% in GN) but its demonstration with EM is exceptional (1.3% in GN). Subendothelial fibrin and its degradation products are especially found in generalized intravasal coagulation [1653]; these deposits are ultimately enveloped and "organized" by BM substance.

Fibrinoid/osmiophilic deposits do not, with certainty, consist exclusively of degraded fibrin residues (contra: [1508]). Giant deposits, as occur in glomerular capillary loop obsolescence, usually contain only IgM and/or C3 as shown with IF. They are—like the analogous arteri-

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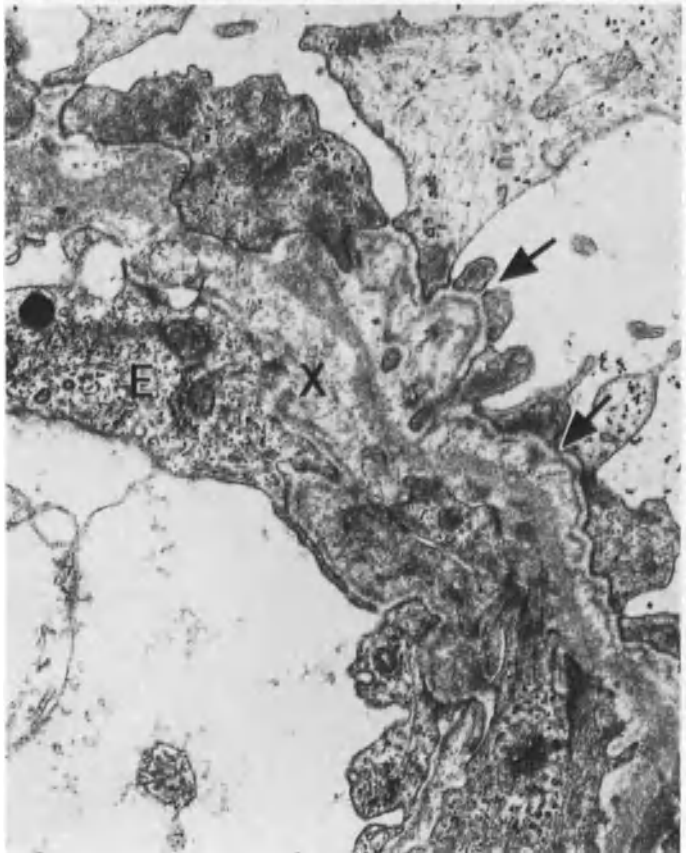


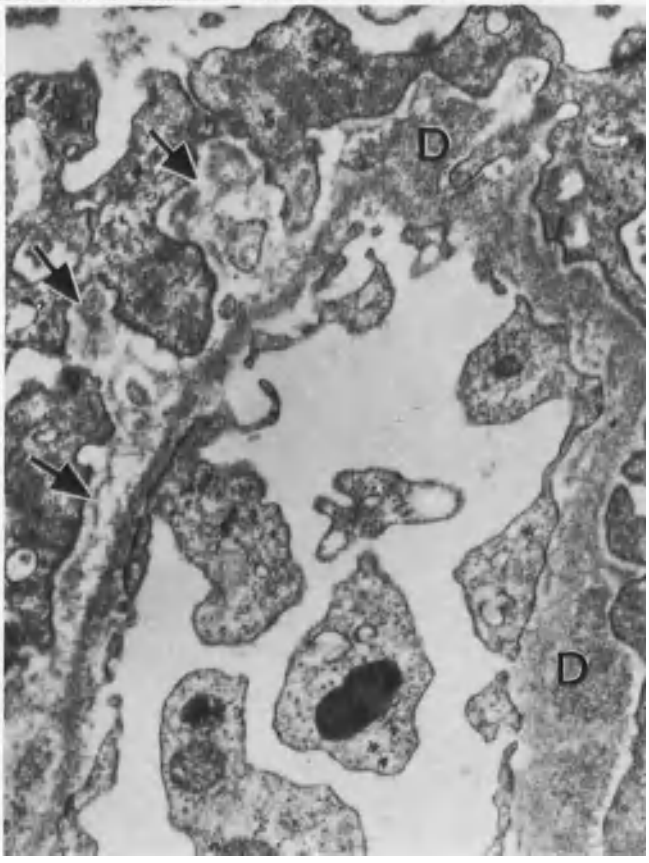


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olar deposits associated with hypertension and the tubular deposits in tubular atrophy—to be interpreted as *insudation deposits*. Similarly, deposits of trapped immunoglobulins, i.e., those not arising directly from immunologic reaction, have been reported subendothelially in 7% of post mortem material from "normal" kidneys [1590]; we have not been able to confirm this finding. Finally, deposits are progressively degraded leaving local erosions of the BM or empty lacunae which often still contain immunoglobulins under IF (Figs. 6.25, 6.26, 6.29, 6.30, 6.31, 6.32, 6.35, 6.41, 6.42, 6.43, 6.44, 6.47, 6.48, 6.49, 6.50).

Fundamentally, four different localizations (subepithelial, subendothelial, intramembranous and mesangial either within the matrix or along the mesangial BM (Fig. 6.34, see p. 178) of osmiophilic deposits have been identified. Not too rarely, all four may occur in the same glomerulus. For frequency and distribution of deposits, see Fig. 6.34.

***Subepithelial Deposits.*** Subepithelial deposits (for frequency see Fig. 6.34 and correlation with other glomerular findings Fig. 6.39) in the form of spherical nodules are termed humps (Fig. 6.35; [832, 834]). Humps are characteristic of the acute serum nephritis produced in animal experimentation and of the poststreptococcal type of GN in humans. They are also encountered in fresh attacks of membranoproliferative GN, in proliferative FGN (Fig. 6.34) as well as in epimembranous GN. The deposits result from the deposition of circulating immunocomplexes and are generally thought to be the expression of an immunocomplex GN. Humps correlate in IF with the presence of C3 and IgG (Fig. 6.39).

They can be seen in semi-thin sections under favorable conditions and in paraplast sections. They appear as isolated subepithelial red nodules with Masson's trichrome/AFOG stain. They are shown to be up to 5 µm in size and with EM to be sharply demarcated by the podocytic cell membrane. Very fresh, small humps lie between the podocyte foot processes and are covered by the fine slit membrane. The deposits are also usually sharply marked off from the l. densa but in later phases this demarcation may become less clear. Oval intramembranous deposits are occasionally found beneath the humps (Figs. 6.36, 6.39).

During their degradation, the humps appear to be perforated, i.e., moth-eaten (Fig. 6.35) and they ultimately become translucent [1628a]. Humps are said to disappear after 6 weeks. In our own material (Fig. 6.38) we found humps in clinically acute GN still present averagely 9 weeks after disease onset, a finding which suggests that the humps may be deposited episodically. If they are found years after the clinical onset of GN, however, their presence indicates a new acute attack of the disease (Fig. 6.38). In 30 cases demonstrating humps, the antistreptolysin titer was normal in 15 cases, slightly increased in 7 and massively increased in 8. This finding possibly indicates that humps are not invariably associated with streptococcal infection.

Humps, as described above, must be differentiated from other subepithelial deposits as found in membranoproliferative or epimembranous GN.

Subepithelial deposits—not infrequently—observed in fresh attacks of membranoproliferative GN are considerably wider, less high and are less sharply delimited from the l. densa than are humps (Figs. 6.34, 6.37).

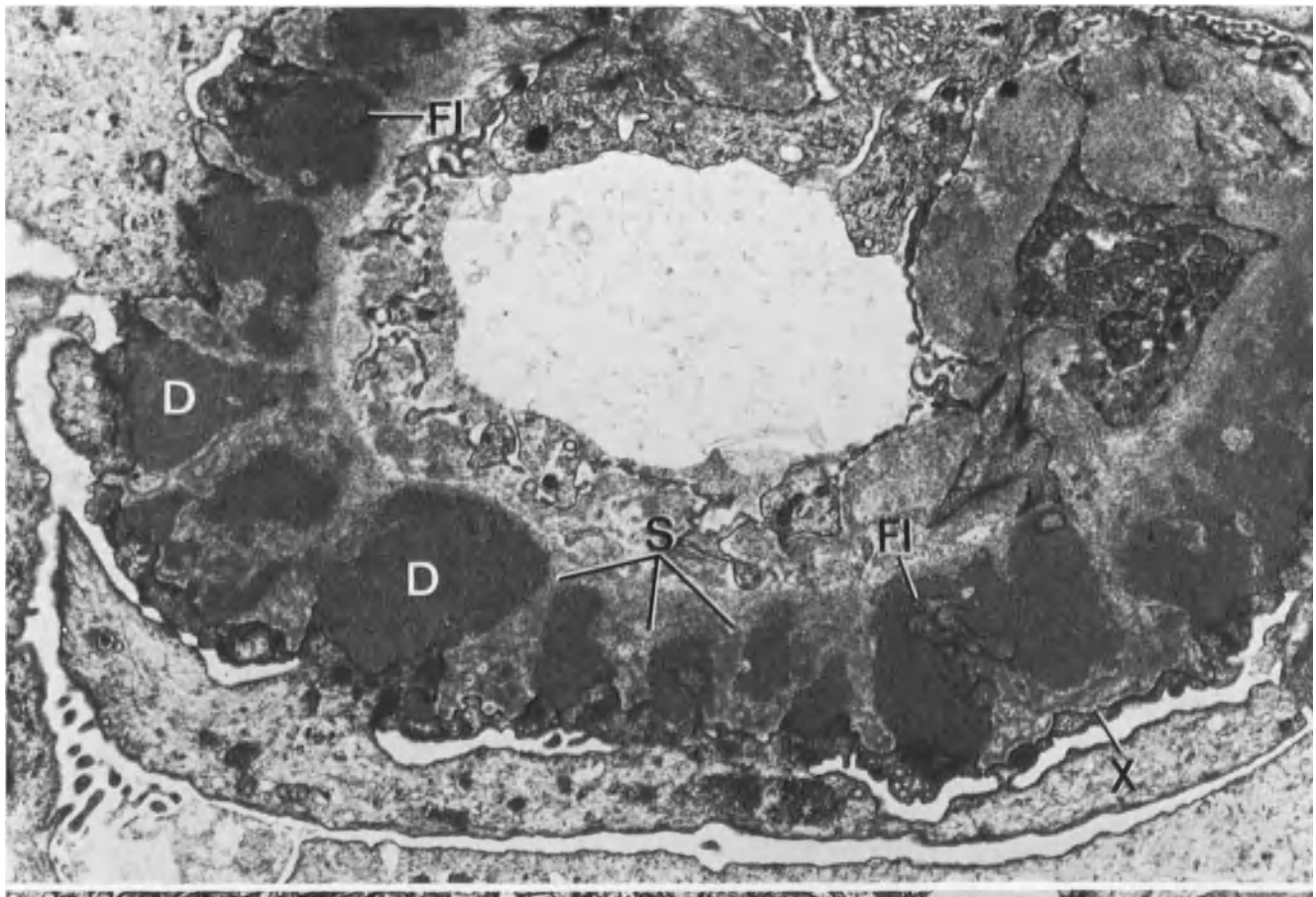
The deposits encountered in epimembranous GN are more lamelliform or round and are far more numerous than humps (Fig. 6.40). They appear to be degraded far more slowly and they can coalesce. A striking feature associated with the deposits is the formation of so-called spikes (brush-like radial densa processes) which originate from the l. densa and grow out between the individual deposits. There, together with newly formed subepithelial BM, they envelop the deposits which ultimately become completely incorporated into the l. densa (Fig. 6.41). The epithelial cover over these deposits shows very pronounced foot process fusion as well as an increase in osmiophilic fibrils (Figs. 6.39, 6.41).

During deposit degradation, surrounding BM material becomes reticular and granular, lacunae develop and the entire BM becomes considerably thicker (Figs. 6.39, 6.41, 6.42). During this process, virus-like particles are frequently observed (Fig. 6.42) as well as thread-like-structures of about 200 Å thickness (Fig. 6.43) corresponding to striated membranous structures [86] and, very rarely, myelin figures (Fig. 6.44).

◁ **Fig. 6.27.** Glomerular capillary loop in scleroderma. Severe thickening of the electron-lucent lamina rara interna (→←) which contains scattered erythrocytes (*). Lamina densa is very wrinkled, and podocytes evidence focal foot process fusion (*FP*). Capillary lumen (*CL*). Female, 62 years. EM (×4320)

**Fig. 6.28.** Severe thickening and humpiness of lamina rara externa (→) in peripheral glomerular BM with new formation of a uniformly thin densa layer in proliferative FGN in Schönlein-Henoch purpura. Lamina rara interna is also partially thickened (X) and suggests new formation of a densa lamella. Podocytes show severe foot process fusion. Endothelium (*E*) is hypertrophied. Male, 6 years. EM (×13,300)

**Fig. 6.29.** Irregular thickening of lamina rara externa (→) in peripheral glomerular BM and occasional osmiophilic granular deposits (*D*) in proliferative FGN. Lamina densa is partly considerably narrowed. Male, 60 years. EM (×21,400)

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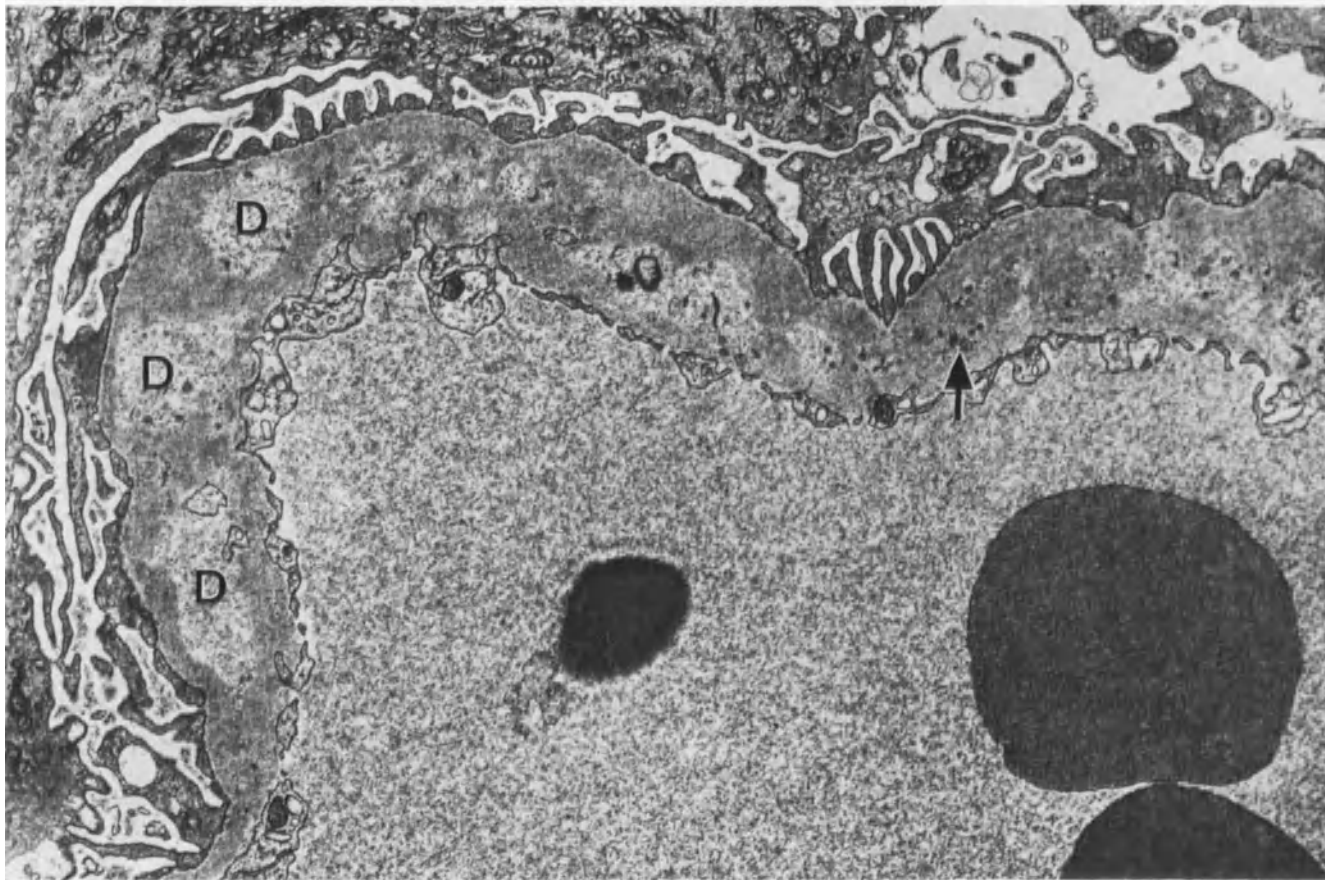



6.31

***Subendothelial Deposits.*** These deposits are often quite large and widespread. They occur in the widened l. rara interna and are mainly found in GN (28.2%) less frequently in transplants (11.9%) and even in non-GN (4.3%). For frequency and general occurrence, see Fig. 6.34; for correlation with other glomerular findings, Fig. 6.39. In GN, they are typically found in membranoproliferative GN as well as in proliferative or sclerosing FGN (Fig. 6.45) and in SLE nephritis (wire-loops) where they may be confused with hyaline thrombi (Fig. 6.46).

Fingerprint-like configurations within the deposits are observed in SLE; they are said to originate from crystallization of lipoprotein molecules [280, 841]. Peculiar crystalloid structures may be found in cryoglobulinemia (see p. 169).

Since these extremely coarse deposits are very often positive for fibrin(-ogen) besides other immunoglobulins and C3 (Fig. 6.39) in IF, it is conjectured that residues of fibrin degradation participate in their formation (see also [454]). In general, the subendothelial deposits encroach upon the mesangial matrix (Fig. 6.45) and are often associated with deposits along mesangial BM as well as mesangial matrix (Figs. 6.39, 6.45).

During the course of their degradation, lighter areas with fine granules appear at their borders (Fig. 6.47) as well as relatively frequent lipid inclusions (Fig. 6.49). A new, thin l. densa is formed under the endothelium and the total capillary loop wall accordingly becomes considerably thicker (Figs. 6.23, 6.48).

Giant deposits (identifiable as hyaline lumps even with LM) frequently develop in association with capillary loop obsolescence (Fig. 6.50). We believe that insudation is far more involved in this development than is the deposition of immunocomplexes. Genuine capillary loop occlusion by very large subendothelial deposits is not infrequently observed in SLE (Fig. 17.21, p. 330) and membranoproliferative GN. In this situation, the deposits are riddled with degenerative vacuoles which contain very scanty electron-lucent material and lipids. Additionally, foam cells, assumedly endothelial, are often encountered.

In anti-BM (Masugi) nephritis and the corresponding human diseases (Goodpasture's syndrome and scattered cases of extracapillary accentuated GN), very thin, slightly electron-opaque deposits—which are formed subendothelially—may be found in the loose l. rara interna (Fig. 14.59, p. 229; [280, 1154]). But EM study is usually negative even though linear deposits are seen with IF. Information relating to coarse nodular subendothelial deposits in hepatic glomerulonephrosis is given on p. 400.

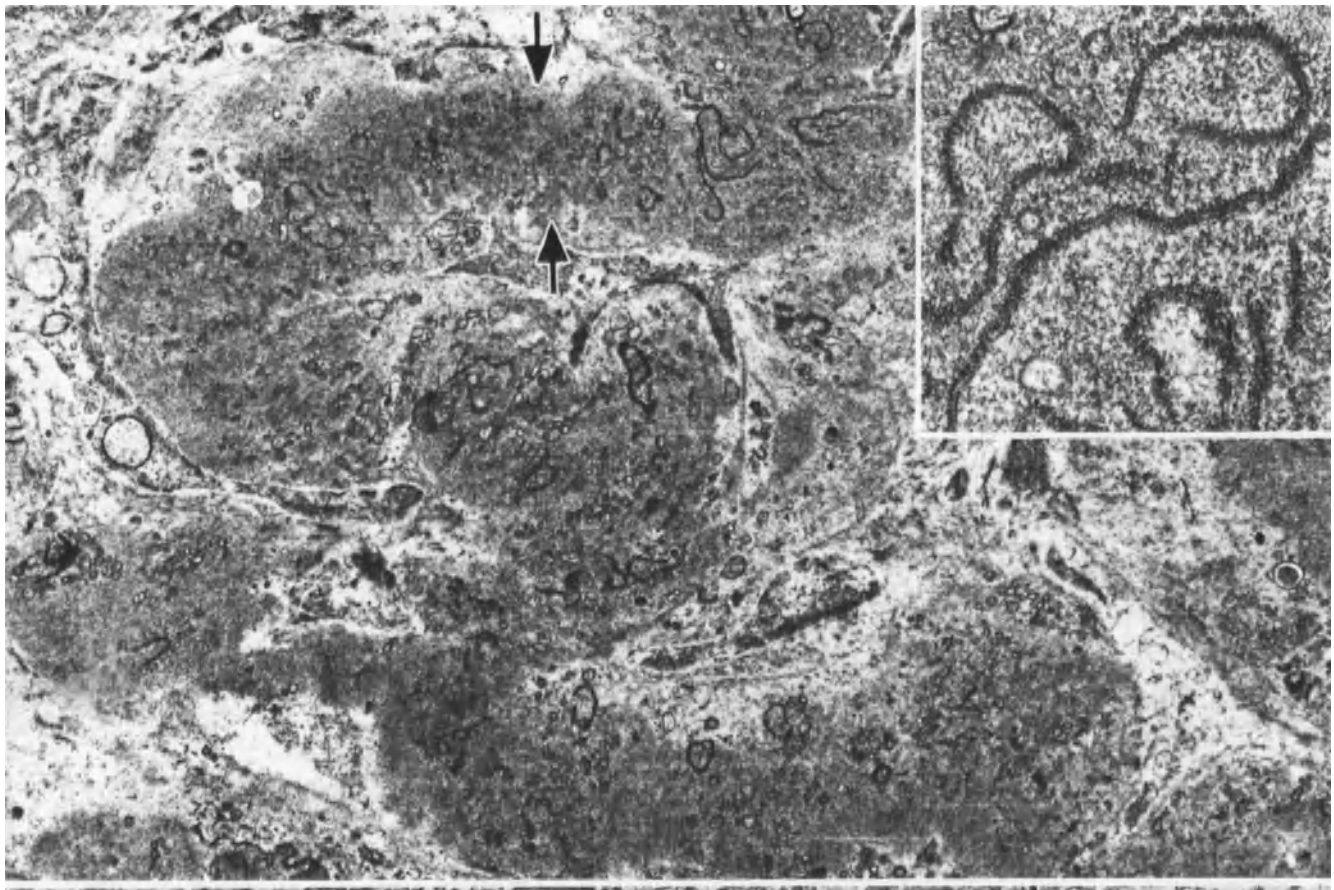
Two possibilities for subendothelial deposit formation can be considered: they are formed either independently of mesangial changes even though partly removed via the mesangium due to their size or as a consequence of overloading of the mesangium with immunocomplexes [401, 544]. Statistical analysis (Fig. 6.39) accordingly, does not permit a conclusion as to the initial site of deposit formation.

***Intramembranous Deposits.*** We distinguish between primary and secondary intramembranous deposits. We consider those deposits as secondary which have become incorporated into the BM by restructuring activities as is observed in epimembranous and membranoproliferative GN (Fig. 6.36; for frequency and distribution of primary deposits, see Fig. 6.34). Primary intramembranous deposits are found in all forms of GN (Figs. 6.34, 6.51) especially with the irrefutable presence of humps (Figs. 6.36, 6.39) as well as in other nephropathies, e.g. diabetes mellitus, arteriolosclerosis, Alport's syndrome where they probably arise from insudation (contra: [1628a]).

A second form of primary intramembranous deposits, which are more massive, i.e., longer and thicker than those mentioned above, is better termed dense osmiophilic material. Their size is such that only a narrow remnant of the original densa remains intact on both sides under the l. rara (Figs. 6.51, 14.103, 14.107). With LM, they are recognizable by the presence of the homogeneously thickened BM associated with extensive mesangial proliferation with deposit formation (Fig. 6.52). Intramembranous GN (see p. 252) is often considered to be a special form of membranoproliferative GN [35, 1136]. More recent study [524] has challenged the assumption that the dense material consists of genuine immune deposits.

◁ **Fig. 6.30.** Epimembranous GN (stage II). Extensive subepithelial osmiophilic deposits (*D*), between which spikes (*S*) are formed. Focal transition to stage III (X), i.e., covering of a deposit by coalescence of spikes. Scattered thread-like structures (*Fl*) are present in the deposits. Complete fusion of foot processes has occurred. Male, 60 years. EM (× 11,500)

**Fig. 6.31.** Epimembranous GN, stage IV; stage I was present bioptically 5 years previously. BM evidences severe thickening and irregularity with degradation granules (→), while at other sites empty deposit lacunae (*D*) may still be recognized. Male, 46 years. EM (× 10,700)



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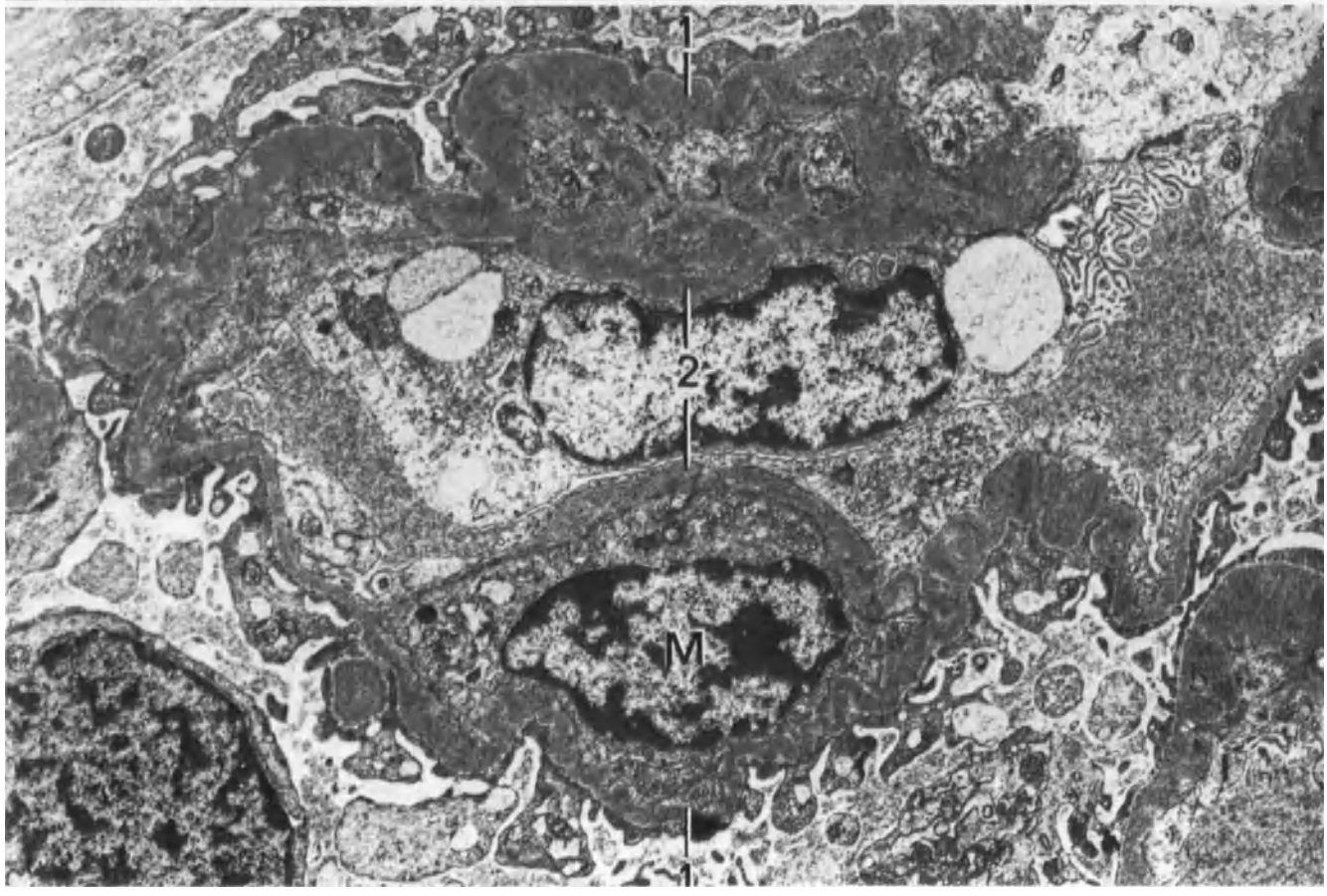


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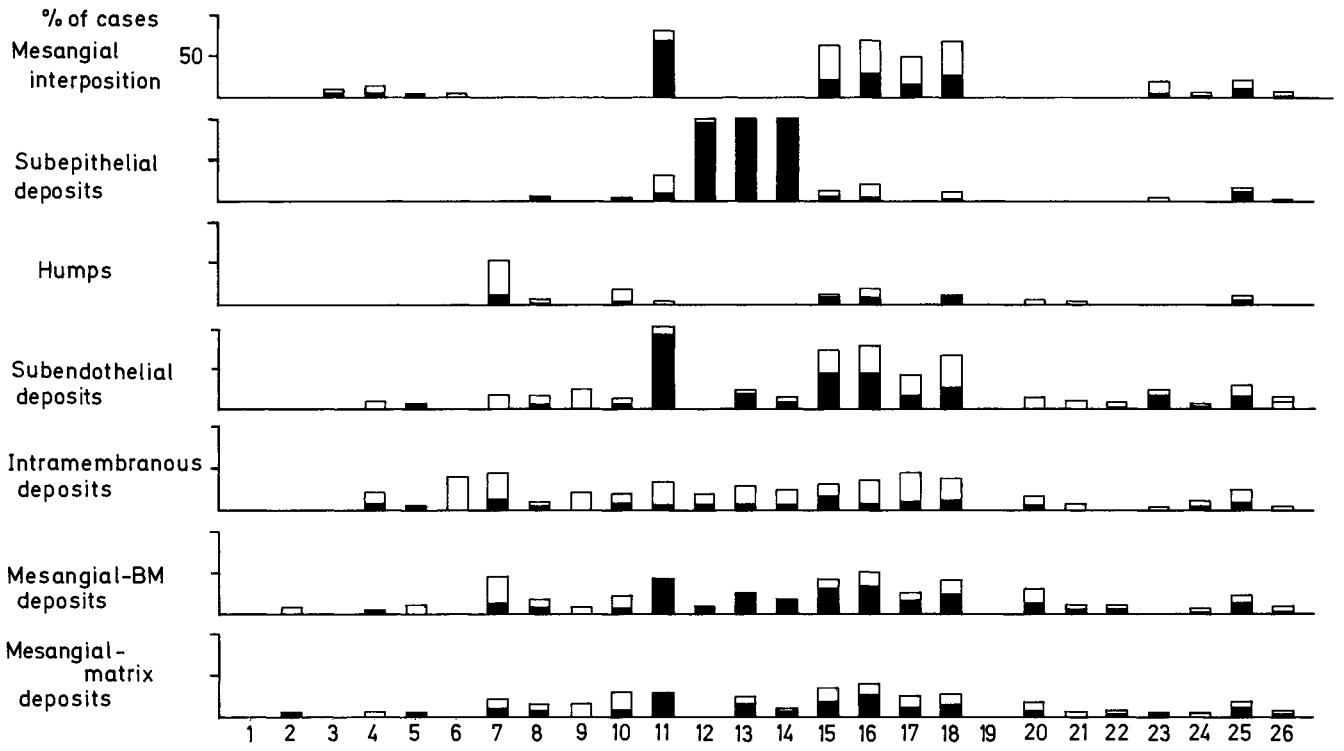


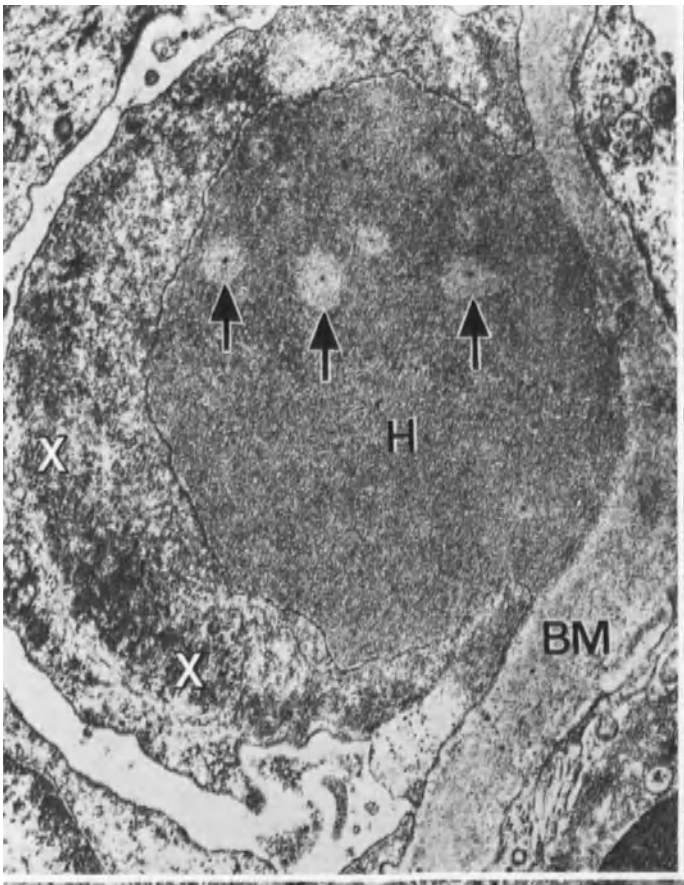

**Fig. 6.34.** Histogram: Glomcrular deposits (*D*). For detailed legend see Figure 6.9. In considering intramembranous deposits, dense material as seen in intramembranous GN was excluded

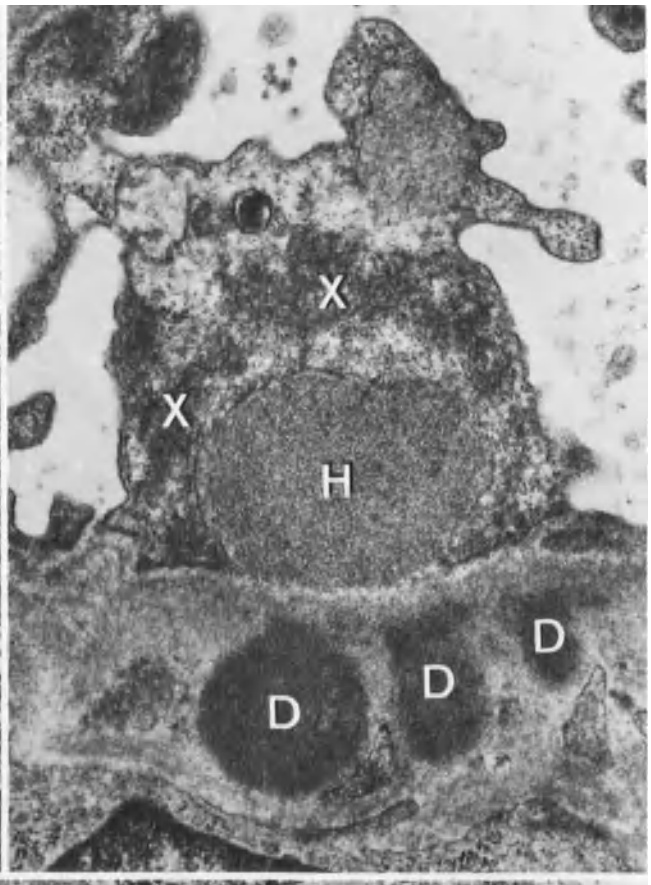
## Further BM Changes

1. *Local translucent areas* in the l. densa, which are not usually clearly demarcated can be observed after dissolution of deposits (Fig. 6.31) and, above all, in conjunction with epimembranous GN (Fig. 6.41).
2. We have observed *collagen* in the BM in one instance of circulatory collapse and in two of GN (Fig. 6.53).
3. *Circumscript interruptions* (Figs. 6.54, 6.55, 17.10) of the entire BM have been observed by us in 13 out of 700 biopsies (12 times in GN and once in a kidney transplant). Local destruction of the BM occurring in GN can be suspected with LM in the presence of a massive filling of the capsular space with erythrocytes and fibrin. In GN, these interruptions occur chiefly in focally accentuated forms (Fig. 6.55) and almost exclusively in the region of subendothelial deposits. They are also encountered occasionally in glomerular minimal change (Figs. 6.54, 6.55). The defects heal by cell proliferation with formation of a new BM (Fig. 6.54; [1565]).
4. Also with EM, a superficial, very slight *erosion* of the l. densa (Fig. 15.34, 18.15) can occasionally be observed under the humps. Larger partial defects are rare (Fig. 15.31) and result in local attenuation of the BM (see also [1595a]). For loop necrosis see p. 56.
   It is a remarkable fact that even in severe proteinuria and/or hematuria, the BM is by and large structurally intact (no interruptions are present). Analogously, proteinuria is not necessarily a consequence of a severely altered BM. Underlying causes decisively involved in these functional disturbances are probably related to factors in the polymerization of the ground substance, in the thickness of the (possibly) crystalloid network (as yet not clearly demonstrable with EM) and in the kind of foreign substances deposited (amyloid, immuno-deposits, etc.). Even though chemical study has shown an increase of the insoluble collagen fraction and a decrease of substances soluble in 0.5 m NaCl in the BM [1110], much more data must be generated before a molecular explanation for functional BM changes can be given (p. 22).
5. *BM thinning* is usually seen in Alport's disease (Fig. 6.24, p. 466); it is supposedly typical for benign familial hematuria (Fig. 6.56, p. 476).

◁ **Fig. 6.32.** Epimembranous GN, stage V; glomerular capillary loop lumens have completely disappeared. BM is highly thickened (→←) and is riddled with degradation granules as well as with thread-like structures demonstrating periodicity (*striated membranes*) shown in inset. Male, 24 years. EM (× 11,600; inset × 36,000)

**Fig. 6.33.** Membranoproliferative GN. Doubling of peripheral glomerular capillary loop BM by interposition of a mesangial cell (*M*). 1. Original BM. 2. Newly formed BM. Male, 66 years. EM (× 5900)

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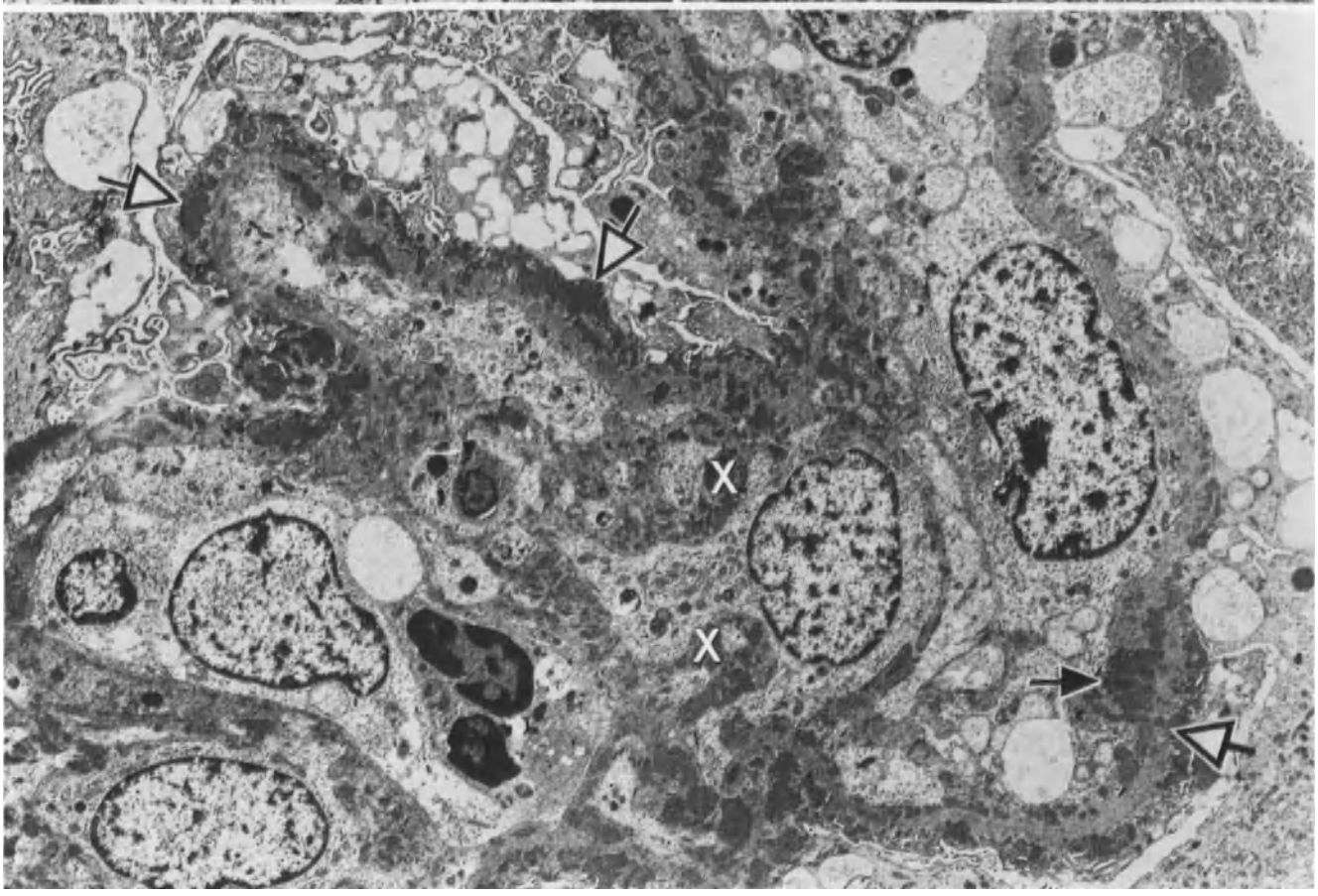


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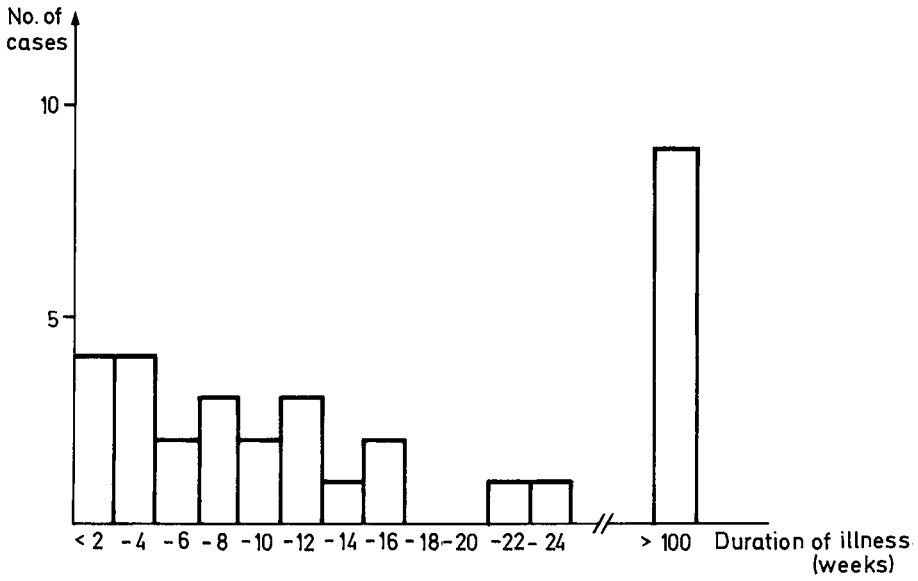



**Fig. 6.38.** Relationship between EM-demonstrated humps and disease duration; average duration of illness is 8.7 weeks ($n=23$). Cases with duration of illness longer than 100 weeks were not considered

## Changes in Other Glomerular Capillary Wall Constituents

### Podocytes (Visceral Epithelium, Pericytes)

(Figs. 6.57, 6.58)

LM-discernible podocyte changes are usually limited to detection of diffuse cyloplasmic and nuclear swelling and of scattered hyaline droplets.

◁ **Fig. 6.35.** Hump (*H*) with signs of incipient dissolution (→). Lamina rara externa is preserved. BM, glomerular capillary loop BM. Note increased osmiophilic substance in covering podocyte (*X*). Endotheliomesangial GN (proliferative stage); clinically acute onset 8 weeks before biopsy. Male, 6 years. EM (× 17,000)

**Fig. 6.36.** Osmiophilic desposits (*D*) in thickened lamina densa below hump (*H*). Increased osmiophilic substance in covering podocyte (*X*). Endotheliomesangial GN with isolated crescents and clinical onset 10 weeks prior to biopsy. Male, 5.5 years. EM (× 24,000)

**Fig. 6.37.** Extensive subendothelial deposits in peripheral glomerular capillary loops (→). Irregularly structured subepithelial deposits (⇨) covered by podocytes, mesangial deposits (X). Mixed epimembranous and membranoproliferative GN in SLE. Female, 15 years. EM (× 9270)

Diffuse and global occurrence of podocytic foam cells are observed in storage diseases (mucopolysaccharidoses and GM gangliosidoses, Fig. 23.1). Very exceptionally, a few isolated foam cells displaying focal-segmental distribution are encountered in GN and transplant kidneys (3 out of 700 of our biopsies).

With the advent of EM, it became possible for the first time to gather and analyse information relating to the nature and extent of podocyte reactions. EM study soon made it apparent that podocytes react quickly and strongly to various injuries and stresses [1154] as can be seen by the frequency of their changes and reaction pattern (Fig. 6.57, 6.58). The typical reaction pattern of podocytes in all types of nephropathies consists. of cellular edema (contra: [1508]) accompanied by nuclear swelling, microvilli (pseudovilli) formation and foot process fusion (see Fig. 6.58). The most well-known change is fusion of foot processes (Fig. 6.59). Whereby slit pores at sites of close apposition between adjacent epithelial cell membranes are suppressed by podocyte swelling [785].

Today, fusion is viewed as the consequence and no longer as the cause of proteinuria [454, 1538]; it is considered to be a reaction to the flowing through of large molecules. Upon remission of the proteinuria, fusion of the foot processes disappears [275].

A slight degree of fusion of the foot processes is very frequent in all nephropathies (Fig. 6.57). Severe and extensive fusion is found predominantly in GN.

The significance of localized, unsharply delimited osmiophilic cytoplasmic condensations (osmiophilic sub-

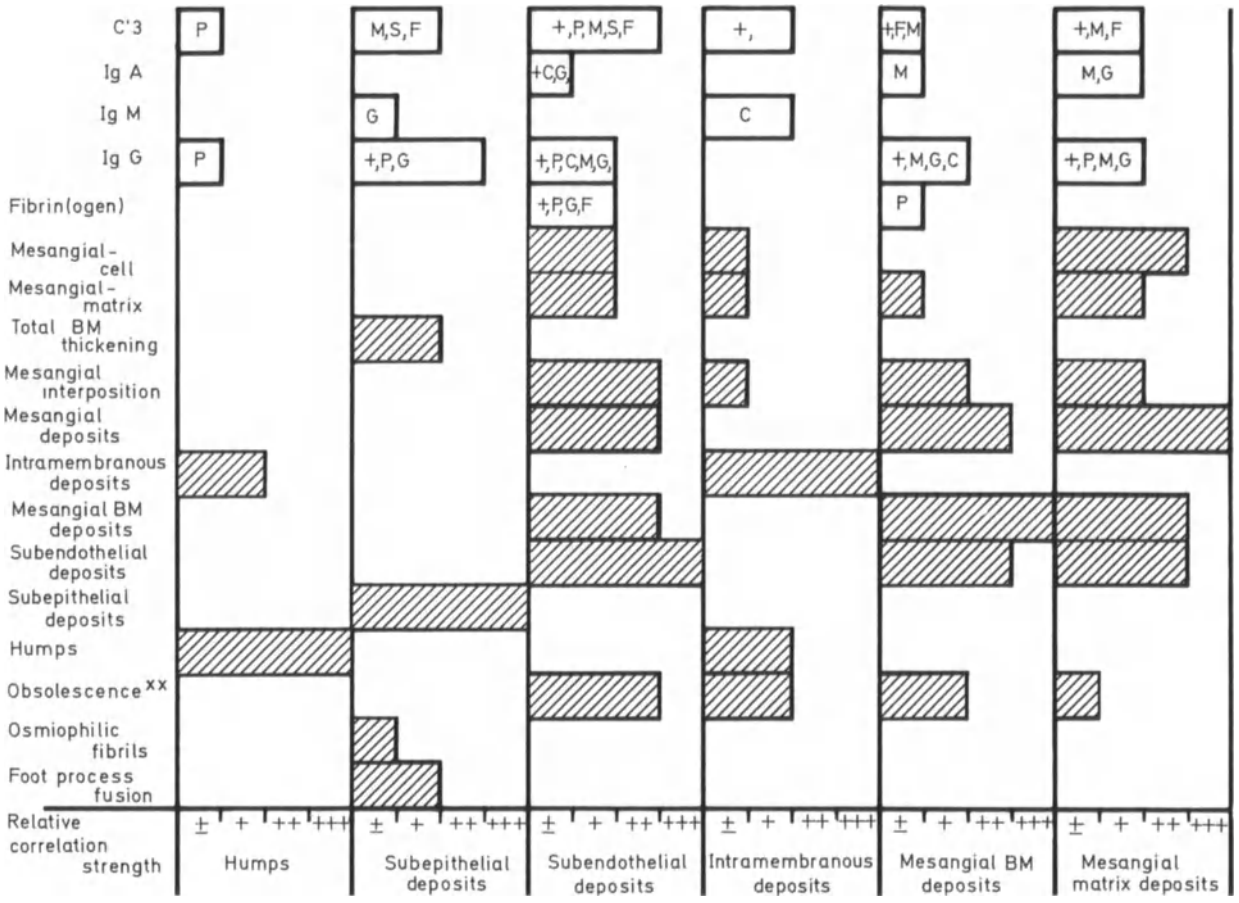



**Fig. 6.39.** Correlation of glomerular deposits in various locations (as seen with EM) with other EM and IF glomerular findings. (+) presence of immunoglobulin independent of distribution pattern; peripheral (*p*), mesangial (*m*), global (*g*), segmental (*s*), fine granular (*f*), coarse granular (*c*). Mesangial cell/matrix refers only to increase. Osmiophilic fibrils used synonymously with substance. Obsolescence of glomerular capillary loops (*xx*) due to proliferation (see also legend of Fig. 6.23)

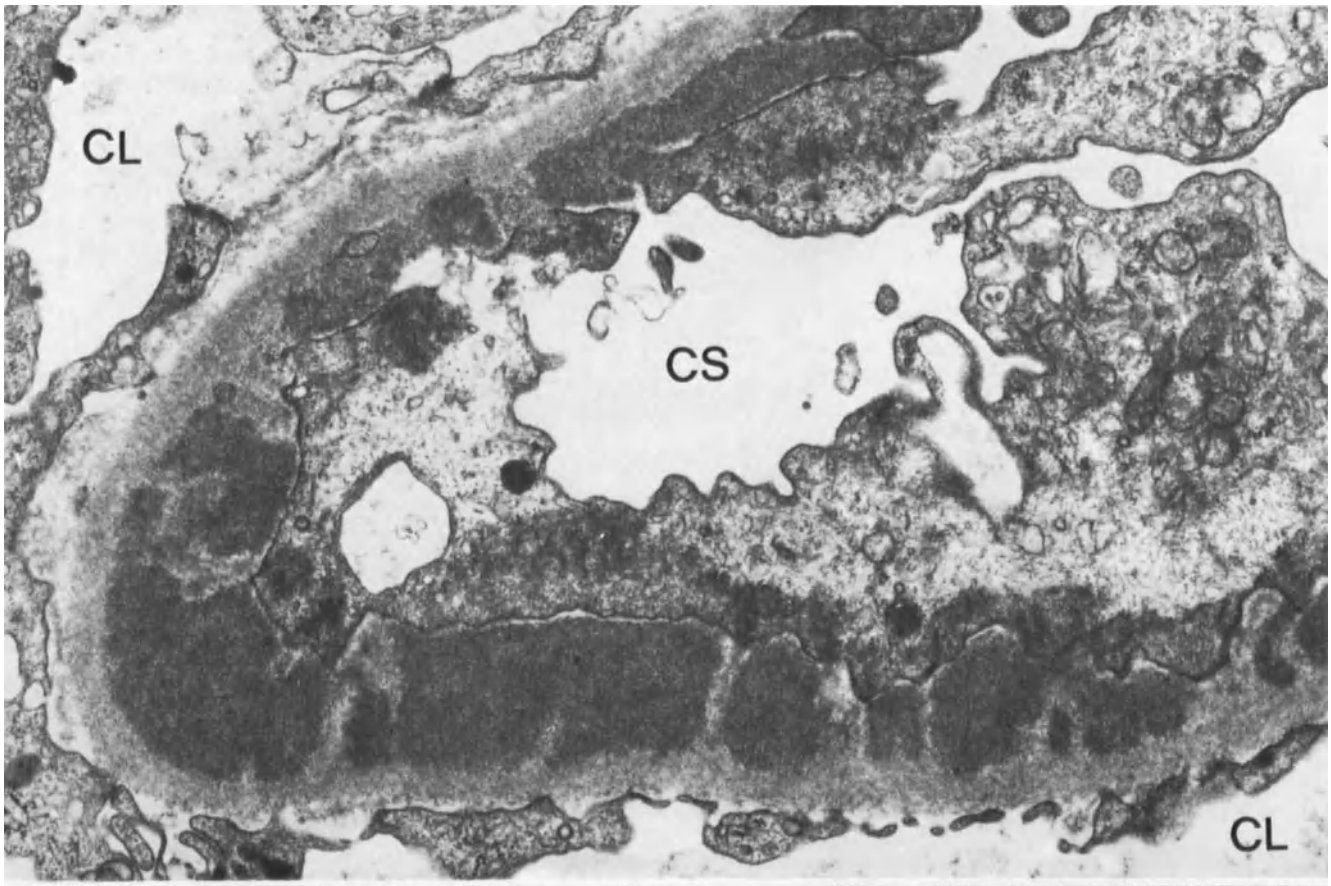
stance = fibrils) in podocytes remains unknown (Figs. 6.56, 6.60). Morphologically, they appear in two forms:

1. Condensations with a very pronounced fibrillar character which indicate an increase of actomyosin fibrils [925, 1633]
2. Condensations which are finely granular or amorphous point to their origin from residues of degraded immunodeposits [205, 1801].

The significant increase of osmiophilic granular/amorphous condensations (Figs. 14.21, 14.22)—especially over subepithelial deposits (Fig. 6.39)—supports the pathogenetic significance of podocytes in the degradation of immunocomplexes (see also [454, 1628a]). Further evidence in support of this view is the fact that the cytoplasmic condensations are expecially frequent in GN (40%) and strongly increased in 15% thereof (see Fig. 6.57) but usually only present in slight amount in nonglomerulonephritic disease and kidney transplants.

**Fig. 6.40.** Extensive osmiophilic deposits in epimembranous GN, stage I–II. Note beginning spike formation between the deposits. Clinical duration of illness 12 weeks. Lumen of glomerular capillary loop (*CL*); capsular space (*CS*). Male, 62 years. EM (×23,100) ▷

**Fig. 6.41.** Osmiophilic deposits (*D*) in dissolution in epimembranous GN, stage III. Empty lacunae arising from complete dissolution of deposits with thread-like structures (*FI*). Complete foot process fusion is present. Glomerular capillary loop lumen (*CL*). Clinical duration of illness 75 weeks. Male, 33 years. EM (×22,600)

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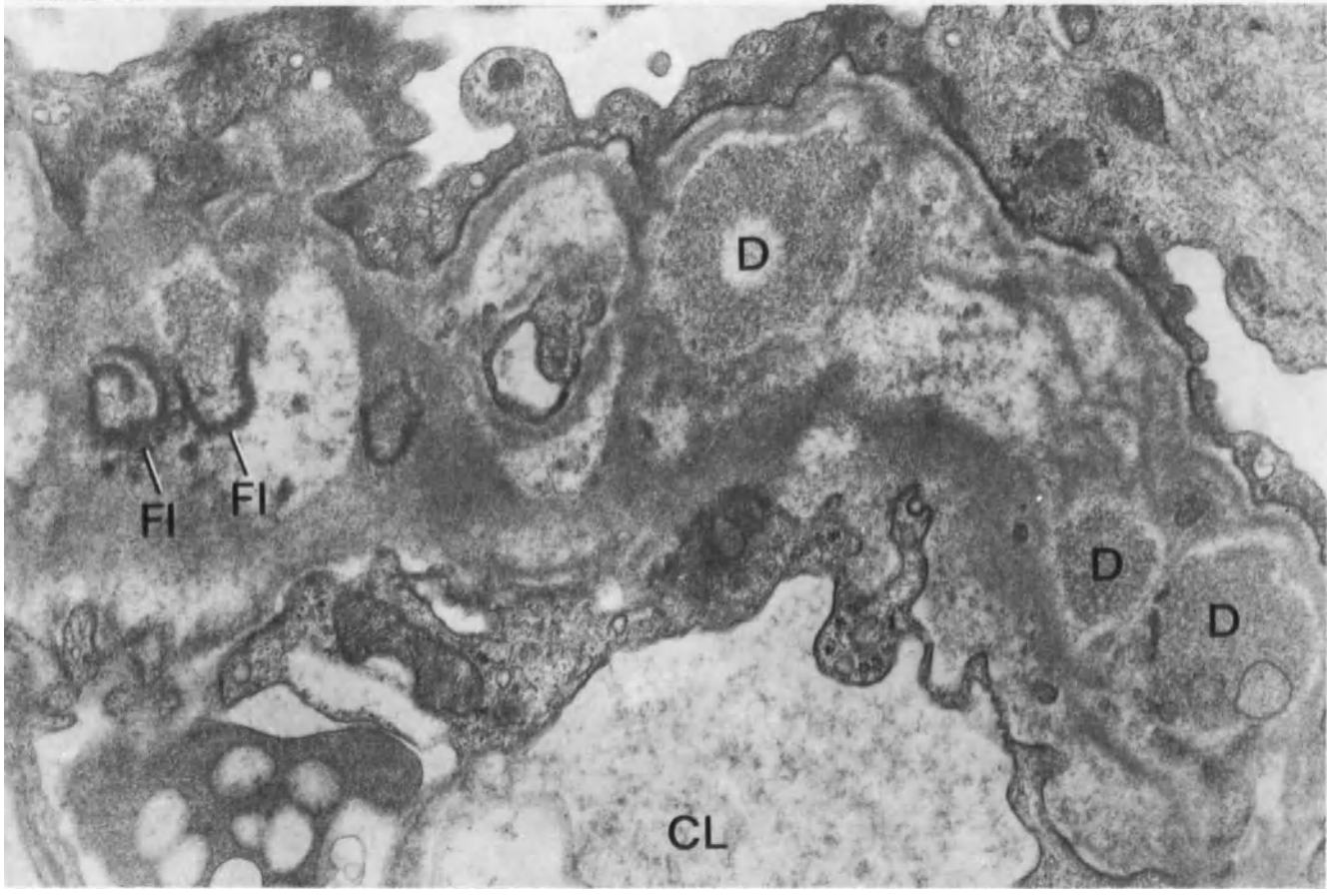


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**Fig. 6.42.** Severe, irregular thickening of lamina rara externa in epimembranous GN; stage III with acute relapse. New formation of a thin lamina densa immediately under the podocytes (⇨). Numerous large, fine-granular residual osmiophilic deposits (*D*) are usually surrounded by virus-like oval structures (→). Lamina densa (*LD*), podocyte (*P*). Tangential section. Duration of illness 50 weeks. Male, 58 years. EM (× 15,800)

**Fig. 6.43.** Same case as in Figure 6.42. A deposit in dissolution is seen with laminated structures, as are virus-like oval particles in which a central osmiophilic zone can be recognized (→) and thread-like structures in the center of the deposit. (Compare Fig. 6.32, inset). Fine-granular osmiophilic deposit (*D*), endothelium (*E*), podocyte (*P*), lamina densa (*LD*). Newly formed subepithelial l. densa (⇨) Male, 58 years. EM (× 29,388)

**Fig. 6.44.** Same case as in Figure 6.42. A myelin structure is present in a large subepithelial deposit (*D*). Wide spikes (*S*), podocyte (*P*), endothelium (*E*). Male, 58 years. EM (× 21,000)

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**Fig. 6.45.** Extensive subendothelial osmiophilic deposits in the glomerular capillary loop periphery in a case of membranoproliferative GN associated with hepatitis B virus. Male, 82 years. Autopsy material. Formalin fixation EM (× 5100)

**Fig. 6.46.** The same case as in Figure 6.45. Large deposits in glomerular capillary loop periphery can easily be mistaken for thrombi. Male, 82 years. PAS (× 200)

**Fig. 6.47.** Dissolution of subendothelial osmiophilic deposits in a case of membranoproliferative GN with beginning new formation of a thin subendothelial lamina densa (→). Female, 17 years. EM (× 16,500)

**Fig. 6.48.** End stage of deposit dissolution in a case of membranoproliferative GN. Lamina rara interna is nodularly thickened. Residues of a deposit undergoing dissolution (*D*). Newly formed subendothelial layer of lamina densa (→) is very thick. Foot processes of podocytes are completely fused. Male, 8 years. EM (× 6700)

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**Fig. 6.49.** Extensive lipid vacuoles (*X*) in subendothelial deposits of membranoproliferative GN in contracted kidney. Male, 23 years. EM (× 10,700)

**Fig. 6.50.** Isolated obsolescent peripheral glomerular capillary loops in a case of sclerosing FGN. Glomerular capillary loops are completely adherent to capsular BM (*CBM*). Loops are full of osmiophilic deposits which contain lipid vacuoles. Male, 18 years. EM (× 5640)

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**Fig. 6.51.** Intramembranous GN. Very dense, ribbon-like osmiophilic material is embedded in lamina densa. Lamina rara interna and externa are partly preserved as narrow strips. Mesangial matrix (*MM*) is frankly increased. Female, 25 years. EM (× 5200)

**Fig. 6.52.** Massive mesangial deposits (*D*) in membranoproliferative GN (lobular variant). Scattered peripheral subendothelial deposits (*D*→). Female, 10 years. EM (× 10,200)

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**Fig. 6.53.** Collagen fibers in a thickened and loosened BM (an extremely rare finding!) in sclerosing stage of endotheliomesangial GN. Podocyte (*P*). Male, 6.75 years. EM (× 33,000)

**Fig. 6.54.** Total BM interruption with secondary reconstruction in glomerular minimal change. Endothelium (*E*). Female, 23 years. EM (× 35,000)

**Fig. 6.55.** BM defect in sclerosing FGN. Endothelium (*E*). Male, 10 years. EM (× 35,000)

**Fig. 6.56.** Focal thinning and slight splitting of BM (→) in a case of persistent hematuria of 2 years. Clinically, no evidence for familial renal disease, in particular Alport's disease. Female, 4 years. EM (× 11,000)

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**Fig. 6.57.** Histogram. Podocyte changes (for details see Fig. 6.9). Vacuoles were not semiquantitatively evaluated. Osmiophilic fibrils synonymous with substance

**Fig. 6.58.** Reaction pattern of podocyte parameters as seen with EM and their correlation to IF findings (for details, see Fig. 6.22). Osmiophilic fibrils synonymaous with substance

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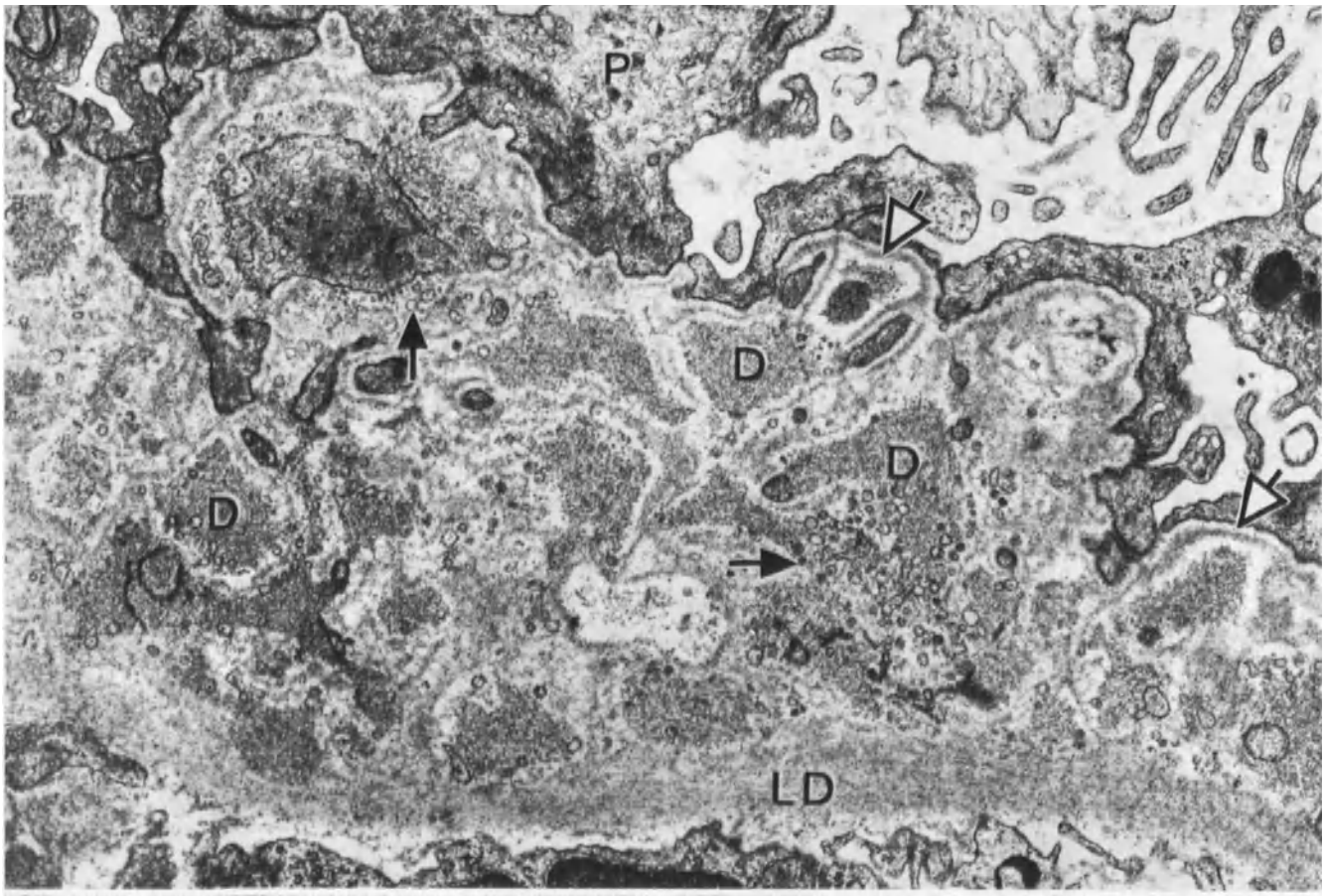
**Fig. 6.59.** Complete fusion of podocyte foot processes which evidence accumulation of osmiophilic substance (→) in glomerular minimal change. Male, 18 years. EM (× 18,400)

**Fig. 6.60.** Extensively increased osmiophilic substance in podocytes (*P*) which is partly fibrillar in character. Endotheliomesangial GN. Endothelium (*E*). Female, 16.5 years. EM (× 46,000)

**Fig. 6.61.** Severe vacuolar degeneration and hypertrophy of podocytes and formation of microvilli (→) in membranoproliferative GN. Very pronounced widening of endoplasmatic reticulum is also present. Female, 31 years. EM (× 3000)

**Fig. 6.62.** Fibrin (→) and very large phagolysosomes (protein droplets, *PD*) in an edematous podocyte during clinically acute attack in membranoproliferative GN known for 6 months. Male, 60 years. EM (× 8600)

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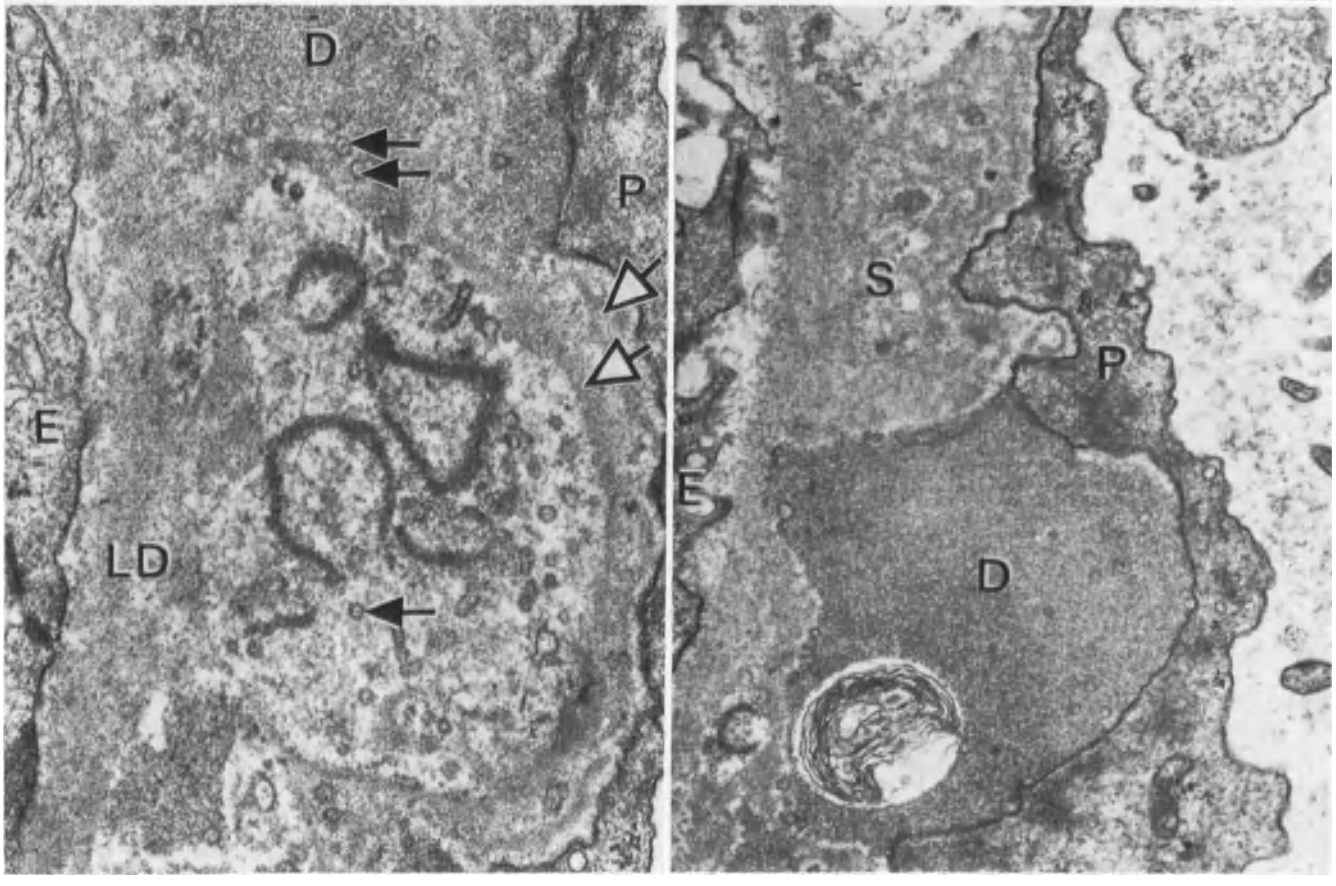


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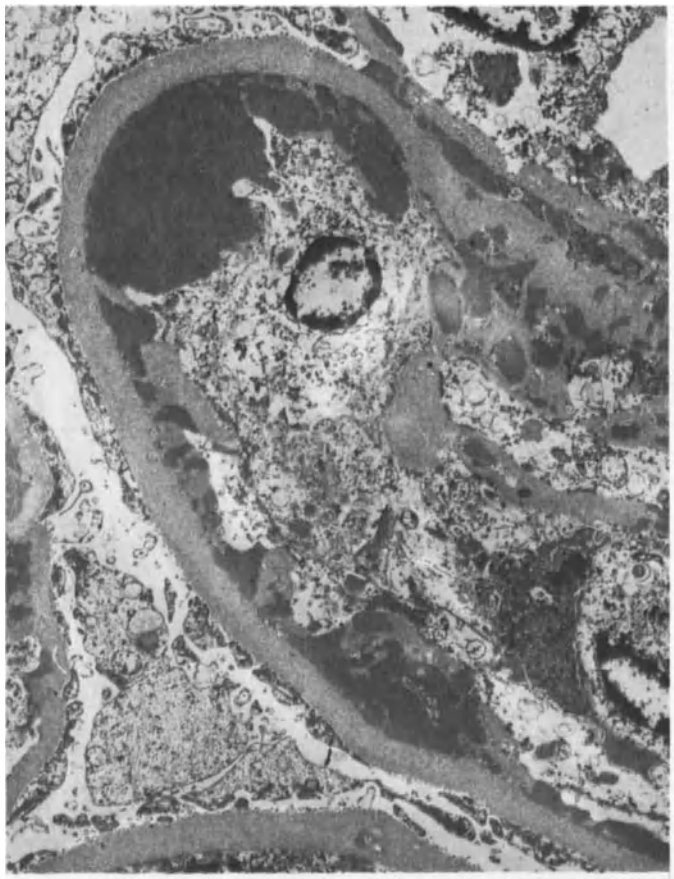

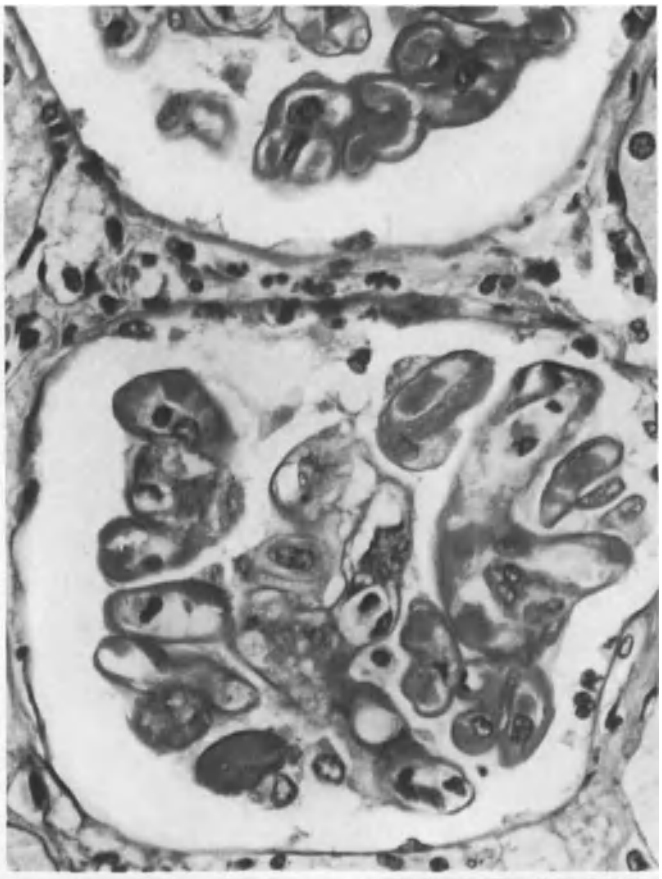

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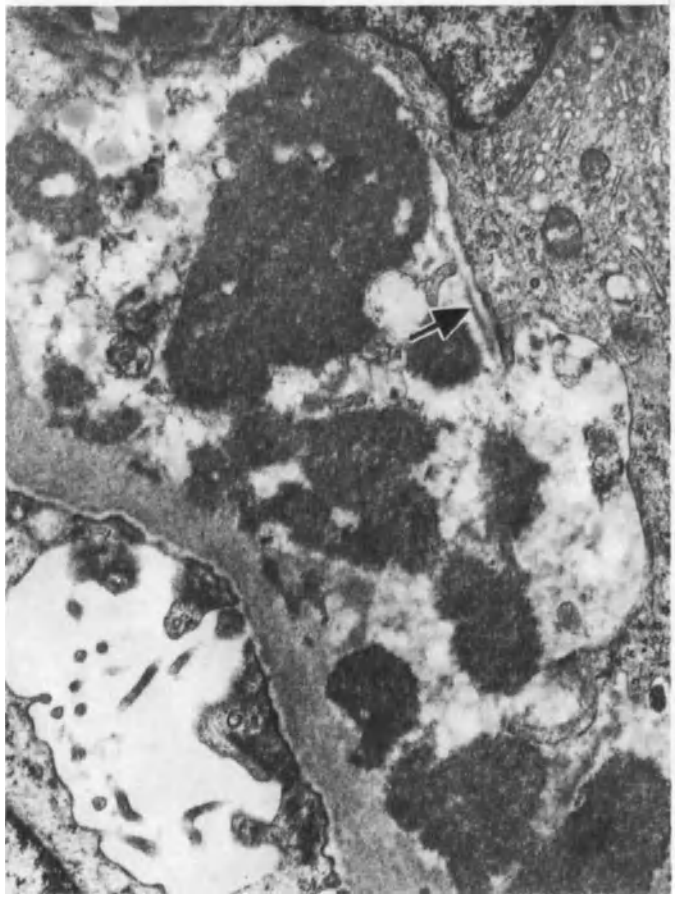

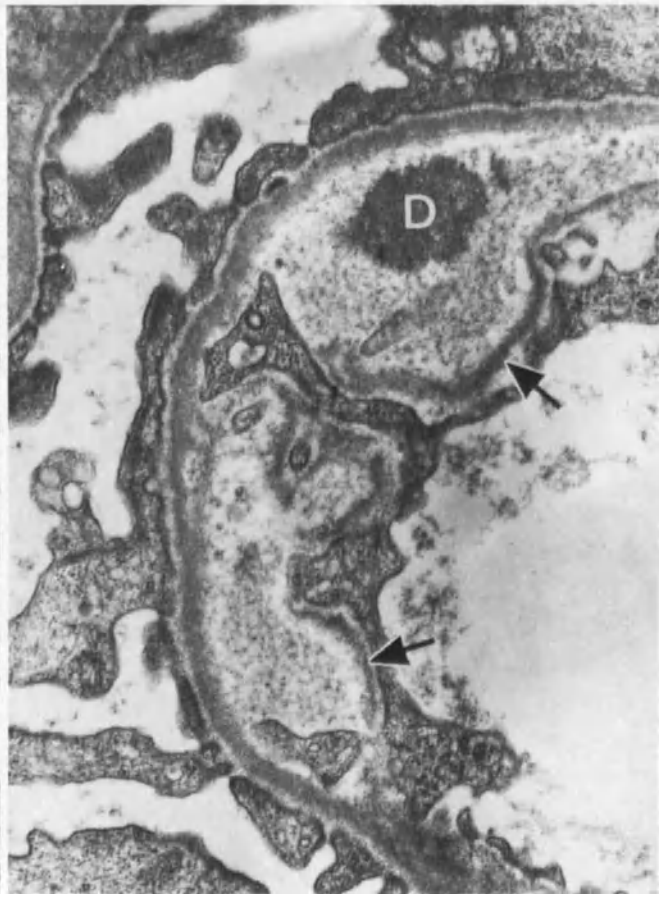


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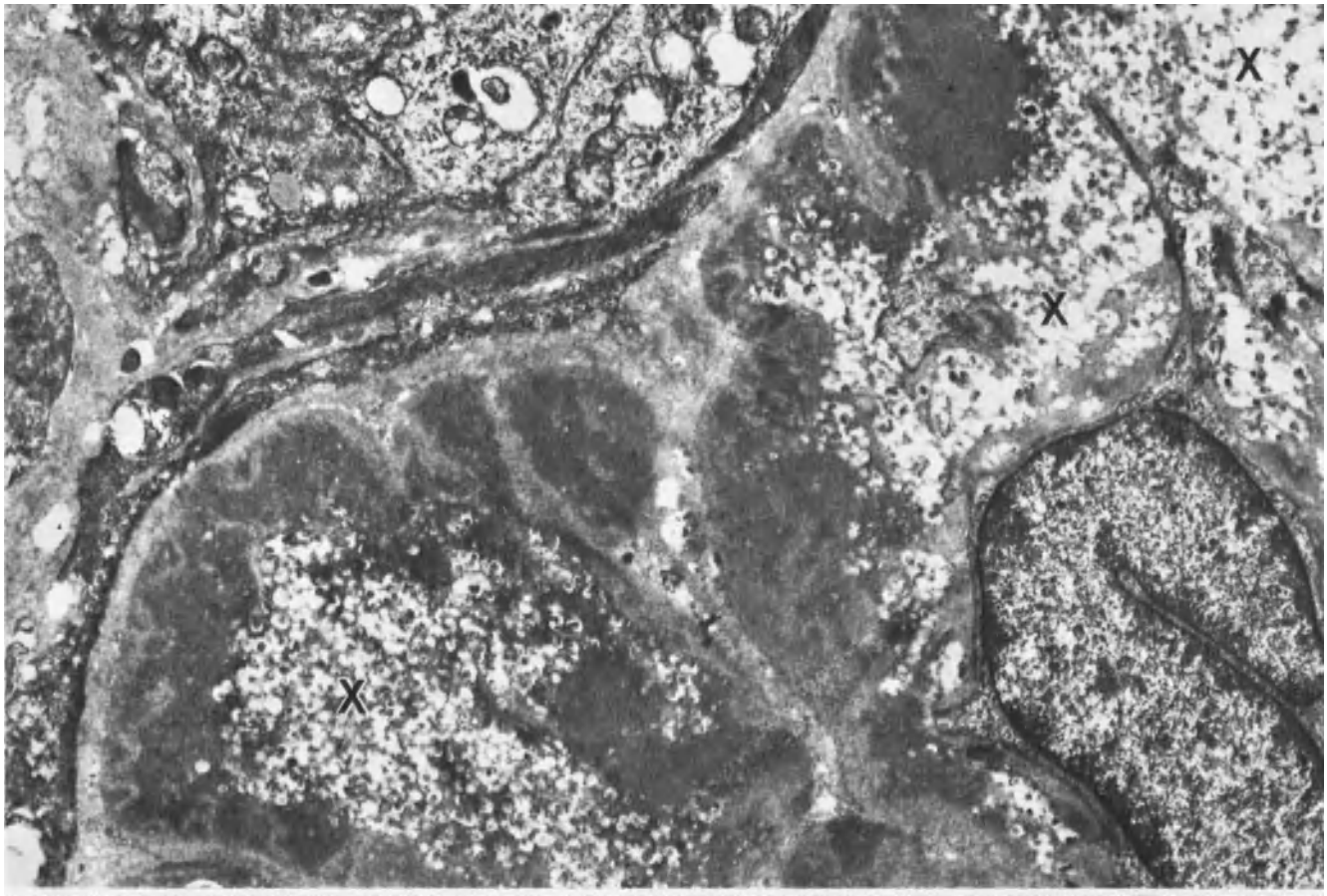


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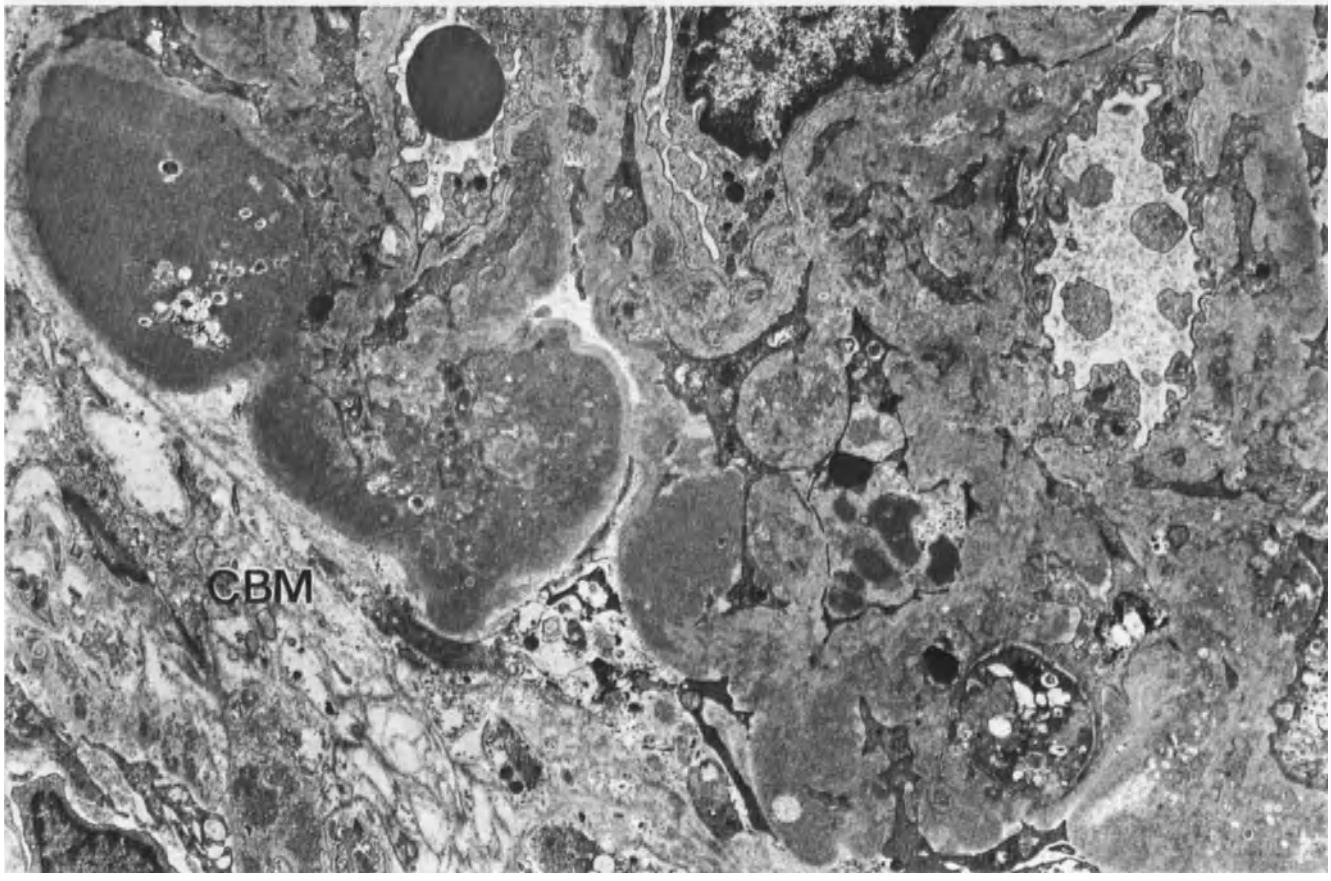


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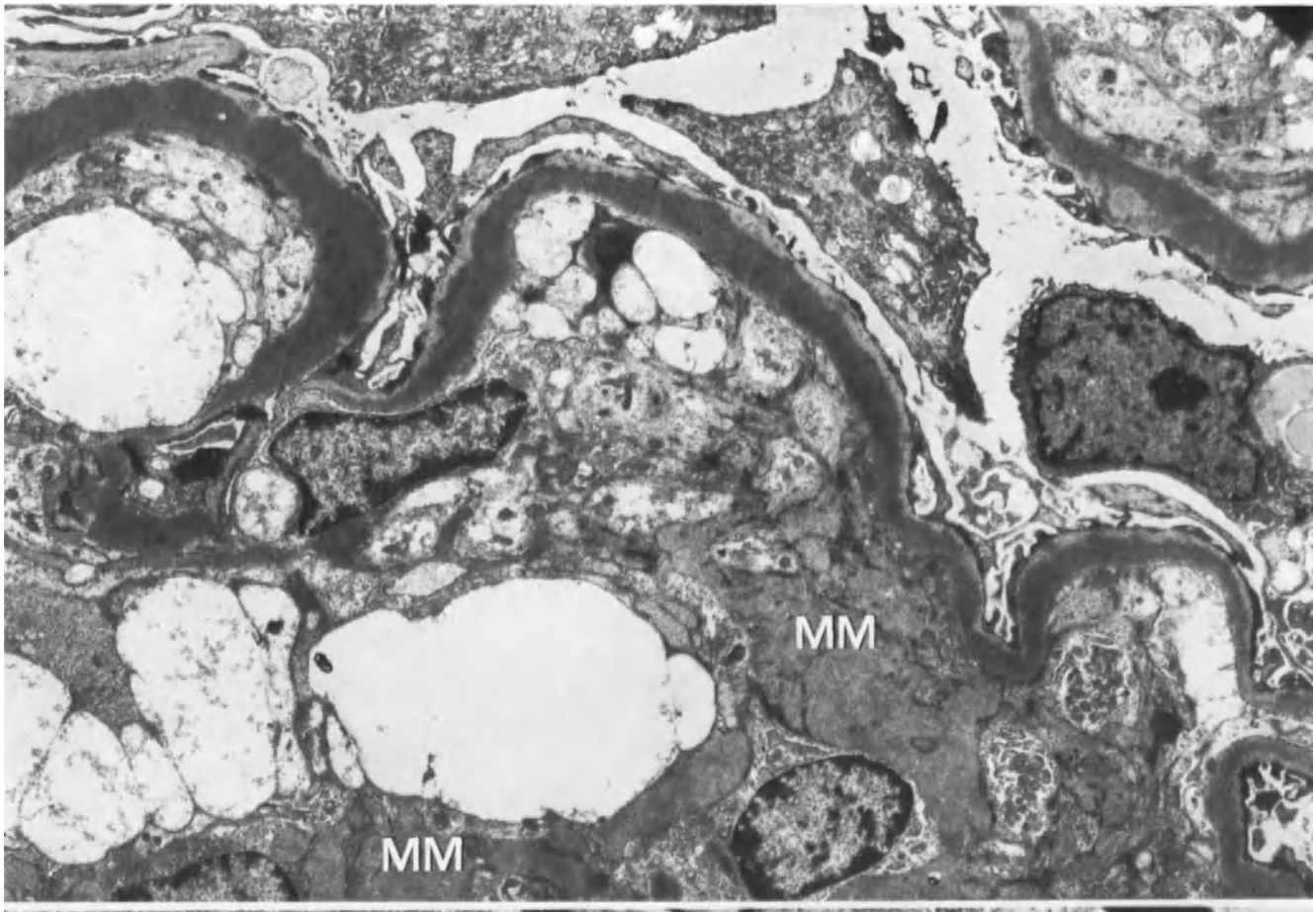


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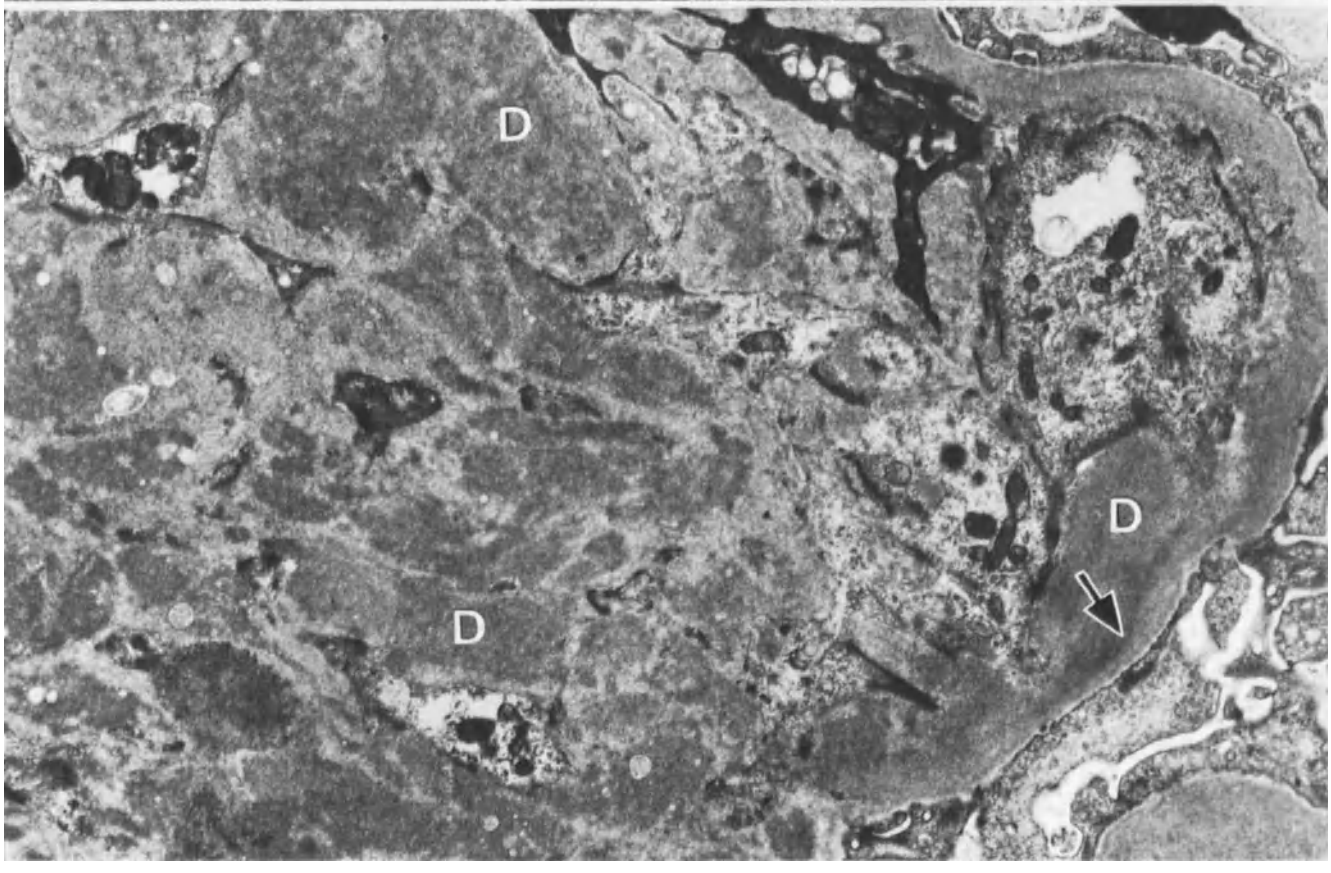


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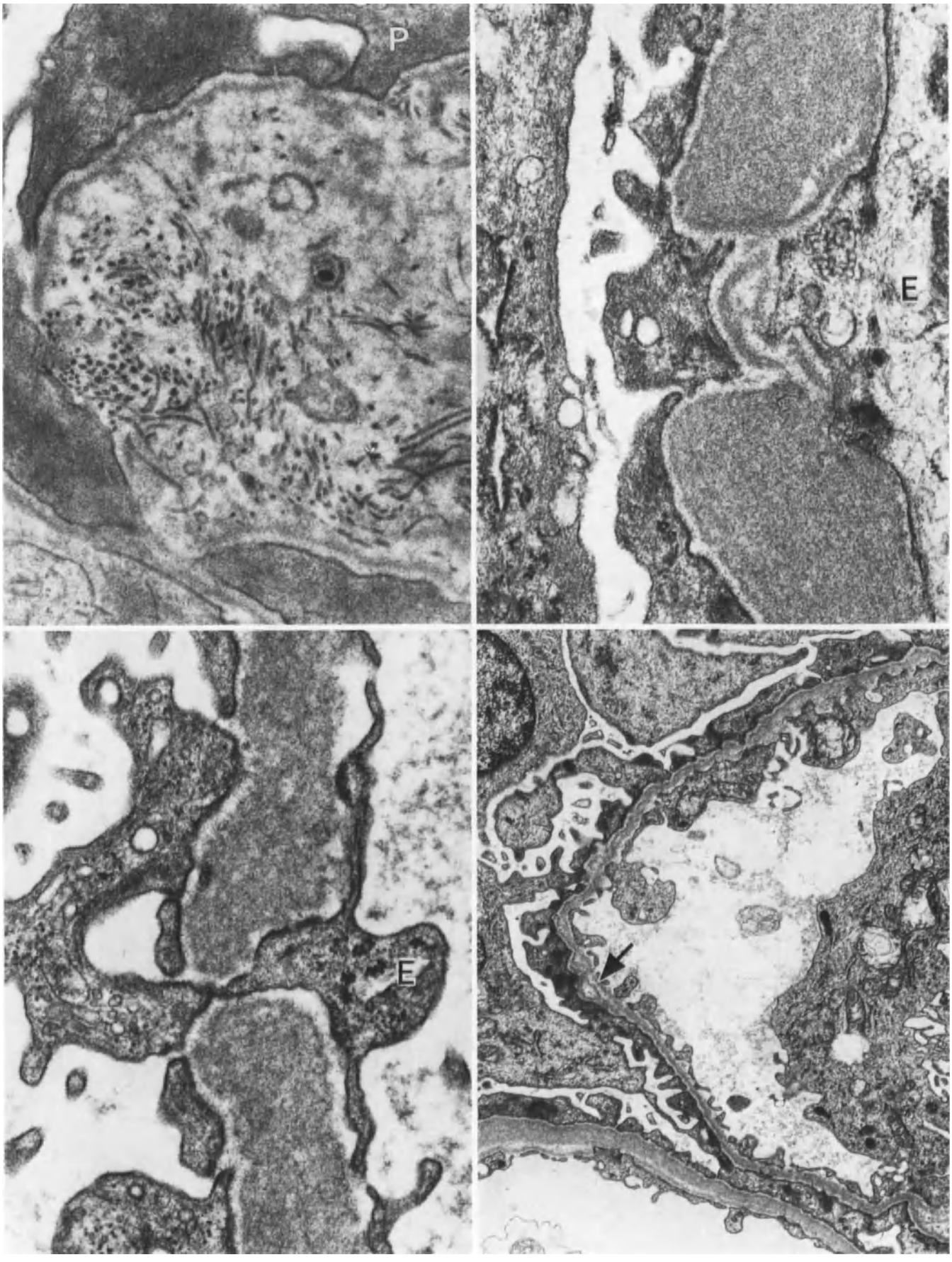


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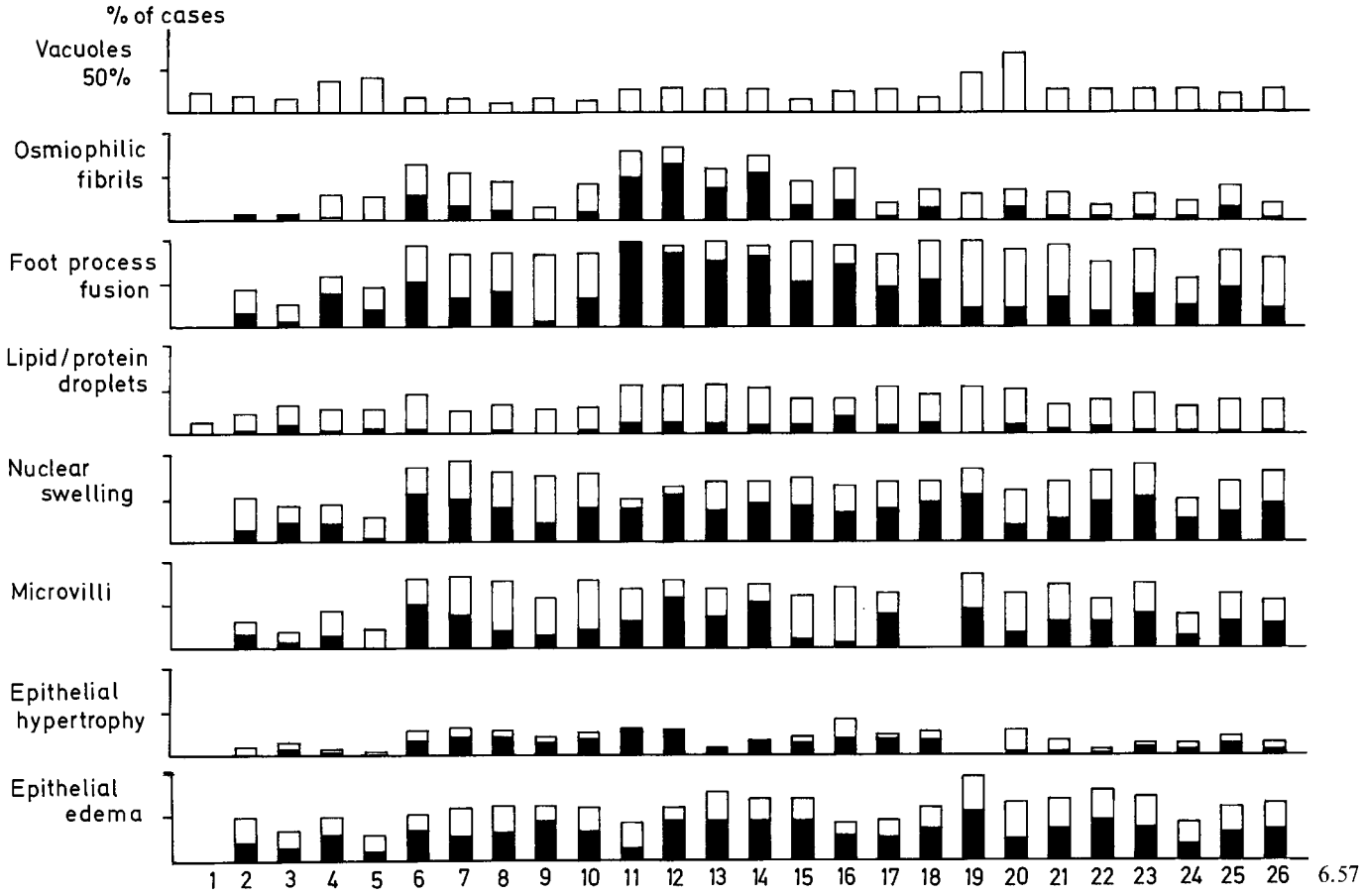
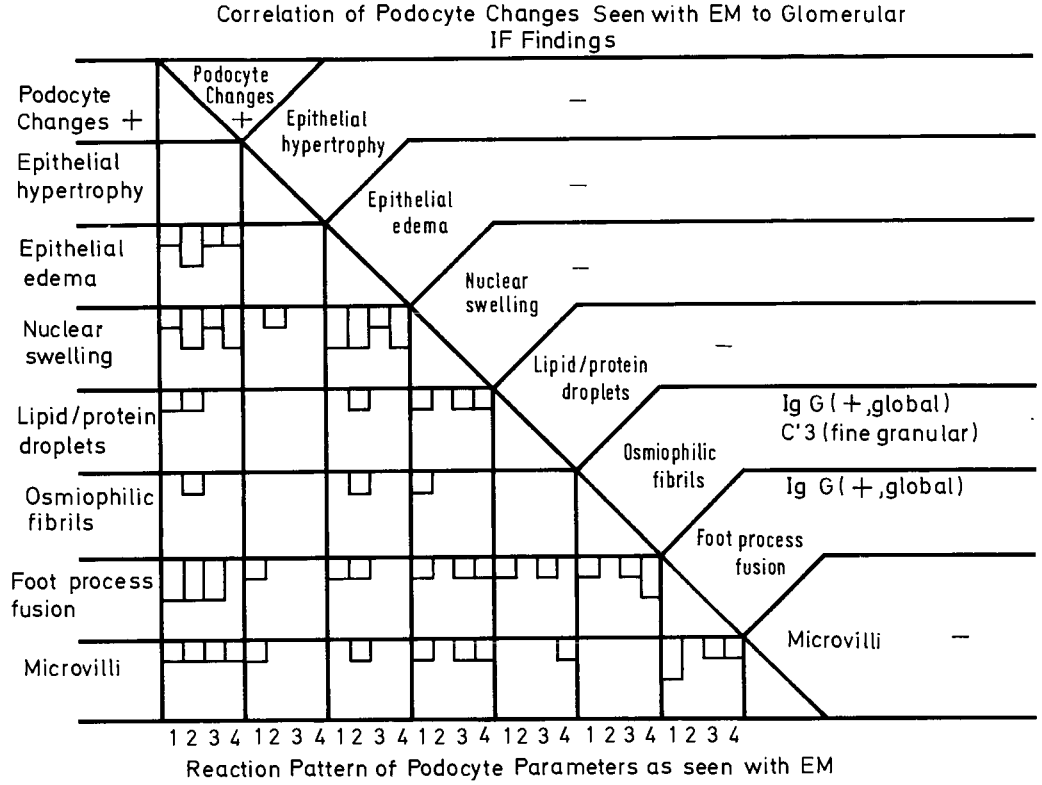
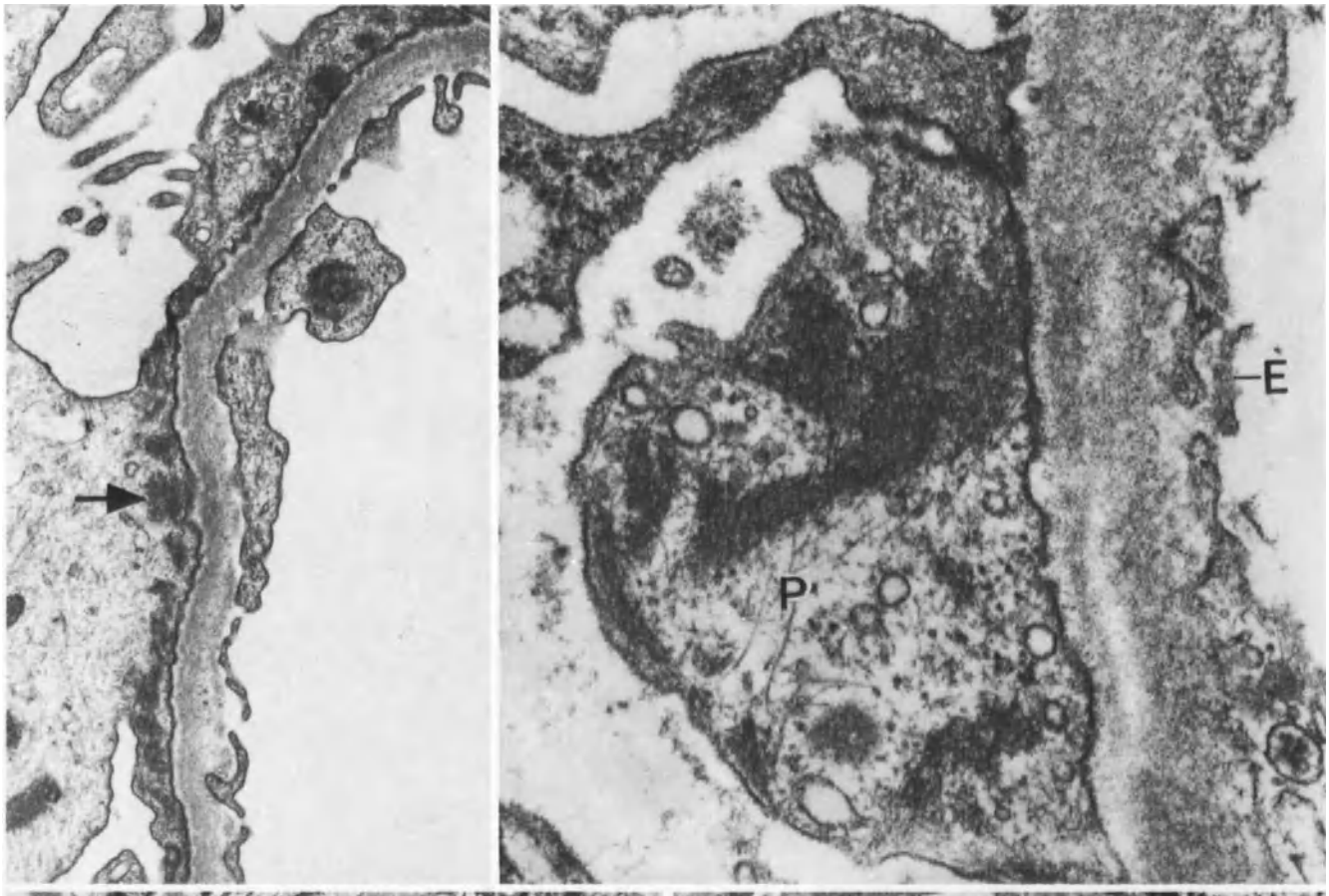

% of cases
Vacuoles 50%
Osmiophilic fibrils
Foot process fusion
Lipid/protein droplets
Nuclear swelling
Microvilli
Epithelial hypertrophy
Epithelial edema
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26

6.57


Correlation of Podocyte Changes Seen with EM to Glomerular IF Findings
Podocyte Changes +
Epithelial hypertrophy
Epithelial edema
Nuclear swelling
Lipid/protein droplets
Osmiophilic fibrils
Foot process fusion
Microvilli
Podocyte Changes +
Epithelial hypertrophy
Epithelial edema
Nuclear swelling
Lipid/protein droplets
Osmiophilic fibrils
Foot process fusion
Microvilli
–
–
–
–
Ig G (+,global)
C'3 (fine granular)
Ig G (+,global)
–
1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4
Reaction Pattern of Podocyte Parameters as seen with EM

6.58

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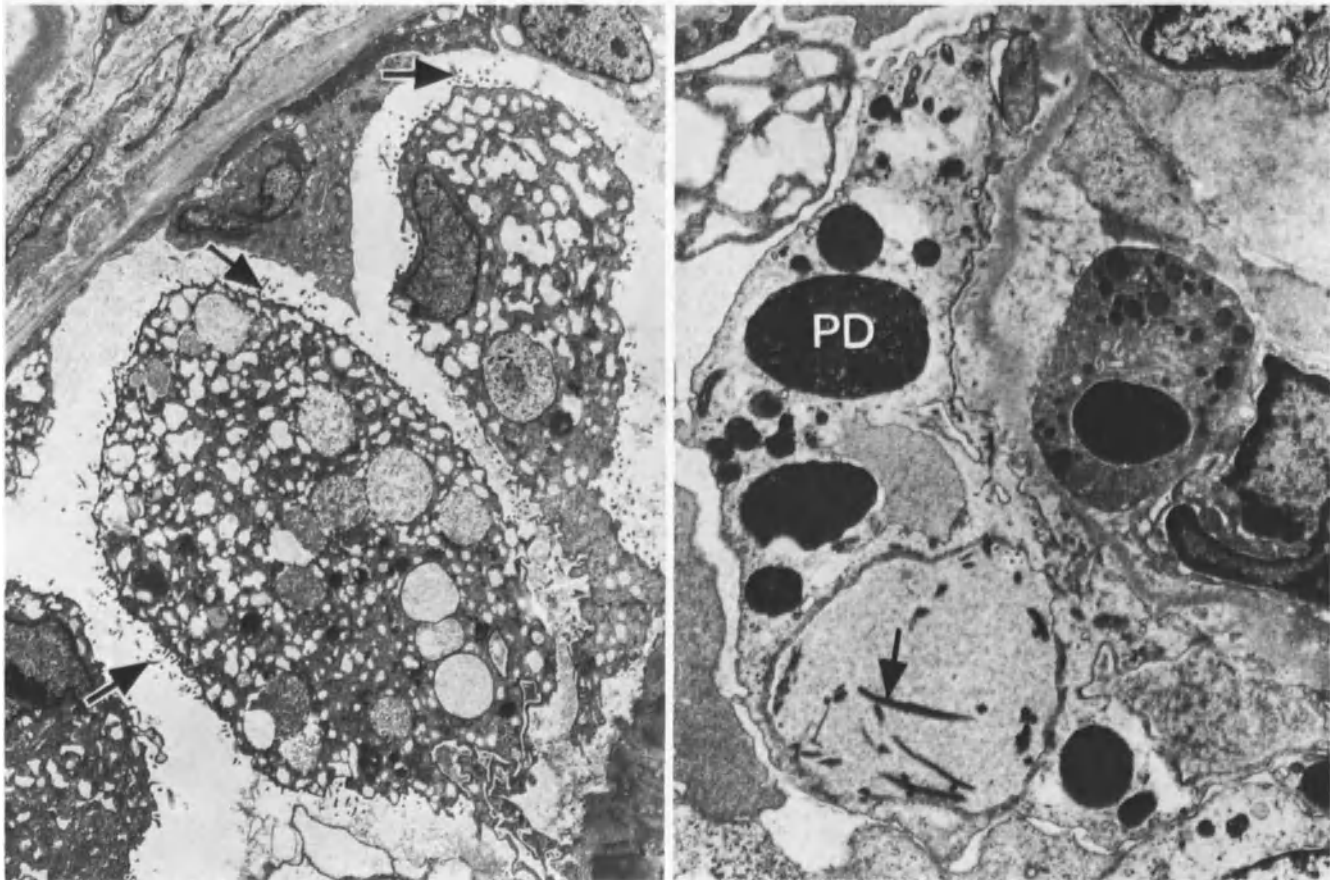


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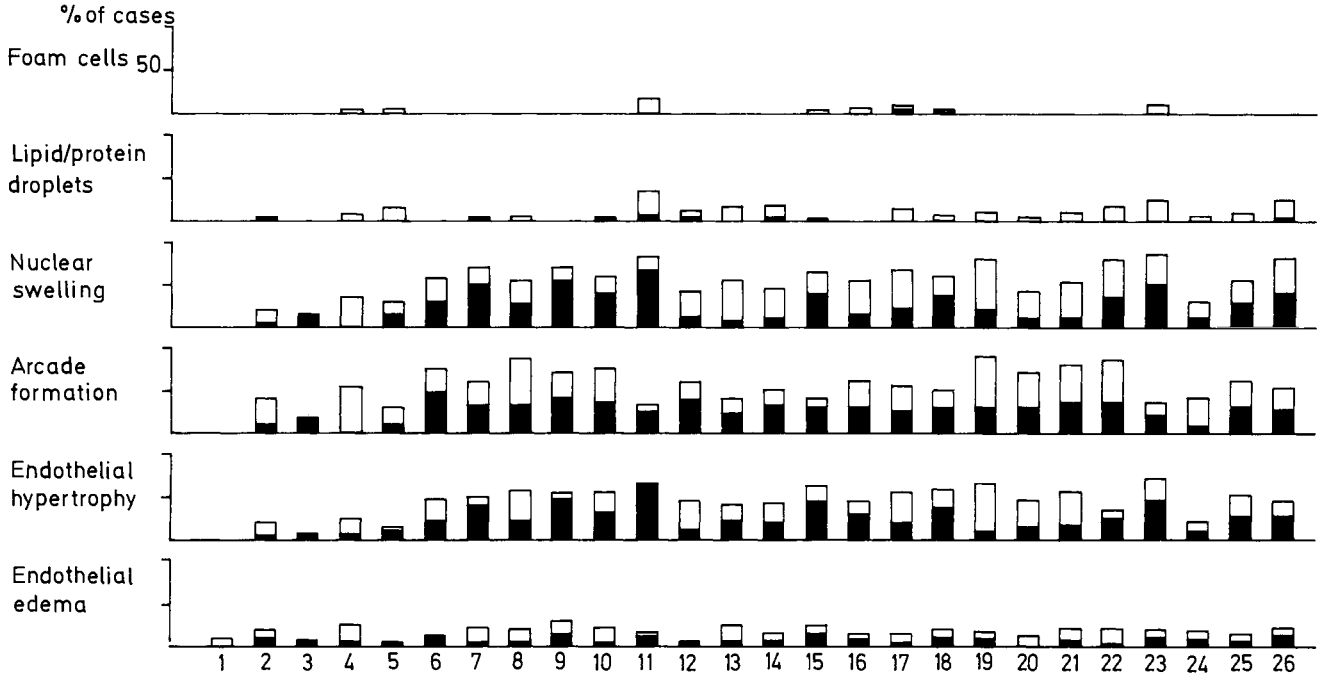



**Fig. 6.63.** Histogram. Endothelial changes in glomerular capillary loops (for details, see Fig. 6.9)

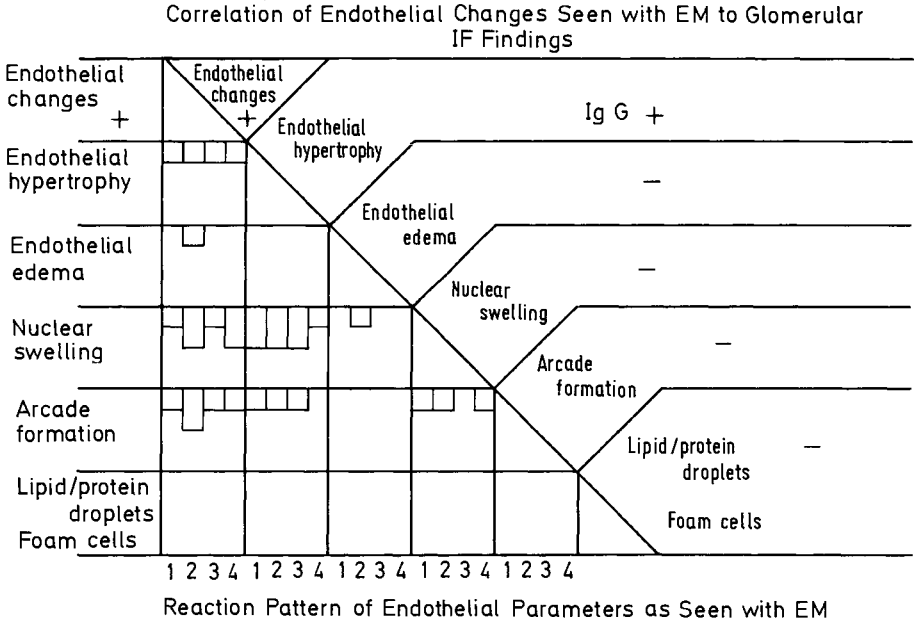


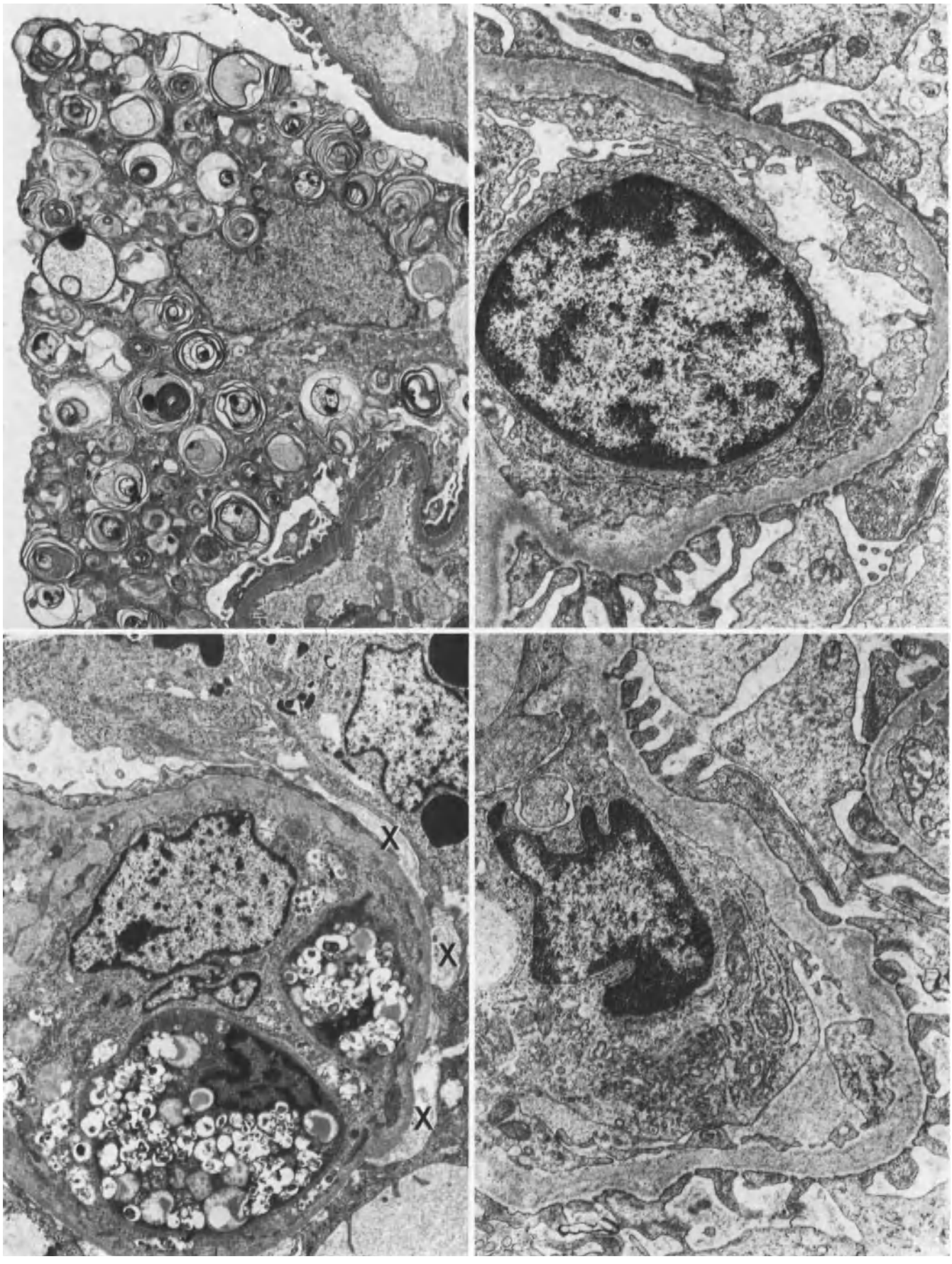

**Fig. 6.64.** Reaction pattern of endothelial parameters as seen with EM and its correlation to glomerular IF findings (for details, see Fig. 6.22)

**Fig. 6.65.** Unusual massive accumulation of myelin figures in a podocyte in pyelonephritic contracted kidney. Male, 61 years. EM (×4600)

**Fig. 6.66.** Highly swollen (hypertrophied) endothelial cell with increase of organelles and severe nuclear swelling in endotheliomesangial GN of 6 weeks' duration. Male, 3.5 years. EM (×12,700)

**Fig. 6.67.** Endothelial foam cells in a glomerular capillary loop ▷ in GN contracted kidney. Beginning subepithelial deposition of fibrillar material (X) indicating obliteration. Male, 34 years. EM (×5900)

**Fig. 6.68.** Endothelial cell with pronounced swelling and lobulation of nucleus as well as increase of organelles. Glomerular minimal change 7.5 months after clinically acute GN. Male, 4.5 years. EM (×14,400)

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6.68

Other investigators consider this podocytic osmiophilic substance to be characteristic for lipoid nephrosis [111]—which we cannot confirm (Fig. 6.57)—or a precursor for BM [1109, 1154].

Hypertrophy of podocytes characterized by increase of endoplasmatic reticulum, Golgi complexes and ribosomes is far more rare (see Figs. 6.57, 6.61). Hypertrophy can also be associated with the formation of microvilli (Figs. 6.61, 6.58). Microvilli formation and foot process fusion do not exclude each other (Figs. 6.57, 6.58).

Protein (Fig. 6.62) and, less frequently, lipid droplets or myelin figures (Fig. 6.65) are observed as cellular inclusions with approximately the same frequency in all nephropathies; cytoloysosomes occur only in severe changes [454]. Finally, heterolysomes with a granular or amorphous content—possibly representing degraded immunocomplexes—are observed in the presence of subepithelial deposits [1628a], a finding which additionally supports the contention mentioned above.

A further change seen in glomerular proteinuria is manifested as a weakening of the colloidal iron stain for sialic acid in podocyte membrances [152].

Cellular necrobioses and necroses (3 out of 700 of our EM biopsies) were found exclusively in glomerular obsolescence. Such cells are very electron-opaque and shrunken and contain strongly dilated endoplasmatic reticulum (Fig. 6.92).

Stereocilia (Figs. 6.16, 6.17; p. 62) are an extremely rare finding (1 out of 700 of our cases) and their significance has eluded explanation. For virus-suspect findings, see p. 92; for podocytic giant cells see Table 8.1, p. 129.

**Endothelium**
(Figs. 6.63, 6.64)

Endothelial changes noted with LM are, as made evident in the histogram (Fig. 6.63), usually far more pronounced than are those of podocytes. Thus, for example, severe swelling of the endothelial cells (Fig. 6.66) accompanied by nuclear swelling which leads to apparent occlusion of the capillary lumen can occur during the exudative stage of GN. An especially marked form of endothelial swelling is seen in toxemia of pregnancy, i.e., simple glomerular endotheliosis [1494, 1540].

It should be borne in mind that what appears to be endothelium with LM can, with EM, be shown to be monocytes, mesangial or endothelial cells. Even with EM, categorical identification of different cell types may often be beset with difficulties.

Endothelial foam cells (Fig. 6.67) are encountered in hyperlipemia, diabetes mellitus, nephrotic syndrome [75a, 1564a, 1568a, b, c] and in storage diseases (Fig. 23.1, [1365]). In the first three diseases, the foam cells demonstrate a focal-segmental distribution while in storage diseases they occur more globally and diffusely. Among the glomerulonephritic diseases, especially in proliferative/sclerosing FGN, we have found isolated foam cells in 3% of our cases and in 1.4% of our non-GN biopsies—exclusively in diabetes mellitus with hyperlipemia. We also noted foam cells in 2% of our renal transplant material (Fig. 6.43).

The typical reaction pattern in EM (Fig. 6.64)—irrespective of the type of nephropathy—usually consists of hypertrophy (Fig. 6.68) characterized by an increase in endoplasmatic reticulum (see also [275]) accompanied by nuclear swelling and notching (Fig. 6.68) and by arcade formation (cytofolds, pseudopod-like processes, Fig. 6.69; [454]). Endothelial hypertrophy is the result of various longer acting stimuli, e.g., the presence of IgG in cases of pronounced changes.

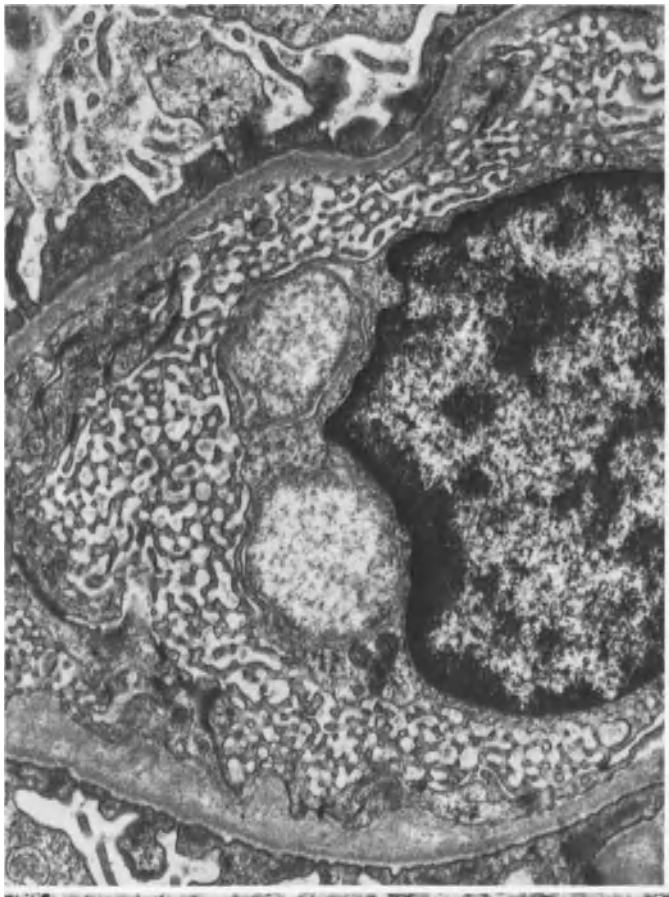
Cellular hypertrophy was present in about 50% of our cases of GN and renal transplants. More rarely we have observed it in nonglomerulonephritic lesions (Fig. 6.63) Endothelial hypertrophy may persist for months subsequent to GN [65a, 446a, 901a, 1010a, 1068, 1436a, 1797, 1718a, 1131a]. It also occurs during regenerative activity in the region of the endothelium, during intensified cellular work and also during aging [8a, 545a, 1549a]. In hypertrophy, endothelial gaps appear whose consequence is an increase in vascular permeability.

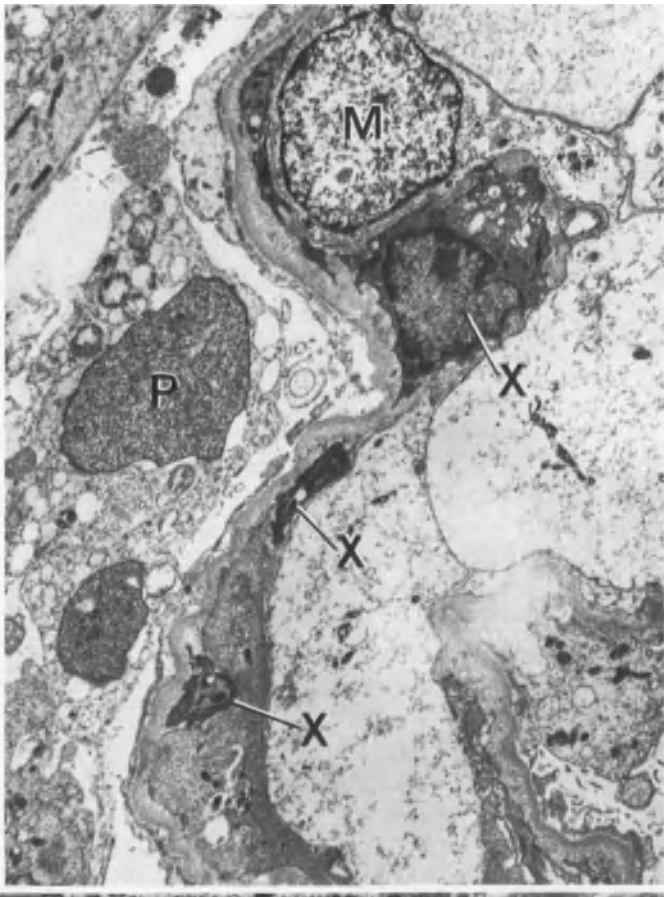
Endothelial edema—with or without nuclear swelling, but without concomitant organelle increase—is an unspecific reaction form which probably can rapidly set in as a response to a wide range of injurious agents and especially to hypoxia [1470]. The edema is usually accompanied by the formation of so-called balloons, i.e., organelle-free evaginations or amputations of cytoplasmic components (see p. 60).

**Fig. 6.69.** Pronounced arcade formation as a sign of endothelial cell hypertrophy and activation in glomerular minimal change. Female, 8 years. EM (×13,700) ▷

**Fig. 6.70.** Necrobiotic endothelial cell (X) in membranoproliferative GN with severe extracapillary involvement. Podocytes (*P*) and the nucleus of a mesangial cell (*M*) are highly degenerated. Male, 46 years. EM (×5500)

**Fig. 6.71.** Severe endothelial proliferation in membranoproliferative GN. Endothelial cells are poor in organelles and lie directly on the BM; this latter finding excludes the presence of mesangial cells. Polymorphonuclear leukocytes (*PL*) are seen in the severely narrowed residual glomerular capillary loop lumen. No deposits are present in this micrograph. Male, 57 years. EM (×4700)



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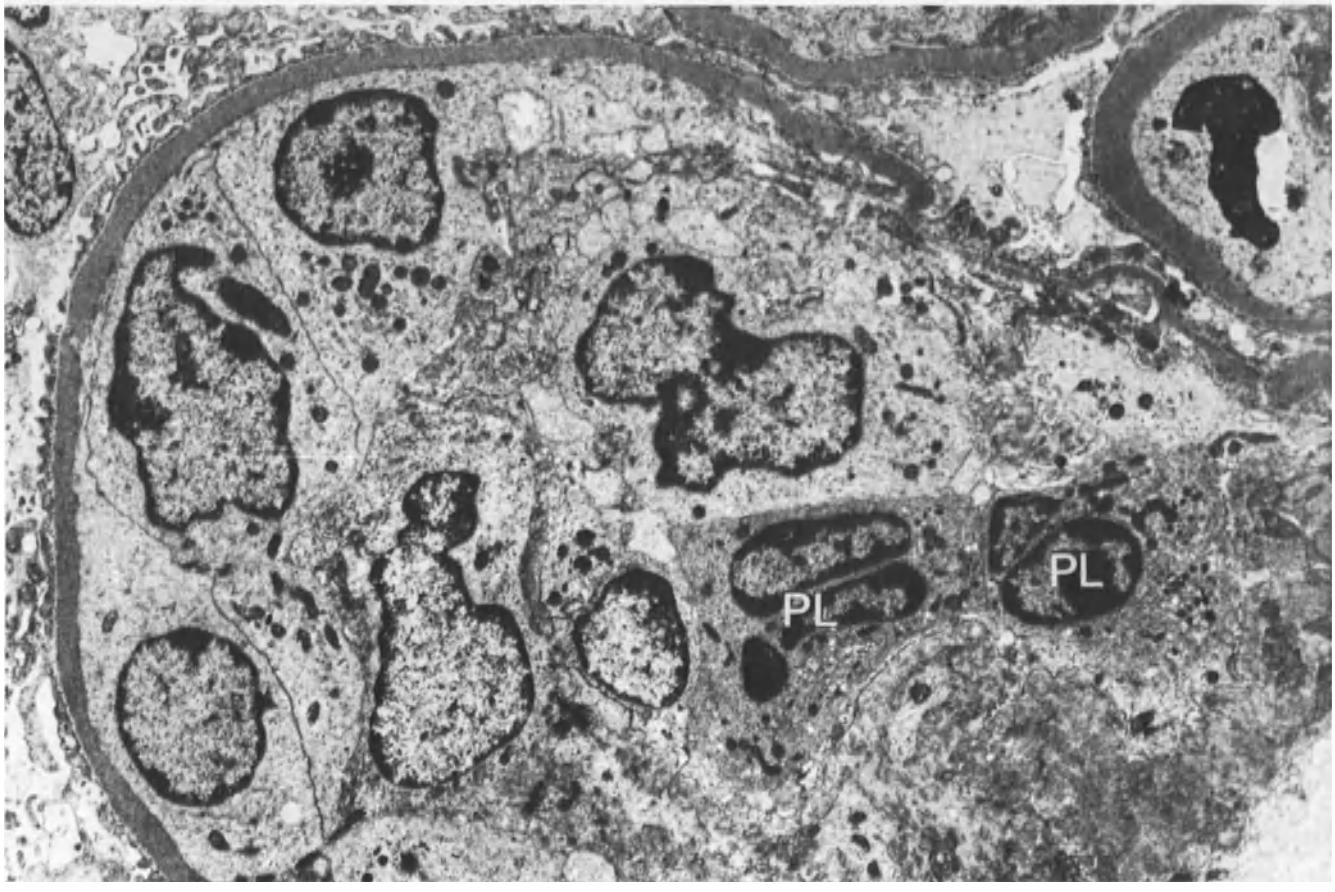



6.71

Lipid and protein droplets are the most common cellular inclusions. They are, however, relatively infrequent (contra: [1508]) but can be occasionally encountered in all nephropathies. In our biopsies from renal transplants alone (see Fig. 6.63), we have observed these inclusions – in relevant amounts – in more than 20% of the cases. However, development to the stage of foam cells (see above) is exceptional.

We observed cellular ferritin three times (Fig. 17.42) and degraded fibrin residues once in GN.

Necrotic endothelial cells are extremely rare (1 out of 700 of our cases). These cells are recognizable by their condensed cytoplasm (coagulation necrosis) with organelle debris (Fig. 6.70). They become detached from the BM and their fenestrated cytoplasmic processes disappear [454]. Pinocytotic vesicles exhibit a remarkable resistence towards cytotoxic phenomena [1010a]. Following endothelial cell detachment, the BM lies freely exposed to the bloodstream and, accordingly, thrombocyte deposition may occur.

Endothelial cell proliferation, to a certain degree, follows endothelial destruction but terminates once the defect has been repaired [454a, 1565a].

This proliferation never results in a multilayered covering of the arteries, arterioles and glomerular capillaries even under the most diverse conditions with regeneration of other vessel-wall constituents [8a, 667a, 831a, b, 901a, 1594a]. There has still not been a clear-cut answer to the question as to whether or not endothelial capillary loop cells can, above and beyond simple replacement, actually proliferate. The problem continues unsolved chiefly because of the almost insurmountable problem – even with EM – of differentiating endothelial from mesangial cells or monocytes (Fig. 6.71).

The presence of PASM- and PAS-positive or osmiophilic material (visible in EM) between proliferated cells may point rather to the mesangial nature of the cells in question.

However, the occurrence of mitoses (2 out of 700: Z, 1 GN, 1 transplant) of endothelial cells in capillary loops as well as the presence of endothelial mitoses in capillaries at other inflammatory body sites (e.g., in wound healing), scarcely leaves room for doubting the proliferative capacity of endothelial cells [1797]. In such cases, we have observed interdigitation of the cytoplasmic processes.

In collapse, occlusion of capillary loops by endothelial proliferation has been clearly demonstrated (Fig. 6.72).

## Virus-Like Particles

Both clinical and serologic data categorically demonstrate that viruses can lead to inflammatory glomerular changes. EM study rather frequently shows virus-like particles especially in inflammatory glomerular processes. But it is not certain whether the particles under observation are effectively viruses or merely degraded, nonviral substances. If serum and biopsy material have not been appropriately maintained by deep-freezing, retrospective demonstration of virus usually proves to be well-nigh impossible.

It is therefore prudent in any case to maintain serum and biopsy material for investigations. Otherwise, a second biopsy with appropriate plans for correct tissue processing should be realized. When the above suggestions are followed, virus – if present – can clearly be demonstrated serologically and with IF [299, 722, 1173, 1531].

In describing such particles with EM, it is advantageous to rely on a purely descriptive nomenclature. We differentiate between round, tubular (filamentous), textile-like, and thread-like structures amongst others. In the absence of unquestionable identification of virus with IF, the term "virus-like particles" should be exclusively used together with the descriptive nomenclature [86].

***Round Virus-Like Particles.*** The operative definition of these forms is that they are round, very dark (Fig. 6.73) or provided with a light center or with a dark nucleus-like central body (Fig. 6.75). Under high resolution, a three-layered membrane can clearly be recognized [230].

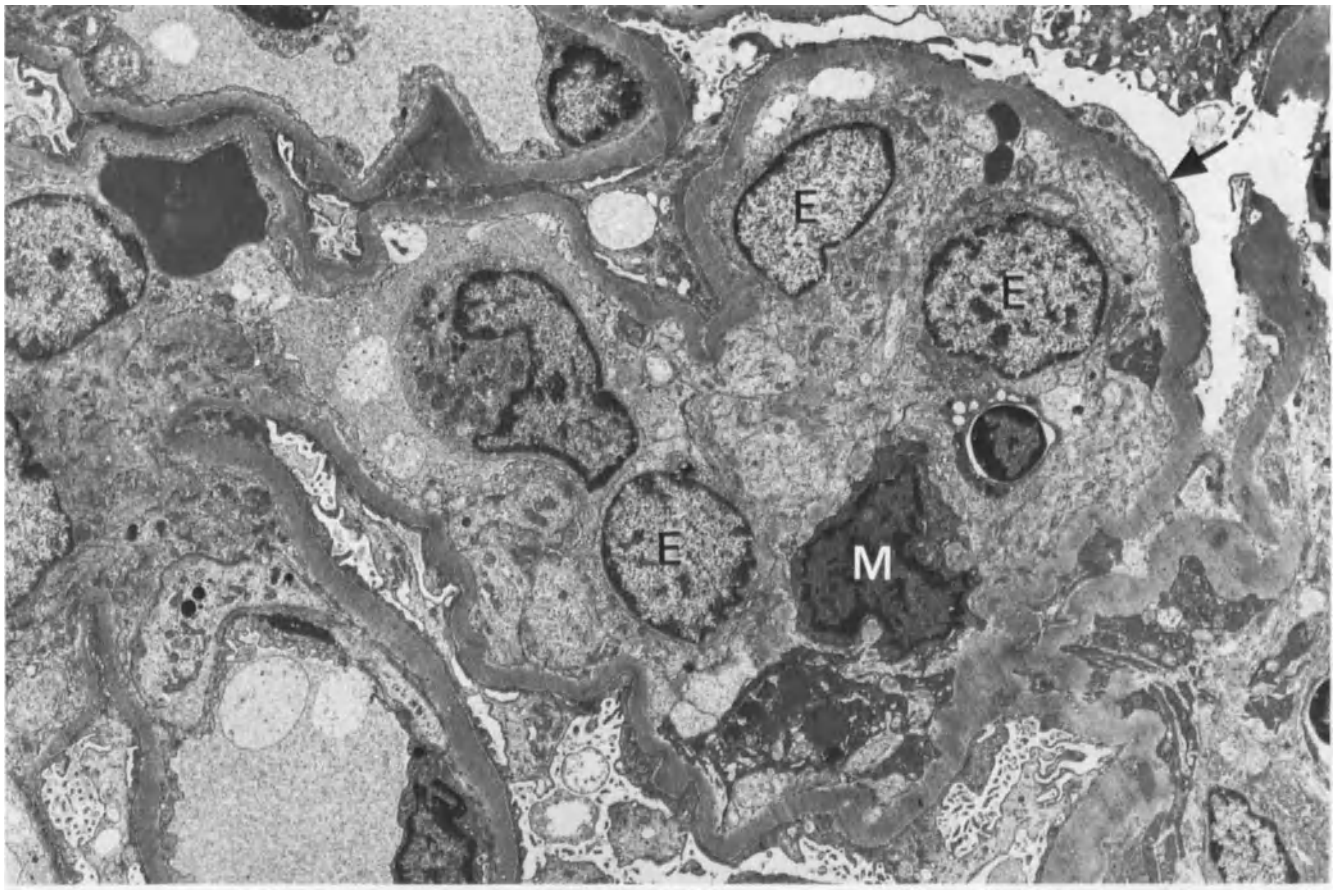
The size varies between 200 and 1800 Å. Considering this parameter only, a particle of about 200 Å could correspond to the hepatitis-B surface antigen (Fig. 6.75), one of 400–450 Å to Dane particles, one of 800–1200 Å to the Barr-Epstein virus (Fig. 6.75) and one of 1500 Å to myxovirus (mumps) [1523]. For further special problems on virus and its morphology see [336].

Round virus-like particles are always extracellular. As a rule, they are found in intimate association with the BM, usually intramembranously, often subepithelially, and more rarely subendothelially (see also [230]). In part, they are also found in relation to osmiophilic deposits [230].

**Fig. 6.72.** Glomerular capillary loop occlusion in slight loop collapse (BM wrinkling) caused by endothelial proliferation (*E*). Severely pyknotic mesangial cell (M). Fusion of foot processes (→). Chronic pyelonephritis with overload glomerulitis. Male, 61 years. EM (×4200) ▷

**Fig. 6.73.** Virus-like granular particles in place of podocytes are seen in membranoproliferative GN of 5 years' duration. Male, 43 years. EM (×15,500)

**Fig. 6.74.** A multivesicular body (→) in a hypertrophied podocyte in congenital nephrotic syndrome. Male, 4 months. EM (×54,000)

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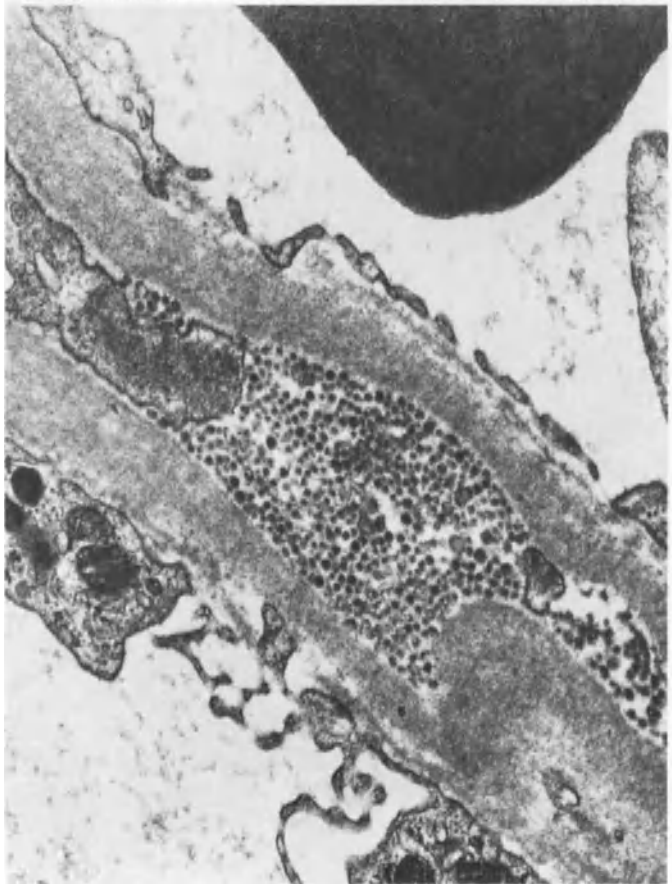

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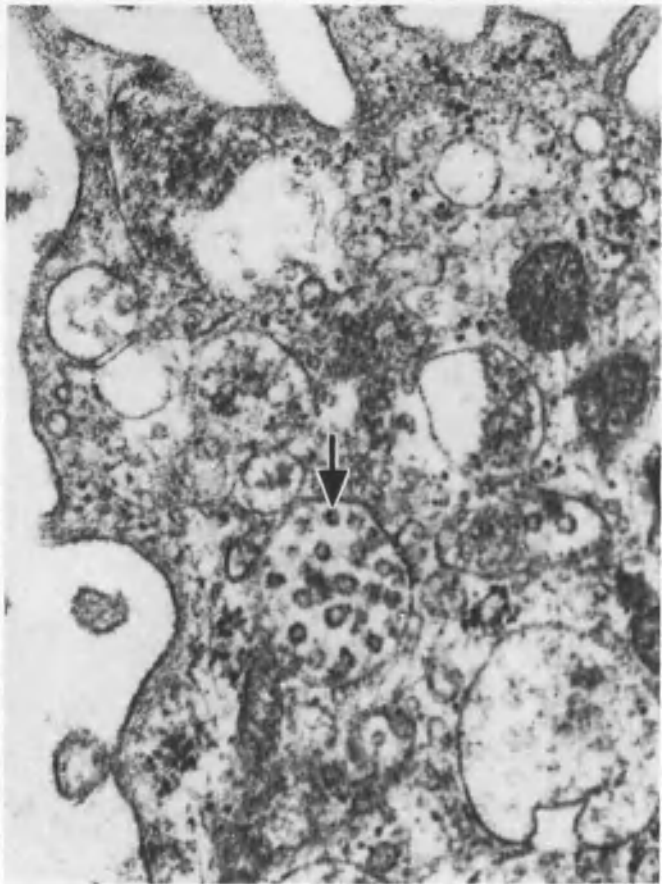

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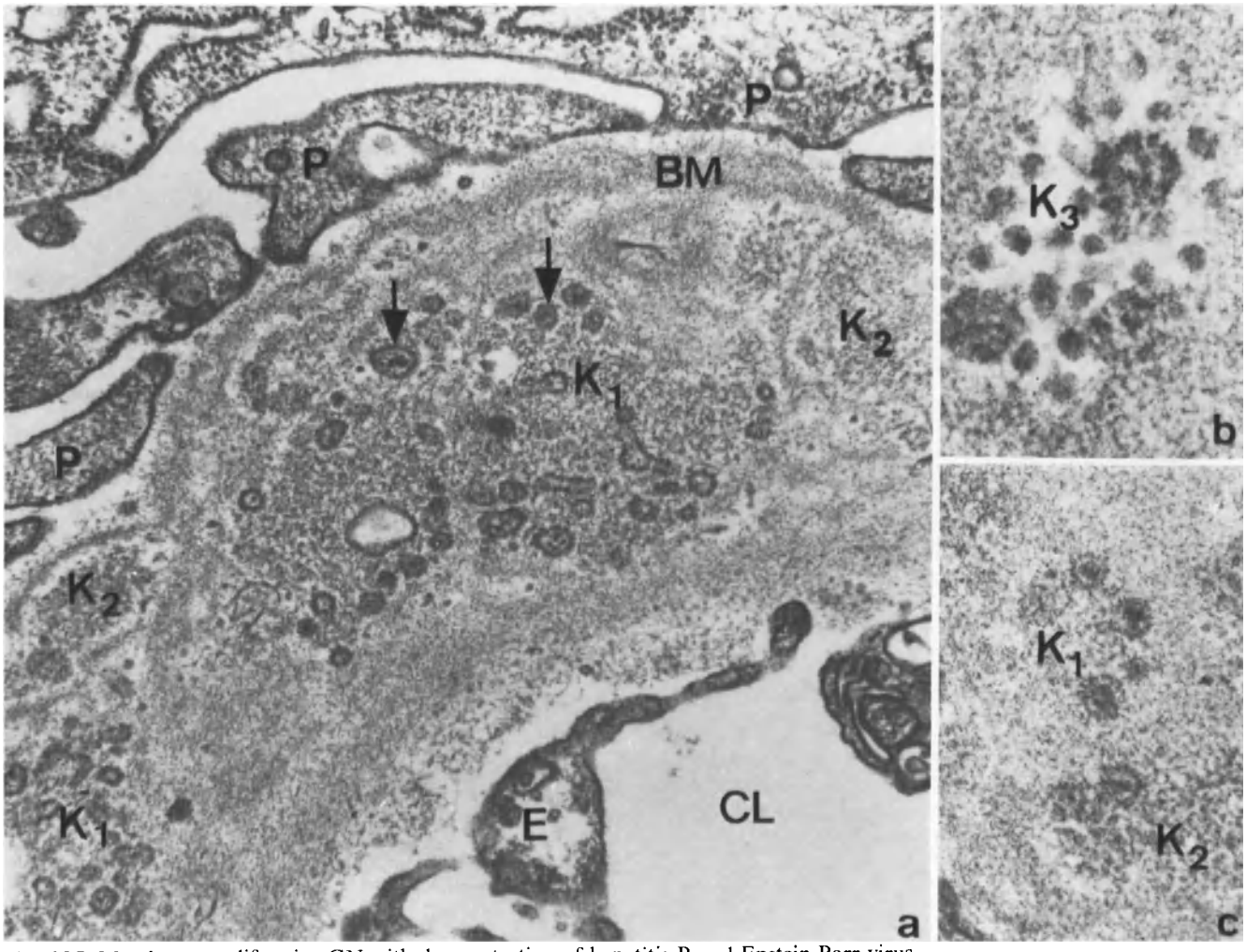



**Fig. 6.75.** Membranoproliferative GN with demonstration of hepatitis B and Epstein-Barr-virus

(a) Part of a glomerular capillary loop wall showing coarse, granular osmiophilic deposit. K 1, large Epstein-Barr-virus particle clearly discernible in deposits (core indicated at →), K 2, deposit without particle. Basement membrane (*BM*), podocyte foot process (*P*), endothelium (*E*), capillary lumen (*CL*). Male, 41 years. EM (× 36,000)

(b) Complex with small particles (K 3) thought to be hepatitis B surface material. EM (× 115,000)

(c) Complex with large particles with core. K 1, Epstein-Barr-virus, K 2 granular osmiophilic deposit without particles. EM (× 50,000). From [1531]

Epimembranous GN is especially often the underlying disease in which the particles are found. They also occur in kidney transplants and, exceptionally, they are found in non-GN. In a careful study of well-kept renal transplant material, the round particles were found in 55 out of 476 cases [230] and in 86 out of 190 [86] respectively.

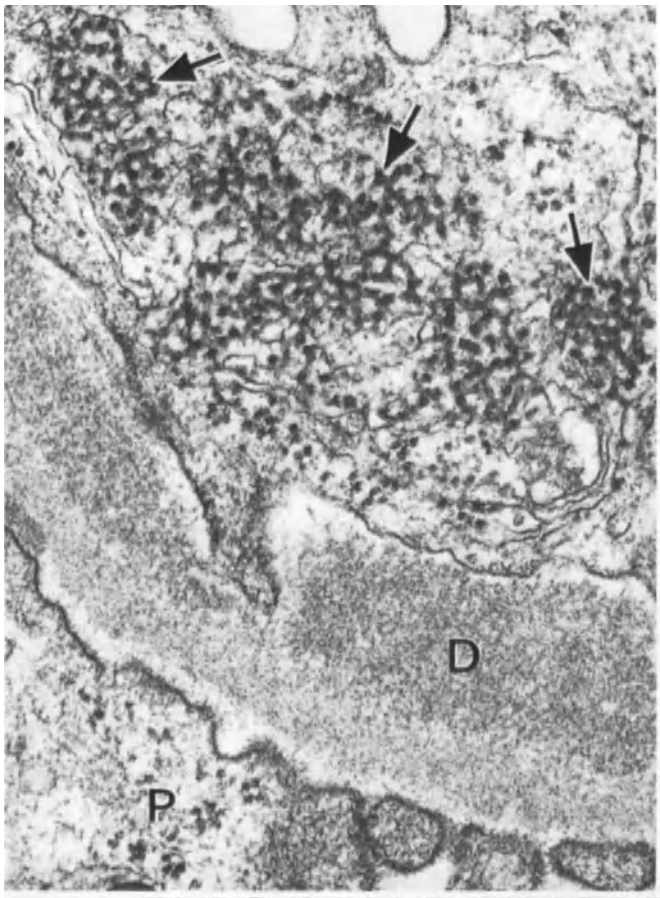
They are found in over 50% of advanced cases of epimembranous GN [787], in gold nephropathy [1628] and in relevant numbers in heroin addicts [357]. The common consensus is that the particles in question usually represent nonviral degradation products [357] and that they are only rarely viruses [230]. Unequivocal demonstration of virus has been exceptional and was usually restricted

**Fig. 6.76.** Part of a peripheral glomerular capillary loop in mixed epimembranous and membranoproliferative lupus GN. Tubular virus-like structures (→). Subendothelial osmiophilic deposits (*D*), podocyte (*P*). Female, 21 years. EM (× 46,000) ▷

**Fig. 6.77.** Fingerprint-like structure in a podocyte in Goodpasture's syndrome. Female, 67 years. EM (× 76,000)

**Fig. 6.78.** Textile-like structure in a podocyte in sclerosing FGN. Female, 5 years. EM (× 51,000)

**Fig. 6.79.** Severe increase and thickening of mesangial matrix bars in a glomerulus of a 2.5 month-old transplant. Foot processes are sometimes absent (→) or sometimes fused (⇨). Massive protein droplets and vacuoles are present in the podocytes. Male, 57 years. EM (× 4220)

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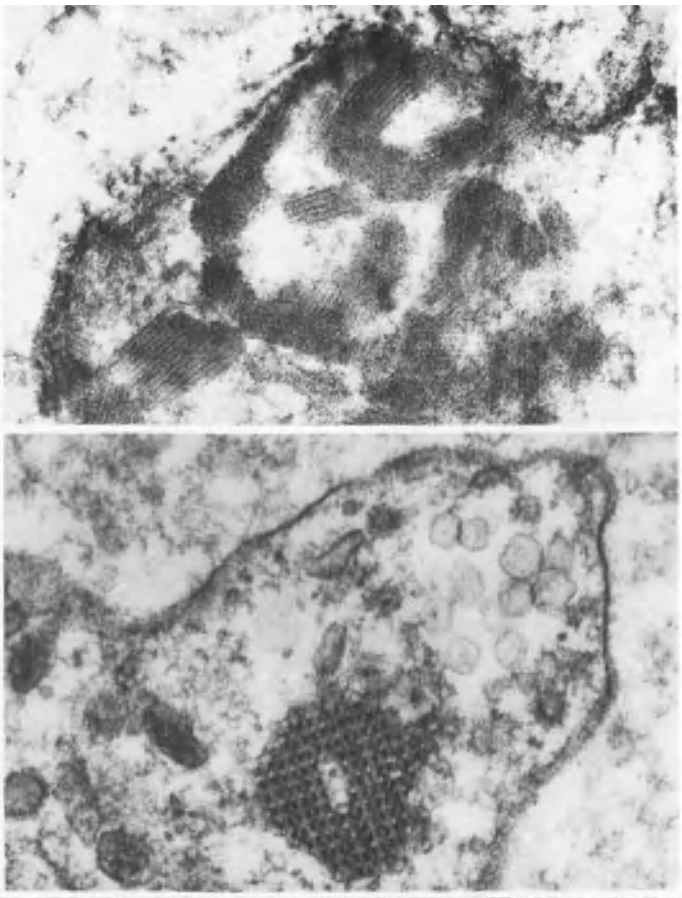

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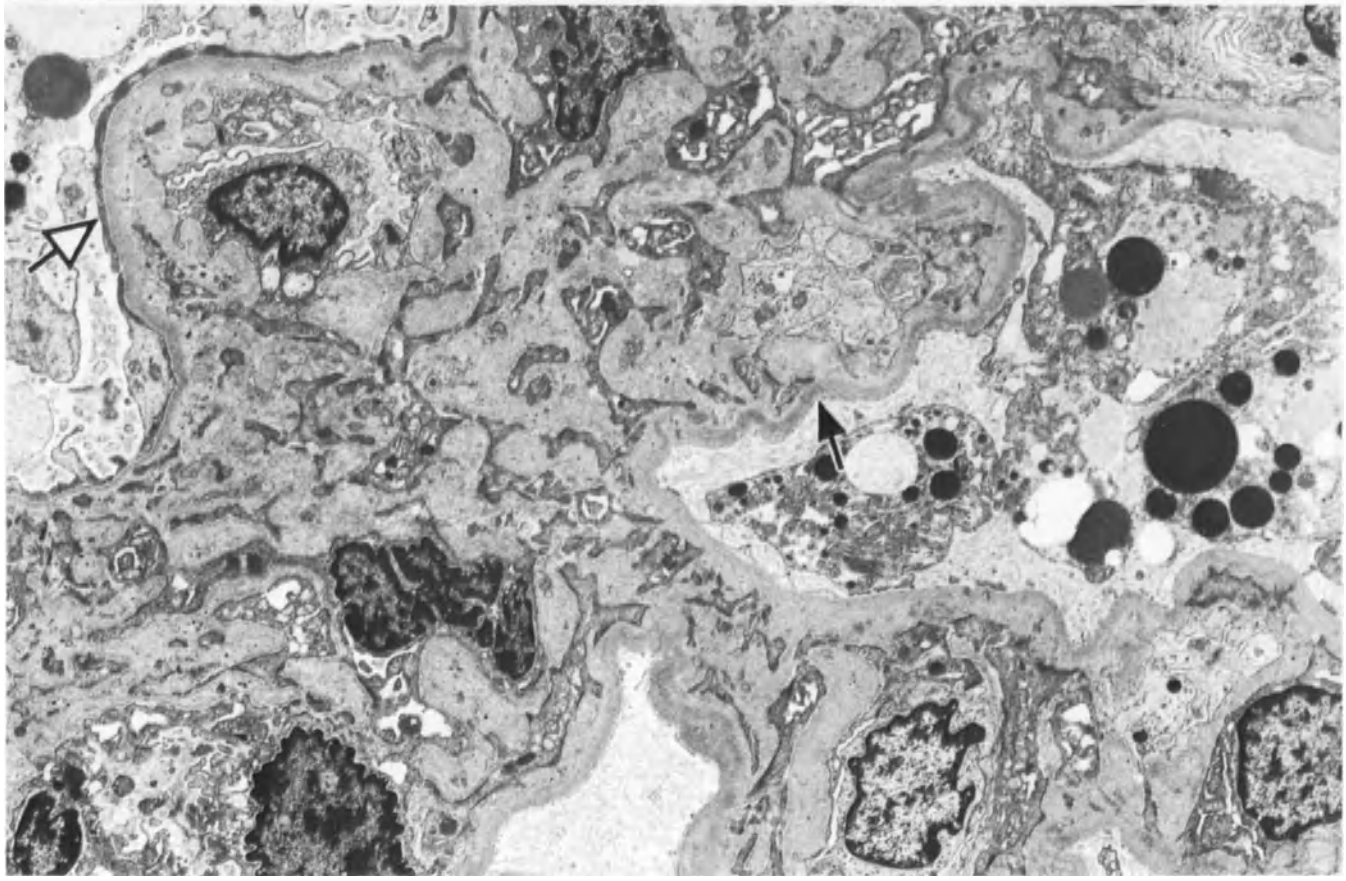


6.79

to hepatitis-B antigen [299, 722, 1531]. In one case, Barr-Epstein virus was found in addition to the hepatitis-B surface antigen [1531].
Nonviral particles may represent either extruded cell products or a crystal formation of lipoprotein in immunodeposits [230, 1757]. These particles must not be confused with multivesicular bodies which are enveloped groupwise by a membrane (Fig. 6.74).

***Tubular (Filamentous) Virus-Like Particles.*** These long, up to 1000 Å [615] tubular forms with a cross-sectional diameter of about 220 Å [105] are mainly found in endothelial cells (Fig. 6.76) and—less frequently—in podocytes or in endothelial cells of intertubular capillaries. They have been described essentially in SLE (Figs. 17.33, 17.34) and initially considered as myxo- and paramyxovirus. Systematic examination [1523] revealed a wide range of primary diseases in which these particles occurred: SLE (98%), renal transplants more than 1 year old (73%), in biopsies of other nephropathies (24.5%). We found tubular virus-like particles in Alport's disease and congenital nephrotic synchrome (see also [346]). They have also been described in scleroderma, synovitis, rheumatoid arteritis, Sjögren's syndrome, polymyositis, gold nephropathy [1628] as well as in normal tissues. In autoimmune disease, the particles have been found in lymphocytes [1431].
The viral nature of the tubular particles is currently regarded as extremely questionable [498]. They are considered to be viral-induced abnormal products of endoplasmic reticulum [852]. Even this latter concept, however, includes recognition of the presence of virus without, of course, relating it to the basic disease.

***Other Virus-Like Particles.*** Textile structures or fingerprint-like forms (Figs. 6.77, 6.78) are occasionally observed in endothelial cells. These forms may consist of cristallized lipoproteins or, moreover, of aggregated crystallized textile-like virus.
We encountered this finding once in a case of chronic lymphatic leukemia associated with epimembranous GN. We are not aware of any extensive studies devoted to the significance of the above-instanced structures.

***Thred-Like Structures (Striated Membranes, Collagen-Like Fibers).*** Finely, uncoiled, thread-like structures which are 200–400 Å wide and up to 2 µm long should be mentioned. We have found them mainly in older deposit in epimembranous GN (Figs. 6.32, 6.42, 6.43). Other investigators have reported them in normal renal tissue as well as in GN and renal transplants [1464]. The thread-like structures exhibit a 100 Å periodicity and, in the surroundings of these structures, round to oval, 800–1000 Å-sized virus-like particles (Fig. 6.43) can be seen. We consider these structures to be degradation products but not viruses.
Concerning cytomegaly, see p. 323.

## Changes of the Mesangium
(Figs. 6.80, 6.81)

In contrast to some of the glomerular structures described in previous sections, extensive and diagnostically significant findings can be obtained in the mesangium using solely LM. To be sure, evaluation of the mesangium with LM alone is extremely difficult. Reference slides cut at the same thickness as the biopsy, taken from healthy individuals of the same age will be found useful to the less experienced.
Factors decisive for correct understanding and classification of mesangial changes are (1) the relationship of the mesangial cell number to the mesangial surface and (2) concordance or discordance between the PAS and PASM stains.
If purely subjective evaluation shows an increase in the quotient mesangial cell number/mesangial surface (morphometric evaluation is hardly feasible for routine work) we speak of mesangial cell proliferation. If the quotient is decreased, we refer to mesangial sclerosis (=matrix increase).
With the above operative definitions in mind, the following four forms of mesangial change can be distinguished:

### *Mesangial Changes Without Cell Increase*

1. Mesangial widening without mesangial matrix increase
   in PAS stain: considerable widening of mesangial surface
   in PASM stain: no (or scanty) increase of silver impregnable matrix (=PAS/PASM-discordance).
   In these cases, the widening of the mesangial surface is due to swelling of mesangial cells.
2. Mesangial sclerosis: concordant widening in PAS and PASM stain of mesangial surface.

### *Mesangial Changes With Cell Increase*

1. Without mesangial sclerosis:
   Discordance between the PAS and PASM stains (due, in this instance, to mesangial cell proliferation and swelling).
2. With mesangial sclerosis:
   Concordant stain results with PAS and PASM.

Reduction of the mesangial surface, mesangiolysis, has been observed in the experimental setting using Habu snake poison [275, 740] and, in humans, in echovirus infection in immune deficiency [1816], in Wegner's Syndrome [1498] and in Schönlein Henoch's purpura (see p. 323, Fig. 17.8).

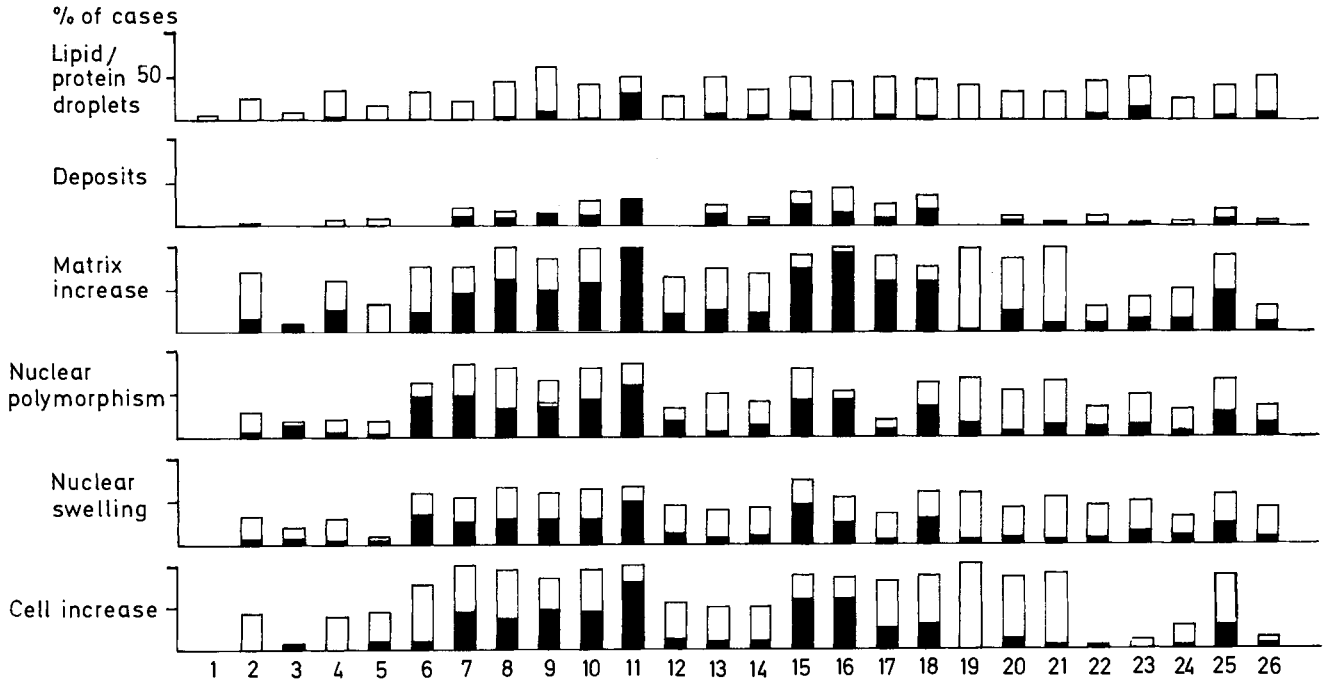



**Fig. 6.80.** Histogram. Mesangial changes (for details, see Fig. 6.9)

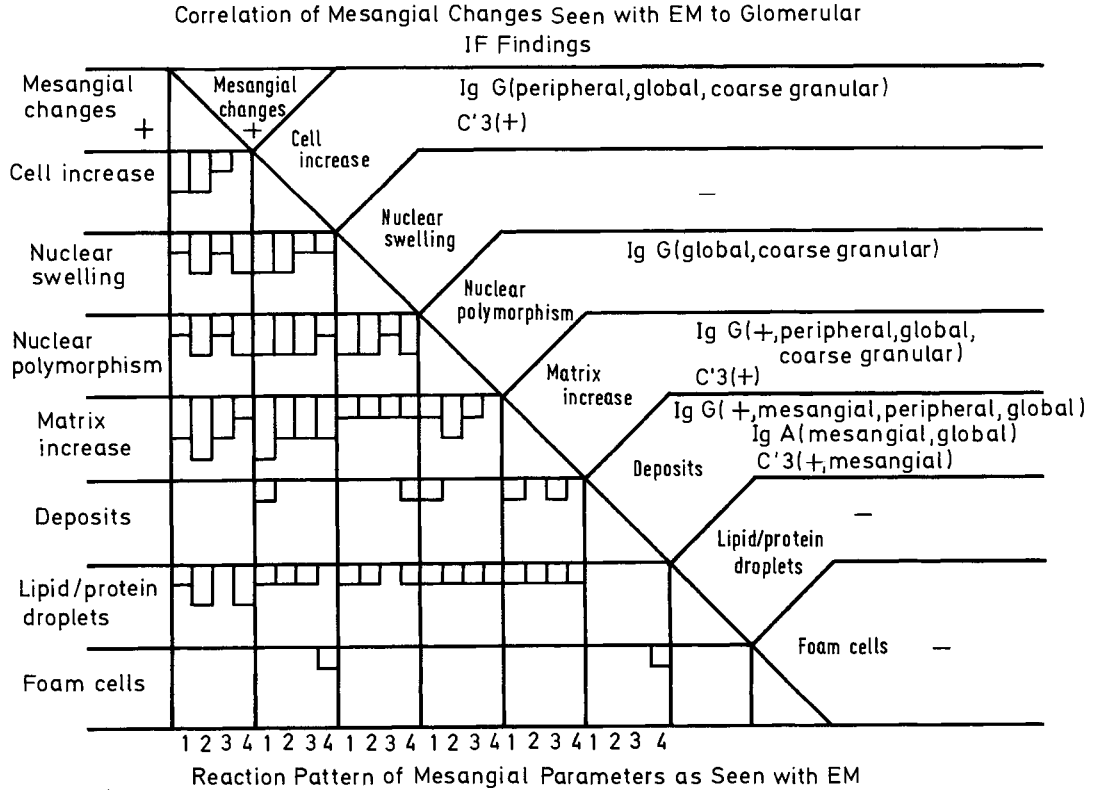



**Fig. 6.81.** Reaction pattern of mesangial parameters as seen with EM and its correlation to glomerular IF findings (for details, see Fig. 6.22)

### Mesangial Widening Without Cell Increase

Mesangial widening without cell increase and with or without mesangial sclerosis corresponds, for the most part, to the picture of glomerulonephrosis and glomerulosclerosis (Figs. 19.1, 19.2, 19.3) respectively and is especially characteristic for mesangial changes in transplant glomerulopathy (Figs. 6.80, 6.81, 6.79). In acute, toxic glomerulonephrosis—as seen in EM—the mesangium is much loosened [1154] and in mesangial cells, an increase in cytoplasmic organelles, nuclear swelling and polymorphism and lipid/protein inclusions is observed (Fig. 6.81). No relevant mesangial matrix increase can be demonstrated with EM. Sometimes, an obvious discordant staining result—considerable widening of the mesangium in PAS stain, no relevant increase of silver—impregnable matrix—may be seen in IgA-nephritis due to mesangial deposits not stained in PASM.

In glomerulosclerosis, on the other hand, there occurs an increase of the mesangial matrix as is seen in hepatic glomerulosclerosis, diabetes mellitus (Fig. 19.18), plasmocytoma (Fig. 19.32), amyloidosis (Fig. 19.7; [275, 1624]) and kidney transplants (Figs. 6.80, 6.81). In amyloidosis, the deposition of amyloid fibrils contributes to the picture of mesangial sclerosis. Rarely, typical collagen is found in old cases of glomerulosclerosis (Fig. 6.82). In this event the diagnosis of glomerulosclerosis with fibrosis is appropriate. In the late stages of GN ('burned-out' GN) the picture of pure mesangial sclerosis may, exceptionally, also occur (Fig. 6.83). Accordingly, infantile mesangial sclerosis [625] may belong to the late-stage GN type of mesangial change (see p. 366).

### Mesangial Widening With Cell Increase

Mesangial widening with cell increase is the most characteristic reaction of the mesangium (Fig. 14.15). The reaction pattern and the associated IF-findings are given in Figures 6.80 and 6.81.

Mesangial widening with cell increase without concomitant matrix increase is seen in exudative and exudative-proliferative GN. During the exudative stage of GN, a few leukocytes or monocytes can be found between mesangial cells [1145]. Mesangial matrix bars are pushed apart from each other by the strongly proliferated and swollen mesangial cells; the bars are not significantly broadened (Fig. 14.19).

Mesangial cells show signs of hypertrophy with an increase of cytoplasmic organelles (Figs. 6.84, 6.85). Simultaneously, a striking swelling and polymorphy of the nuclei is also often present (Figs. 6.80, 6.81). In later stages of GN, for example during the proliferative-sclerosing stage, there occurs a progressive loosening (Fig. 6.86) and an increase of the mesangial matrix accompanied concurrently by a decrease in cellular swelling and proliferation.

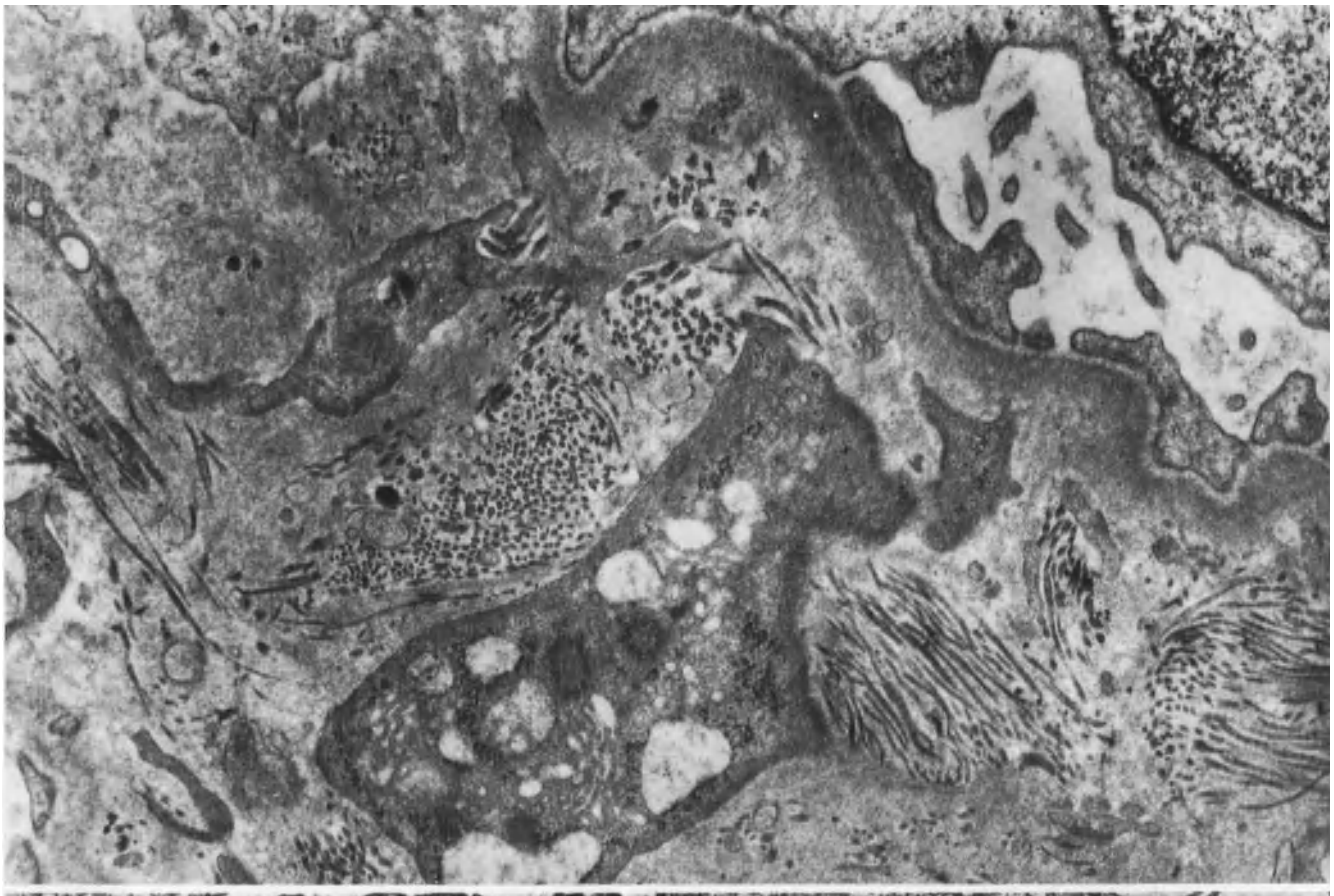
The subdivision of mesangial changes presented above and based primarily on LM is not as obvious under EM. This is so because under EM, cell increase—also in non-GN cases—is frequently more evident than it is with LM (Fig. 6.80). This explains why the EM reaction pattern encompasses both a cell and matrix increase not only in GN, but also in non-GN diseases. However, the EM reaction pattern also demonstrates that cell and matrix increase are not necessarily dependent upon the presence of deposits. On the other hand, cell and matrix increase as well as nuclear polymorphism—as seen under EM—correlate with the IF-demonstrated immunoglobulins and complement factors, thus indicating that these factors are the most important triggers of mesangial reaction (Fig. 6.81).

From a quantitative point of view, we differentiate *pan-mesangial* widening if the entire mesangium is widened and *axial* widening if the mesangial islands as seen in cut sections merge to form an axis from the periphery to the vascular pole and '*minimal* change' if the widening is slight, insular, 'spotty' and discontinuous, (see p. 180). The occurrence of no more than 3–5 mesangial nuclei embedded closely together in a PAS-positive mesangial matrix in often hardly more than 10% of glomeruli is characteristic for glomerular minimal change. This form of mesangial widening may be found in Alport's disease with, however, specific BM changes demonstrable with EM. Foci of this kind of mesangial widening are also observed in severe cases of hypertension [1090] as well as in a wide variety of other non-GN diseases (Figs. 6.80, 6.81).

With EM, lipid and protein droplets (heterolysomes) can often be demonstrated in mesangial change (Fig. 6.80). We have observed them in GN in 39.3%, in nonglomerulonephritic disease in 25.9% and in renal transplants in 51.2% of our cases. Mesangial foam cells (Fig. 6.87), on the other hand, are very rarely observed. Their differentiation from endothelial foam cells is usually difficult even with EM. We encountered mesangial foam cells in 0.6% of GN and 2.8% of renal transplants. They occur diffusely and globally in storage diseases only (e.g., GM l-gangliosidosis; Figs. 23.1, 23.2).

**Fig. 6.82.** Collagen fibers in the mesangium (an extremely rare finding) from a 4.5 month-old transplant. Male, 37 years. EM (×23,000) ▷

**Fig. 6.83.** Thickening of mesangium without cell increase in sclerosing stage of endotheliomesangial GN. Female, 36 years. EM (×10,000)



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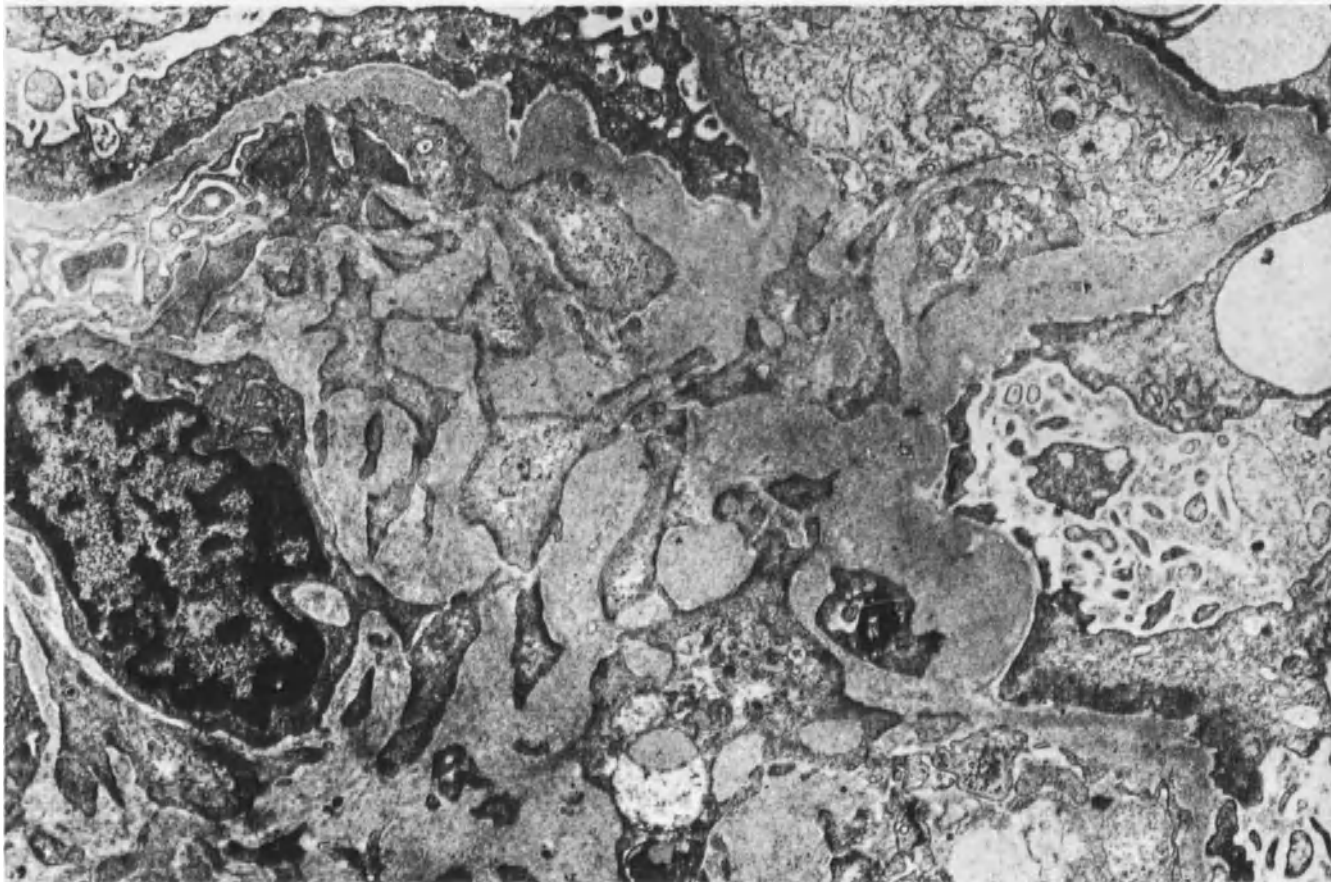


6.83

It is not yet possible to determine reliably whether or not mesangial changes are active, i.e., progressive (see p. 173). Indicative of activity are cell increase, nuclear swelling and, with EM, marked emphasis of nuclear lobulation and endoplasmatic reticulum increase.
Some investigators [1284] differentiate three types of mesangial cells: resting, active and dark. The dark ones are reported to be characterized by being shrunken, degenerated and by having dense, notched nuclei. They have been described as occurring in a scattered fashion in normal kidneys and in considerable numbers in the region of large immunodeposits. We have not been able to identify these dark cells in any of our biopsies.
A characteristic property of mesangial cells is their tendency to wander between BM and endothelium in the capillary loop periphery in chronic inflammation. This behavior is termed mesangial interposition (circumferential interposition or intussusception Figs. 6.18, 6.33; [40, 275, 454]. This change is best recognizable in thin PASM-stained sections by the presence of a double BM (so-called tram-track picture, see p. 62). Massive mesangial interposition is found in the region of subendothelial deposits and, accordingly, almost exclusively in membranoproliferative GN and focally accentuated GN.
Massive mesangial deposits are found in a special form of GN, namely, mesangial IgA-GN (Fig. 17.62, see p. 350; [123, 128]). Scattered mesangial deposits are also encountered in almost all of the other forms of GN and even non-GN (Figs. 6.34) and are usually associated with mesangial matrix and cell increase (Fig. 6.39). They are, however, scanty and usually too small to be demonstrable with LM. Fairly frequently, mesangial deposits can be massively present in membranoproliferative GN (Fig. 6.52, p. 231). A deposite-like mesangial widening is also observed in association with amyloid deposition (see p. 382).

## Changes of the Glomerular Capsule
(Figs. 6.88, 6.89)

### Parietal Epithelium (Capsular Epithelium)

It is noted that parietal epithelial cells respond considerably less markedly than the visceral ones (see histogram Figs. 6.88, 6.57).
Epithelial hypertrophy and lipid or protein droplet inclusion (Fig. 6.93) can occur in all nephropathies (Figs. 6.88, 6.89). Lipid and protein droplets (Fig. 6.93) are occassionally seen in cases with normal urinary findings in different nephropathies but are usually found in GN (Fig. 6.89). Epithelial necroses are rare and occur mainly in non-GN (Fig. 6.88). Cylindrical or papillary metaplasia of the parietal epithelium is only observed with tumors and above all with those of the liver [1068, 1314].

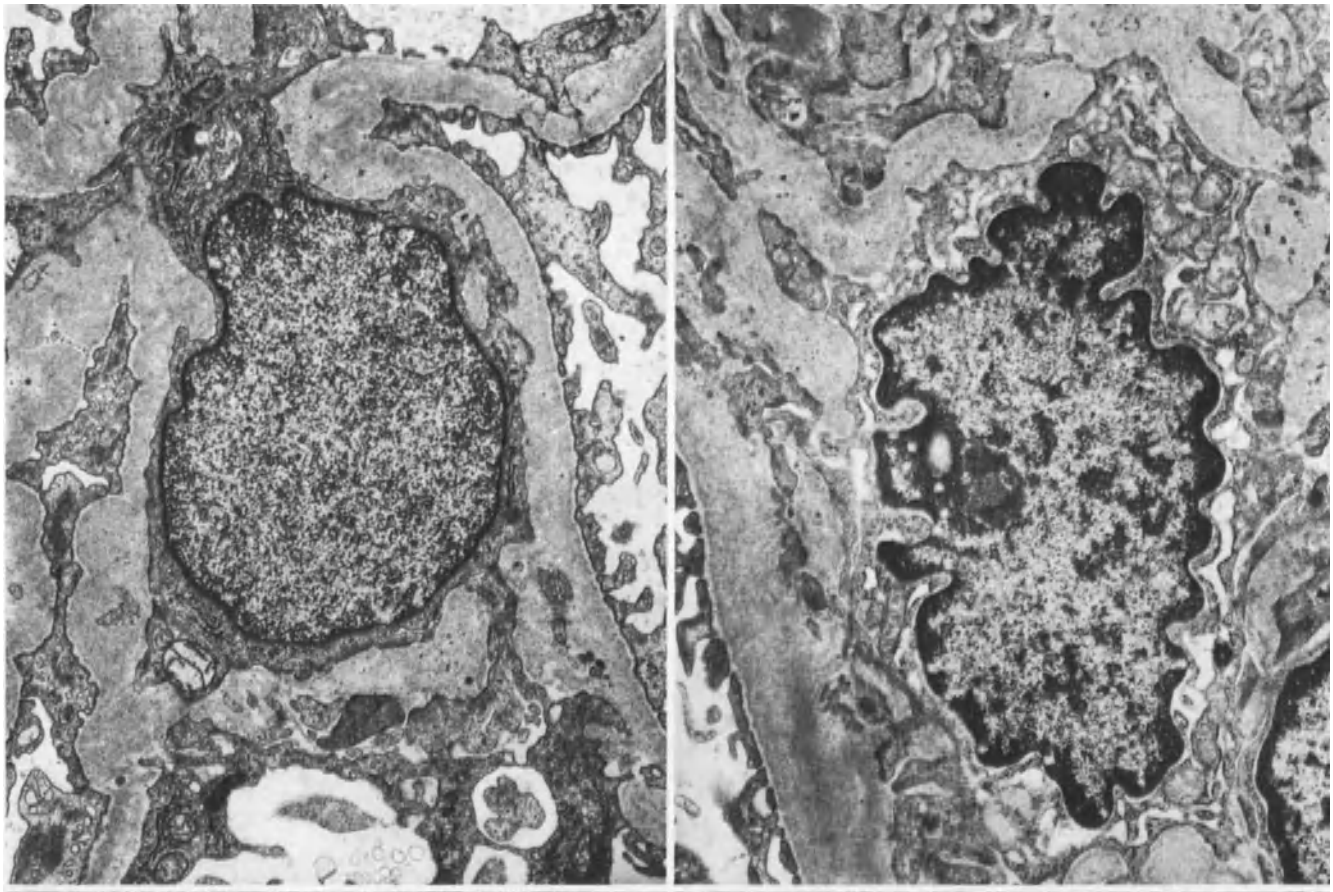
***Crescents:*** Proliferation of capsular epithelium globally, respectively totally (encompassing the entire circumference of the glomerular capsule, Fig. 6.90) or segmentally, respectively partially (parietal crescents involving only a segment of the capsule space, Fig. 6.91) represents a requisite condition for subsequent development of synechia. Both correlate with the presence of fibrin (-ogen) in the glomerulus (Fig. 6.89). Moreover, fibrin within the capsular space is considered as a prerequisite condition for crescent formation. True capsular epithelial proliferation is to be differentiated from pericapsular connective tissue proliferation with LM. The majority of the proliferating cells constituting crescents are of capsular epithelial origin. These cells appear light with EM (Fig. 6.92), can phagocytize and transform into fibroblasts. Between the proliferating cells, isolated dark podocytes exhibiting markedly cystoidally widened endoplasmatic reticulum – as seen with EM – can always be found (Fig. 6.92). A few capsular epithelial cells may undergo destruction or become transformed into foam cells (Fig. 6.92). It is assumed, exceptionally, that hematogenous monocytoid cells are significantly involved in the proliferative process [876]. We have not been able to convince ourselves about this even though monocytoid elements – in addition to neutrophilic leukocytes – can be observed in the glomerular capillaries in the exudative stage of GN [229]. These cells are assumed to wander into the capsular space through defects in the BM [1146] and to proliferate and transform there into 'epitheloid' cells as in a tubercle. We have never encountered this type of cell and do not believe that this is the regular course of events. A coarse granular exudation, occassionally with fibrin fibers, is always found between the cells of the crescent relatively early (Fig. 6.94; [1653]). Both elements are replaced quickly by BM-like substance initially (Fig. 6.95) and by collagen subsequently (Fig. 6.96; [789, 1064]).

**Fig. 6.84.** Normal mesangial cell with very scanty cytoplasm ▷ (for comparison with Fig. 6.85). Male, 62 years. EM (× 12,700)

**Fig. 6.85.** Hypertrophied activated mesangial cell with nuclear polymorphism, increased cytoplasm and organelles in sclerosing FGN (poor fixation of material). Male, 40 years. EM (× 12,700)

**Fig. 6.86.** Severely loosened mesangial matrix in acute transplant rejection (27 days after transplantation). Male, 44 years. EM (× 18,000)

**Fig. 6.87.** Mesangial foam cells with numerous lipid-containing vacuoles in IgA mesangial GN. Female, 31 years. EM (× 13,000)



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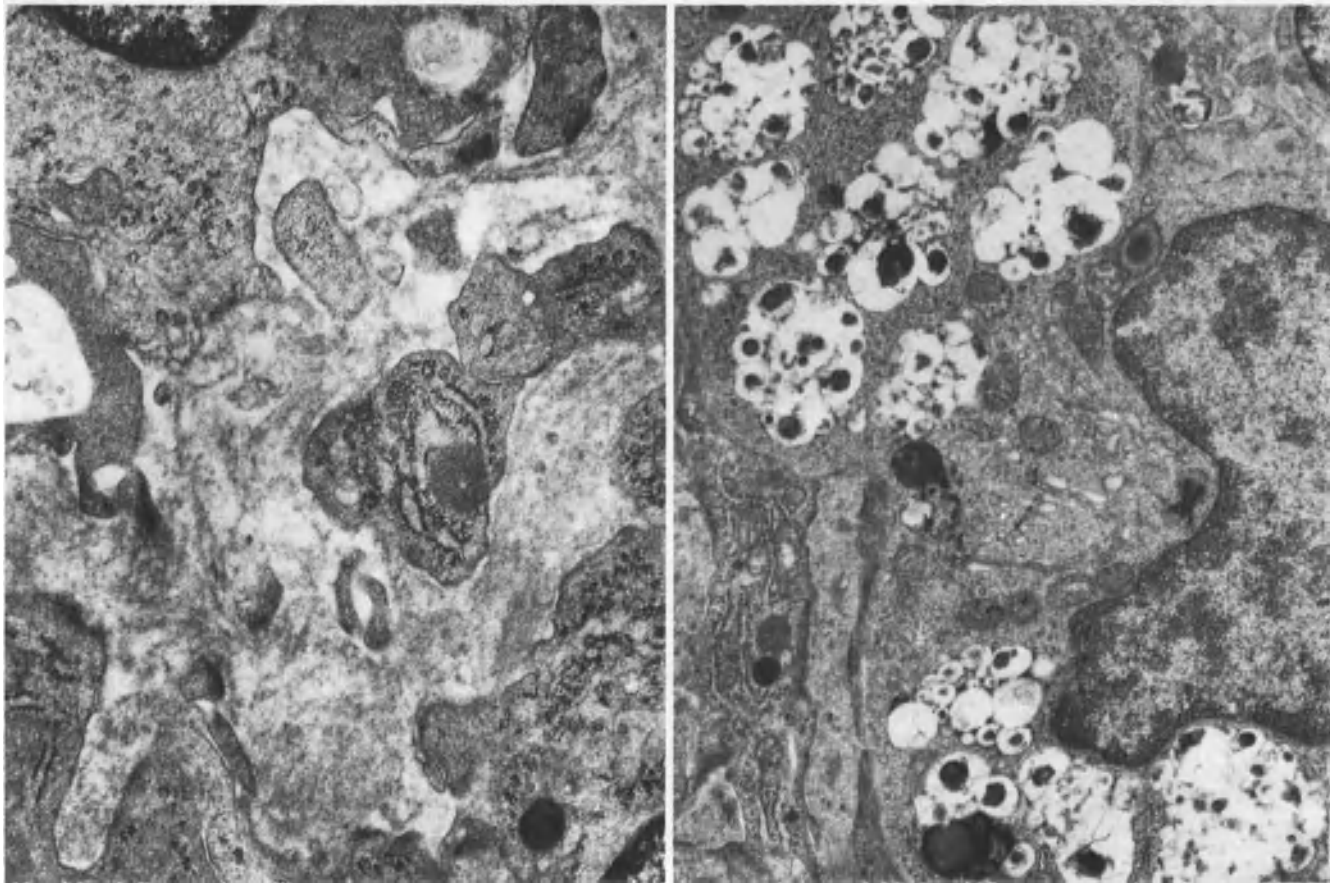

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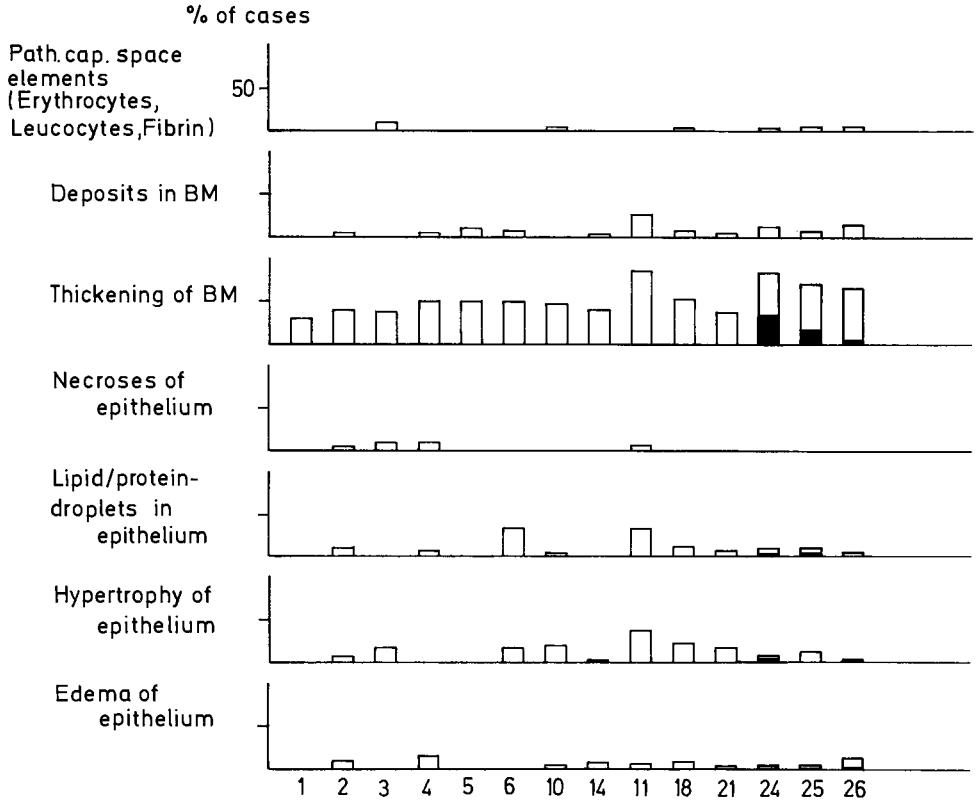


**Fig. 6.88.** Histogram. Changes in Bowman's capsule and its contents (for details see Fig. 6.9). No semiquantitative differentiation for any of the parameters of individual diseases. Number of cases differs from those given in Figure 6.9: $n$: 1=14; 2=25; 3=11; 4=20; 5=14; 6=12; 10=63; 11=16; 14=20; 18=56; 21=74; 24=131; 25=284; 26=60.

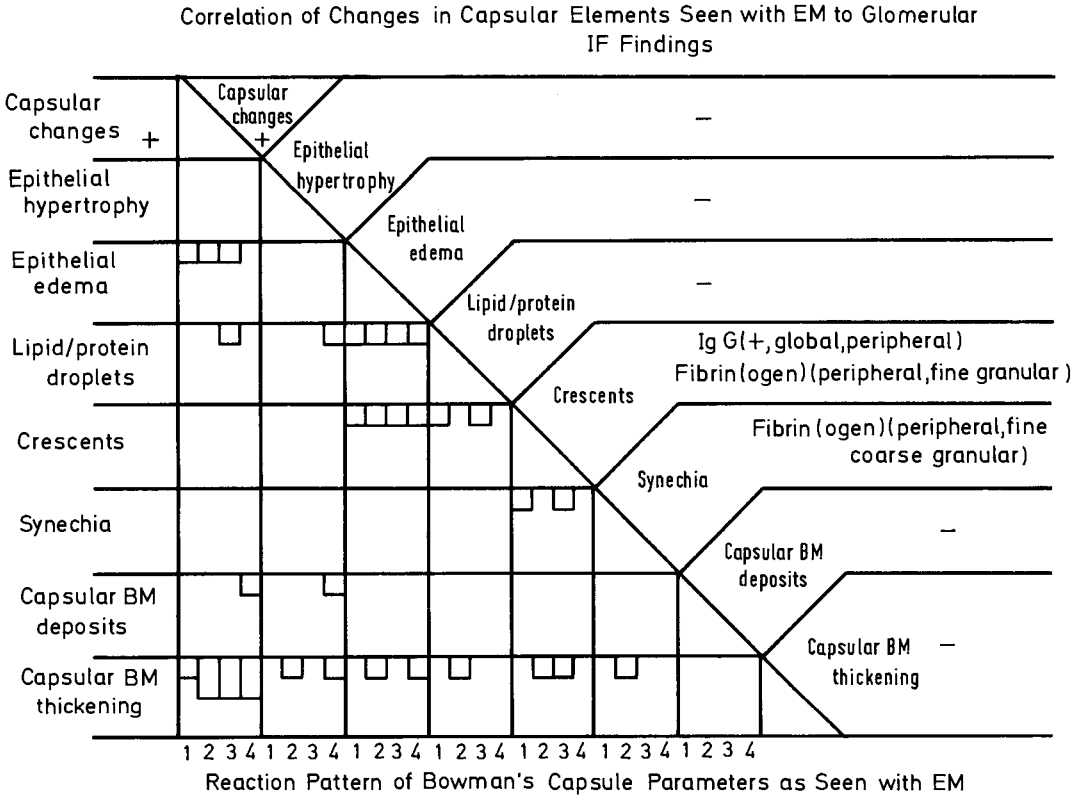


**Fig. 6.89.** Reaction pattern of parameters of Bowman's capsule as seen in EM and its correlation to glomerular IF findings (for details, see Fig. 6.22, for number of cases see Fig. 6.88).

Proliferation of capsular epithelium is thought to be by and large reversible and at least so in the absence of a heavy fibrin network. Coring of proliferated epithelium leads to so-called pseudotubule formation (=adenomatoid structures, Fig. 6.97). Pseudotubuli lumens are frequently covered with podocytes under which a thin BM is formed. In the final phase, the cells disappear and a coarse collagenous fiber network with a few fibrocytes remains behind.

***Synechiae*** (Figs. 6.98, 6.99) arise by fusion of capillary loop BM and capsule BM [1508] (Fig. 6.100). During this process, it appears that fibrin extravasated into the capsular space is a precondition (see Fig. 6.94) and template for the BM substance [779]. Indications of forthcoming synechia formation have been reported on the twelfth day of exudative GN [206]. Such formations, however, are more likely adhesions than true synechiae. Occurrence of synechiae point very strongly to a primary inflammatory glomerular disease. It is recalled, however, that they can, on occasion, occur following capillary loop thrombosis and necrosis, e.g., at the edge of infarcts, in malignant nephrosclerosis and other lesions.

## Capsular Basement Membrane

Capsular BM, in both LM and EM, is often thickened (Fig. 6.88) and always so in glomerular collapse. It may also be fragmented (Fig. 6.101) in the diseased as well as in the normal kidney. BM is severely fragmented in pyelonephritic obsolescence and often infiltrated with connective tissue cells. It is destroyed in Wegener's disease (see p. 348) and less pronouncedly in Goodpasture's disease (see p. 339) but rarely in other forms of GN. With EM, the BM occassionally has a network-like appearence and demonstrates vacuoles and lipid droplets (Fig. 6.101); these findings cannot be regularly associated with other renal changes.

Fibrinoid, coarse spindle-like or ovoid thickenings—the so-called capsular drops (Fig. 19.27)—are considered characteristic for diabetes mellitus (see p. 393). They are rarely found in a variety of other nephropathies.

Dense intramembranous capsular BM deposits are usually present in intramembranous GN. A few osmiophilic deposits are also found in other forms of GN (Fig. 6.88) and slightly more frequently in transplants, chronic pyelonephritis and an isolated few even occur in the normal kidney (Figs. 6.88, 6.89, 6.102). Their significance is unknown.

## Capsular Space

Material from a needle biopsy viewed with EM frequently contains in the capsular space cell elements encompassing mitochondria, protein droplets, and parts of the brush border of proximal tubules (Fig. 6.103) which must be considered as artifacts. The presence of erythrocytes, leukocytes, and fibrin in the capsular space is unquestionably pathologic; they are found mainly in GN and renal transplants (5% of our cases; see histogram, Fig. 6.88).

Bowman's capsular space, which accounts for 30–50% of the glomerular cross-sectional area in the normal kidney, is almost totally filled with loop convolutes in severe GN.

In glomerular collapse, on the other hand, the capsular space is often enormously expanded; it is especially prominent in pyelonephritis of Montaldo's type (Fig. 20.54; see p. 340).

Page 104

**Fig. 6.90.** Global (total) crescent with preserved capsule BM (→) in extracapillary accentuated GN of 6 weeks' duration. In the center, glomerular capillary loops are completely collapsed. Female, 62 years. PAS (×500)

**Fig. 6.91.** Segmental (partial) crescents in Goodpasture's syndrome. Proliferated capsular epithelial cells (→) evidence numerous (hyaline) protein droplets. Note glomerular capillary loop synechiae (*SY*). Female, 70 years. PAS (×525)

**Fig. 6.92.** Crescent in extracapillary accentuated GN in anti-BM-type GN (Masugi type). Foam cells of capsular epithelium (*F*), podocyte with cystoid-widened endoplasmatic reticulum and marked osmiophilic cytoplasm (*P*), osmiophilic deposits (*D*) in capsular BM. Remaining cells are proliferated capsular epithelial cells. Female 60 years. EM (×3900)

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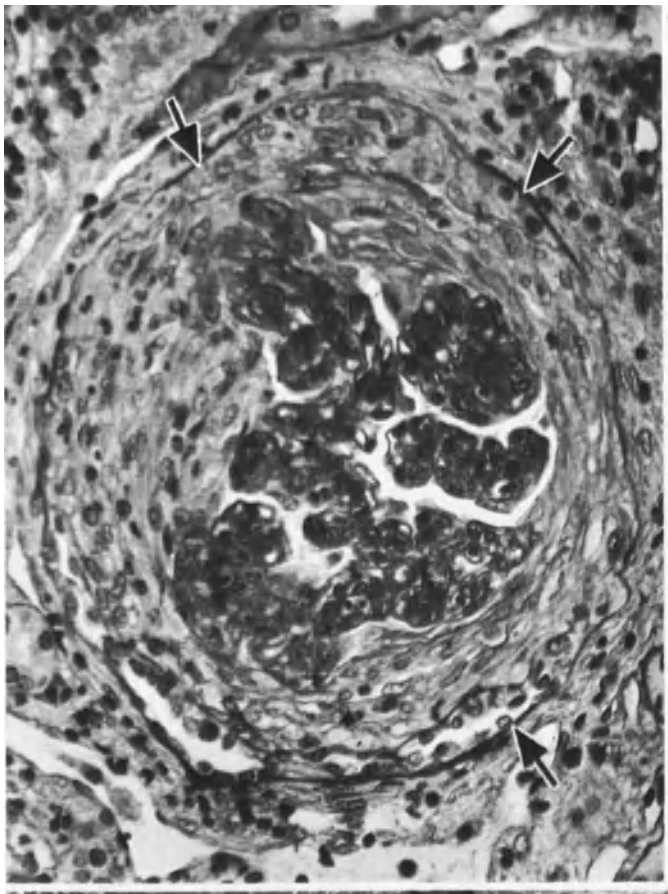
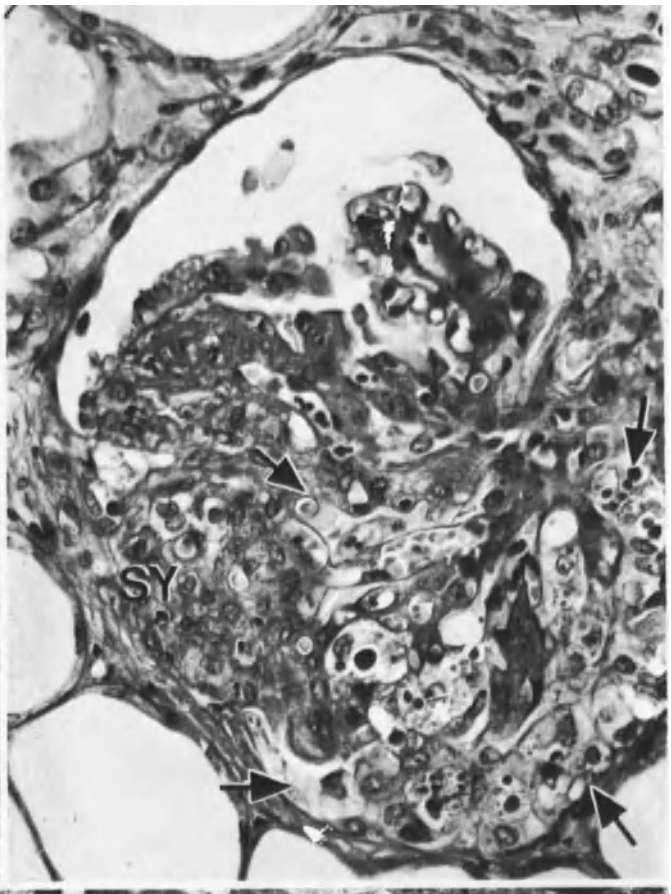
**Fig. 6.93.** Numerous protein droplets in capsular epithelium in congenital nephrotic syndrome. Female, 6 months. EM (×2400)

**Fig. 6.94.** Coarse fibrin strands (→) between proliferated capsular epithelial cells in extracapillary accentuated GN of the anti-BM-type (Masugi type). Glomerular capillary loop BM (←*BM*) is unchanged in this section. Female, 60 years. EM (×3700)

**Fig. 6.95.** Formation of BM-like material (→) is seen between proliferated capsular epithelial cells in endotheliomesangial GN with some crescents. Clinically, 4 months' duration. Male, 63 years. EM (×7800)

**Fig. 6.96.** Same case as in Figure 6.94. Collagen fiber formation (*C*) between proliferated capsular epithelial cells and podocytes in late phase of crescent formation. Female, 60 years. EM (×8900)



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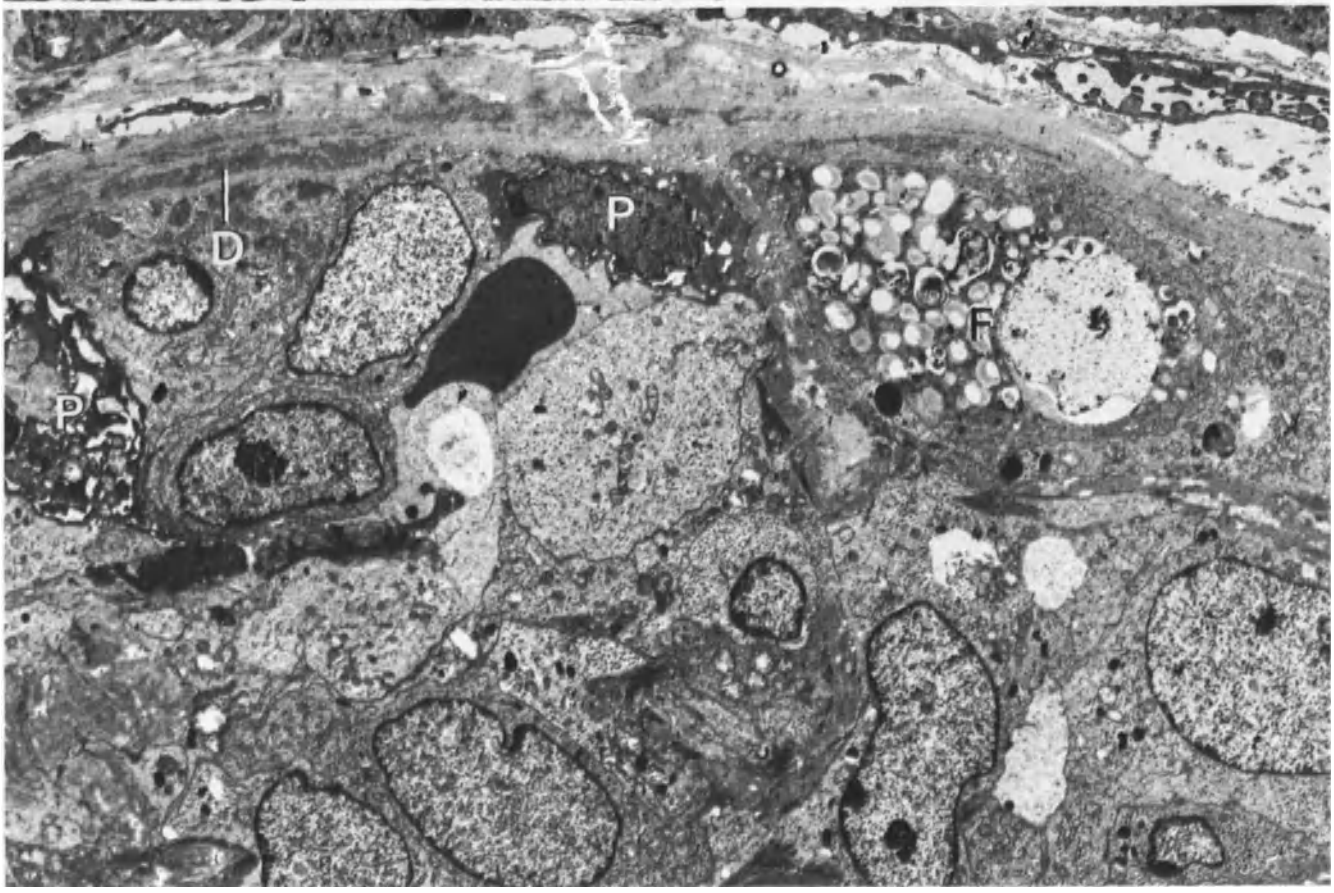


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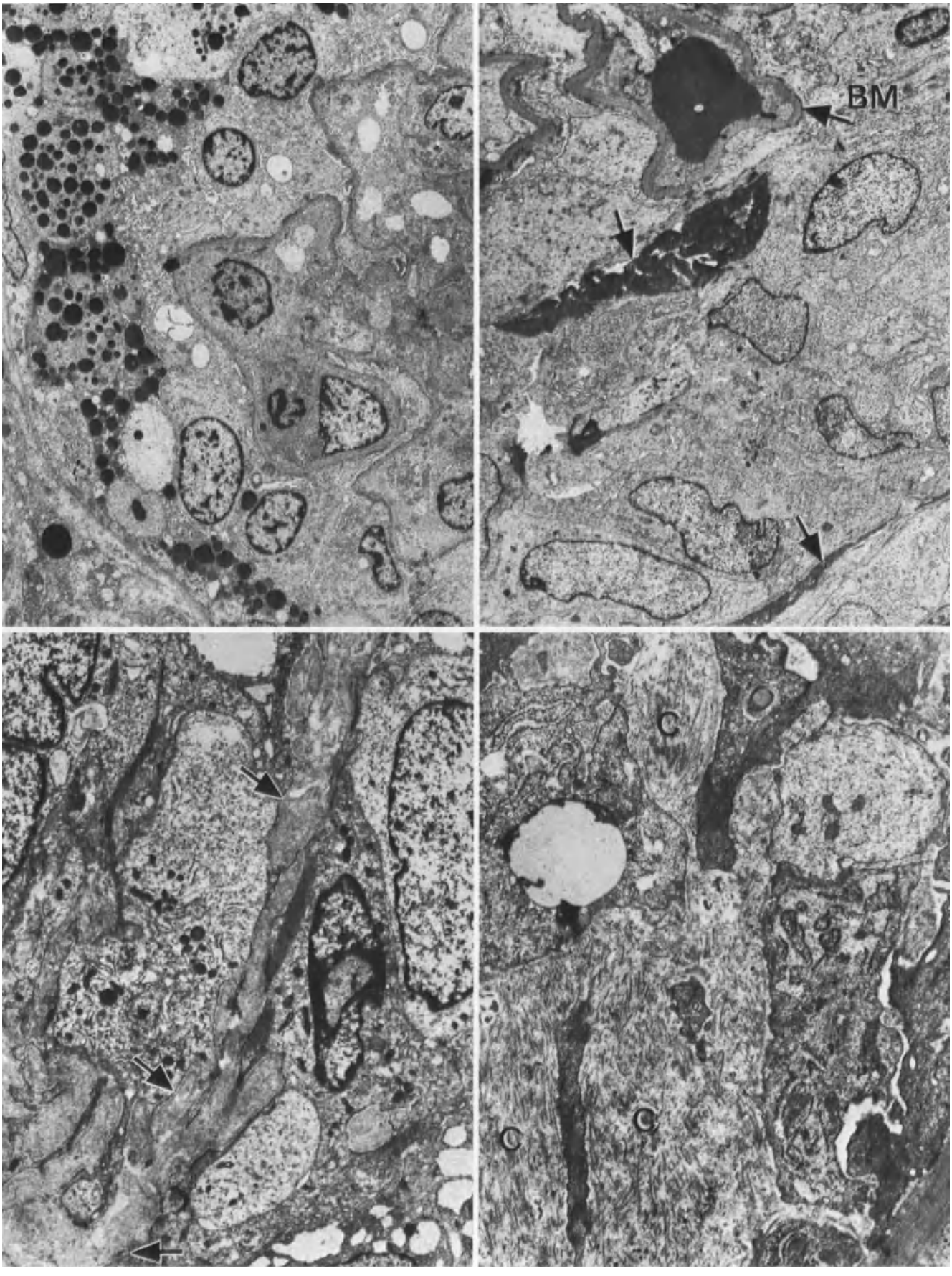


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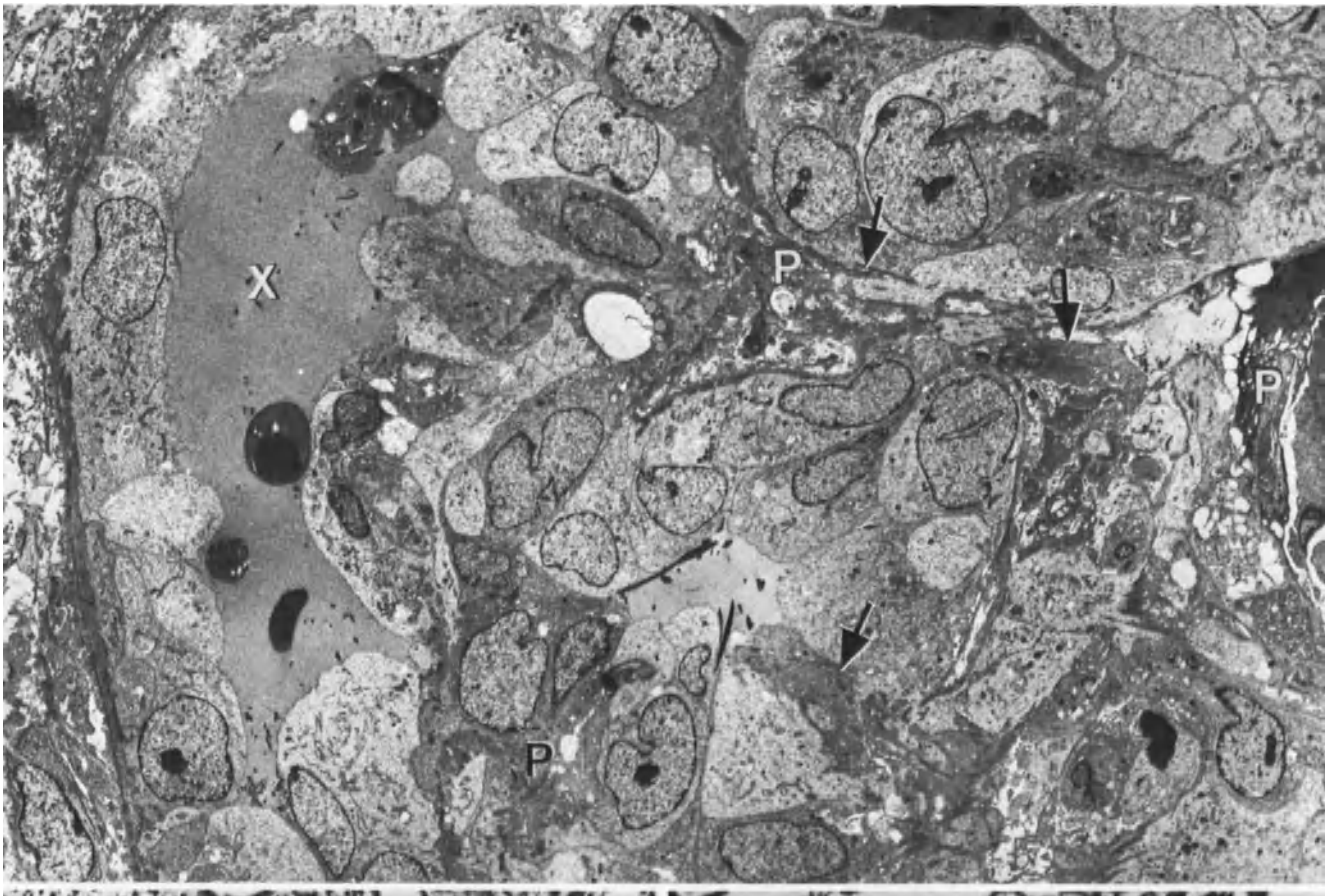


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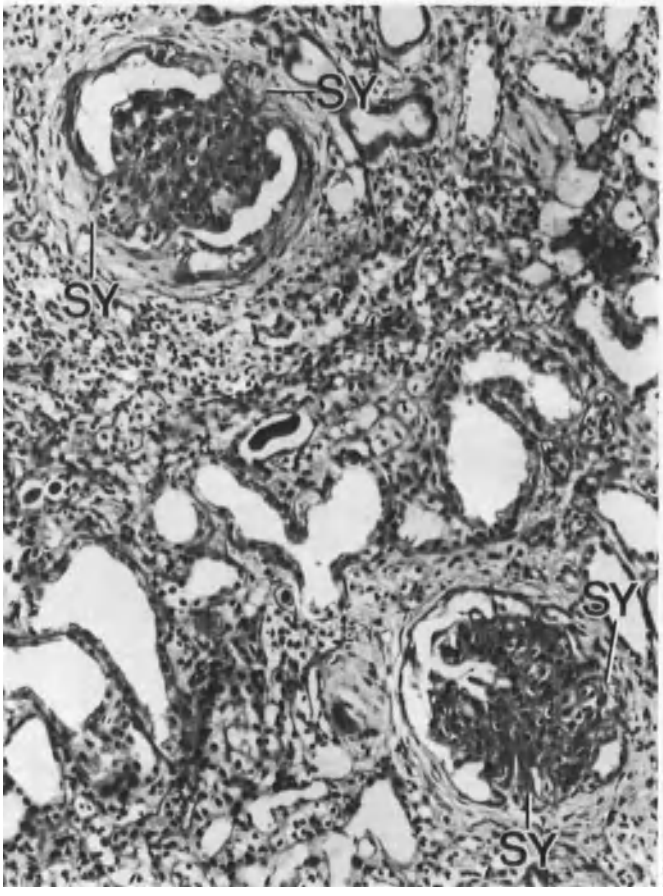


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## Glomerular Obsolescence

A few isolated completely (globally) obsolescent glomeruli are consistently encountered in normal kidneys (see Table 4.1). With glomerular obsolescence, it is important to determine whether it is diffuse or focal and whether the involvement is segmental or global.

The focal segmental form of glomerular obsolescence is especially found in all forms of GN associated with and due to crescents and in sclerosing FGN.

Three different types of obsolescence can be differentiated with LM [216]:

1. Glomerulonephritic proliferative type
2. Ischemic, vascular (collapse/infarct) type
3. Pyelonephritic destructive type.

In general, however, analysis will be based more on the study of neighboring regions and attendant changes than on that of a single obsolescent glomerulus since differentiation as to type of obsolescence on a single glomerulus is very often impossible, and especially so with EM (see also [1179]). IF is of no significant help in the differentiation, since the predominant immunoglobulins found in obsolescent glomeruli of different types and in different nephropathies are IgM and C3 (see Fig. 11.17). The matter is further complicated by the fact that the three types can occur simultaneously and in close proximity in the same case. Frequency of distribution of the three types in relation to renal disease is given in Table 6.1.

Table 6.1. Relative frequency of the various types of obsolescent (hyalinized) glomeruli in our material

| Nephropathy | Type of obsolescence | | | |
|---|---|---|---|---|
| | GN-type (%)[c] | Pyelo-type (%) | Col-lapse-type (%) | Non-differ-entiable (%) |
| Glomerulonephritic contracted kidney ($n=30^a/318^b$) | 9.6 ±19.4 | – | 53.4 ±43.9 | 26.9 ±43.1 |
| Pyelonephritic contracted kidney ($n=10/290$) | 3.0 ±4.8 | 15.9 ±14.8 | 61.1 ±29.2 | 19.0 ±19.3 |
| Ischemic, vascular contracted kidney ($n=11/600$) | 2.3 ±4.1 | 1.4 ±3.2 | 74.9 ±20.1 | 21.7 ±16.1 |

[a] No. of cases.
[b] No. of obsolescent glomeruli.
[c] % of obsolescent glomeruli ($\bar{x}$, SD).

### Glomerulonephritic Type of Glomerular Obsolescence

This type of obsolescence (centrifugal: [1127]) is often only recognizable by the confused arrangement of both the capillary loop BM and mesangium in the completely coalesced capillary loops.

Two forms are recognizable: obsolescence without crescent formation and collapse (Fig. 6.104) and obsolescence with both (Fig. 6.105). In the more or less intact glomeruli—at least in diffuse GN—synechiae and pseudotubuli are occassionally encountered in the region of old crescents (see p. 100; Fig. 6.109). Capsular BM is sometimes well preserved but is usually fragmented and less strongly collagenized than in the pyelonephritic destructive type.

De novo formation of shunt vessels through transformation of individual capillary loops leading to formation of arteriolae rectae verae is quite common (Fig. 6.104). Their presence is thought to explain the absence of necrosis in surrounding parenchyma which is supplied by the vasa efferentia.

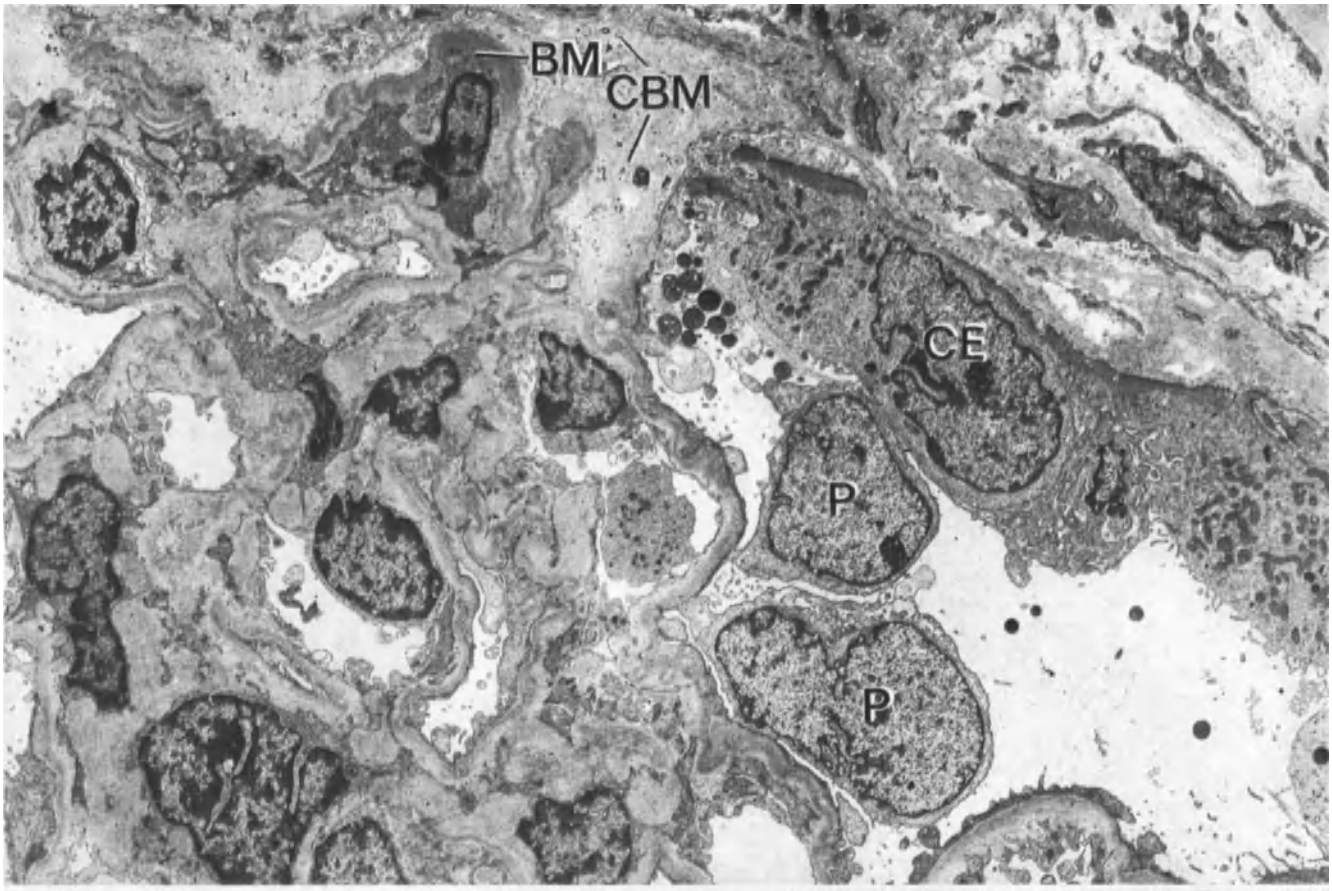
With EM, the original capillary loops are usually still recognizable by their coarse, wrinkled, electron-opaque BM (Fig. 6.106). They can be filled in with osmiophilic masses. On the inner aspect, BM exhibits marked osmiophilic finely granular deposits (Fig. 6.106) which probably arise by insudative processes. These deposits now and again contain extensive lipoid vacuoles and degeneration granules. Analogous changes are demonstrable in pure collapse glomeruli.

We have repeatedly found a tenuously fibrillar or granular electron-loose material on the capillary loop surface

◁ **Fig. 6.97.** Same case as in Figure 6.94. Adenomatoid structure (pseudotubule: X) in a crescent containing fibrin strands. Clear cells are proliferated capsular epithelial cells between which BM-like material (→) is seen. Degenerated podocytes (*P*). Female, 60 years. EM (×1500)

**Fig. 6.98.** Sclerosing stage of membranoproliferative GN. Both glomeruli show synechiae (*Sy*) and considerable loop obsolescence. Extensive inflammatory infiltration in interstitium and atrophy of tubules are present. Female, 26 years. PAS (×175)

**Fig. 6.99.** Synechia (⇾) over isolated, parially obsolescent glomerular capillary loops in proliferative FGN. Male, 34 years. PASM (×350)

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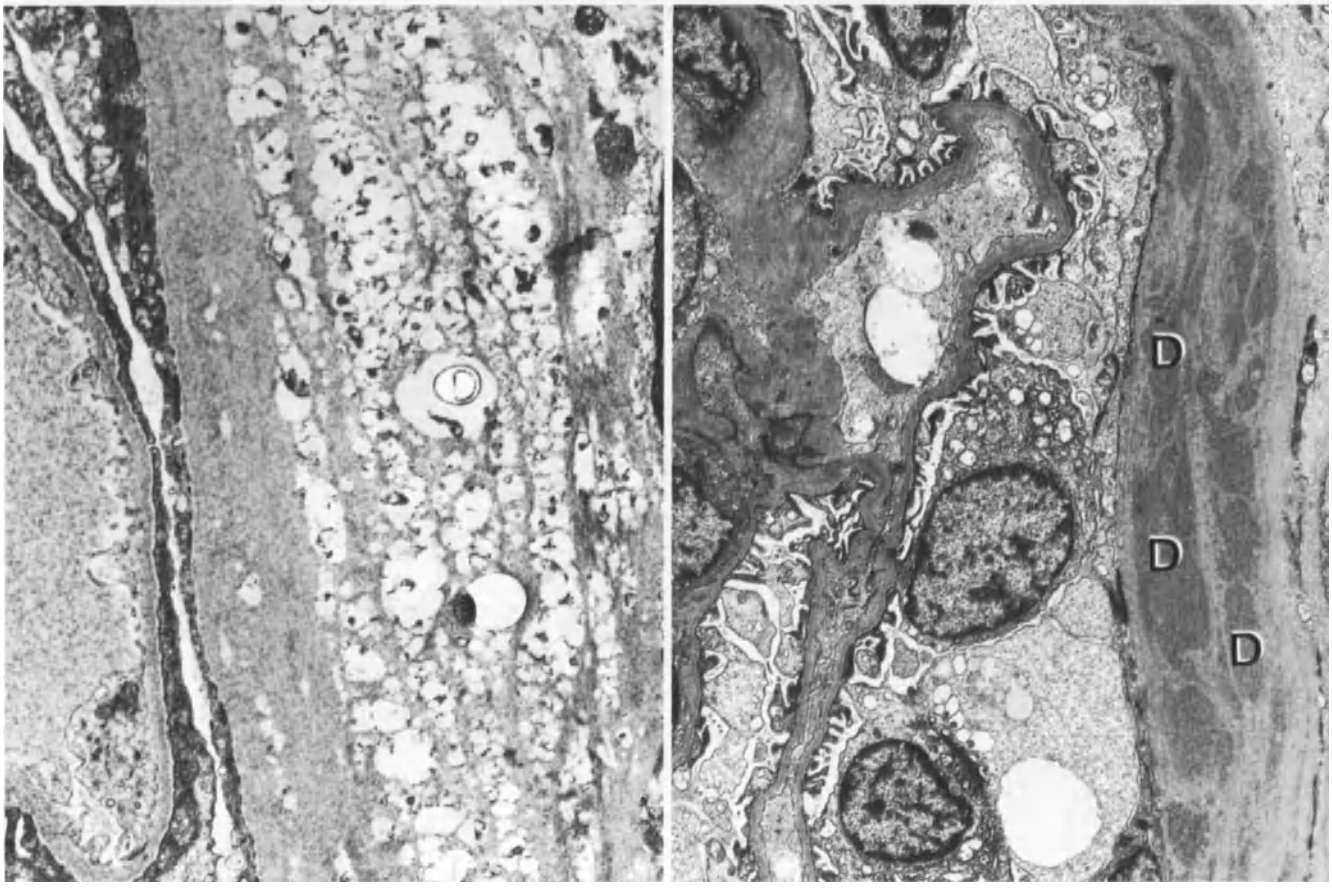


6.101
6.102

resting directly on the BM. This material bridges the spaces between the individual capillary loops; it is covered by degenerated podocytes (Fig. 6.109; see also [597]).
Directly under the podocytes in this situation there is frequently found a very thin, new l. densa which appears to have the same finely fibrous structure as the previously mentioned material.
The remnant capsular space is rarely filled out with proliferating epithelium which undergoes secondary changes (see p. 100). Far more frequently, the space is occupied by finely granular masses with numerous, unequally large amorphic particles (Figs. 6.107, 6.108). Peripherally, this material often demonstrates a thin, newly formed l. densa upon which are found the degenerated podocytes towards the exterior (Fig. 6.108).
The granular exudative masses in the capsular space are partially permeated with BM-like substance originating in part from capsular BM and in part from podocytes. Later, collagen fibers appear (Fig. 6.109; [779, 1179]).
Only rarely there is a complete loss of capsular BM with replacement by connective tissue and attendant severe periglomerular fibrosis. The capsular BM may also be found completely intact (Fig. 6.107).
In the capsular BM, we rarely observed osmiophilic deposits which we suppose to be of insudative origin.
The cause of the glomerulonephritic type of obsolescence is inflammatory glomerular loop destruction. Analogous obsolescence is also present in Alport's syndrome, occasionally in pyelonephritis (hematogeneous foci), in diabetes mellitus as well as in ischemic contracted kidney.

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**Fig. 6.103.** Free contents in the capsular space in endotheliomesangial GN. Free mitochondria (*MI*), epithelial fragments with mitochondria (*X*), stereocilia (→), capsular epithelium (*CE*), basement membrane of a peripheral glomerular capillary loop with preserved foot processes (*BM*). Male, 10 years. EM (×4620)

**Fig. 6.104.** Glomerular obsolescence in GN contracted kidney. No residues of capsular epithelial proliferation are recognizable. Tubules are highly atrophic, and their BM is not particularly thickened. Shunt vessel (*SV*). Male, 37 years. PAS (×160)

**Fig. 6.105.** Type of collapse obsolescence of glomerulus with severely thickened capsular BM. PAS (×480)

**Fig. 6.106.** Obsolescent glomerular capillary loop in so-called overload glomerulitis in a case of chronic pyelonephritis. There are extensive osmiophilic deposits with vacuoles and lipids in the subendothelial space. Podocyte (*P*), fibrillar subepithelial thickening (*). Original lamina densa (→←). Male, 32 years. EM (×8970)

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◁ **Fig. 6.100.** Synechiae in sclerosing FGN. There is fusion of the dark peripheral glomerular capillary loop BM with that of the capsule (*CBM*) which is much loosened. Capillary loop obsolescence is noted under synechiae. Podocytes (*P*) and their nuclei are considerably swollen as is the neighboring capsular epithelium (*CE*). Male, 27 years. EM (×3500)

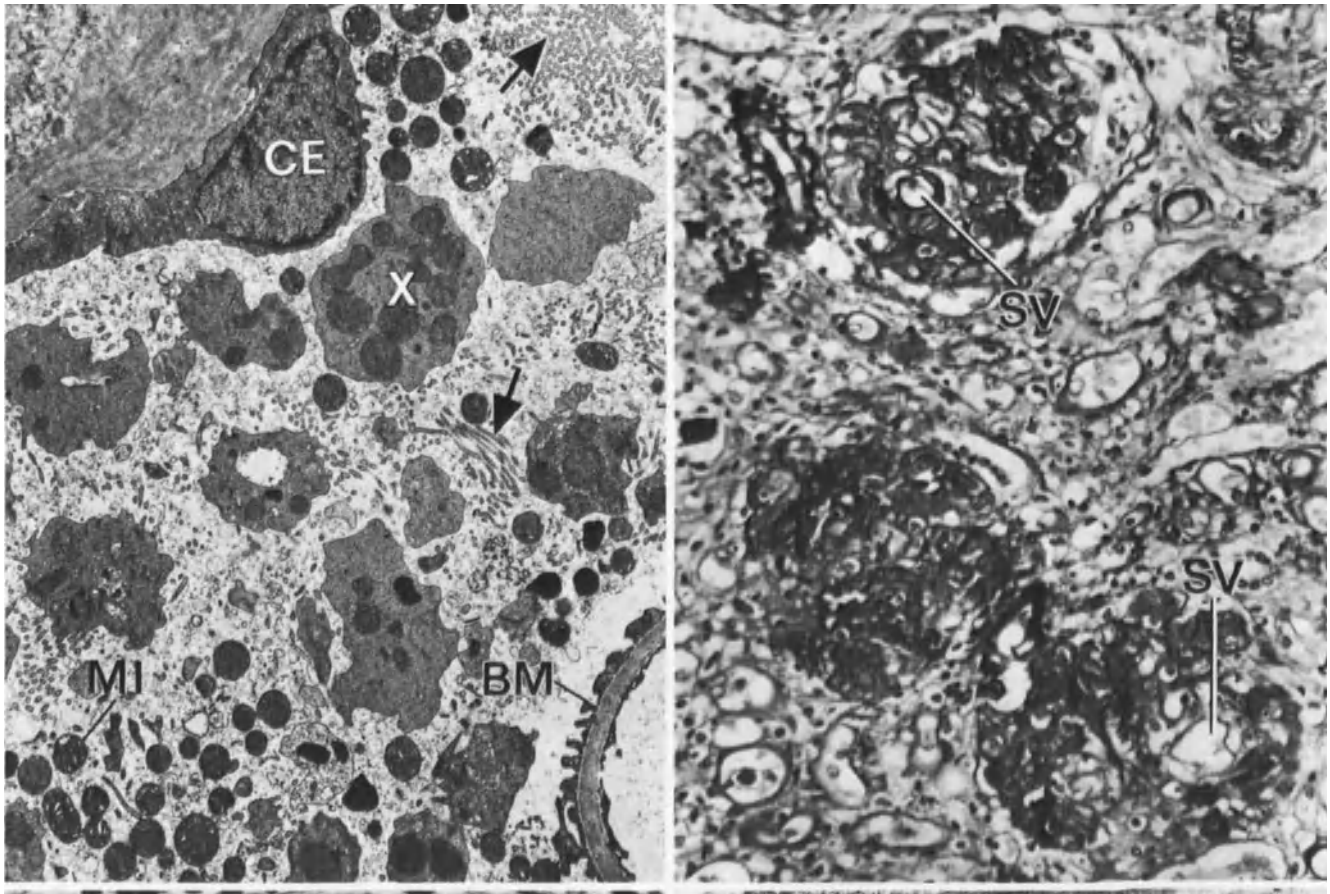
**Fig. 6.101.** High degree of splitting, thickening and vacuolization of the capsular BM which shows numerous lipid-containing vacuoles and severe foot process fusion of a neighboring glomerular capillary loop in a case of endotheliomesangial GN. Female, 36 years. EM (×8700)

**Fig. 6.102.** Thickening of the capsular BM by extensive osmiophilic deposits (*D*) in an otherwise unchanged kidney. Female, 25 years. EM (×4290)

**Fig. 6.107.** Obliteration of capsular space in GN contracted kidney. Capsular basement membrane (CBM) is not thickened. The capsular space is filled up with collagen-containing masses in which an adenomatoid-like lacuna is seen (*), lined by endothelial-like cells attached to a typical BM. Male, 40 years. EM (×3500)

**Fig. 6.108.** Same case as in Figure 6.107. Granular material with isolated collagen fibers and irregularly formed particles in the former capsular space are in evidence. Podocyte (*P*), thickened basement membrane of an obliterated glomerular capillary loop (*BM*). Male, 40 years. EM (×17,000)

**Fig. 6.109.** Obliterated capsular space is rich in collagen fibers. Adenomatoid spaces (*) surrounded by a rather thick BM are lined by podocytes demonstrating formation of microvilli. Male, 40 years. EM (×5600)

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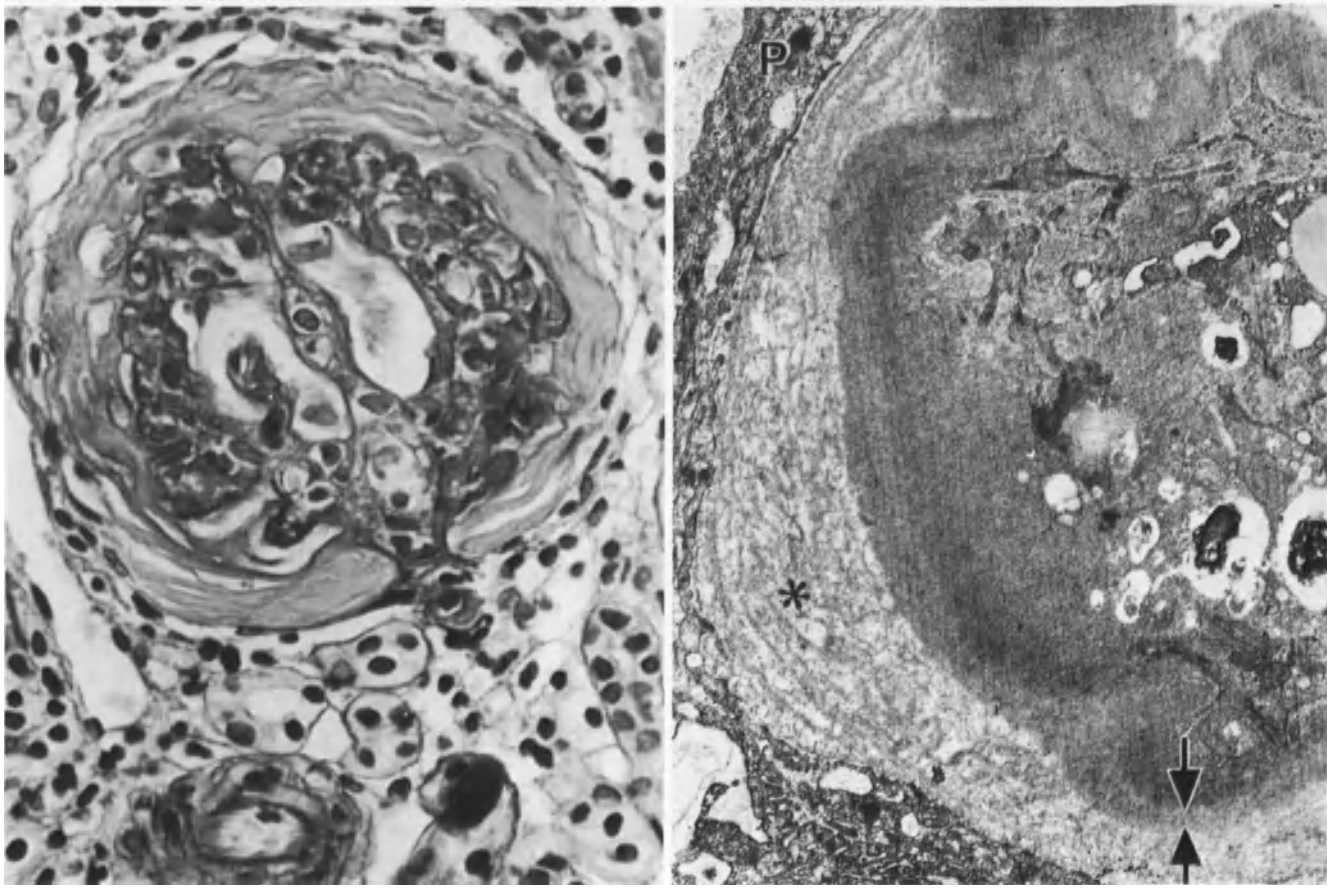


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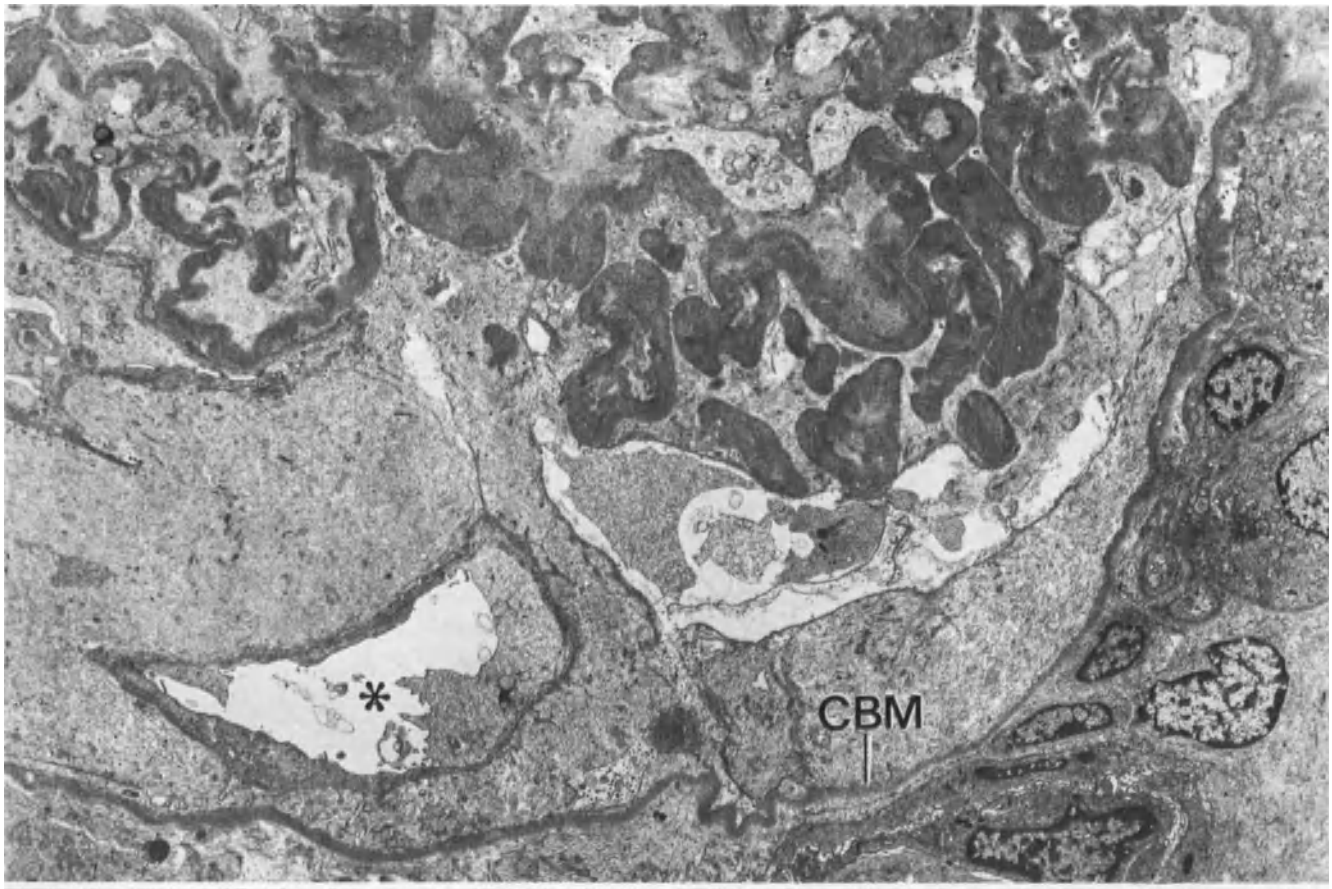


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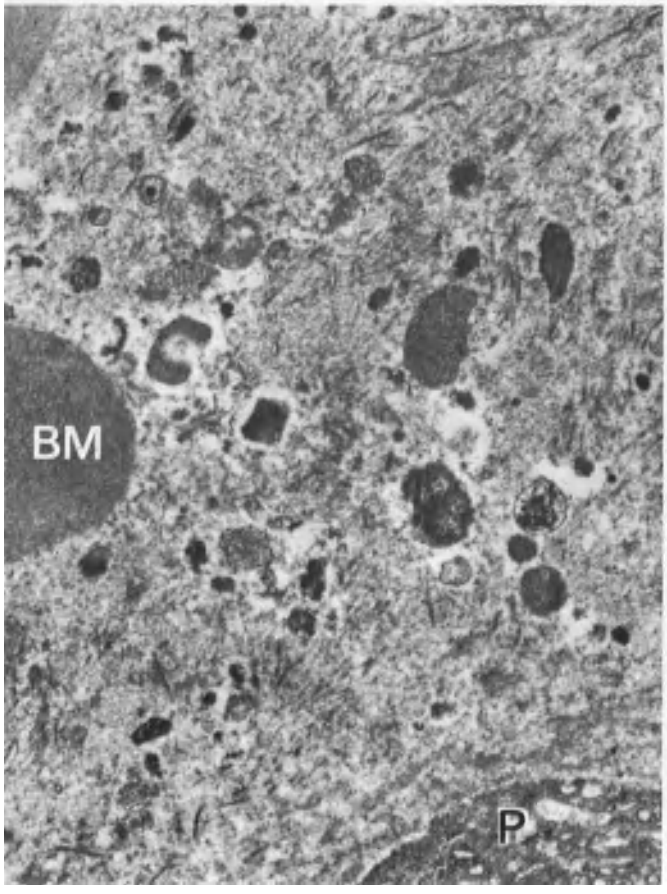


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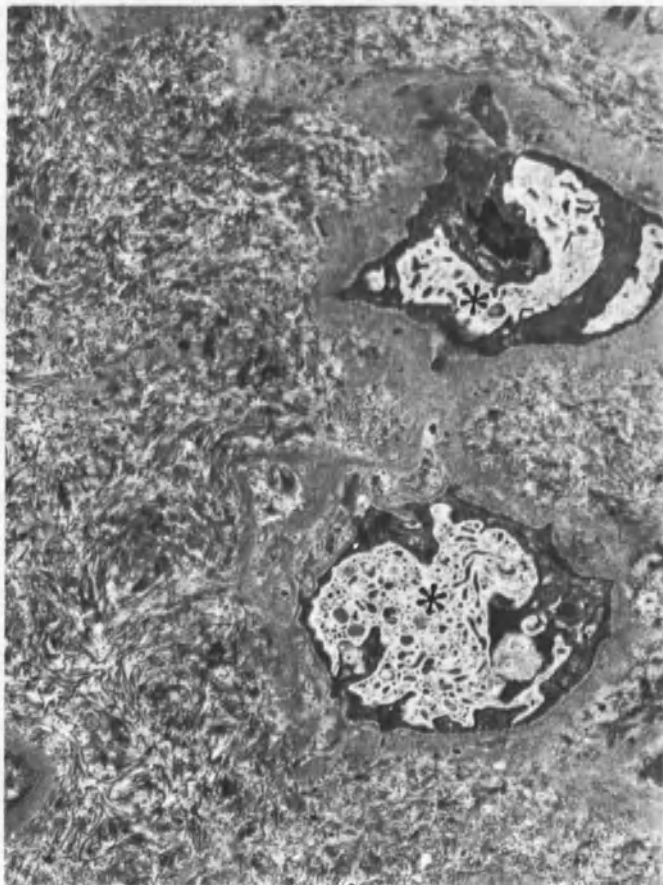


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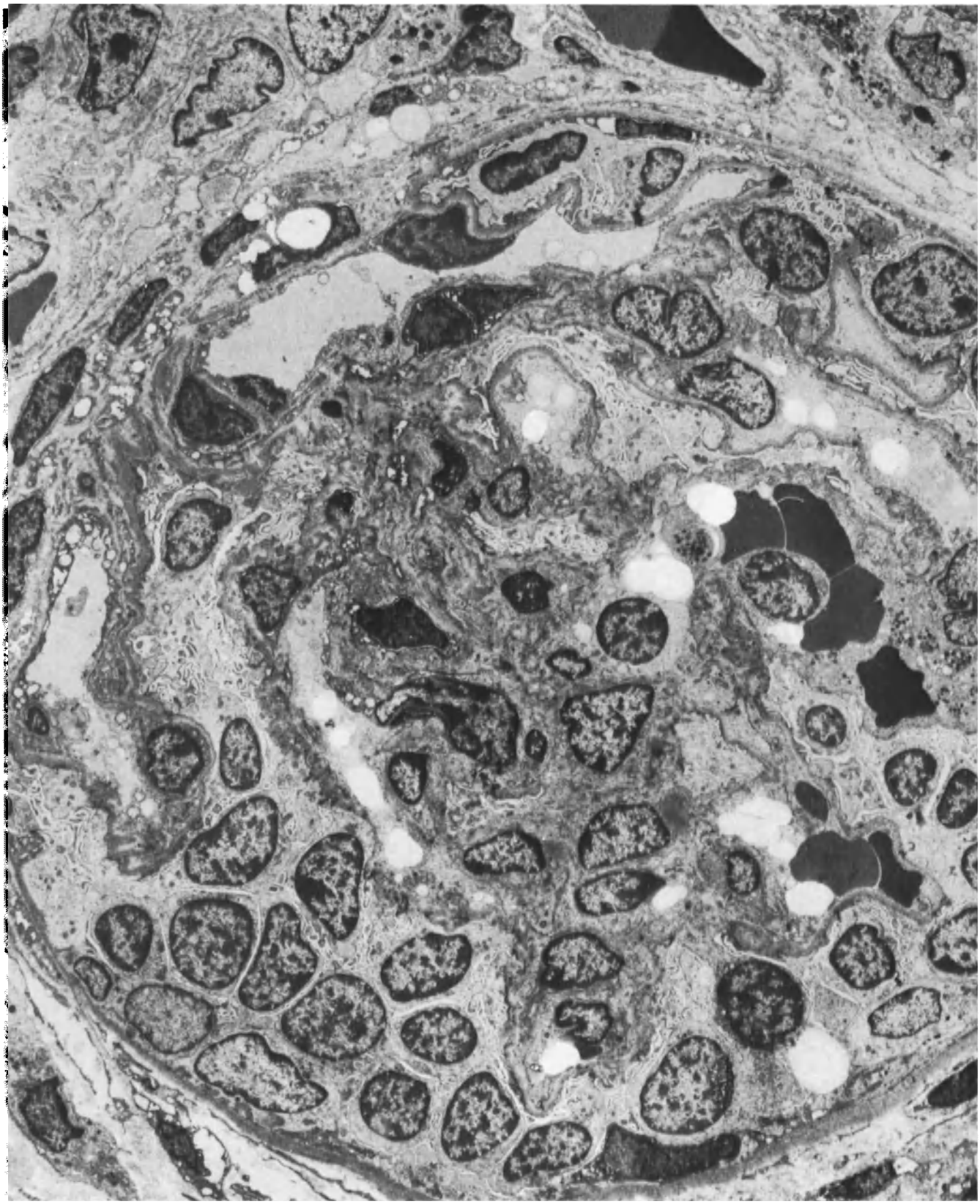


**Fig. 6.110.** Collapse glomerulus in chronic pyelonephritis. Glomerular capillary loops are completely collapsed, which is clearly evident in the center. Podocyte increase and edematous swelling is obvious. Male, 1 year. EM (×2400)

## The Ischemic Type of Glomerular Obsolescence

***Collapse Type.*** This type is the most frequent of those of vascular origin. It develops slowly. Its most striking characteristics are: the thickening and, above all, the wrinkling of capillary loop BM (Figs. 6.110, 6.111). Additionally, mesangial cells disappear and there occurs a simplification of the entire glomerulus. Podocyte proliferation is clearly apparent in infants and small children; these podocytes are especially large and almost cubic (Fig. 6.110).

The capsular space is progressively filled by masses which are van Gieson yellow and PAS negative or slightly positive and which quite often contain collagen fibers. Due to their van Gieson yellow staining, they are variously designated as fibrinoid or as hyaline and are said to be rich in 5-nucleotidases [1064].

Fibrin stains are negative. It is assumed that the masses are of exudative origin arising from increased capillary loop permeability caused by ischemia. An exudation through capsular epithelial cells is held to be unlikely [1179].

Shunt vessels are very rarely encountered. Nevertheless, cortical parenchyma in these areas is usually not necrotic since its requirement for blood is probably low due to severe ischemic injury. The capsular BM is usually homogeneously thickened and fragmented (Fig. 6.111). Additionally, a slight, perifocal interstitial fibrosis scantily infiltrated with lymphocytes is usually found.

With EM, large fibrinoid osmiophilic masses containing lipid vacuoles are often demonstrable in the capillary loops, a finding we believe to be indicative of secondary insudation into the original capillary loop lumen. The finely fibrillar and granular material between BM and podocytes with formation of a new thin l. densa (Fig. 6.108) is encountered now and again. We once observed a very old capillary loop obsolescence underneath a very fresh partial crescent. Such changes must not be taken as proof of glomerulonephritis.

The capsular BM is always prominently thickened, often fragmented, and displays, in part, lipid-containing degeneration vacuoles. It can be interspersed with fibrocytes or even—as seen in one case—be completely missing. The capsular space shows far richer collagen formation in the finely granular masses than is the case in GN obsolescence. With LM, the masses are initially seen at the glomerular hilus (Fig. 6.112).

The direct cause of collapse obsolescence is hypoxic injury of the capillary loops. Indirectly, it is attributable to severe proximal vascular stenosis involving arteries of every caliber but especially arterioles (arteriolosclerosis). A more frequent cause of collapse is primary pyelonephritis with secondary vascular disease whereby, along with the collapse glomerulus, pyelonephritic obsolescence is also observed. Collapse-type obsolescent glomeruli constitute the bulk of obsolescent glomeruli not only in ischemic contracted kidney and pyelonephritis but also in GN and other nephropathies (e.g., chronic interstitial nephritis/hydronephrosis) (Table 6.1).

Accelerated obsolescence, reported as characteristic and almost pathognomonic for malignant nephrosclerosis [783], shows, in addition to capillary loop collapse and fragmentation of capsular BM, a simplification of the vascular bed in which, nevertheless, the loops contain erythrocytes. With EM, a peculiar, irregular thickening of the l. rara interna can be recognized. Between this lamina and the endothelium, a second, very thin layer of l. densa is present. Corresponding pictures of this finding [783] (Fig. 6.27) concur exactly with ours in scleroderma. This investigator also observed the finding in scleroderma, and he considers it similar to that found in severe transplant glomerulopathy, in which we also found l. rara thickening—of greater degree—as well as new formation of a l. densa layer. In our material, the described so-called accelerated obsolescence could not be found in malignant nephrosclerosis.

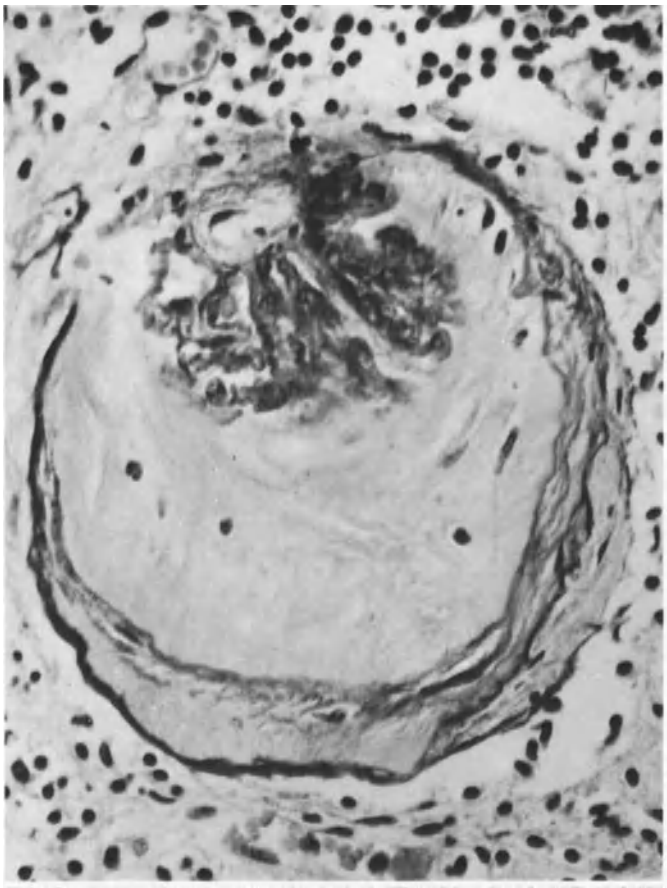
***Infarct Type.*** A second form of ischemic glomerular obsolescence is encountered in renal infarct. In this form, in contrast to the collapse type, the glomerular capillary loops are dilated and filled with erythrocytes and thus come to occupy the entire capsular space. It is in this way that ball glomeruli arise. Initially, they are granular and later PAS positive. Collagenous fibers are not formed for a considerable length of time in the postinfarct period. These glomeruli are yellow or orange with van Gieson staining (Fig. 6.113).

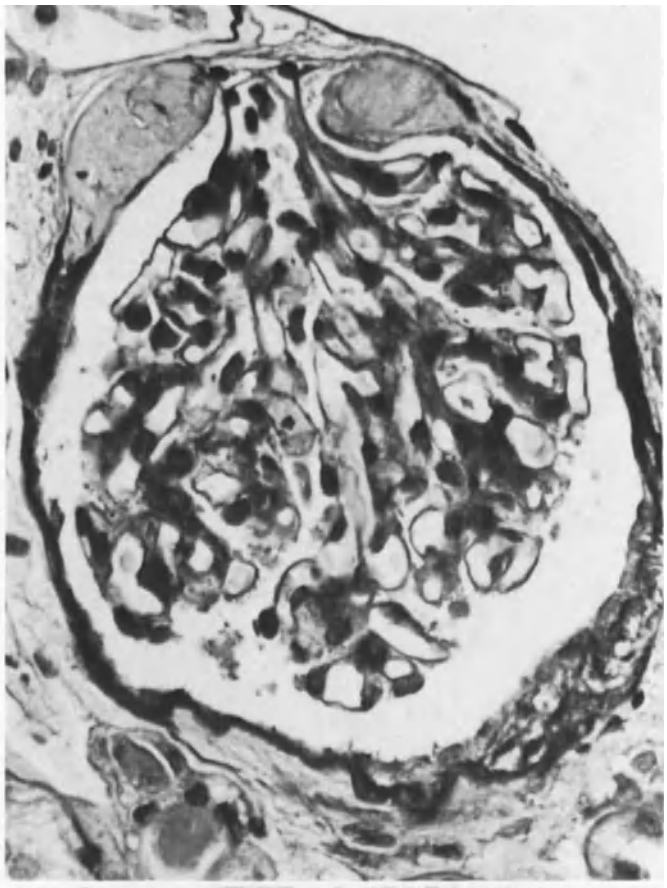
Pathogenetically important factors in this type of glomerular obsolescence include instantaneous and complete ischemia due to complete vascular occlusion, as well as capillary loop blood stasis.

## Pyelonepritic or Destructive Type of Glomerular Obsolescence

In this form, Bowman's capsule (proceeding from the interstitium) is loosened and infiltrated with collagen (Fig. 6.114; see [779, 1154]). As a rule, a very pronounced periglomerular fibrosis with numerous small lymphocytes is present.

The original capsular space may be rich in van Gieson-yellow amorphic masses. In infantile pyelonephritis as in early infantile glomerulonephritic contracted kidney (see p. 356), completely torn down glomeruli, in the form of so-called spider scars are easily overlooked. In both pyelonephritis and chronic interstitial nephritis, doubling of the capsular BM with exudation between the layers—with an empty capsular space—is fairly frequently observed (Fig. 6.114). An exudate may arise from the interstitium and pass through the capsular BM. The find-





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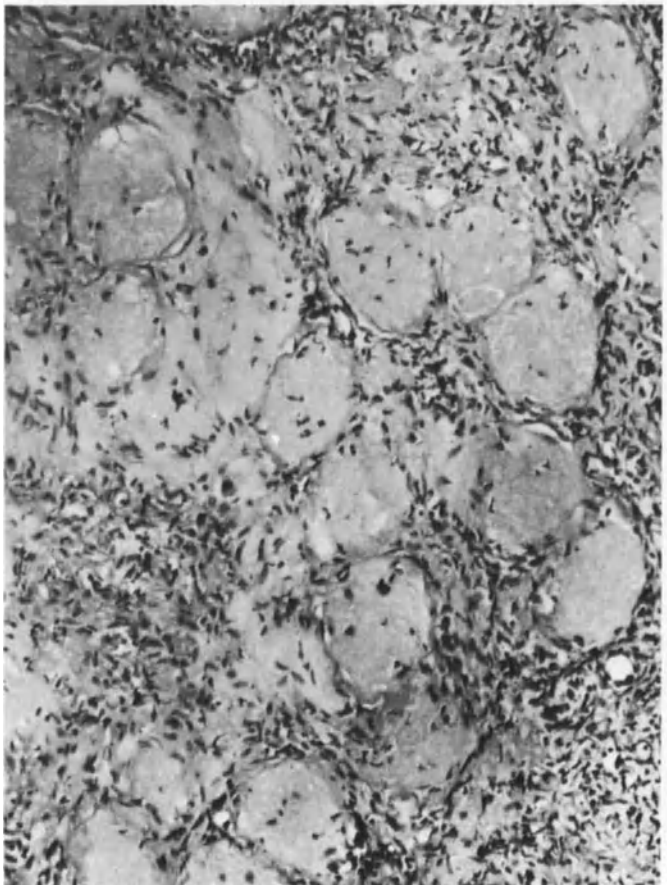

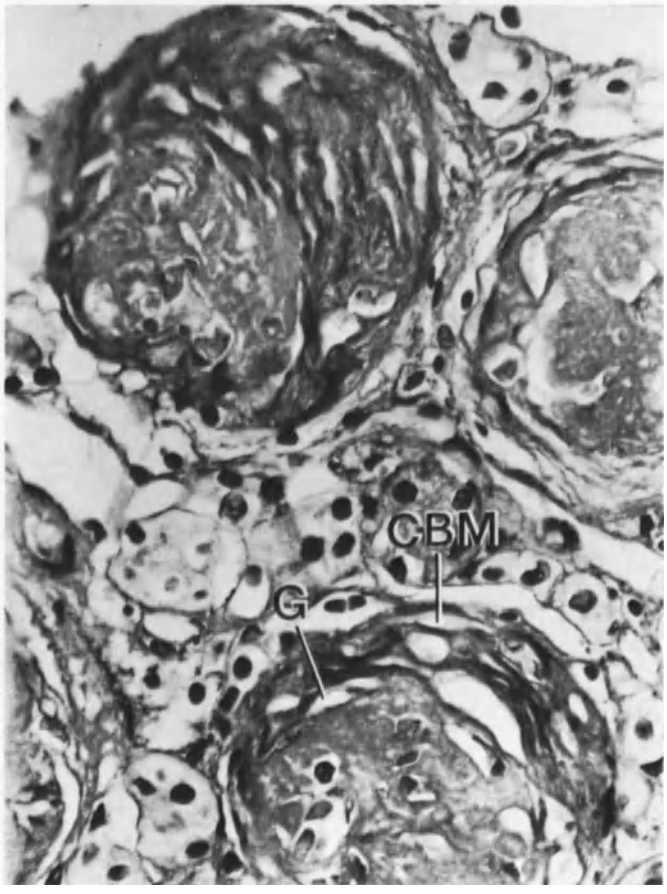


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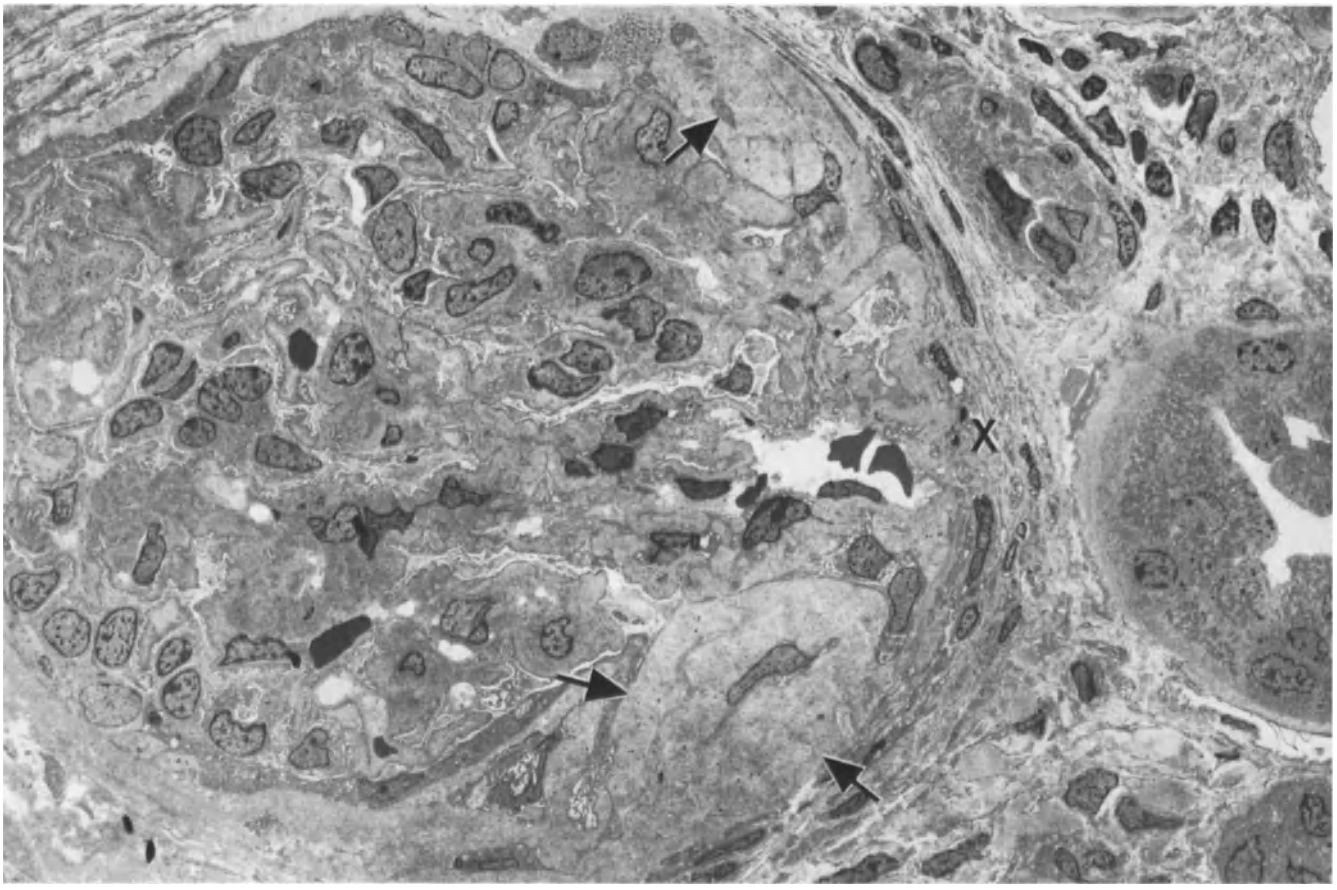



**Fig. 6.115.** Glomerular obsolescence in chronic pyelonephritis. Glomerular capillary loop collapse and splitting of capsular BM permeated by connective tissue (X). Capsular space is filled with amorphous material (→). Female, 25 years. EM (× 1000)

◁ **Fig. 6.111.** Glomerular obsolescence of collapse type in chronic interstitial nondestructive nephritis after mushroom poisoning (*Amanita phalloides*) 5 years previously. Glomerular capillary loops are completely collapsed and their BM is severely wrinkled. Capsular space is totally filled with a homogeneous mass which is very poor in nuclei. Capsular BM is splintered. Male, 51 years. PAS (× 230)

**Fig. 6.112.** Incipient collapse obsolescence of a glomerulus in arteriolosclerosis associated with hypertension. Very fine-granular, LM homogenous and, occasionally, coarse clumpy masses are discernable in the split capsular BM at the glomerular hilus. Entire capsular BM is clearly thickened and, at times, already doubled. Female, 62 years. PAS (× 550)

**Fig. 6.113.** Completely obsolescent (van Gieson yellow-orange stained) glomeruli (appearing-pale in micrograph) in an infarct scar. No tubular residues are present. Interstitium is very shrunken and, accordingly, the glomeruli are densely packed. Van Gieson (× 230)

**Fig. 6.114.** Glomerular obsolescence in chronic pyelonephritis. With the van Gieson stain as used here, the glomerulus (*G*) appears yellow-orange and the splintered and thickened capsular BM (*CBM*) red. Female, 42 years. Van Gieson (× 480)

ings with EM are by and large consistent with those already described (Fig. 6.115).

Pathogenetically, a centripetal mechanism seems to be operating [836, 1127]. The inflammatory process encroaches on the glomerulus from the interstitium. The capillary loops collapse secondarily due to the exudation.

### Glomerular Destruction

Complete glomerular destruction occurs in embolic purulent hematogenous FGN (Fig. 5.7), miliary tuberculosis (Fig. 20.53) and in the pyelonephritis of early childhood as noted above. It is also encountered in Wegener's syndrome—in this case caused by granulomatous periglomerulitis (Fig. 17.46)—and, more rarely, in Goodpasture's syndrome. Finally, complete glomerular destruction is observed in the glomerulonephritic contracted kidney of early childhood (so-called oligonephronia). The consequence of the destruction is scar formation or coiled BM remnants in the form of socalled spider scars (Fig. 17.65).

# 7. Histopathology of the Juxtaglomerular Apparatus (JGA)

## Limiting Factors Imposed by Biopsy

Diagnostic possibilities for interpreting JGA changes in renal biopsy are limited by the small number of glomeruli obtained by biopsy procedure. At least 25 JGA sections are said to be required for meaningful quantitative determination of cell number or JGA surface with LM [1089]. However, other data have shown that evaluation of 10 JGA sections will give the same results as obtained when 25 are studied [174, 330]. If only 10 JGA sections are studied, diagnostically relevant conclusions are only possible in the presence of very pronounced pathologic changes (100% of the control value); otherwise, the variability of findings is too extensive to be of diagnostic significance. From 10 to 40 sections through glomeruli are required to obtain sections through 6 JGAs (if serial sections which encompass all JGAs are not made). A further limiting factor is the fact that significant differences are present in JGAs taken from different parts of the kidney [1245, 1529].

## Prognostic Value in Renal Hypertension

A few centers use results from the quantitative evaluation of the JGA (also with frozen sections) to predict the success of surgery in renal hypertension.

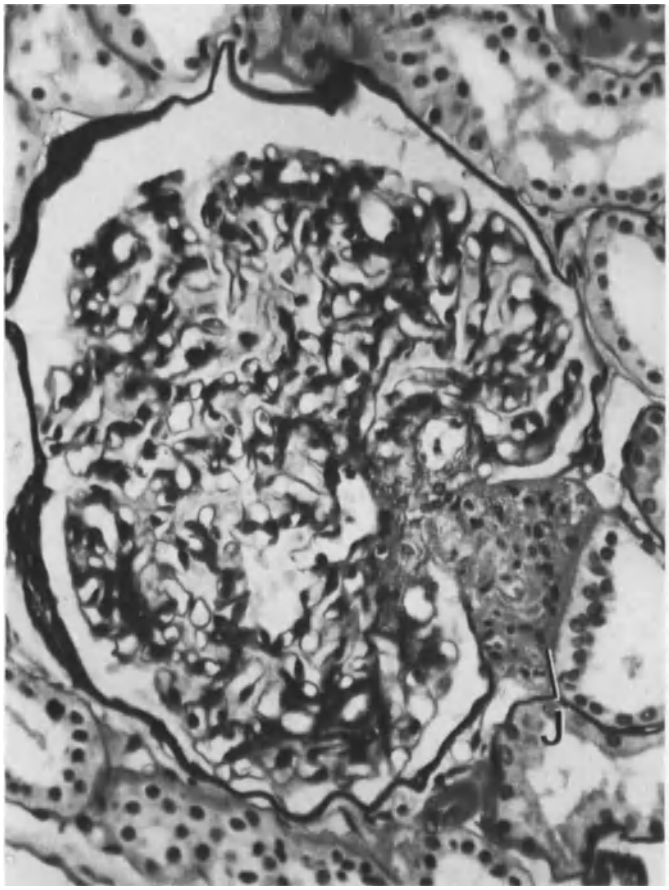



**Fig. 7.1.** Hyperplasia of the juxtaglomerular apparatus (*J*) in Addison's disease. PAS ( × 500)

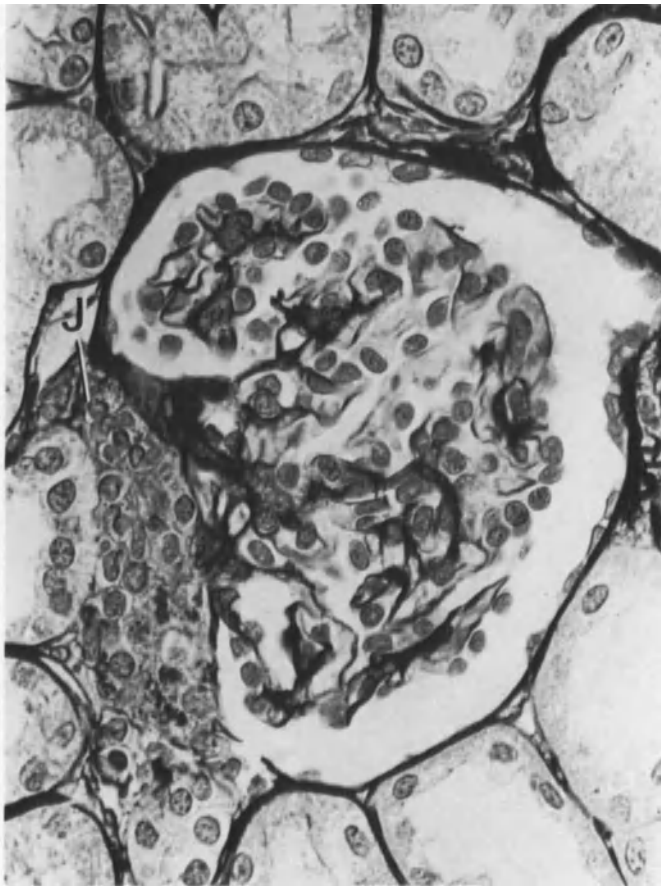



**Fig. 7.2.** Hyperplasia of the juxtaglomerular apparatus (*J*) in Bartter's syndrome. PASM ( × 800)

If biopsies from both kidneys are compared with each other, the influence of a surgical procedure on blood pressure can be predicted with a measurable degree of certitude, i.e., decrease in blood pressure associated with an obvious difference in JGA size between the two kidneys [330, 448]. Preoperative measurement of renin from each renal vein separately gives the same magnitude of prognostic assurance [81, 175]. We have not been able to confirm a correlation between semiquantitative study of JGA morphology in biopsies and of success prediction of surgical procedures in renal hypertension.

Renin granules are clearly identifiable with ultrastructural techniques (Fig. 4.16) (see p. 32). Therefore, in the presence of cytologic findings characteristic of increased synthetic activity, e.g., enlargement of rough endoplasmatic reticulum and Golgi fields and an increase in granules, hypertrophy of individual JGAs can be diagnosed [487, 1089, 1383].

## Increase in JGA Size

Increase in JGA cell number and size, and, accordingly in overall JGA size, is regularly observed in conditions of acute or chronic decreased renal blood flow. A classic example of a chronic decrease in renal blood flow is central renal artery stenosis. Other conditions resulting in decreased renal blood flow include contracted kidneys of various etiology, kidney in shock, liver cirrhosis, eclampsia and Addison's disease (Figs. 7.1, 4.12, 4.13, 4.14, 4.15, 4.16); enlarged JGA due to impaired blood flow is also seen in renal transplants (Fig. 30.74, p. 606) and in tissue bordering kidney scars [21, 240, 270, 436a, 449, 1089, 1808]. Since central renal artery stenosis is often associated with hypertension, it is assumed, with the support of experimental evidence as well, that activation of the renin-angiotensin-aldosterone system is the cause of renal hypertension [601a].

In Addison's disease (Fig. 7.1) and in Bartter's syndrome (Fig. 7.2), both of which evidence intense stimulation of the renin-angiotension-aldosterone system in the face of normal blood pressure, it is noted, however, that JGA activation and size increase are not necessarily accompanied by hypertension [919].

## Decrease in JGA Size

In Conn's syndrome (primary hyperaldosteronism with hypertension and hypervolemia) the JGA is atrophic [270, 1084, 1090, 1698].

# 8. Histopathology of the Renal Tubules

[103, 263, 655, 1068, 1156, 1571a]

## Problems in Evaluation

The evaluation of renal tubular lesions from biopsy material—especially with respect to specific disease states—is not easy. Some of the factors responsible for difficulties encountered in renal tubular study are given below.

1. Under normal conditions, immersion fixation can lead to tubular collapse with reduction in the size of the lumen which, in turn, causes a change in the surface component of the various cell compartments due to cellular swelling. This change is not found regularly in man as it is in experimental animals (rat) and it may indicate that the time required for development of tubular collapse in man is longer that it is in the rat.
2. Even under physiologic conditions, neighboring nephrons do not function identically, so that findings vary from nephron to nephron. This is also true for diseased kidneys. For example, in shock kidney, a few nephrons with collapsed tubules are always present among those with typically dilated tubules.
3. Morphologic findings in a single nephron show that functional differences among the individual tubular cells of the nephron exist. An example of this is the physiologic cell turnover which, as measured by the urinary excretion of tubular epithelium, is slight when the subject is at rest, but considerably increased with physical stress or after administration of diuretics [748].
   Degenerative and regenerative tubular epithelial changes are also regularly demonstrable under controlled conditions. Therefore, differences in disease states are, accordingly, quantitative and not qualitative.
4. Atrophy is the most frequent tubular change. It is due to primary vascular, glomerular or interstitial kidney disease. No specific morphologic changes permitting correlation to underlying disease processes can be evaluated from the atrophic tubules.
   Mindful of the above, it is readily seen that tubular changes seldom assume diagnostic significance except, for example, in shock kidney, in cytomegalovirus infections, or in specific storage diseases.

## Histopathology of Complex Tubular Changes

### Necrosis

Tubular necrosis (Fig. 8.1) is characterized by eosinophilia, loss of nuclei, cytoplasmic degeneration, and, ultimately, detachment and removal of necrotic epithelial cells which are flushed out in the urine. Regeneration of the tubular epithelium occurs in a proximal to distal sequence, i.e., in the direction of urine flow.

With EM, necrobiosis becomes perceptible in the form of cellular shrinkage and nuclear pyknosis (Fig. 8.2). Organelles often exhibit vacuolar degeneration (Figs. 8.3, 8.6) which is particularly evident for the basal labyrinth (Fig. 8.4). In anoxia, there first occurs a flattening of the epithelium as is seen in shock (Fig. 8.5).

In toxic tubular injury this change is less clearly pronounced (Fig. 8.6). Necrotic cells are partially or completely detached into the lumen (Fig. 8.7) with signs of ballooning (Fig. 8.6).

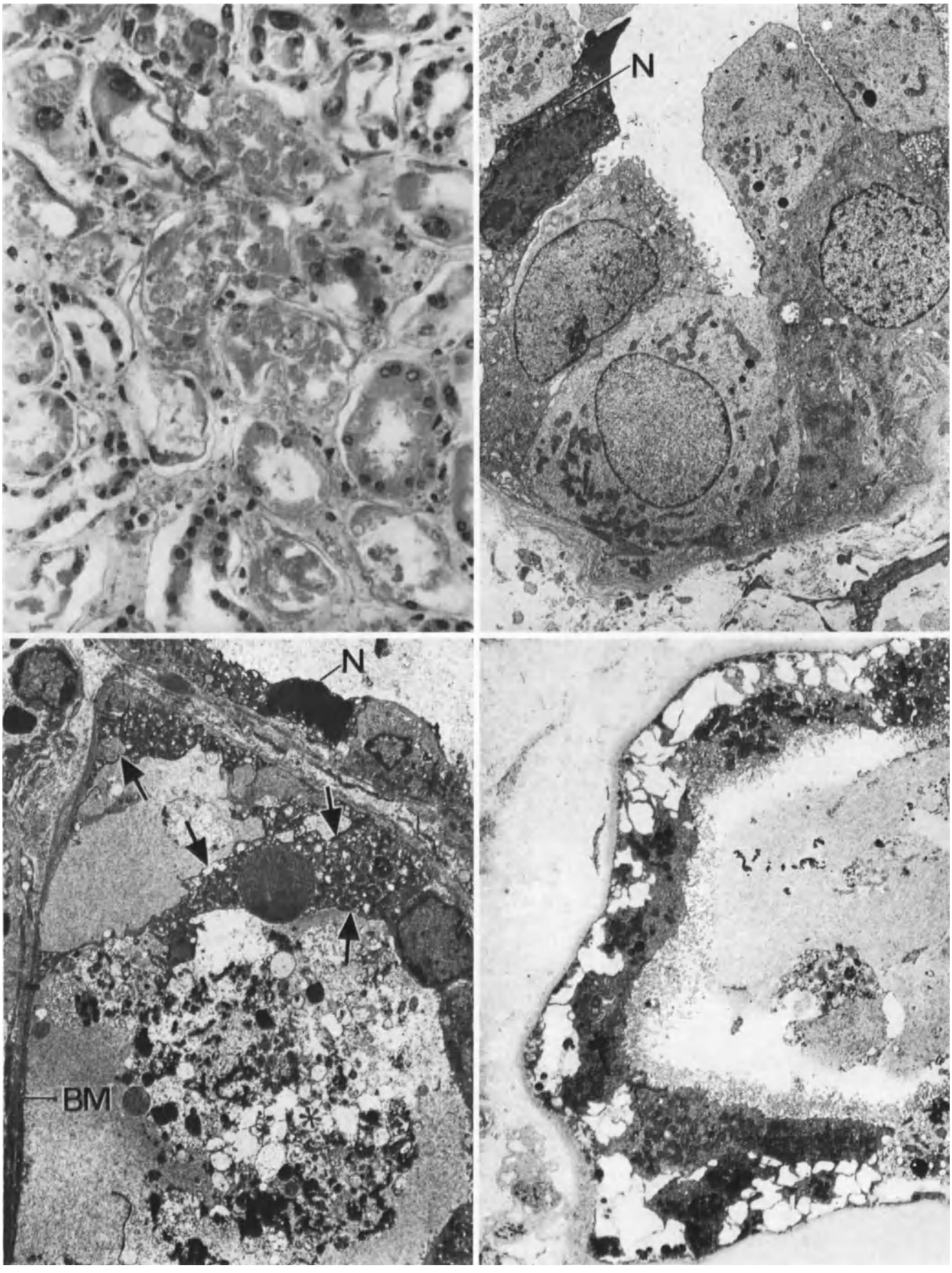
For proper regeneration to occur, the BM must be intact since it functions as a growth template [1674]. Data from animal experimentation indicate that tubular regeneration is at its maximum 3 days after a single injury with necrotic sequelae [213].

**Fig. 8.1.** Fresh tubulonecrosis in head injury. Autopsy specimen. Female, 38 years. HE (×600) ▷

**Fig. 8.2.** Necrobiotic cell in a collecting duct (*N*) shows nuclear shrinkage and severe condensation of the cytoplasm. Male, 22 years. EM (×3500)

**Fig. 8.3.** Kidney 1 h after transplantation with severe tubular cell injury: Necrotic tubular cell in situ (*N*); detritus in tubular lumen and desquamated necrotic epithelial cell (*); denuded tubular basement membrane (*BM*). Vacuolar transformation of organelles and cell detachment form BM (→). Female, 48 years. EM (×2800)

**Fig. 8.4.** Severe anoxic injury of the proximal tubular epithelium in a 21-day-old transplant with acute interstitial rejection. Basal labyrinth is much widened and the epithelium is slightly flattened. Male, 34 years. EM (×2080)

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Regenerating cells are low, have basophilic cytoplasm, large nuclei and numerous mitoses (Fig. 8.8). The brush border is at first absent from the proximal convoluted tubules but reappears following completed regeneration.

Ischemic injury, such as occurs in renal infarction or extensive intravasal coagulation, is the main cause of tubular necrosis. A few isolated necrotic cells are found in acute renal failure of various etiology (see p. 419). Accordingly, the designation, 'acute tubular necrosis' used to characterize acute renal failure is not appropriate from the morphologic point of view [403, 1213, 1453]. The extensively studied tubular necrosis observed in animals following experimental poisoning with heavy metals is only rarely observed today in humans [502].

### Atrophy

Two morphologically different forms of tubular atrophy can be discerned. The first form (Figs. 8.9, 8.10) consists of atrophy with a decrease in the outer diameter, lumen, and size of the tubular cells with water-clear transformation of the cytoplasm (Figs. 8.9, 8.11). When atrophy is extensive, the resulting finding is referred to as an "endocrine kidney" (see p. 508). In this condition, the tubular BM is partially thickened by deposition of new BM substance on the inner aspect of the original BM (Fig. 8.10). This thickening is often accompanied by thinning of the BM at other sites [1808] (Fig. 8.11). In the second form of atrophy, the outer diameter of the tubules is not changed, the epithelial cells are flattened (Figs. 8.12, 8.13) and often demonstrate ischemic injury (Figs. 8.13, 8.14). The tubular lumen, which is widened due to cellular atrophy, is stopped up with urinary mucoid (Fig. 8.12). When many neighboring nephrons are implicated in the process, the atrophy is referred to as a pseudostruma configuration or thyroid-like picture (Fig. 8.12, see p. 50).

As mentioned previously, the first form is attributable to ischemic injury such as occurs with stenosis of the renal artery or thrombosis of the renal vein [1808]. A similar form of atrophy is also encountered in primary and secondary Fanconi syndrome in which tubular microdissection techniques have brought to light a swan neck-like transformation of the proximal convoluted tubules [343].

The second form of atrophy characteristically occurs in chronic pyelonephritis [1492a]; it is, however, also encountered in conditions associated with impairment of blood flow.

### Hypertrophy

Hypertrophy of a few isolated nephrons characterized by an enormous increase in the outer diamter of the tubules, but with a normal cellular complement does occur and almost exclusively in the contracted kidney (Fig. 8.15). It is obviously an expression of a compensatory effort of the few remaining intact renal tubules. Similar findings are also found in advanced stages of so-called oligomeganephronia; see p. 356; [5, 428, 593, 626].

### Dilatation

Tubular dilatation is defined as an increase in the inner and outer tubular diameter. In this condition—as in postnecrotic regeneration—some of the tubular cells dedifferentiate, while others show no LM characteristics distinguishing them from the normal state (Figs. 8.14, 22.1, 22.2, 22.3). The cause of tubular dilatation is to be found

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**Fig. 8.5.** Severe flattening of tubular epithelium and interstitial edema in anoxia. Proximal tubule (*PC*), distal tubule (*DC*). Same case as Figure 8.4. Male, 34 years. EM (×2200) ▷

**Fig. 8.6.** Acute tubulonecrosis following therapy with gentamicin and keflin. Marked flattening of the epithelium (→) and ballooning of cytoplasmic elements (*B*). Mitochondria are severely swollen in preserved tubular cells. Male, 66 years. EM (×3480)

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**Fig. 8.7.** Same case as in Figure 8.6. There is obvious desquamation of necrotic masses with complete denudation of tubular BM (→). Vacuolar transformation of cytoplasm in better preserved cells due to swelling of the organelles is present. Interstitium (*) is practically unchanged. Male, 66 years. EM (×1288)

**Fig. 8.8.** Regenerating tubular epithelium with mitoses (→) in tubulonecroses following formic acid poisoning. Desquamated detritus from necrotic tubular cells (*). There is coarse vacuolar degeneration of the tubular cells. Female, 68 years. HE (×600)

**Fig. 8.9.** So-called endocrine kidney (contracted kidney due to renal artery stenosis). Dedifferentiation of tubular epithelium, which evidences clear cytoplasm and almost complete disappearance of the tubular lumen, are present. Tubular BM is usually somewhat variably thickened. PASM (×530)

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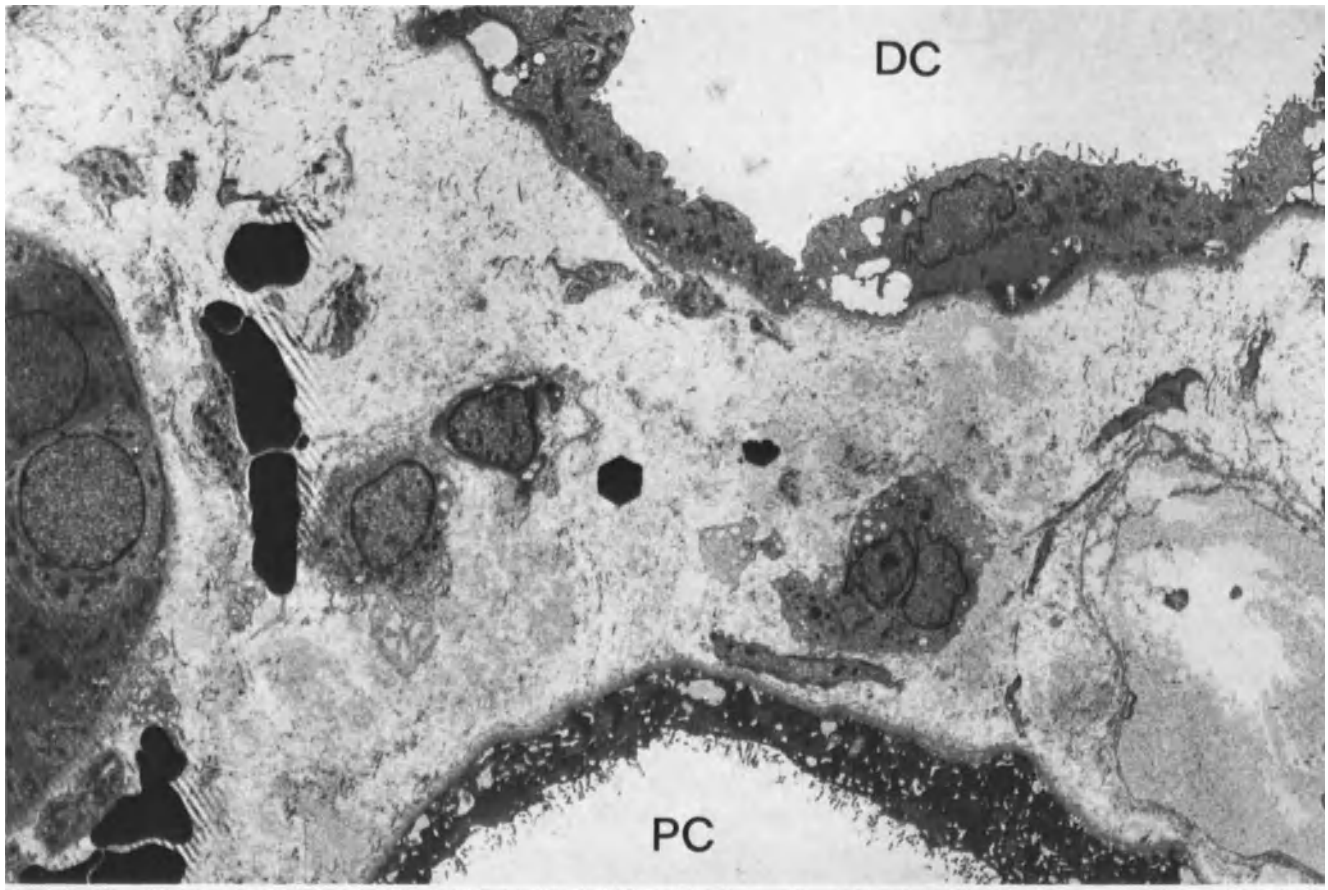
**Fig. 8.10.** Severe tubular atrophy with dedifferentiation of epithelium and pronounced thickening of tubular BM in pyelonephritic contracted kidney. Two phagocytes are lying between the layers of split tubular BM. New formation of a second BM subepithelially (→). Interstitium is severely fibrosed and demonstrates lymphohistiocytic infiltrates. Male, 52 years. EM (×3500)

**Fig. 8.11.** High degree of dedifferentiation of a proximal tubule of the so-called endocrine type in contracted kidney due to stenosis of renal artery. Tubular lumen no longer discernible. Tubular BM is thinned and in several places completely missing (→). Numerous residual bodies (pigment) are present in the tubular cells. Male, 51 years. EM (×5500)

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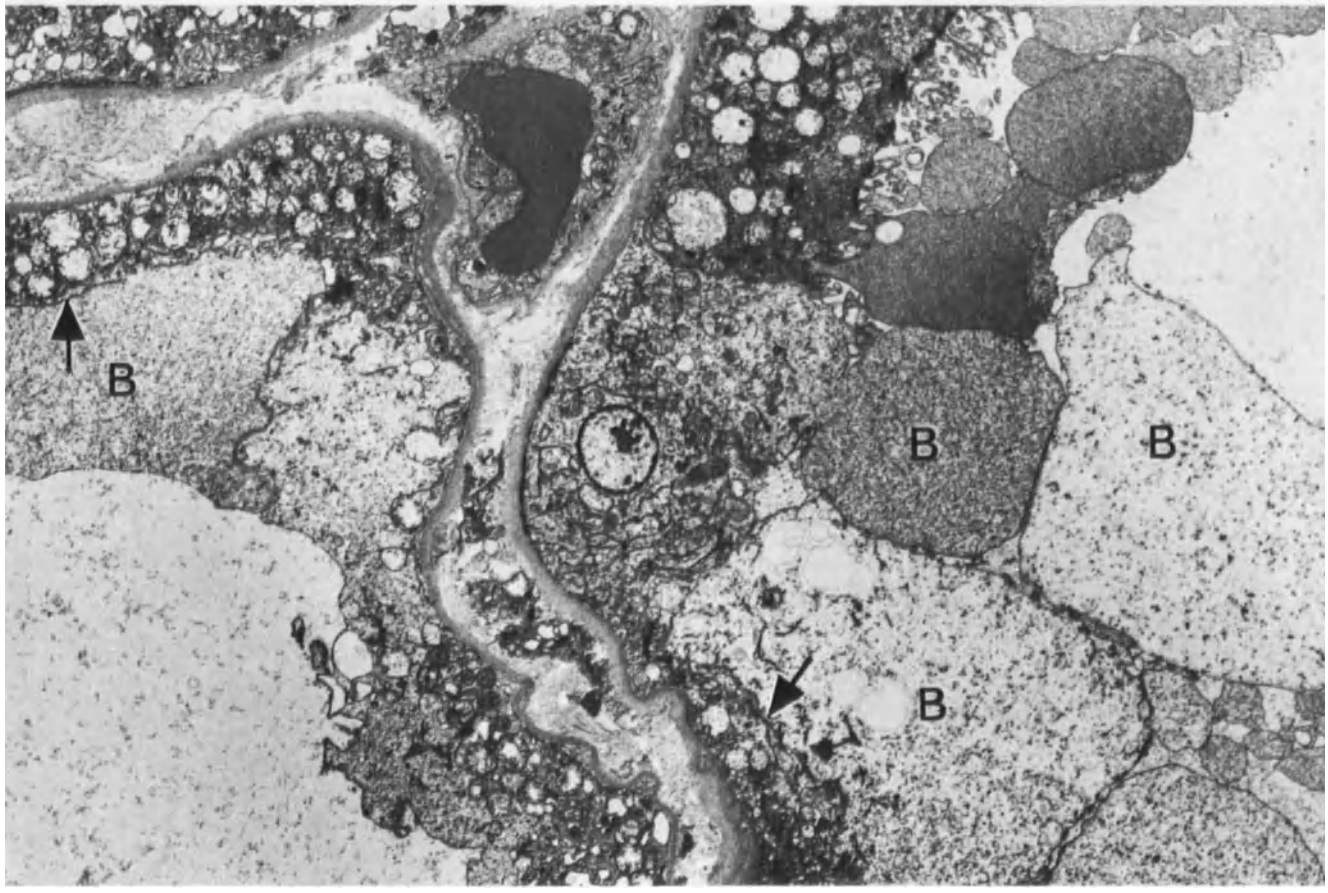


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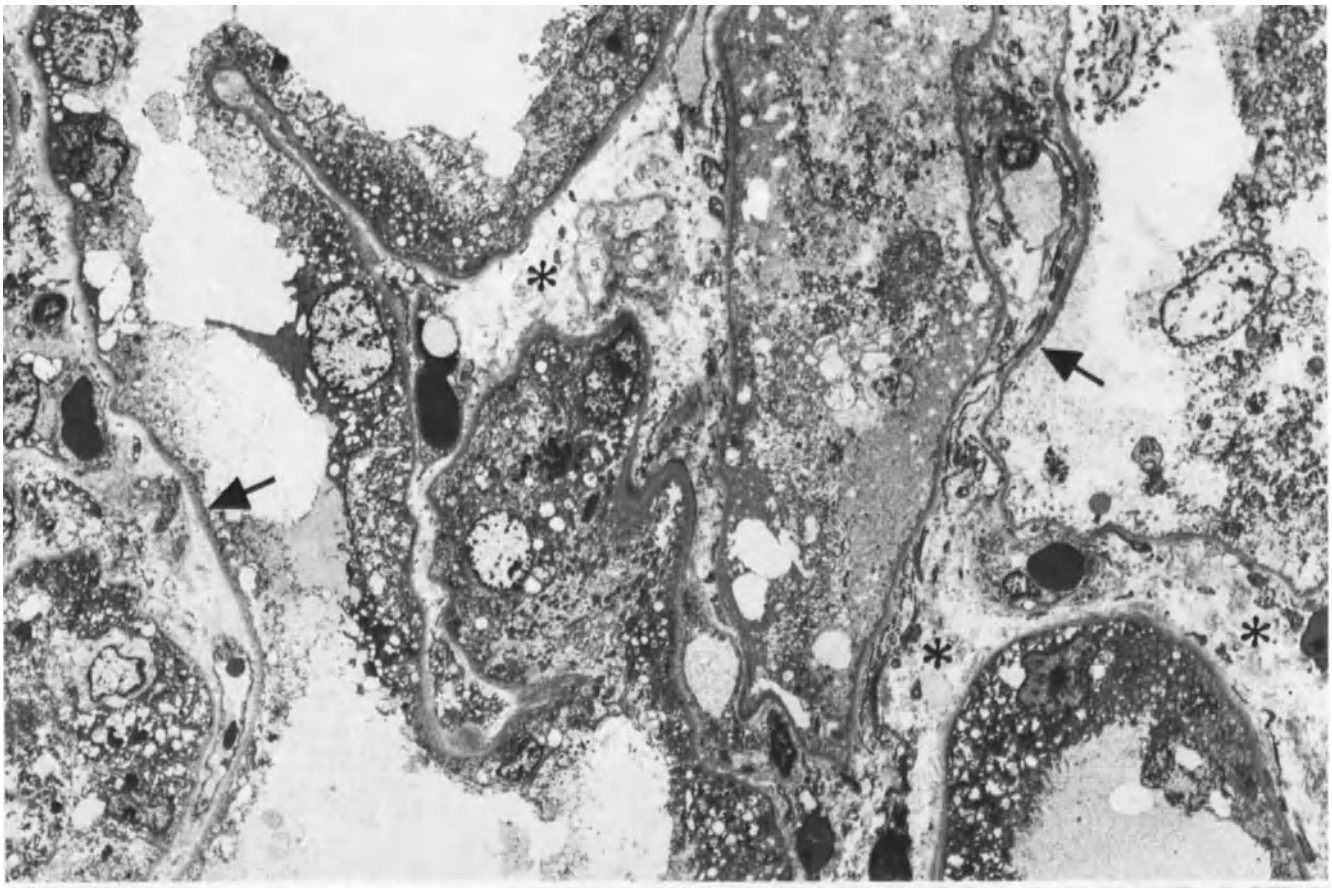

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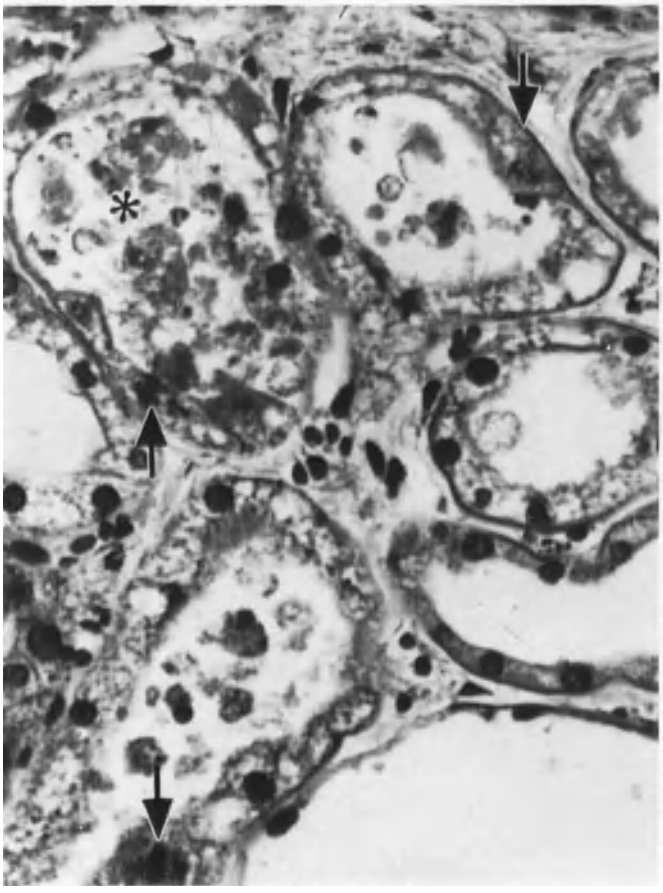

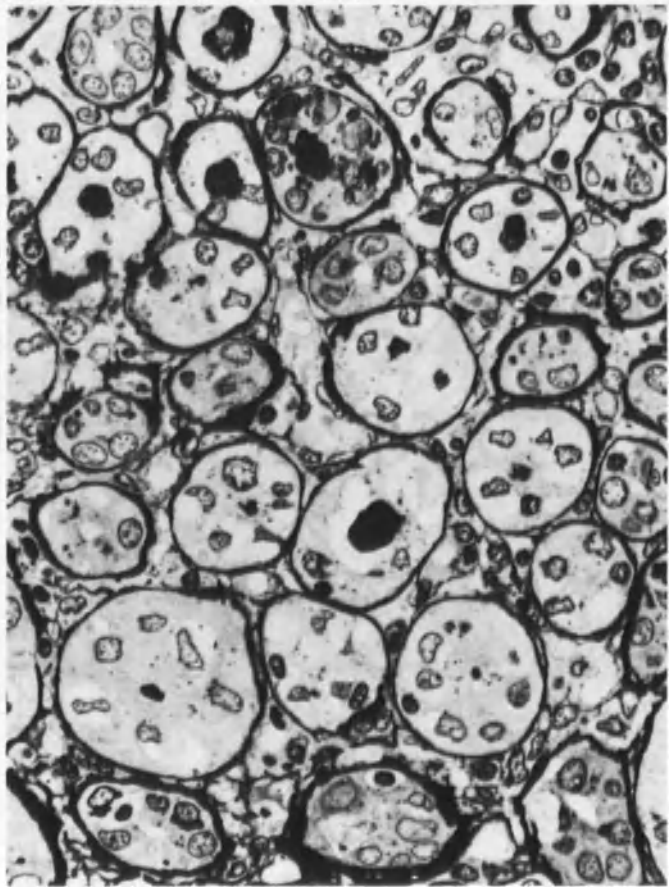

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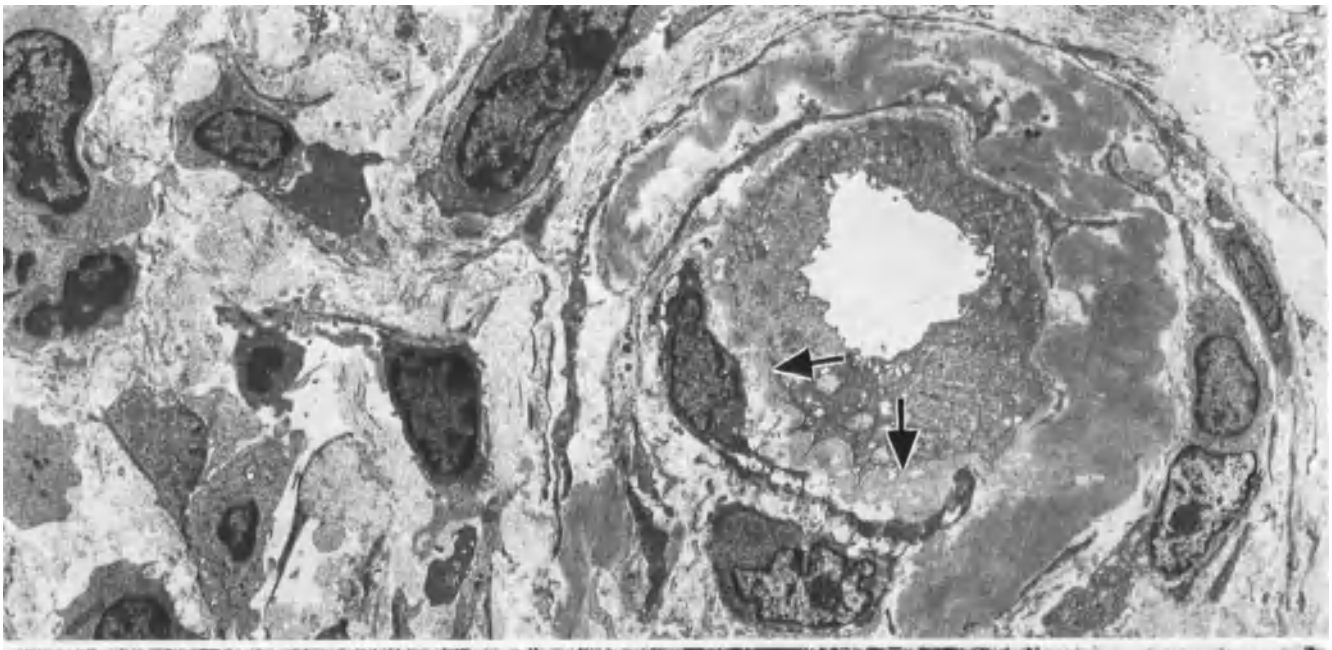

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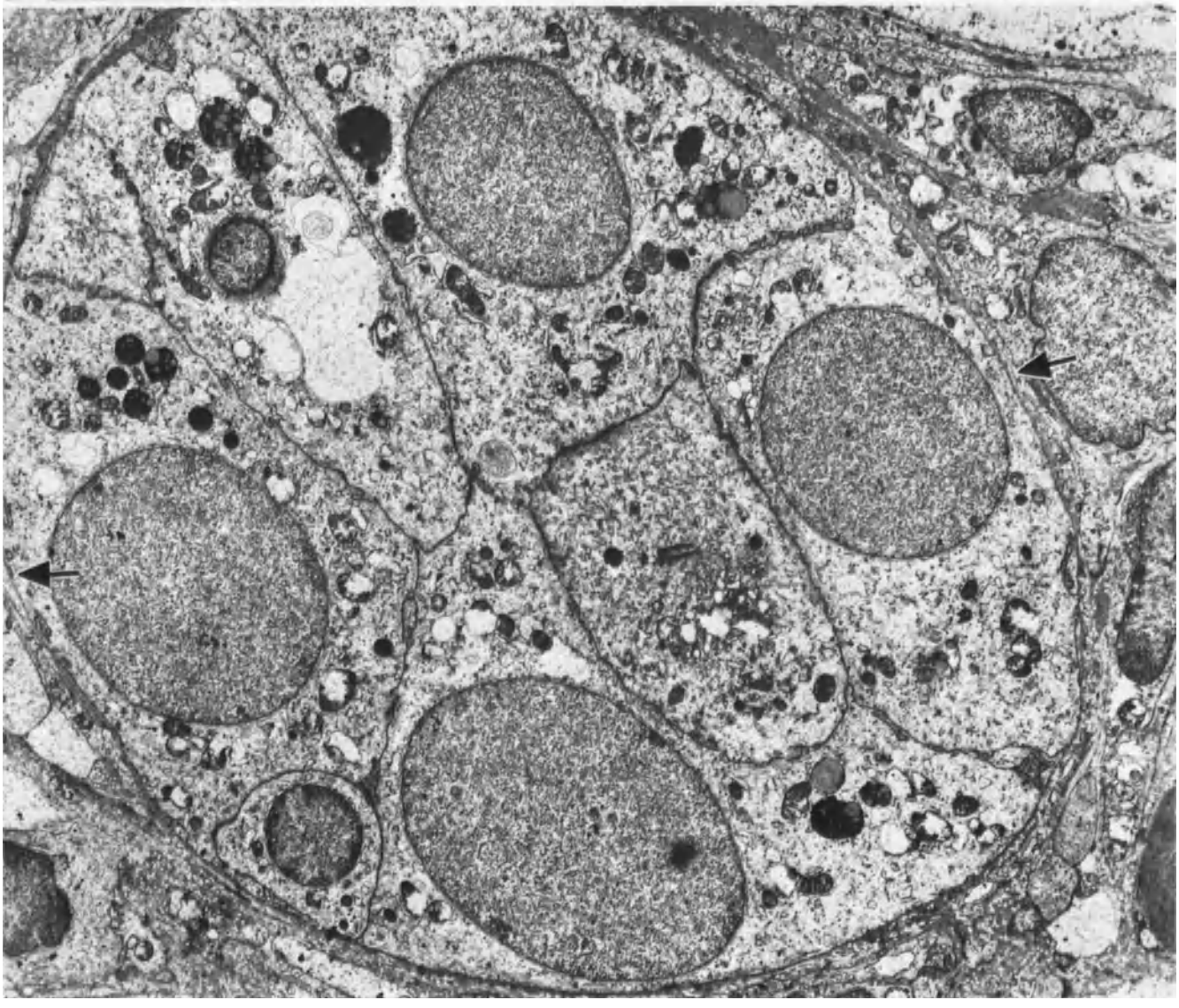

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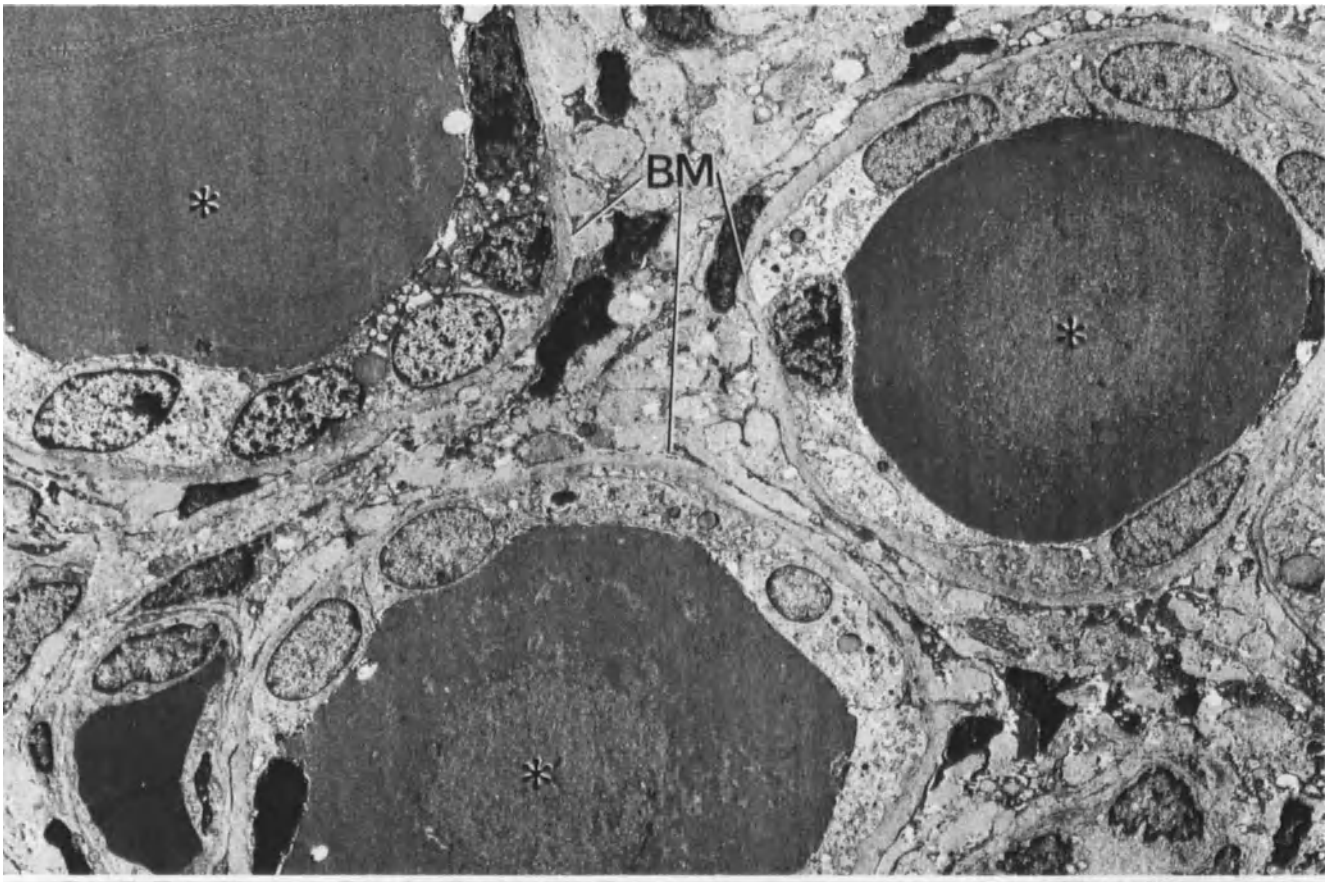


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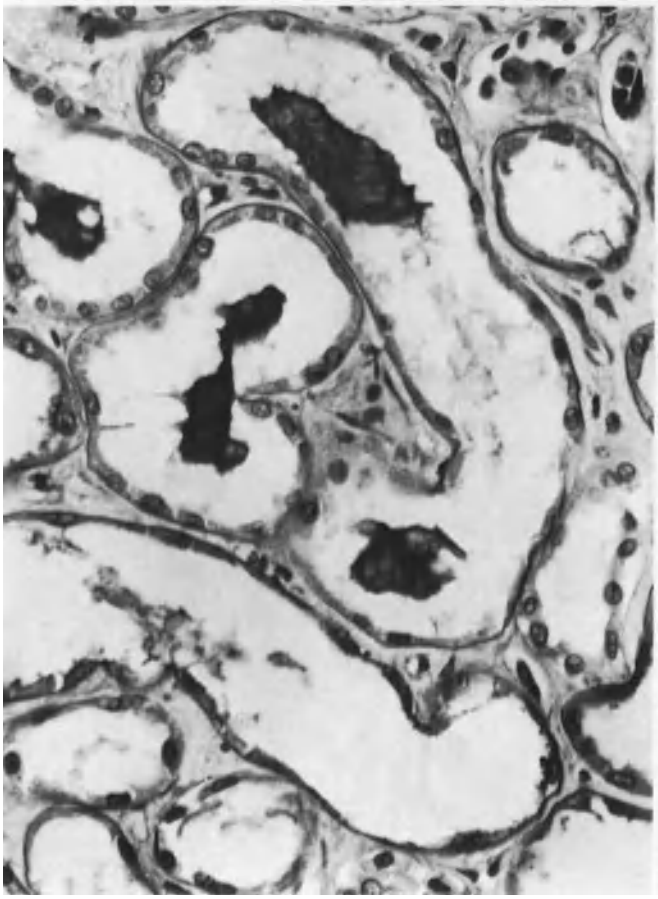

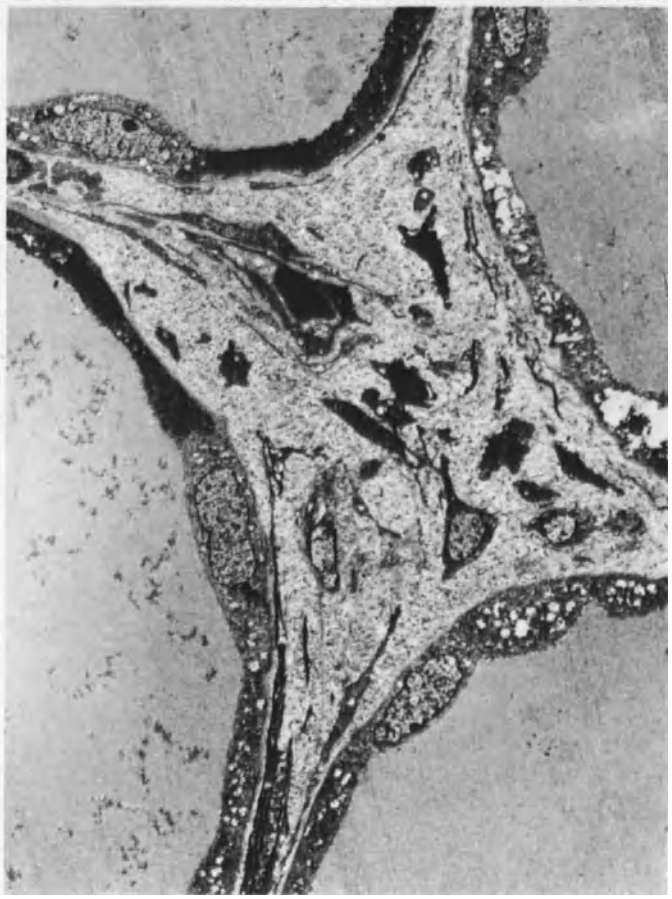

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in an increased intratubular pressure such as is present in hydronephrosis (due to tubular obstruction) or in the polyuric stage of acute renal failure [378, 726, 1453].

### Diverticulae

The occurrence of diverticulae in the distal convoluted tubule has been conclusively demonstrated using microdissection techniques (Fig. 4.19c, see p. 34). The number of diverticulae increase linearly with age. The pathogenesis and significance of tubular diverticulae are unknown [347].

## Cytoplasmic Changes of the Tubular Epithelium

### Vacuolar Changes

***Fine Vacuolar Form (Osmotic Nephrosis, Carbohydrate or Sugar Storage Nephrosis, Fally Degeneration).*** This form is mostly observed in extreme storage of glomerularly filtered carbohydrates such as glucose, dextran, mannitol etc. (Figs. 8.16, 8.17).

Fine vacuolar change arises if (a) the amount of a carbohydrate in the tubular lumen or capillaries is increased or (b) in the presence of cellular insufficiency. The cause of cellular insufficiency may be associated with ischemic injury in cardiovascular collapse or with lysosomal enzymatic insufficiency which occurs in certain storage diseases [313, 568, 692, 918].

The frequently observed concomitant appearance of severely changed nephrons—together with completely normal ones—(Fig. 8.16) indicates circumscript vascular impairment to be an important co-factor in the change. With EM, highly engorged lysosomes are observed (Fig. 8.18) in which the stored carbohydrate can be identified autoradiographically [1352].

◁ **Fig. 8.12.** Thyroid-like foci in early childhood pyelonephritis. Tubular epithelium is severely flattened and dedifferentiated. In the lumen, intensely osmiophilic, uniformly compact (hyalin) casts (*) are present. Tubular basement membrane (*BM*) is obviously thickened. Coarse-fibered fibrosis of the interstitium is seen with scattered fibroblasts and small lymphocytes. Female, 27 years. EM (×21,500)

**Fig. 8.13.** Hypoxic tubular damage showing severe flattening of the proximal tubular epithelium in GN contracted kidney. Autopsy specimen. Female, 67 years. PAS (×340)

**Fig. 8.14.** Severe atrophy of proximal tubular epithelium with cystoid widening of the lumen in GN contracted kidney. Numerous vacuoles arising from cystic widening of endoplasmatic reticulum and mitochondria are present. Male, 34 years. EM (×1500)

Fine or middle-sized vacuolar transformation of the cytoplasm is also demonstrable in paraffin sections in cases of neutral fat storage arising from phosphorus or chloroform poisoning and in cases of liver dystrophy (Figs. 8.19, 8.20) or lipid storage in nephrotic syndrome. Toxic injury to the tubular cells by poisons is the cause of neutral fat storage and hyperlipemia is involved in the lipid storage associated with so-called lipoid nephrosis.

Lipid-containing foam cells are occasionally observed in a variety of disparate nephropathies. We found foam cells in 5.6% of 200 unselected biopsies of GN and glomerular minimal change (Fig. 18.3), but they occur in about 40% of cases of Alport's syndrome ([521] see p. 466).

***Coarse Vacuolar Form.*** Coarse cytoplasmic vacuoles are observed in association with long-lasting hypokalemia in which they are very prominent in the proximal convoluted tubules (Fig. 8.21). They may persist for some time after normalization of serum values.

Findings with EM indicate that the condition is attributable to either intracellular vacuoles surrounded by membrane or to an extracellular widening of the basal labyrinth [275, 684, 1537]. Similar vacuolization of the convoluted tubules is observed in diethylene glycol poisoning in which extensive oxalate crystal precipitation is also encountered [1068, 1492a].

A further cause of vacuolar degeneration is the extensive storage of glycogen in proximal convoluted tubules as occurs in van Gierke's disease [684, 1068] and in the straight segments of the proximal tubules in long-lasting diabetic hyperglycemia (Armanni-Epstein cells, [1492a, 1625]).

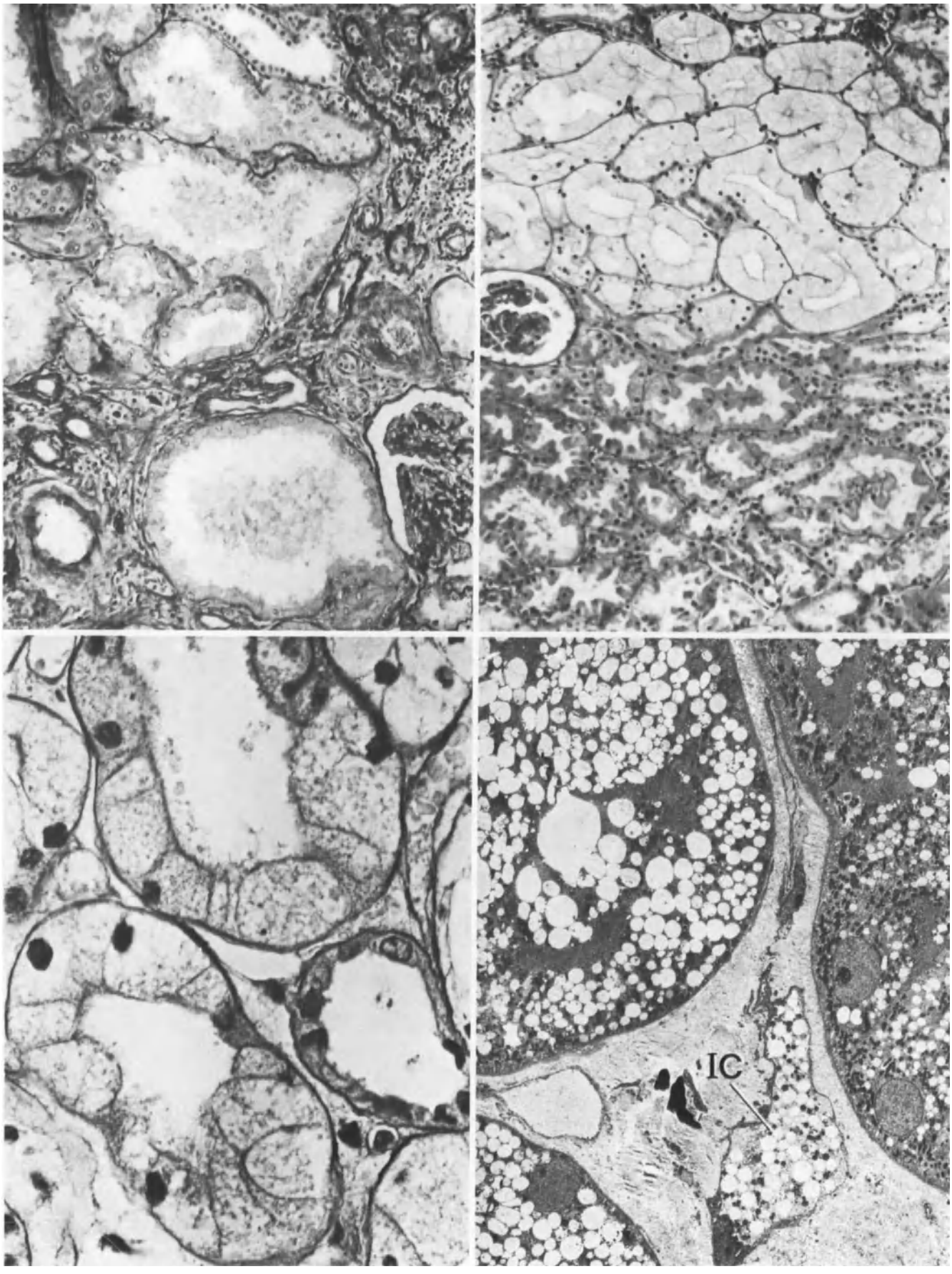
### Protein (Hyaline) Droplet Storage

This change depends on a massive increase of protein-storing phago-(hetero-)lysosomes (Fig. 8.22). The protein storage is observed almost exclusively in the proximal convoluted tubules. Increased availability of tubular (luminal) protein as occurs, for example, in GN, is the cause of the increased number of these cellular organelles. For frequency and composition of protein storage in IF-material, see Fig. 11.17.

Peritubular capillaries are said to contribute to the tubular pool of protein [259]. Disturbances of intracellular protein turnover and transport may also be involved as indicated in the Chediak-Higashi syndrome [446, 692].

### Pigments

Intracellular pigment deposition (hemoglobin, myoglobin, melanin, bilirubin, lipofuscin) occurs by two mecha-

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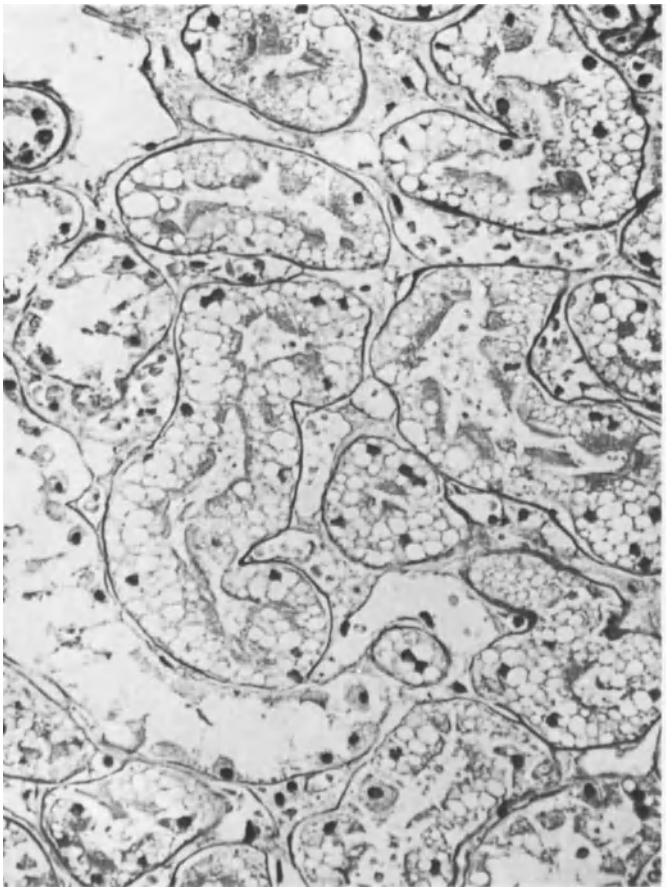


**Fig. 8.19.** Vacuolar degeneration of proximal tubular epithelium due to massive fat accumulation in liver dystrophy. Male, 75 years. PAS (× 200)

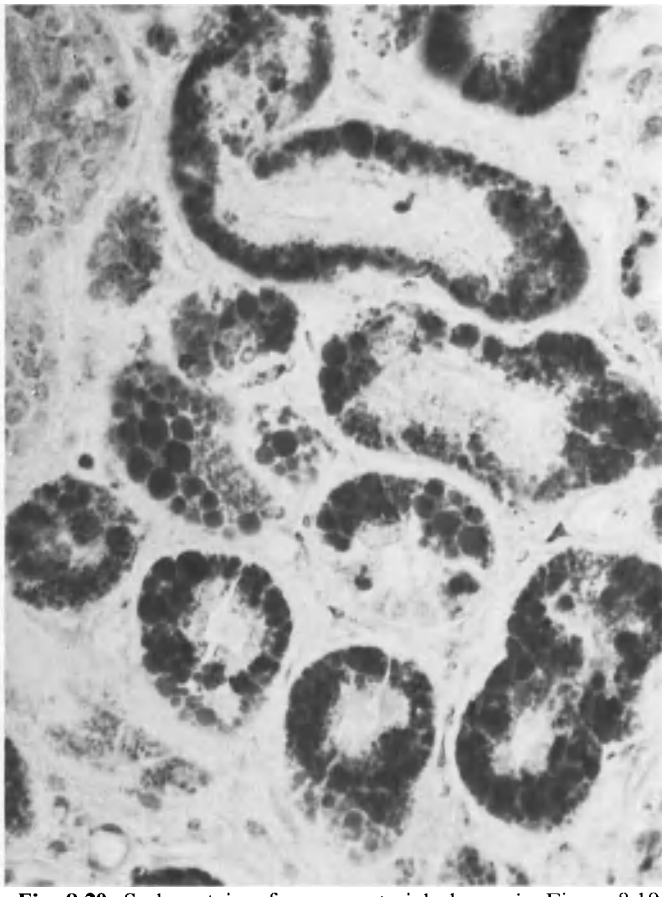


**Fig. 8.20.** Sudan stain of same material shown in Figure 8.19. Male, 75 years (× 200)

◁ **Fig. 8.15.** Compensatory hypertrophy and cystoid widening of proximal tubules in GN contracted kidney. Male, 52 years. PAS (× 130)

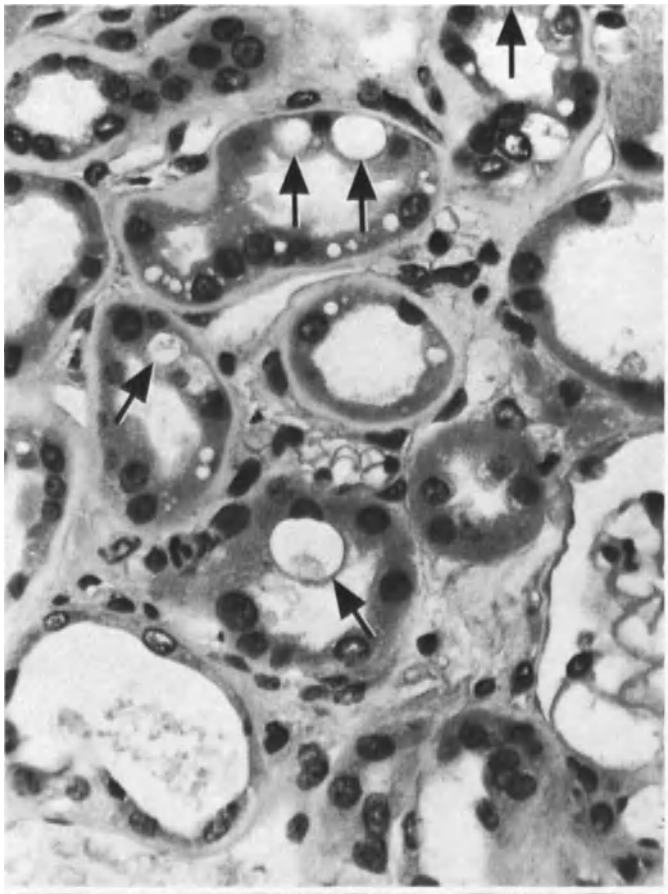
**Fig. 8.16.** Carbohydrate storage in proximal tubules characterized by fine vacuolar transformation of their epithelium. Severely changed and unchanged nephrons lie side by side. Autopsy specimen. Male, 77 years. PAS (× 130)

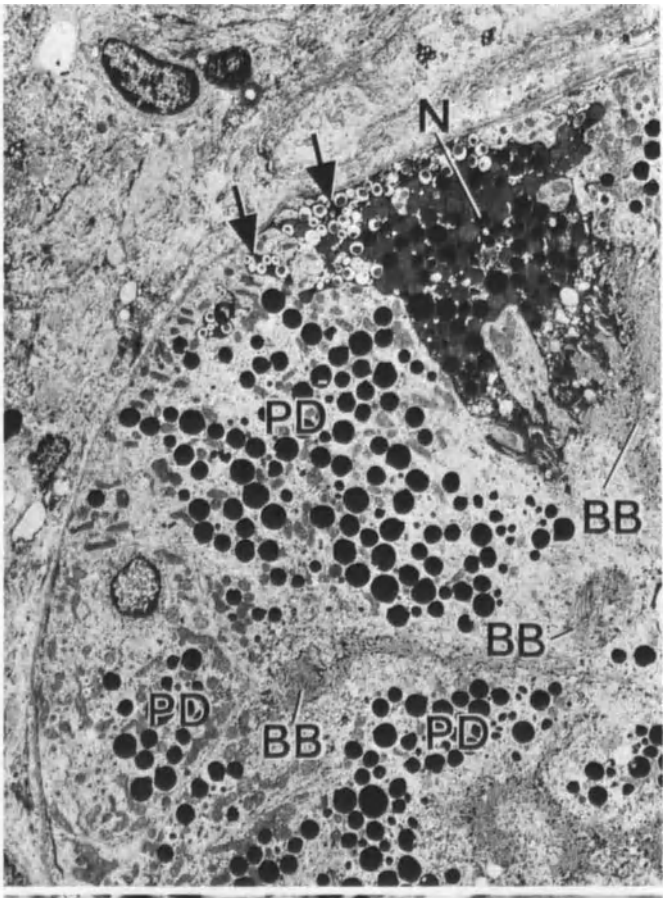
**Fig. 8.17.** Higher magnification than preceding figure, showing an extremely fine vacuolar change of proximal tubules caused by carbohydrate storage with secondary water uptake. Autopsy specimen. Male, 77 years. PAS (× 520)

**Fig. 8.18.** Carbohydrate storage in proximal tubules in acute interstitial nephritis showing bulky, cystic expanded lysosomes of somewhat unequal size. Analogous change is also present in the endothelium of an interstitial capillary (*IC*). Female, 48 years. EM (× 1100)

nisms. One mechanism is based on an excess of glomerularly filtered pigments in tubules (possibly excessive pigment concentrations in peritubular capillaries) which become resorbed and stored by the proximal tubules [1791] and partially transformed intracellularly, e.g., hemoglobin→hemosiderin [1318].

The second mechanism depends on a primarily intracellular process. There occurs an increase in the number of cytolysosomes attending an increased breakdown of cellular organelles, e.g., in age, and in phenacetin addiction [607, 1791], see p. 440). Lipofuscin is the chief pigment arising from this wear and tear of cellular constituents. Intracellular processes are relevantly involved in the deposition of pigment occurring in hemochromatosis. The thick limbs of Henle's loop are the sites of hemosiderin deposition in hemochromatosis , whereas the convoluted tubules are chiefly involved in hemosiderosis [1318].



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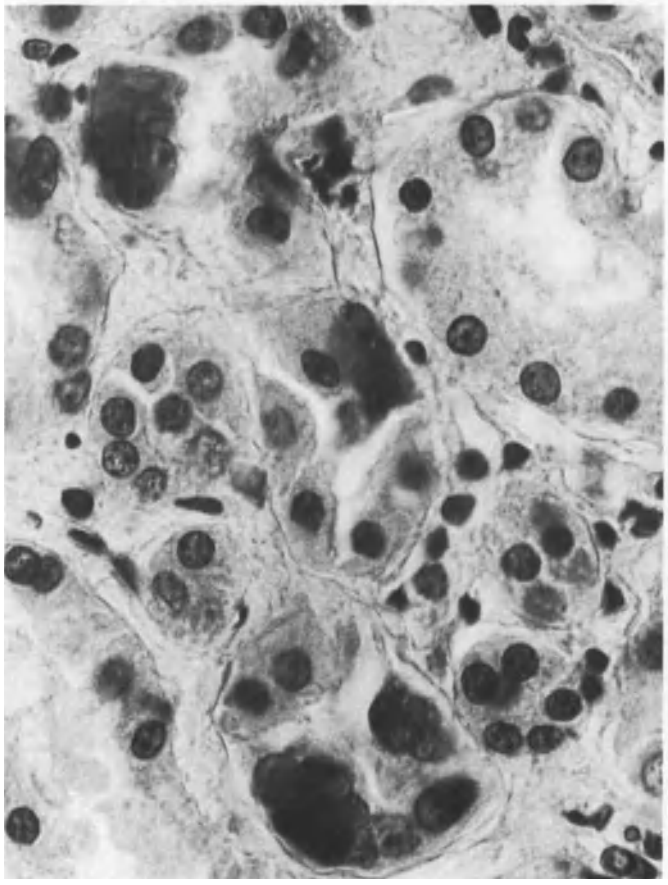

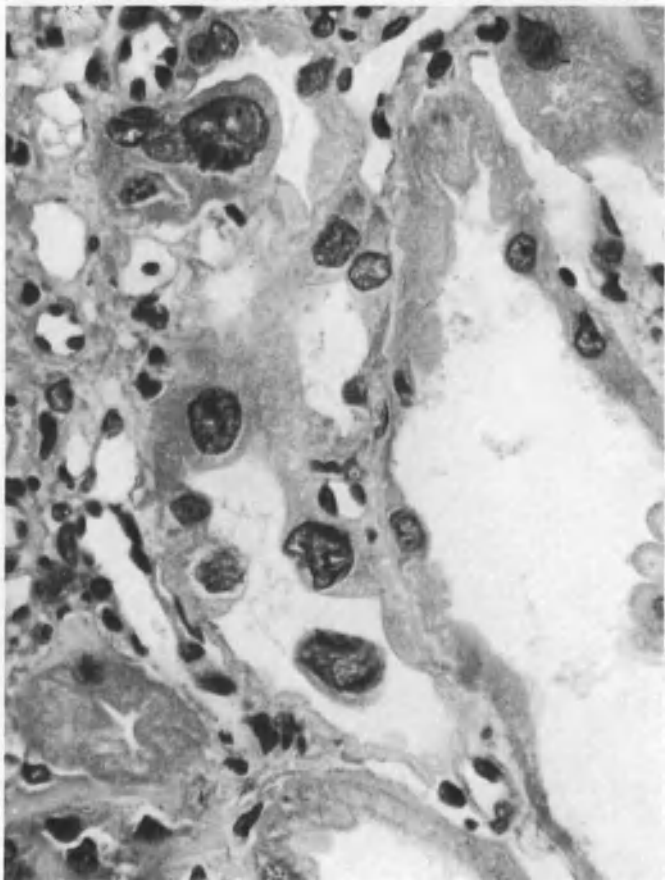

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Table 8.1. Giant cells

| Associated with granuloma | Tubular giant cells | | | Glomerular giant cells |
|---|---|---|---|---|
| | Multinuclear | Mononuclear | | |
| Tuberculosis<br>Sarcoidosis<br>Brucellosis<br>Aspergillosis<br>Actinomycosis<br>Toxoplasmosis<br>Echinococcus<br>Plasmocytoma<br>Foreign body giant cells (bleeding, cholesteatoma, sutures, etc.)<br>Allergic granulomatous arteritis | Old transplants<br>Interstitial nephritis<br>Congenital nephropathy<br>Fanconi's syndrome with and without cystinosis<br>Plasmocytoma<br>Contracted kidney<br>Senescence | With cytoplasmic/intranuclear inclusion bodies:<br>Lead<br>Bismuth<br>Gold<br>Cytomegalovirus<br>Other viral infections possible (varicella, herpes, poliomyelitis, measles, adenovirus infections [774]) | Without inclusion bodies:<br>Busufane® therapy<br>Transplants<br>Contracted kidney (esp. pyelonephritis)<br>Kidney in X-ray injury<br>Liver cirrhosis<br>Hepatoma<br>Idiopathic | Glomerular capillary loop necroses in GN<br>Goodpasture's syndrome<br>Other nephropathies extremely rare:<br>Plasmocytoma<br>Fanconi's syndrome with and without cystinosis<br>Amyloidosis<br>Nail patella syndrome |

## Nuclear Changes of the Tubular Epithelium

Three different types of tubular nuclear changes can be recognized:
(1) Multinuclear giant cells, (2) mononuclear giant cells and (3) nuclear inclusion bodies (see Table 8.1).

***1. Multinuclear Giant Cells.*** Independent of any underlying disease process, multinuclear giant cells are present in the convoluted tubules and with greater frequency with increasing age, e.g., in 2% of material from patients up to 40 years of age and in 3% of 60–80-year-olds [662]. They are also found in significant numbers in conditions associated with increased regeneration as, for example, in older renal transplants (Fig. 8.23) as well as in a few cases of cystinosis (own observation; [1459, 1573]). Multinuclear giant cells arising as a reaction to protein casts—especially in plasmocytoma—are observed in the distal tubules [60, 1457, 1791].

◁ **Fig. 8.21.** Coarse vacuolar degeneration (→) of proximal tubular epithelium in hypokalemia associated with laxative abuse. Female, 58 years. HE (×520)

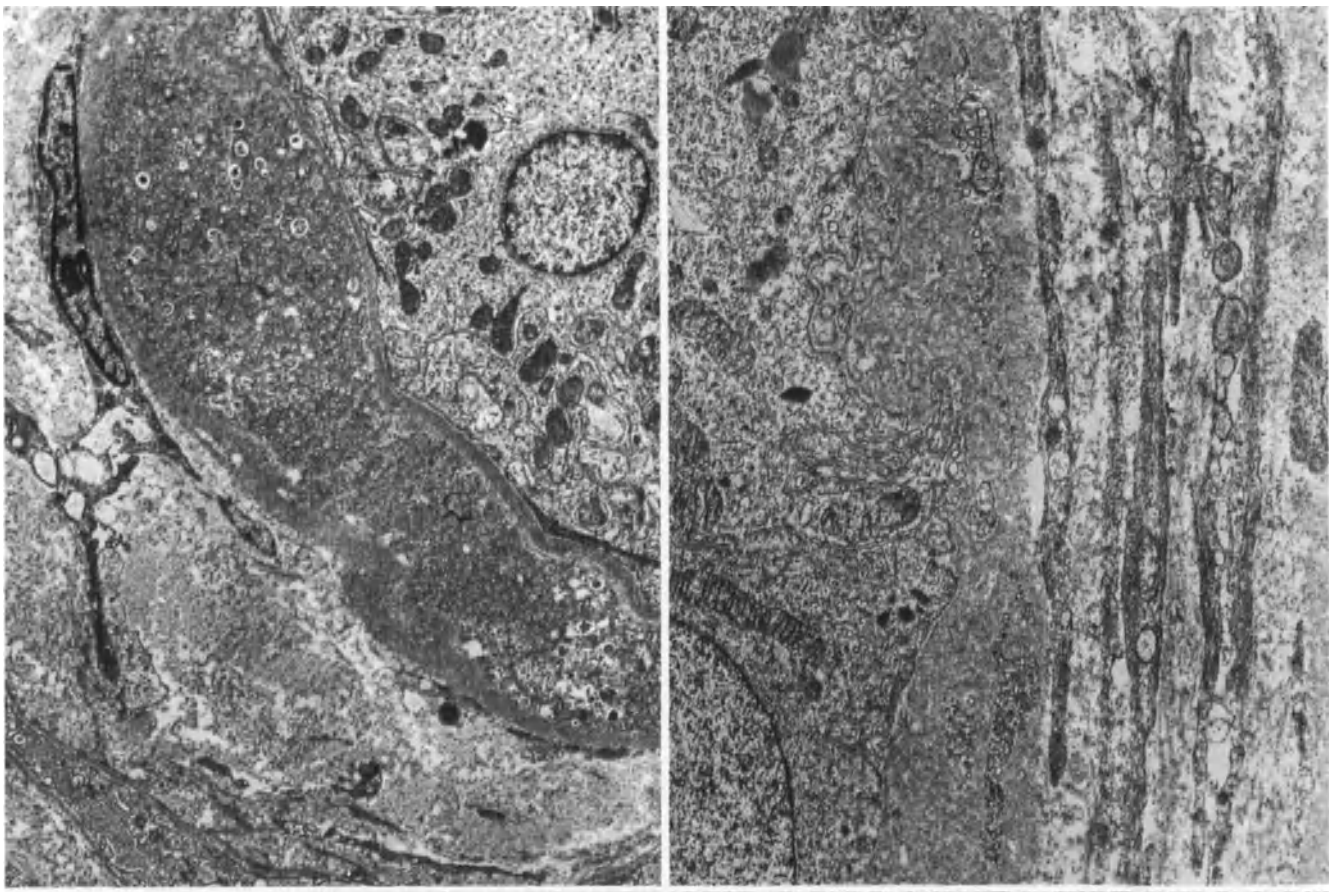
**Fig. 8.22.** So-called hyaline (protein) droplet (*PD*) storage of the proximal tubular epithelium in glomerulonephritis. Isolated lipid-containing vacuoles (→) at the cell base are also present. Necrobiotic cell (*N*), brush border (*BB*). Male, 60 years. EM (×21,000)

**Fig. 8.23.** Tubular multinuclear giant cells as sign of regeneration in a case of chronic pyelonephritis. HE (×690)

**Fig. 8.24.** Idiopathic renal karyomegaly. Numerous predominantly mononuclear cell giants are seen in the proximal tubules. Male, 32 years. HE (×310)

***2. Mononuclear Giant Cells (Cells Giants).*** These cells are far less frequently encountered than the multinuclear variety of giant cell. They are characterized by marked karyomegaly and nuclear polymorphy. These cells are found now and again in pyelo- and glomerulonephritic contracted kidneys and are an expression of impaired regeneration (see also [1068]).
The mononuclear giant cell is frequently found in kidneys which have received radiation therapy (see p. 543) as well as in those of patients who have received cytostatics, especially Busulfane®. In one case of ours in which a cytostatic was used, we also observed these cells in the pancreas, uterus and lungs (see also [1685]). Many of these giant nuclei are found occassionally associated with liver cirrhosis and hepatoma [234, 1774].
In three of our own patients (two of whom were brothers) we have observed, in 20% of the tubular cells in all parts of the nephron, mononuclear giant cells with nuclear diameters of up to 30 µm. In these cases, none of the mentioned causes could be found for this tubular karyomegaly (Fig. 8.24). All three patients suffered from chronic interstitial nephritis and came to terminal renal insufficiency during the fourth decade of life (gold, bismuth, lead or other metal poisoning was excluded by microradiographic and/or neutron activation analysis).

***3. Nuclear Inclusion Bodies.*** Nuclear inclusion bodies are of great diagnostic value in such diseases as cytomegalovirus infection (Fig. 21.7, p. 446) or lead and bismuth poisoning (Table 8.1).



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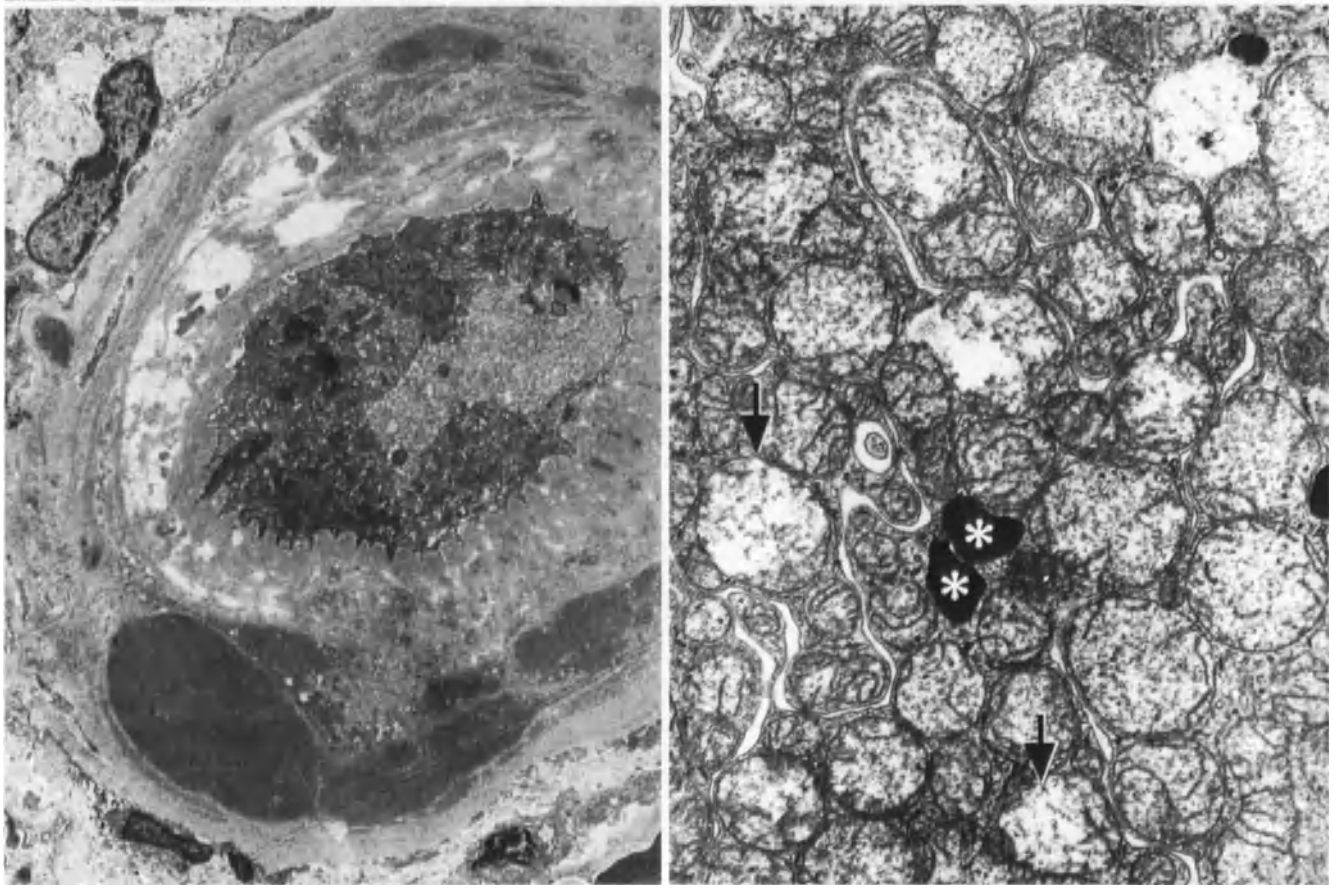

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## EM Pathology of the Renal Tubules

### Tubular BM

It appears reasonable to assume that tubular BM also is subjected to turnover as is known to occur with the BM of the glomerulus. Interstitial fibroblasts and tubular epithelial cells may be involved in the synthesis of tubular BM [263] as indicated from morphologic studies.

In tubular atrophy, there may be massive thickening of the BM through external lamellar deposition or through formation of new BM within the original BM which has become too wide (Fig. 8.25). In addition to thickening, there may also occur a thinning of the BM (Fig. 8.11) and even its complete loss with the result that tubular epithelial cells wander out into the intersitium [1808].

The cause of BM narrowing and loss is to be found either in insufficiency in epithelial or fibroblastic synthetic capability or in acceleration of tissue breakdown by collagenases released from lysosomes [1649].

In addition to thickening and thinning, the BM also demonstrates granular or vesicular inclusions (Figs. 8.25, 8.26).

These findings, as well as lamellation of tubular BM, are unspecific and independent of the underlying disease and they cannot in any way be used in the diagnosis e.g. of Alport's syndrome [521, 695].

Osmiophilic deposits, which are similar to glomerular deposits, are rarely found. But exceptionally and equally rarely very pronounced deposits (Figs. 8.27, 17.34) may be present in SLE [194]. In intramembranous GN far more massive, partly sausage-like material of high electron density is encounterd (Fig. 14.109, p. 257) which is more rare than similar material in Bowman's capsule BM, but more frequent than vascular deposits of the same character. No correlation exists between immunoglobulin deposits (usually IgM) and complement (demonstrated with IF) and the morphology of tubular BM. The only striking feature is that IF findings are especially marked in atrophic tubules and in tubules of kidney transplants (see p. 167).

### Basal Labyrinth

The pronounced interdigitation between tubular cells, which is especially marked in the proximal convoluted tubule and in the straight part of the distal tubule, becomes very obvious when cells next to each other exhibit different degrees of hydration. Dilatation of the extracellular space between the labyrinth folds is found in hypokalemia and in ischemic injury [275, 684, 1537]. But this finding requires careful interpretation since a similar phenomenon is encountered in the center of a tissue block which has been inadequately fixed during processing.

In regenerating cells following tubular necrosis, the basal labyrinth is by and large absent (Figs. 22.6, 22.7), a finding which represents the morphologic correlate of the loss of specific tubular transport function. Because of a decrease in surface area, amongst other factors, appropriate transepithelial fluid transport is no longer assured. Cells of the dilatated tubules in nephrohydrosis complicated by flow impairment or acute renal failure are also characterized by this dedifferentiation [378, 1156, 1213].

### Apical Cell Membrane

The apical cell membrane is especially prone to changes in configuration. For example, during immersion fixation, fluid flows into the cell which is not removed to the peritubular capillaries. The resulting swelling is particularly pronounced in the apical region of the cell where the cytoplasm bulges bleb-like into the lumen accompanied by loss of the brush border (Fig. 8.6, p. 121). Constriction of rather large apical cell segments results in their amputation and sheding into the lumen. This condition is frequently observed in childrens' kidneys even with optimal fixation procedure.

The brush border is practically absent from regenerating cells. Reconstruction of the brush border appears to be initiated from the lateral cell borders. The loss of brush border is regularly observed experimentally in acute disturbance of transepithelial fluid transport such as occurs with acute ischemia [1608]. Ischemic injury due to handling of the biopsy material may also be the cause for this phenomenon in renal biopsies.

◁ **Fig. 8.25.** Severe thickening of tubular BM by osmiophilic deposits with massive degradation particles in membranoproliferative GN. Male, 61 years. EM (×4700)

**Fig. 8.26.** Irregular thickening of the inner aspect of tubular BM with occasional wood chip-like structure of thickened BM and degradation granules. Endotheliomesangial GN. Male, 17 years. EM (×10,000)

**Fig. 8.27.** Extensive nodular osmiophilic deposits in an extremely thickened—and partly loosened—tubular BM in membranoproliferative GN (intramembranous GN was excluded with certainty). Male, 35 years. EM (×3000)

**Fig. 8.28.** Ischemic injury of mitochondria of proximal tubular cell. Swelling and partial dissolution of the mitochondrial cristae and matrix (→). Microbody (*). Nephroptosis. Female, 32 years. EM (×10,000)

### Mitochondria

Corresponding to the physiologic turn-over of cells and organelles, all stages of mitochondrial degeneration—culminating in their uptake into cytolysosomes (Fig. 4.22)—have been observed even in normal kidney tissue. In shock kidneys and in the early post-transplant stage (depending on the severity of ischemia) mitochondria exhibit extensive reversible or irreversible ischemic injury ([1608, 1636, 1637]; Fig. 8.28). Giant mitochondria are a rare finding in the nephrotic syndrome and their functional significance is obscure [263, 1463, 1609].
It is important to note that mitochondria are very prone to fixation artifacts for which the patchy dissolution of the matrix represents a characteristic finding (Fig. 8.28).

### Lysosomes

Lysosomes in the proximal tubule, straight segment of distal tubule and collecting ducts display a great variety of configurations [442, 1030].
Corresponding to their resorptive function, phagolysosomes are abundantly present in the proximal tubules and especially in the convoluted segment.
They contain, for example, proteins or carbohydrates (e.g., glucose, mannitol and dextran) along with water (Figs. 8.18, 8.29).
Massive increase of phagolysosomes indicates—in addition to an increased luminal supply of material—tubular injury such that extrusion or degradation of material supplied can no longer be performed adequately by the cells [313, 692].
Another reason for phagolysosome increase is its uptake of nondigestible material such as polyvinyl-pyrolidon. Additionally, a lysosomal enzyme defect resulting in a storage disease can lead to a corresponding generalized increase of lysosomes [692].
In cytolysosomes, cell constituents (e.g., rough endoplasmatic reticulum, mitochondria) are degraded (Fig. 8.29). Cytolysosomes can thus remove noncompetent structural elements from the cell. This mechanism is also operative under unfavorable environmental conditions to maintain cell viability.
Lipofuscin granules are regularly encountered in all tubular sections, and above all in collecting ducts in old patients. These granules are reportedly increased in subjects addicted to phenacetin, a statement supported by experimental findings in the rat [607, 932, 1626]. However, we could not confirm this in an autopsy series of age and sex matched groups of patients with and without phenacetin addiction. The lipofuscin granules are telolysosomes (Fig. 4.23, see p. 36) in which nondigestible material from phago- and cytolysosomes is stored.

### Lipid Droplets

Fine lipid droplets are often seen in atrophic tubules and are much more pronounced in so-called lipoid nephrosis and lead to the formation of foam cells (see Fig. 8.30). In addition to hyperlipidemia, cell injury with concomitant lipid phanerosis may be responsible for the condition (see p. 132). The lipid droplets lay in the ground cytoplasm, are sharply delineated and are not enveloped by membrane (for lipid droplets see Figs. 8.19, 8.20, 8.31, p. 132).

### Endoplasmatic Reticulum

Vacuolization of rough endoplasmatic reticulum is the earliest sign of ischemic injury [1537, 1635] (Fig. 8.32). Later on, the characteristic mitochondrial changes develop. Regenerating cells are characterized by an increase in rough endoplasmatic reticulum and, mainly, in polyribosomes (Fig. 24.9, p. 492). Increase in smooth endoplasmatic reticulum, seldom encountered in human renal tubules, probably represents cellular adaptive activity whose functional significance has even eluded experimentation [1334, 1639].

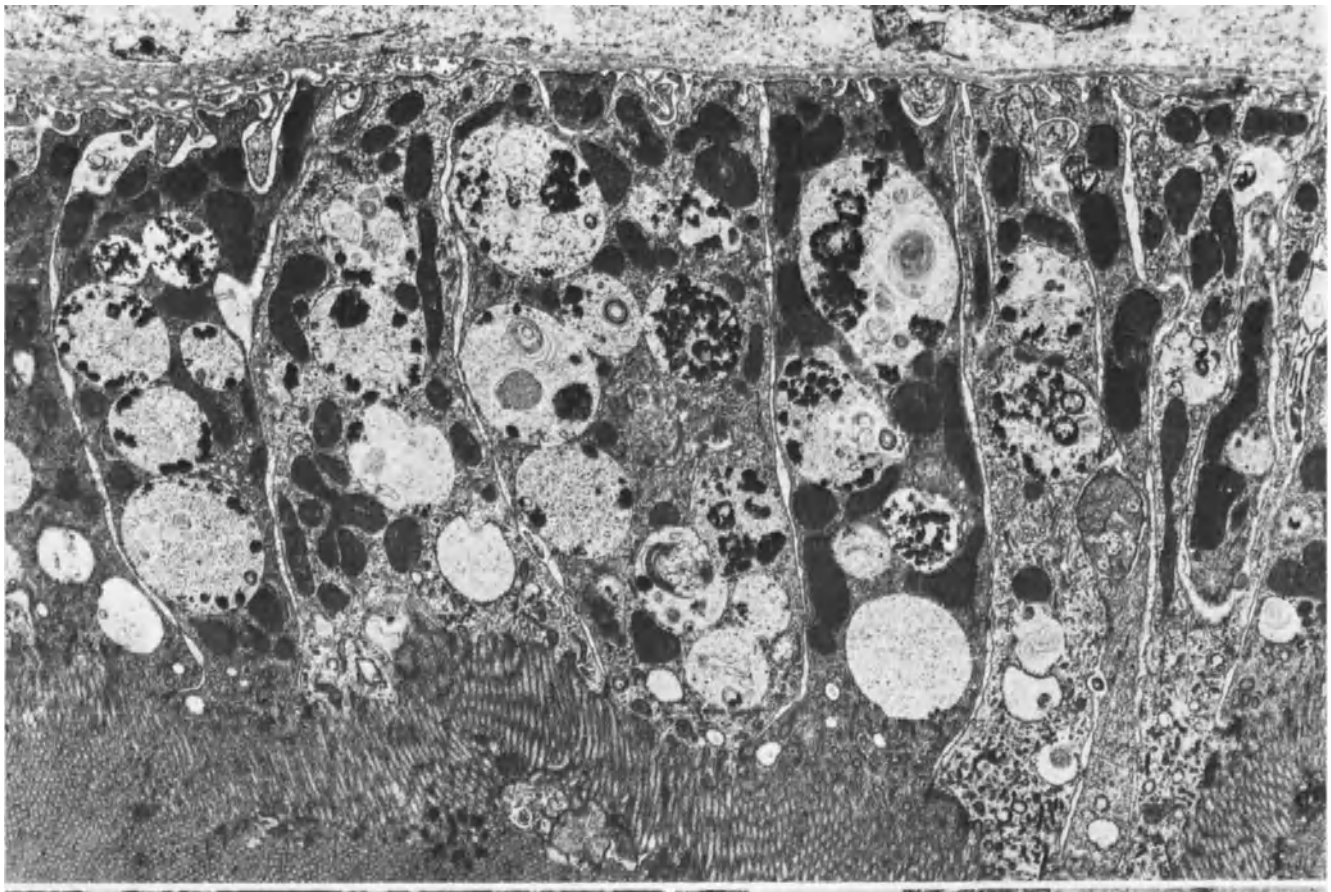
### Nucleus

The most frequent EM nuclear change is degeneration attendant on cell death, which progresses from initial chromatin clumping to karyolysis or karyorrhexis (Figs. 8.2, 8.3). As contrasted to the oval form of the nucleus at rest, the nucleus in regenerating tubules demonstrates pronounced increase in surface area which is achieved by lobulation (Fig. 8.31).
For nuclear inclusion bodies and giant cells with one or more nuclei, see Table 8.1.

**Fig. 8.29.** Proximal tubular cell with very numerous auto-(cyto-) and hetero-(phago-)lysosomes in a 5-month-old kidney transplant with pyelonephritis. Male, 47 years. EM (×6500) ▷

**Fig. 8.30.** 'Interstitial' foam cells in renal amyloidosis. Foam cells are partly surrounded by a clearly recognizable BM (→). Male, 22 years. PASM (×800)

**Fig. 8.31.** Tubular foam cell with numerous cytoplasmic lipid vacuoles, which are occasionally surrounded by a membrane, in a case of membranoproliferative GN. Male, 57 years. EM (×8200)



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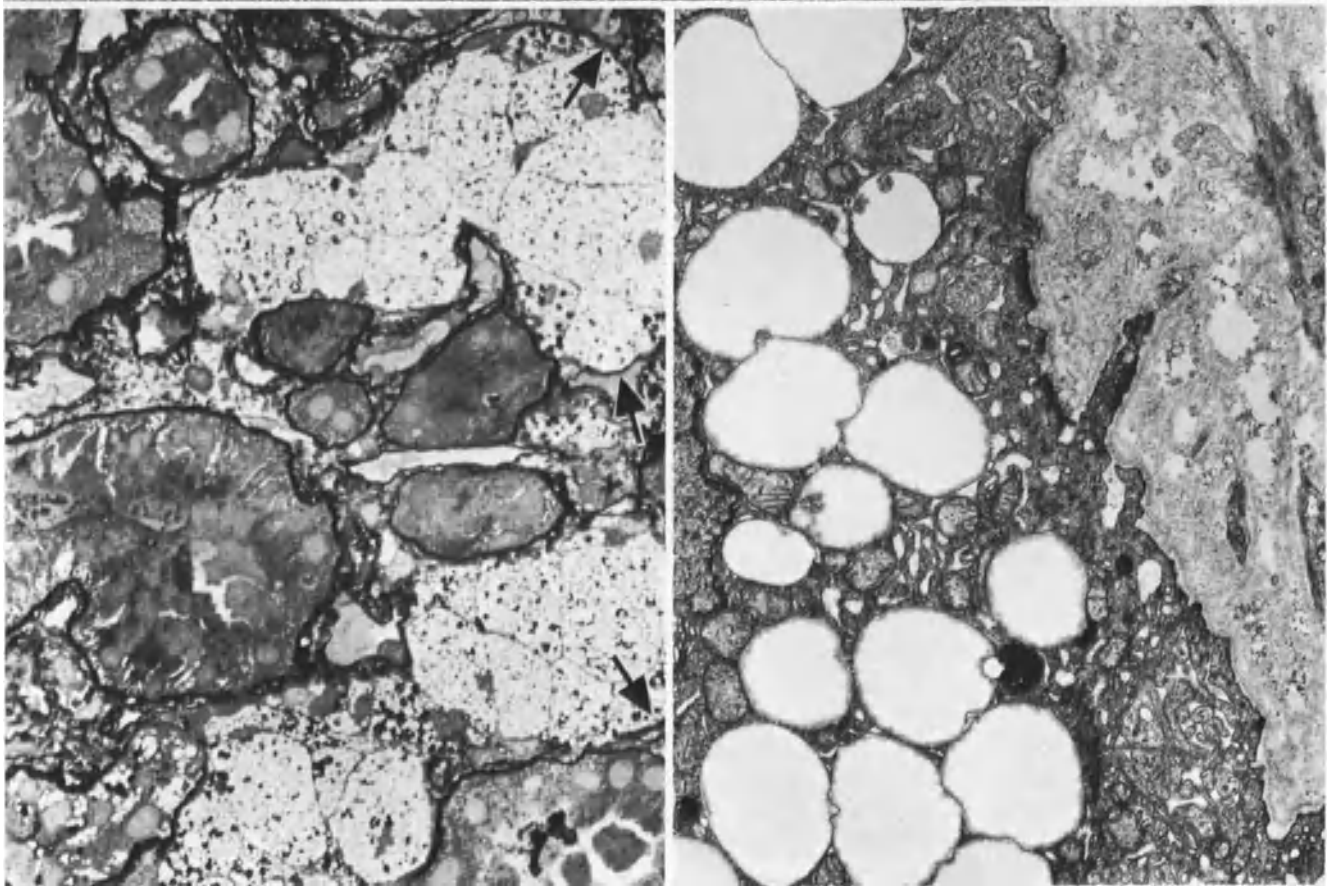


8.30
8.31

## Casts

The diagnostic value of casts in renal biopsy is rather small since their morphology tends to be the same irrespective of the underlying disease. The majority of casts are located in the distal tubules and collecting ducts of the medulla.

### 'Hyaline' Casts

The above-mentioned limiting factors are especially valid for hyaline casts which are also—rarely—found in normal kidney. IF examination indicates that hyaline casts—the frequency of which is similar in all nephropathies—(see for frequency in IF material Fig. 11.17) are composed of plasma proteins (see p. 167) and/or tubular mucoprotein [1062, 1403]. The latter may be especially, but not always, true for the hyaline casts in pseudostruma foci in chronic pyelopnephritis (Fig. 8.12) since the involved glomeruli are obsolescent. An example of the contrary are casts in plasmocytoma (see p. 404).

### Granular Casts/Chromoprotein Casts

With the exception of chromoprotein casts, granular casts do not throw any light on the nature of the underlying disease. With the HE stain, chromoprotein casts have a unique brown color and are positive to the peroxidase test (benzidine reaction). With EM, they appear as clumped, very electron-dense material (Fig. 8.33). The tubular lumen often simultaneously contains granular (lysosomal) chromoprotein masses (Fig. 8.34). Their occurrence points to hemolysis or myolysis in connection with shock or transplant rejection [1791].

### Cell Casts

In tubular necrosis, the detached necrotic tubular cells are pushed together in the distal tubule and are usually recognizable as such. In advanced necrosis, the decaying tubular cells cannot be differentiated from the granular casts consisting of aggregated proteins. With EM, however cellular origin can still be discerned from the presence of organelle fragments (Fig. 8.34).

Leukocyte casts are most frequently found in acute pyelonephritis. After immigration from peritubular capillaries, the neutrophilic leukocytes aggregate into casts in the distal regions of the nephrons. Leukocyte casts also are formed in severe glomerular injury, e.g., extracapillary accentuated GN with severe necrosis. Thus, they are not of pathognomonic significance for the diagnosis of pyelonephritis in the absence of significant bacteriuria.

Erythrocyte casts are usually indicative of severe glomerular injury and they are often accompanied by fibrin, especially so in acute renal transplant rejection (Fig. 8.35). It is noted that only an occassional erythrocyte is ever seen actually wandering through the glomerular BM [229]. This discrepancy is explicable in terms of the rapid passing of erythrocytes through the BM gel as well as in terms of probability—which is very small—of seeing the passage since a large BM surface area exists per glomerulus (ca. 0.5 $mm^2$) compared with the maximal surface area of an erythrocyte (ca. 50 $\mu m^2$). Furthermore, the erythrocyte is deformed as it passes the capillary loop wall. This means that the required area for erythrocyte transit through the BM becomes correspondingly smaller and the probability of viewing the actual passage even less.

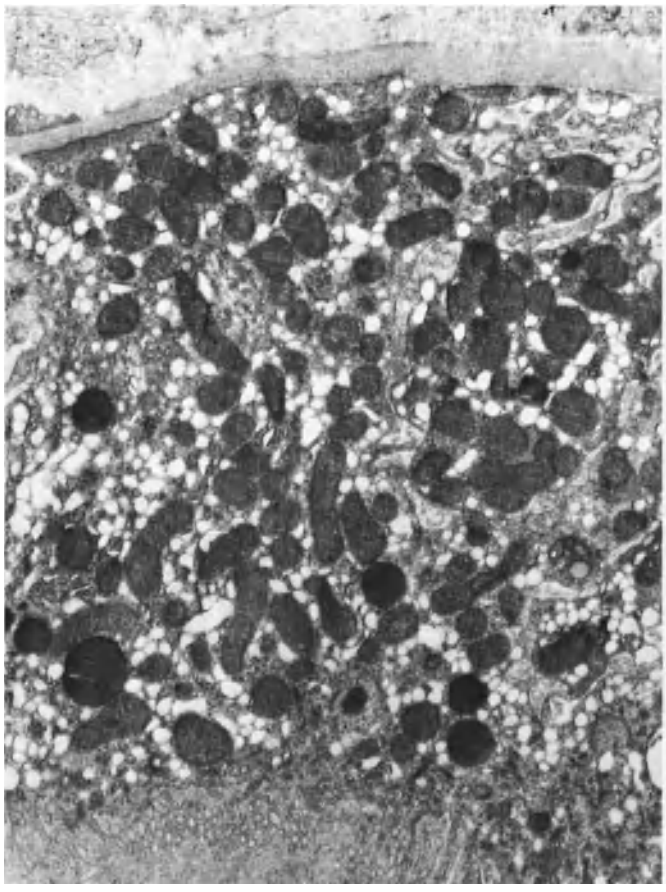
### Other Casts

Calcium casts arise either by intratubular precipitation of calcium salts or by agglomeration of detached metastatic or dystrophic calcified tubular epithelial cells into casts (see p. 484).

Endogenous metabolic products (e.g., bilirubin, uric acid, oxalate, cystine) or exogenous substances (e.g., sulfonamides administered therapeutically) can precipitate intratubularly and go on to cast formation which may give rise to tubular obstruction. Such precipitation can only occur when the solubility product is exceeded. It may occur either in the presence of high concentration or of pH changes which reduce the solubility of the substance in question. Since urine concentration and pH change occur in the renal medulla, the distal tubules and collecting ducts are the structures of predilection for cast formation and it is from these structures that the casts are flushed out with the urine to become accessible for clinical examination. Crystalline and plasmocytoma casts, however, may remain in the tubules and, with continuous renal filtration, lead to nephrohydrosis in the proximal part of the implicated nephron.

### Addendum: Lymph Vessel Casts

Especially in urine retention (hydronephrosis), the kidneys frequently exhibit fibrillar masses in the perivascular lymph vessels which are strongly PAS positive and which can fully obstruct the vessel lumen (Fig. 8.36). Additionally, analogous masses may be found in the slightly infiltrated interstitium where they are only partially surrounded by endothelial cells (Fig. 8.37).



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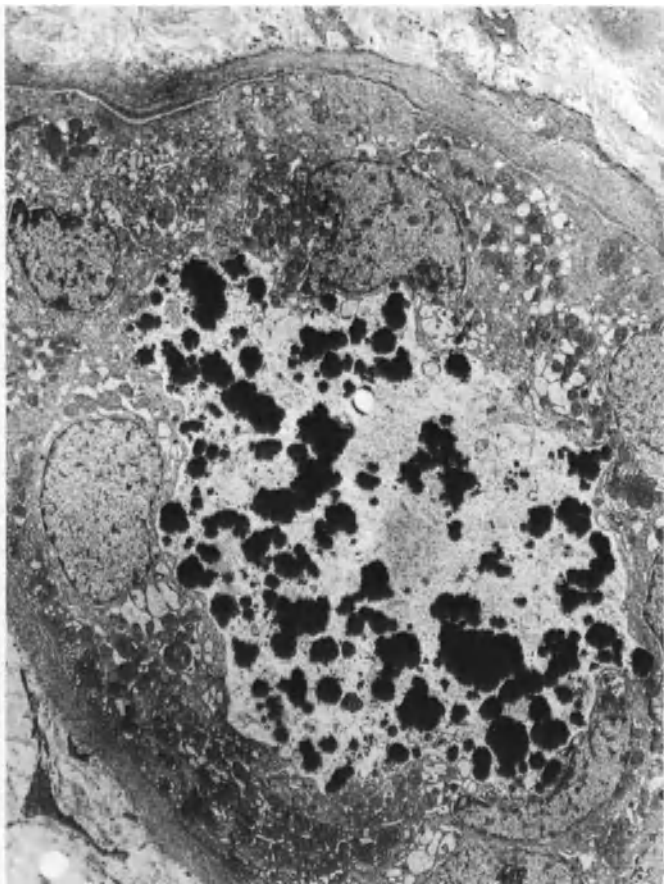

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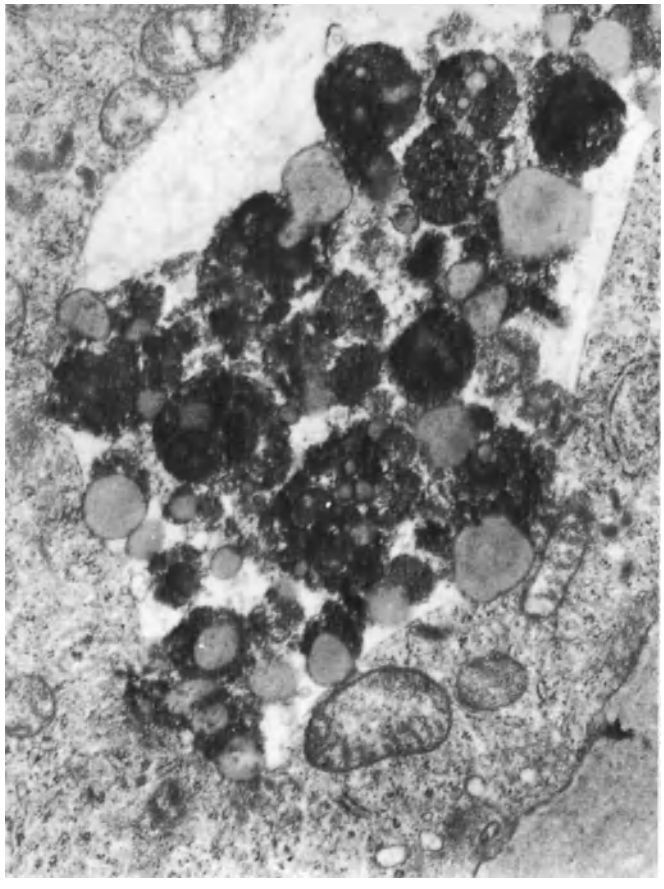
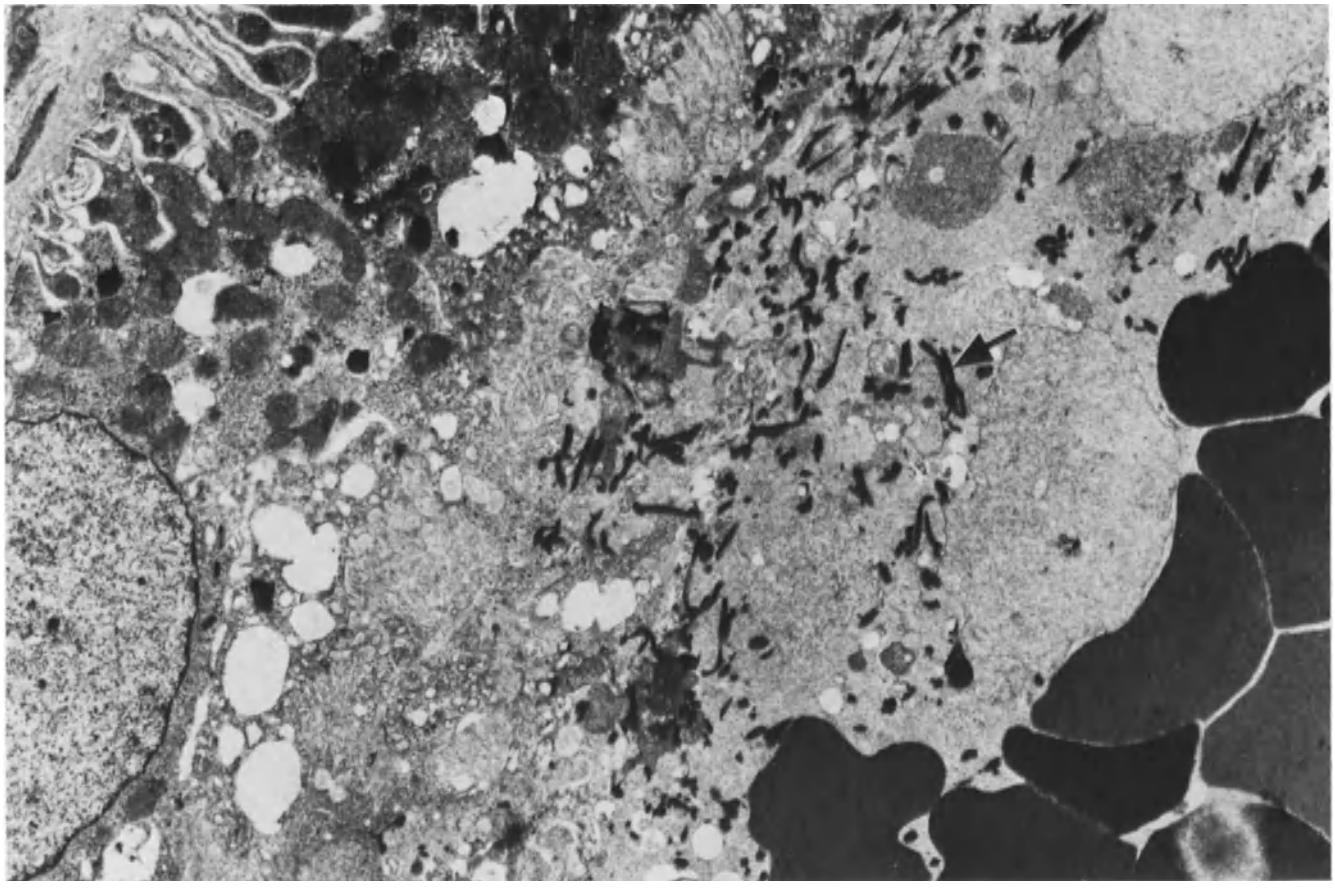


8.34

**Fig. 8.32.** Prominent small cystoid widening of endoplamatic reticulum in proximal tubular cells in nephroptosis. Female, 22 years. EM (×8700)

**Fig. 8.33.** Numerous chromoprotein casts in tubular lumen in a 19-day-old transplant undergoing acute rejection. Male, 22 years. EM (×2600)

**Fig. 8.34.** Granular lysosomal chromoprotein and other protein masses (probably arising from necrotic cells) in the tubular lumen after carbon tetrachloride poisoning. Female, 26 years. EM (×18,000)



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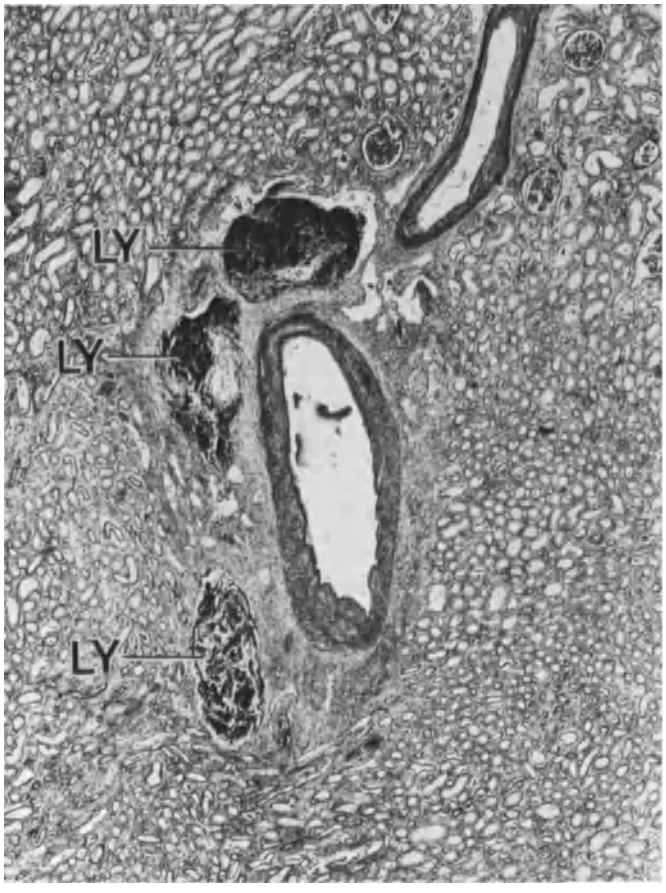
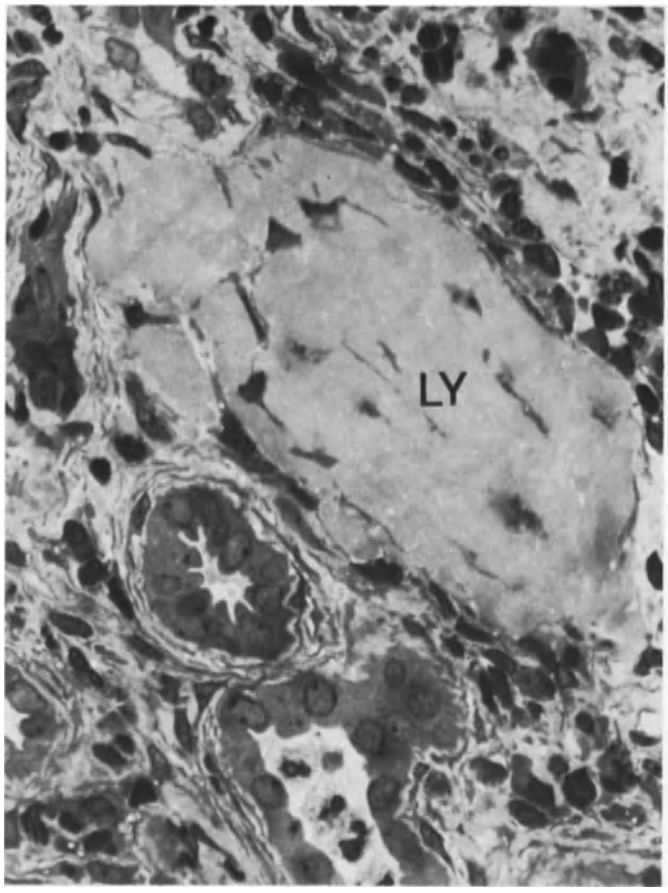


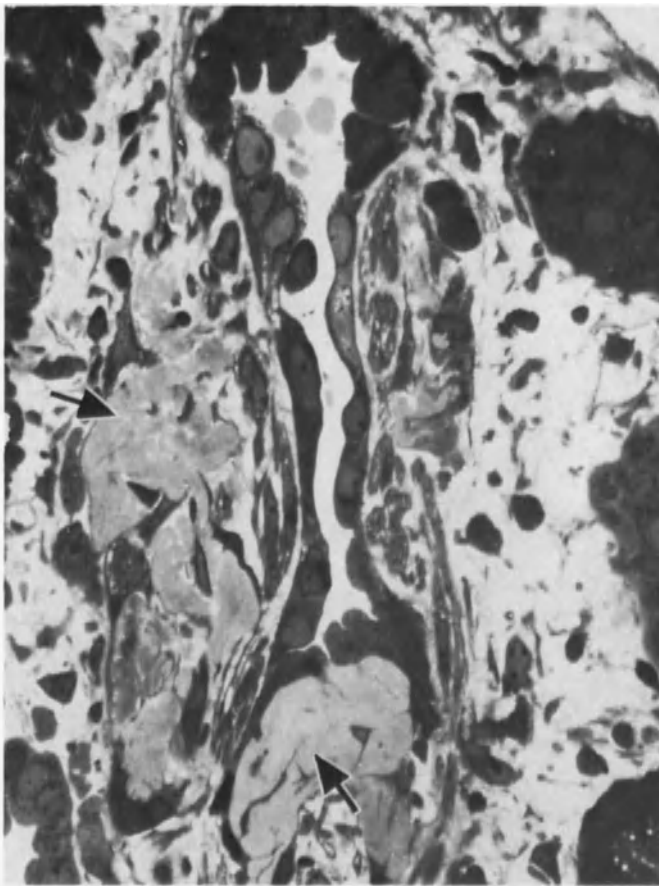

8.36

**Fig. 8.35.** Fibrin strands (→) in tubular lumen in a 20-month-old transplant without signs of acute rejection. Erythrocytes in lumen probably represent an artifact from needle puncture. Male, 32 years. EM (× 5950)

**Fig. 8.36.** Extensive periarterial lymph vessel casts (*Ly*) in nephrohydrosis due to occlusion of the ureter. Female, 52 years. PAS (× 27)

8.37
8.38



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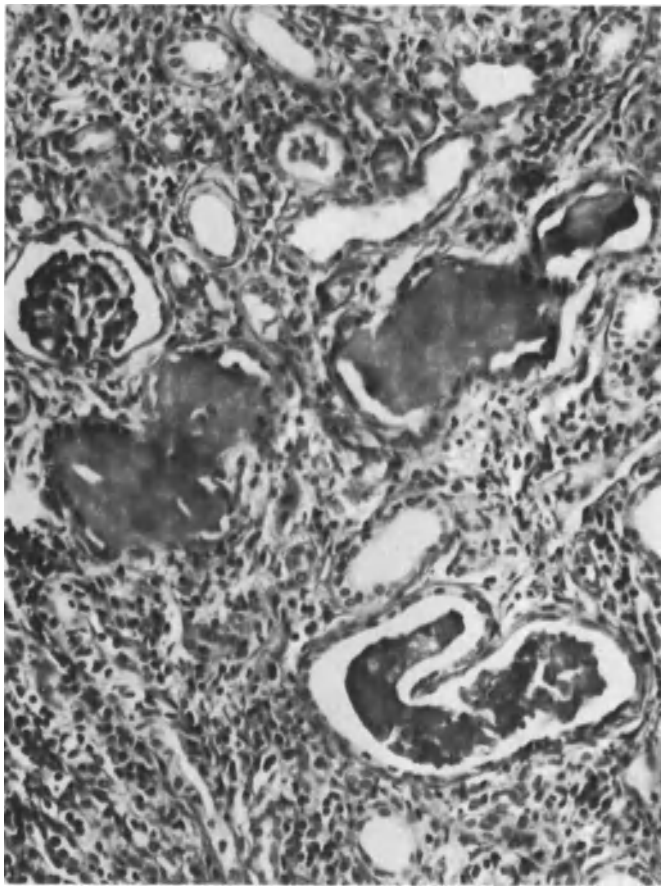


**Fig. 8.37.** Lymph vessel cast (*Ly*) partially permeated by phagocytes is surrounded by an inflammatory infiltrate in a case of ureterocele. Female, 10 months. Toluidine blue, semi-thin section (× 500)

**Fig. 8.38.** Lymph vessel cast (→) is seen pushing the tubular epithelium foreward in a 5-week-old renal transplant with ureter necrosis. Male, 45 years. Toluidine blue, semi-thin section (× 800)

**Fig. 8.39.** Three lymph vessel casts are present in the tubules. Same case as in Figure 8.37. Female, 10 months. PAS (× 160)

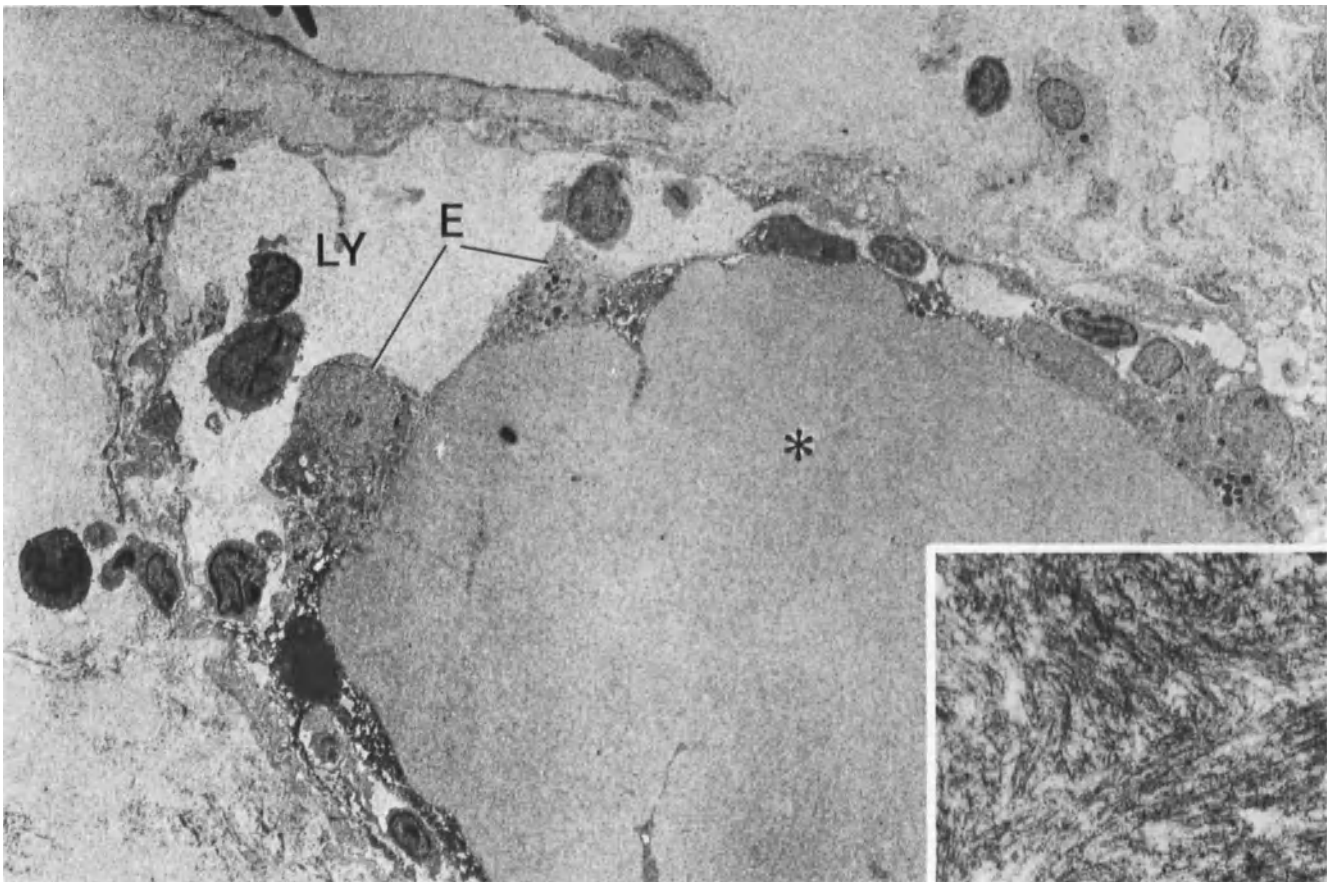



**Fig. 8.40.** Lymph vessel cast (*) probably covered with endothelium (*E*) in the wall of an interstitial lymph vessel (*Ly*); 18-month-old transplant. Female, 47 years. EM (× 1300). Inset: fibrillar structure of lymph vessel cast EM (× 32,000)

This latter situation is often observed in nondestructive acute interstitial nephritis and occassionally in pyelonephritis. The fibrillar masses push into the tubular lumen initially by separating the tubular epithelial cells (Figs. 8.38) and later after their total anoxic destruction so that ultimately the majority of the lymph vessel casts appear to lie within the tubular lumen (Fig. 8.39).

We do not feel that sufficient information is available to determine whether or not true venous thrombi also penetrate the tubuli in this manner (tubulovenous anastomosis). In any case, our EM studies always reveal that only lymph vessels are in contact with the fibrillar masses where severe injury of the tubular epithelium is strikingly apparent.

With high magnification, a very finely fibrillar fretwork is clearly recognizable in the masses (Fig. 8.40). The fibrils certainly do not consist of collagen nor of typical fibrin.

The significance of these still highly controversial masses is, most likely, that they indicate extra- or intrarenal urine retention during which there occurs retrograde lymph flow (to the cortex instead of the hilus). It can be assumed that retrograde flow leads to overloading of the extremely widened lymph vessels, and probably to stasis.

Although lymph vessel casts may be encountered in intra- as well as in extrarenal urine retention and are rare in kidney biopsy, their presence should however always give rise to consideration of extrarenal urinary retention. In our experience, lymph casts were the only sign of clinically unknown cases of ureteral obstruction (e.g., retroperitoneal fibrosis, ureteral necrosis in kidney transplants).

# 9. Histopathology of the Renal Interstitium

Interstitial changes are often treated in a cursory fashion in renal biopsy evaluation. This is to be discouraged since findings in the interstitium such as edema, fibrosis, and inflammatory infiltration often provide important information.

In more or less diffuse widening of the interstitium, edema, sclerosis and fibrosis must be rigorously differentiated from each other. In EM study, it is important to bear in mind that, depending on the osmolarity of the fixation media, edema may be simulated or disappear [1029]. It is also noted that the interstitial connective tissue increases with age and in amount towards the papilla. Finally, we wish to recall that tubules and glomeruli are found to lie further apart in all forms of interstitial widening.

## Edema

Edema (Fig. 9.1 a) is characterized by the pale staining of the interstitium and by the extremely loose arrangement of very tenuous, usually argyrophilic fibers. Edema occurs in acute interstitial nephritis, anoxemia (shock, acute infarcts), acute interstitial transplant rejection, thrombosis of the renal veins, and in the immediate vicinity of acute inflammatory pyelonephritic foci.

## Sclerosis

As contrasted to edema, the fiber network in sclerosis is exceedingly coarse, although the number of fibrocyte nuclei is scarcely increased (Fig. 9.1 b). The fibers stain red with van Gieson and consist, accordingly, of collagen (note difference in designation with respect to mesangial changes, see p. 48). In most cases, tubular BM becomes associatedly thickened.

Interstitial sclerosis may be viewed as a sequel to chronic edema. It occurs chiefly with persistent anoxia but is rather infrequent in the anoxemia occurring with partial ischemic contracted kidney (subinfarct; [1808]). We have noted slight interstitial sclerosis in the chronically congested kidney.

Severe interstitial sclerosis is a highly characteristic finding in chronic urinary edema and in nondestructive chronic interstitial nephritis sui generis or accompanying GN [1782]. Very small intertubular sectors of such severe sclerosis are now and again encountered in idiopathic glomerular minimal change, and they may be the result of prior glomerular inflammation.

## Fibrosis

Fibrosis (Fig. 9.1 c) is the terminal phase of a destructive, e.g., granulomatous inflammation. Tubuli in the implicated area are always destroyed. Occassionally, residues of broken-down tubular BM can be seen (especially with PASM stain and EM).

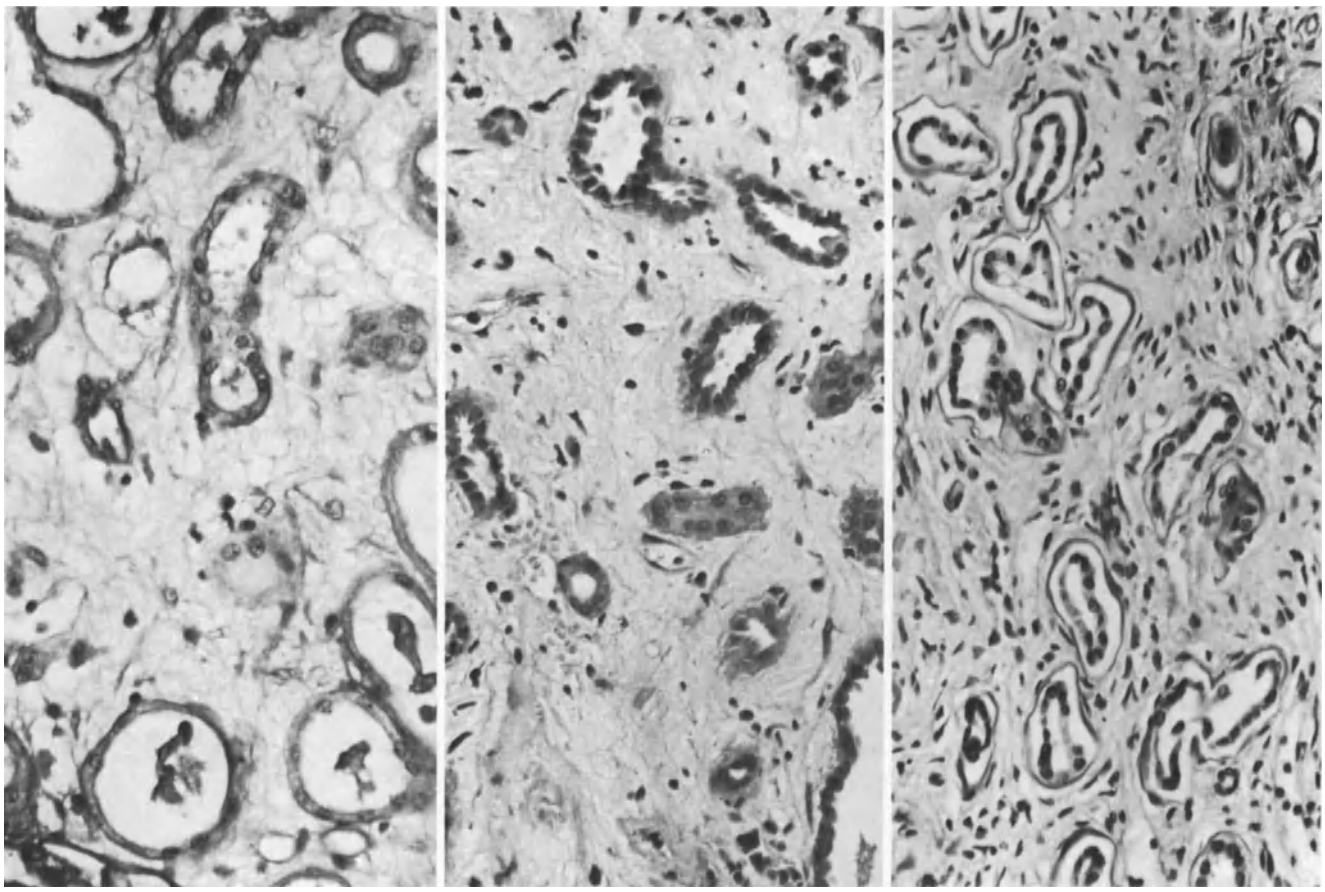
The interstitial fiber network stains very strongly red with van Gieson and the number of fibers and fibrocyte nuclei is considerably increased with respect to normal and sclerotic states. The majority of fibrotic foci evidence lymphohistiocytic infiltrates.

## Inflammatory Infiltrates

The character and composition of interstitial inflammatory infiltrates are governed by the primary disease and its phase. For frequency and composition see Figure 9.2, and for individual cellular constituents of the infiltrates, see Figures 9.3, to 9.6.

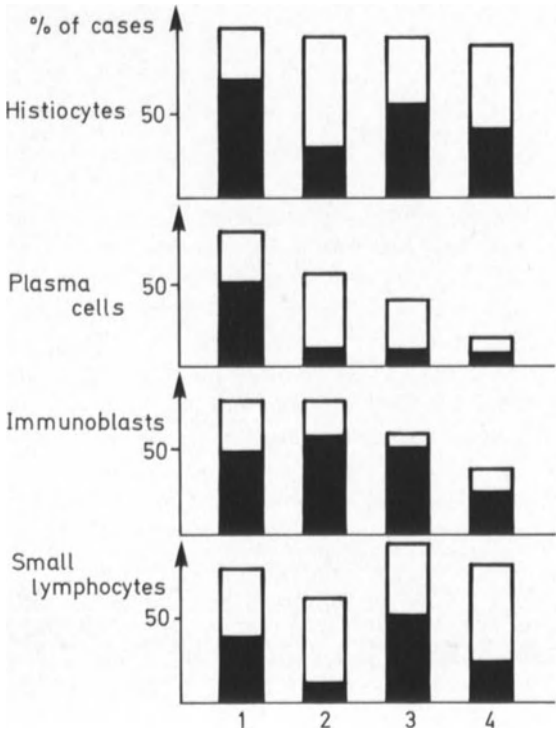
In acute pyelonephritis, polymorphonuclear leukocytes usually predominate, while in the chronic cases as well as in renal scar tissue, small lymphocytes constitute the major cellular element (Fig. 9.7).

In acute nondestructive interstitial nephritis there occurs a mixture of histiocytes, plasma cells, large and small lymphocytes and immunoblasts all with about the same frequency (Figs. 9.8, 9.2). In renal transplants, on the other hand (Fig. 9.9), the infiltrate consists chiefly of large lymphocytes and immunoblasts with only a few scattered small lymphocytes and plasma cells (Fig. 9.2). The two conditions cannot, however, be differentiated



9.1a
9.1b
9.1c

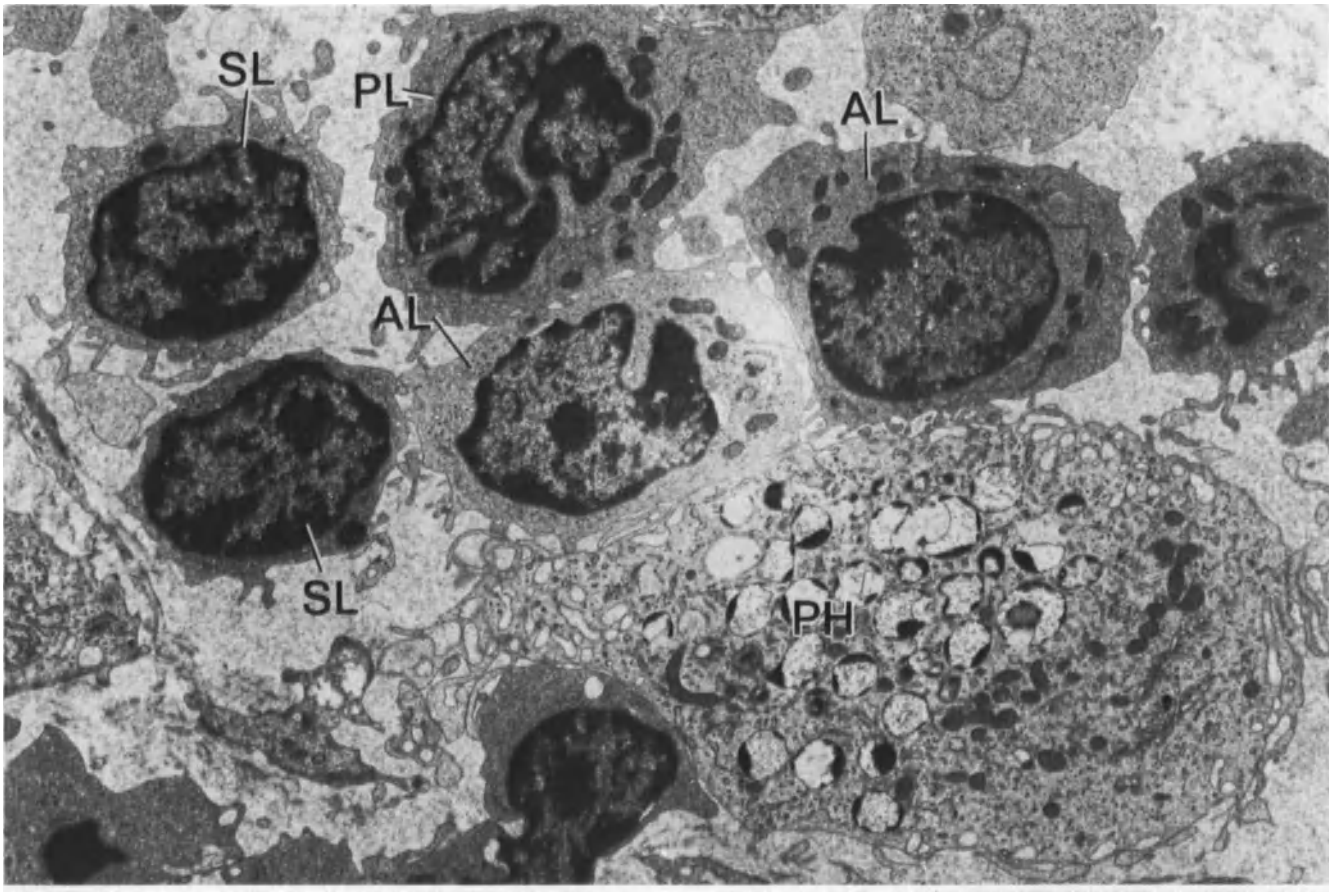
**Fig. 9.1a–c.** Histological comparison of (a) interstitial edema, (b) interstitial sclerosis and (c) interstitial fibrosis. In (a) considerable amount of edema fluid is present in the interstitium which demonstrates a uniformly loose, delicate fiber network. In (b) the fiber network is coarse and irregular and evidences very few nuclei. In (c) coarse, parallel-oriented fibers with numerous nuclei are seen. PAS ( × 532)




◁ **Fig. 9.2.** Histogram: Composition of inflammatory infiltrates in various renal diseases as seen with EM. (1) acute interstitial nephritis ($n=10$); (2) kidney transplant ($n=43$); (3) chronic pyelonephritis ($n=21$); (4) concomitant interstitial inflammation in GN ($n=81$). Total height of the columns gives relative number of positive cases, while black columns indicate moderately severe to severe findings. Under the designation "immunoblasts", activated large lymphocytes are also included

**Fig. 9.3.** Twelve-day-old transplant undergoing acute rejection. ▷ Foam cell of histiocytic origin in the interstitium (*PH*); small lymphocyte (*SL*); polymorphonuclear leucocyte (*PL*); activated lymphocyte (*AL*). Male, 34 years. EM ( × 6300)

**Fig. 9.4.** Seven-day-old transplant undergoing acute rejection. Interstitial edema and infiltrates: phagocyte (*PH*); activated lymphocyte (*AL*); obvious interstitial edema is present. Male, 42 years. EM ( × 11,200)

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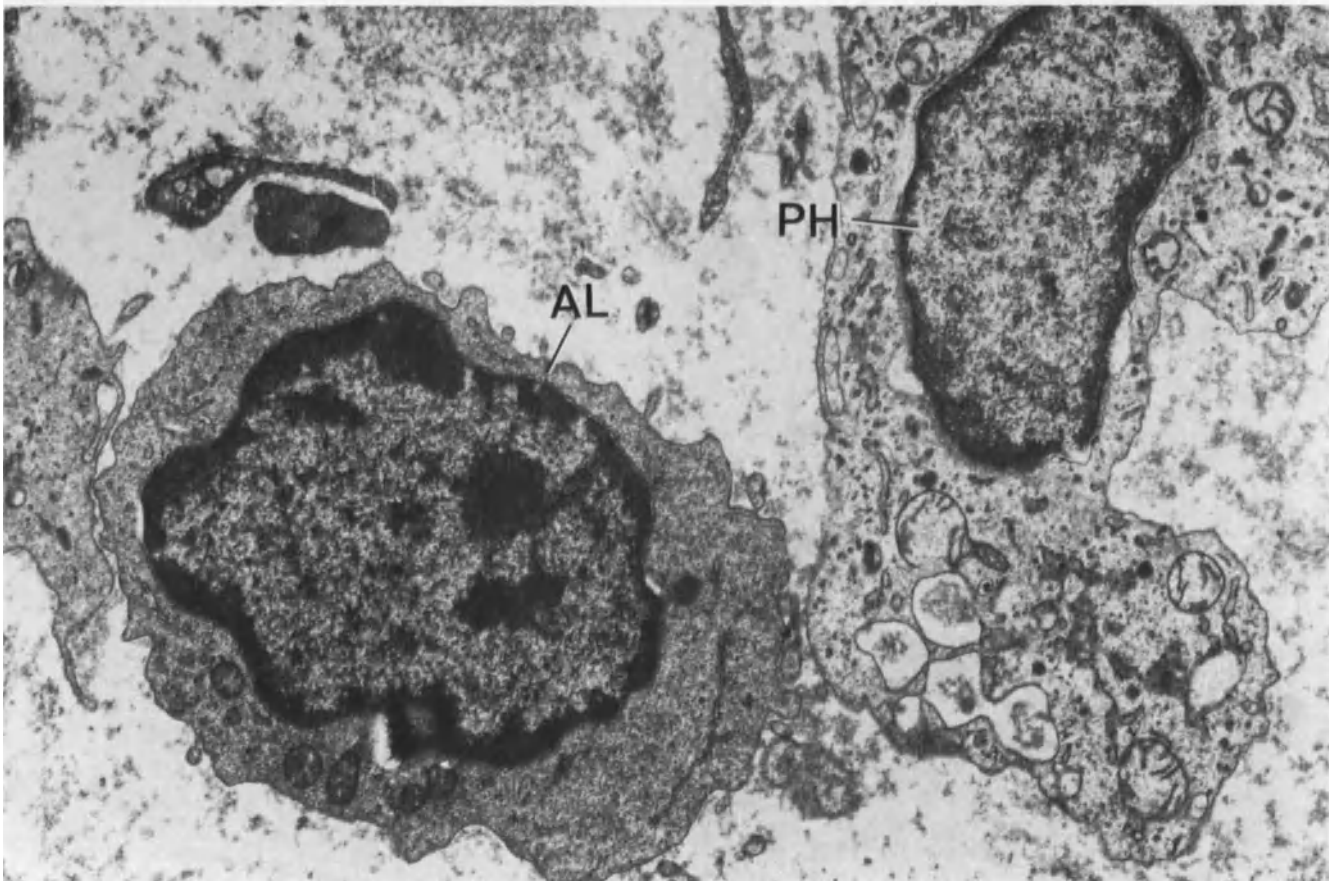


9.4

on the basis of the cellular composition of the infiltrates alone.

The accompanying interstitial nephritis in "active" GN which demonstrates very polymorphic infiltrates is not clearly differentiable from chronic nondestructive interstitial nephritis (Figs. 9.2, 9.10) except by the smaller amount of plasma cells in GN.

In general, the presence of large lymphocytes as well as immunoblasts and plasma cells strongly suggests the existence of an active inflammatory immunologic process while the occurrence of mainly small lymphocytes is usually suggestive that they are components of residual infiltrates of a 'dormant' inflammation.

Pyelonephiritis in infants and small children often leads to large-scale development of lymph follicles which must not be falsely interpreted as a malformation even if one is confronted with a dysplastic kidney with secondary pyelonephritis (Fig. 9.11). Follicular centers are characterized by dividing germinocytes and germinoblasts which have a broad cytoplasm rich in polyribosomes, mitochondria and Golgi organelles (Figs. 9.13, 9.14).

## Foam Cells

Interstitial foam cells are found in transplants (Fig. 9.9), in xanthomatous pyelonephritis, and, more rarely, in the various forms of chronic GN (Fig. 9.12) and in Alport's syndrome. With EM or PASM staining, it can often be demonstrated that the foam cells arranged in clusters are not of histiocytic but often of epithelial (tubular) origin as shown by the presence of a surronding BM (Figs. 9.12, 8.30, 8.31; [1353], see p. 125).

## Deposits

We have observed massive interstitial fibrin deposits in two cases of Wegener's disease, in one case each of acute pyelonephritis and acute interstitial nephritis (Fig. 20.10) as well as in two cases of severe hypertension, one of which was malignant nephrosclerosis. With IF, fibrin (-ogen) can be often demonstrated and especially in transplants (for the frequency of fibrin (-ogen) and immunoglobulin deposits see Fig. 11.15).

More rarely occurring interstitial deposits such as urate crystals, calcium, amyloid and cystine crystals are treated in other sections of the text.

**Fig. 9.5.** Immunoblast in the interstitium with bulky polyribosomes. Same case as in Figure 9.4. Male, 42 years. EM (×11,200) ▷

**Fig. 9.6.** Part of activated histiocyte with strikingly prominent organelles. Same case as in Figure 9.4. Male, 42 years. EM (×14,000)

**Fig. 9.7.** Interstitial infiltrate in chronic pyelonephritis consisting mainly of small and middle-sized lymphocytes and a few scattered phagocytes (*PH*) but no immunoblasts. Severe edema is present. Female, 42 years. EM (×4700)

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**Fig. 9.8.** Acute interstitial nephritis. Activated lymphocyte (*AL*); small and middle-sized lymphocyte (*SL*); phagocyte (*PH*). Female, 59 years. EM (×6500)

**Fig. 9.9.** Twelve-day-old transplant with acute interstitial rejection; small lymphocyte (*SL*); plasmoblast (*); plasma cell (*PS*); phagocyte (*PH*); foam cell of histiocytic origin (*F*). Same case as in Figure 9.3. Male, 34 years. EM (×5500)

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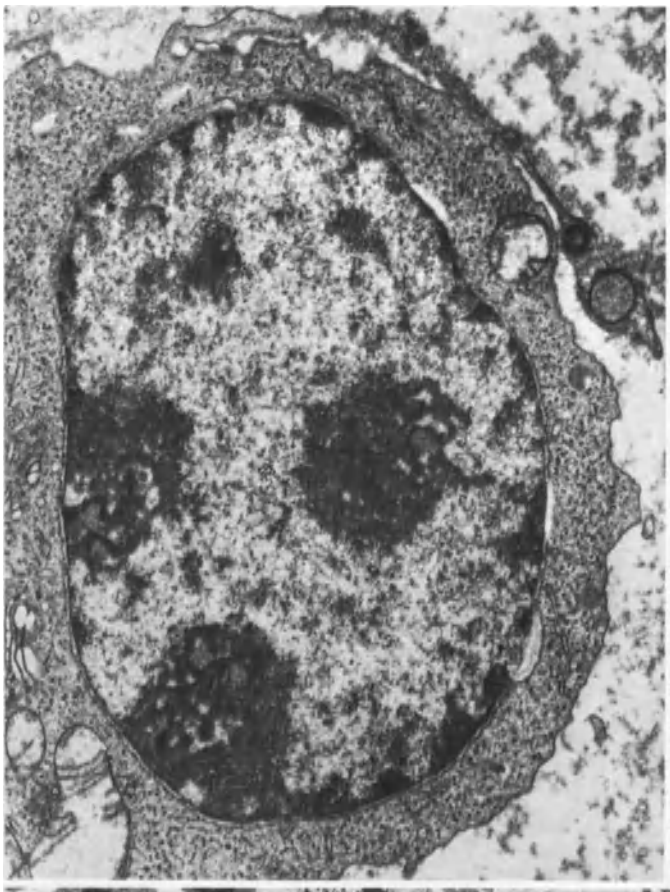
**Fig. 9.10.** Interstitial accompanying nephritis in membranoproliferative GN consisting of a mixture of numerous activated lymphocytes, isolated plasma cells and moderately numerous phagocytes. This is not a specific finding. Female, 42 years. EM (×3700)

**Fig. 9.11.** Dysplastic focus with secondary pyelonephritis in nephrectomy specimen: cartilage (*); lymph follicle (*LY*); glomeruli (*G*). Male, 13 years. HE (×130)

**Fig. 9.12.** 'Interstitial' foam cell under LM which, under EM is seen to be of tubular origin as indicated by the surrounding BM. Proliferative FGN in SLE. Male, 48 years. EM (×3100)



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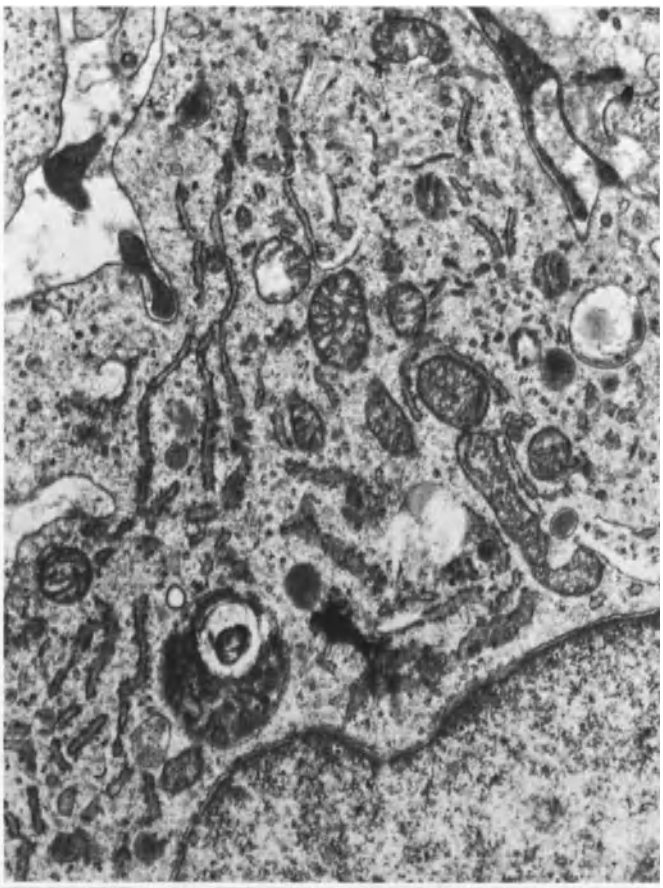

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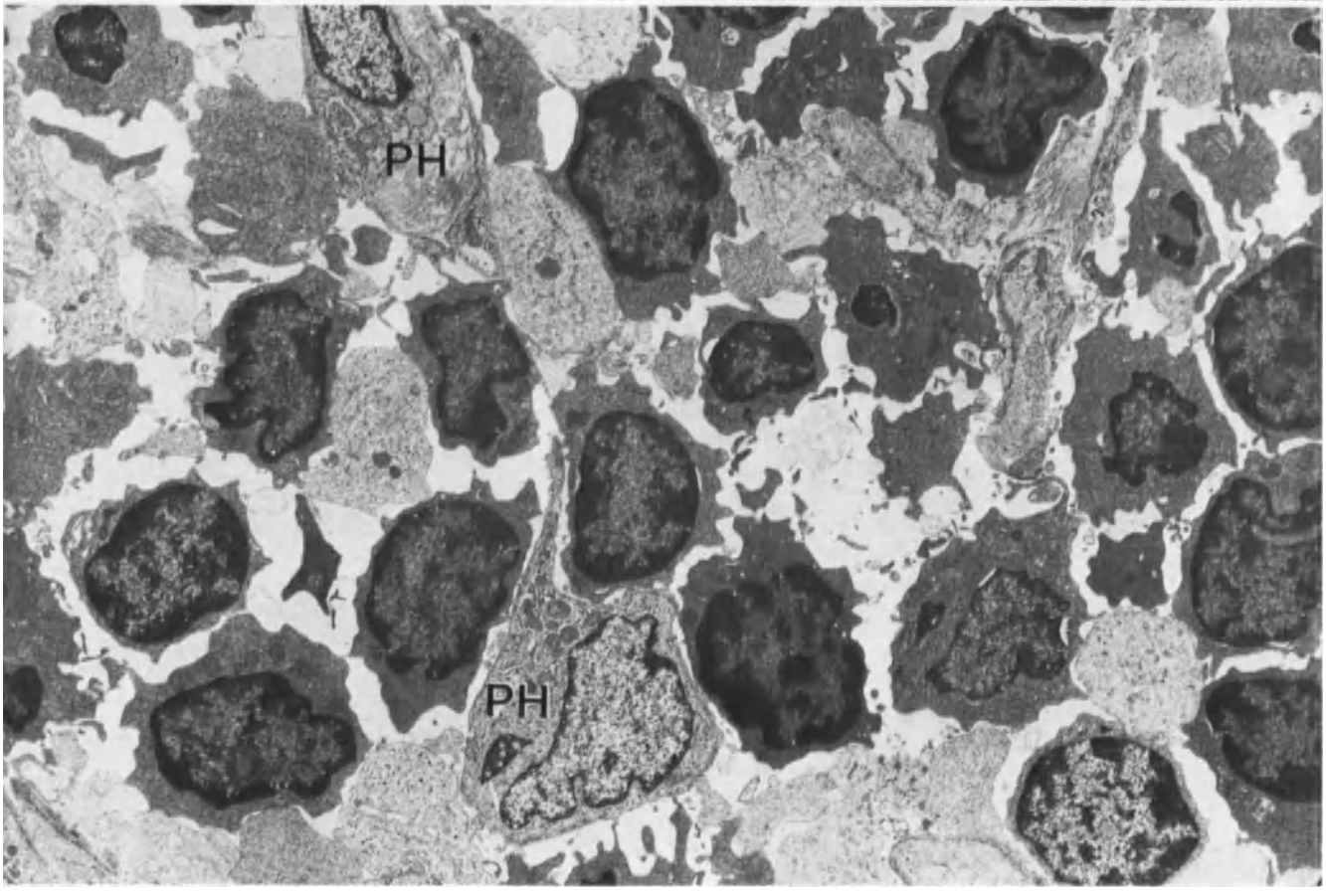


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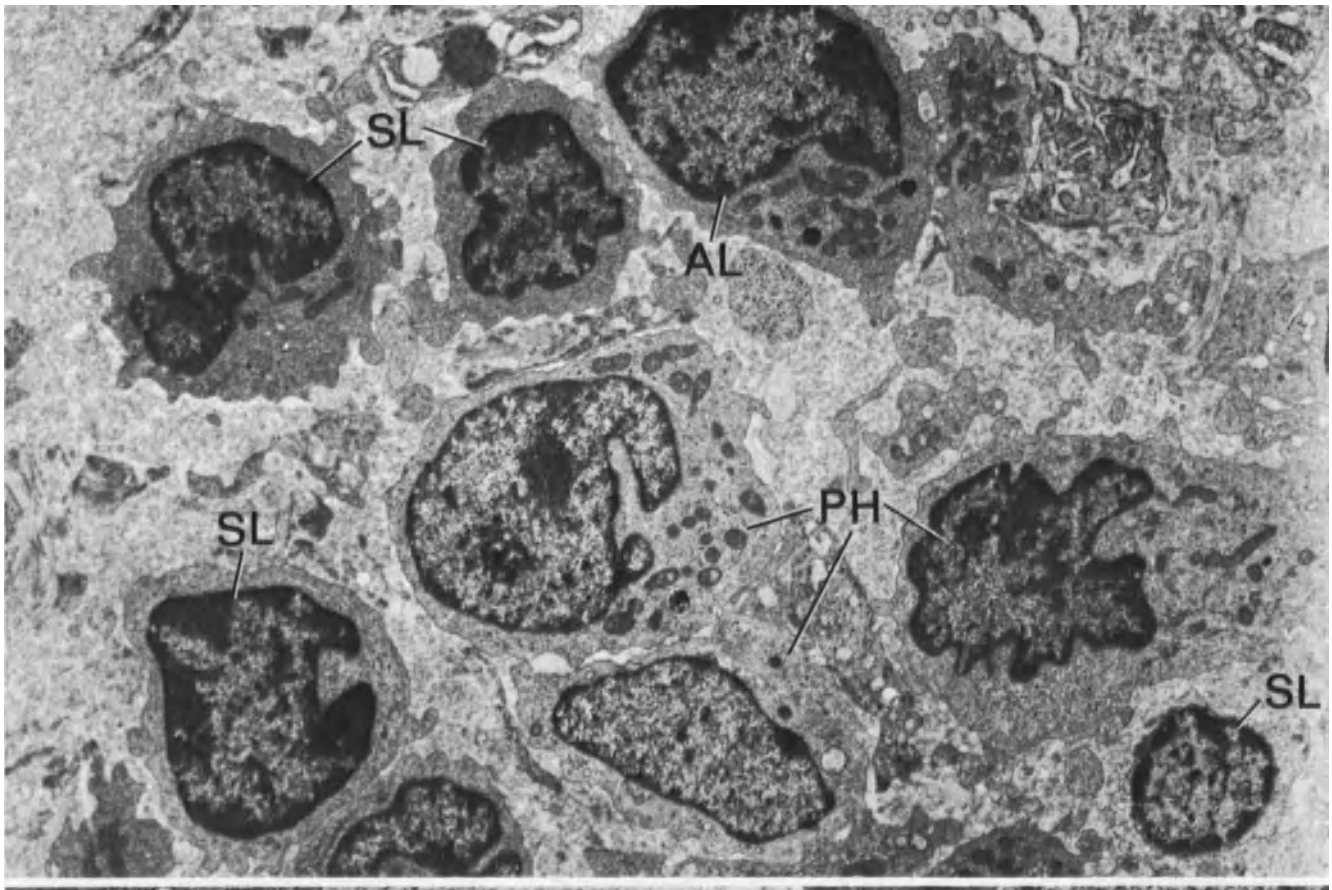


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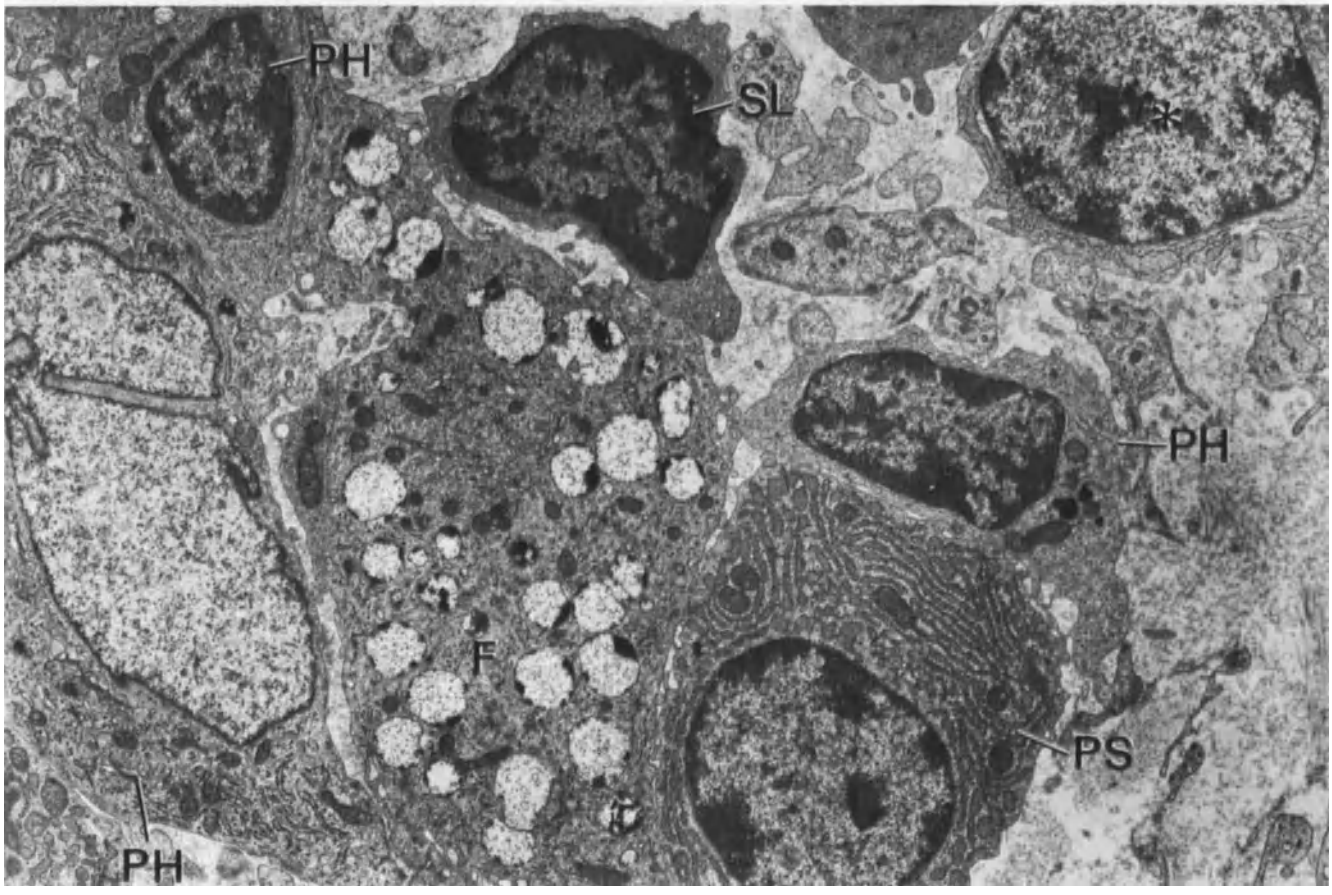


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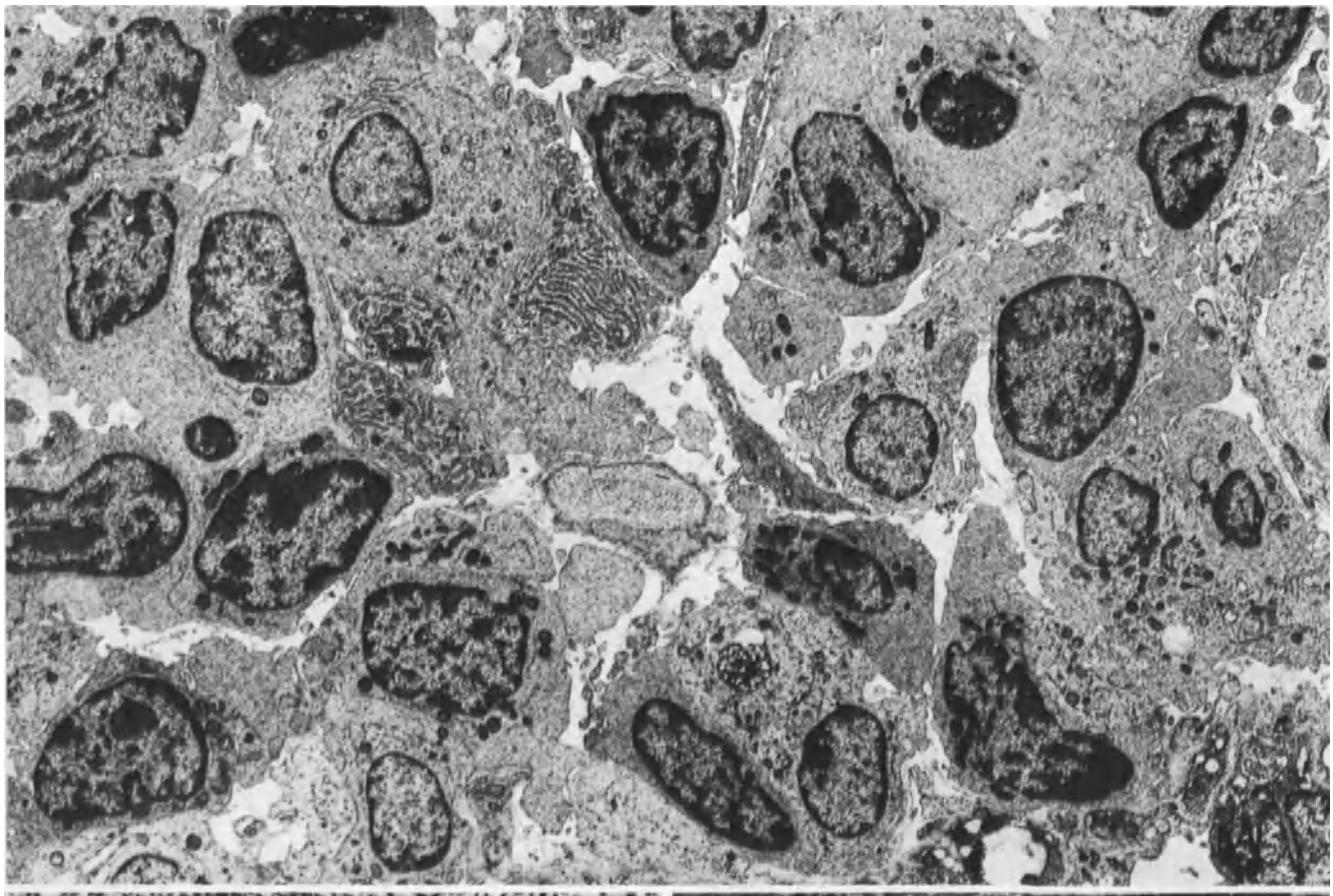

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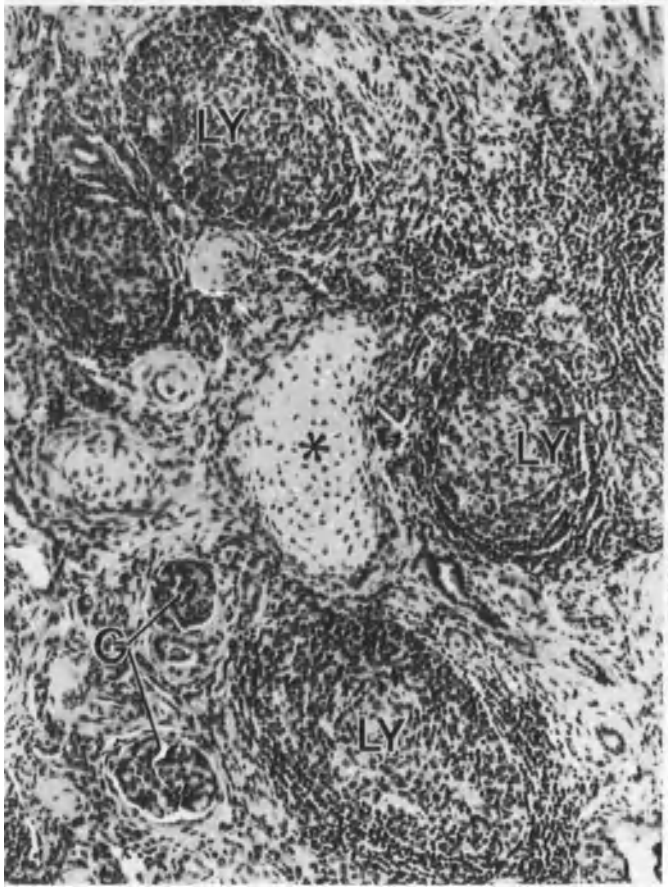


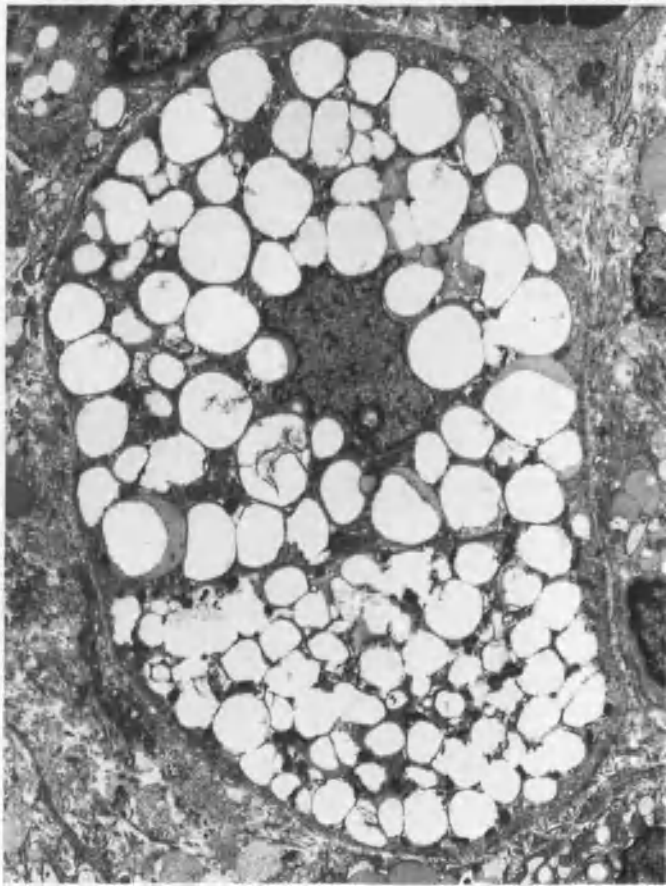

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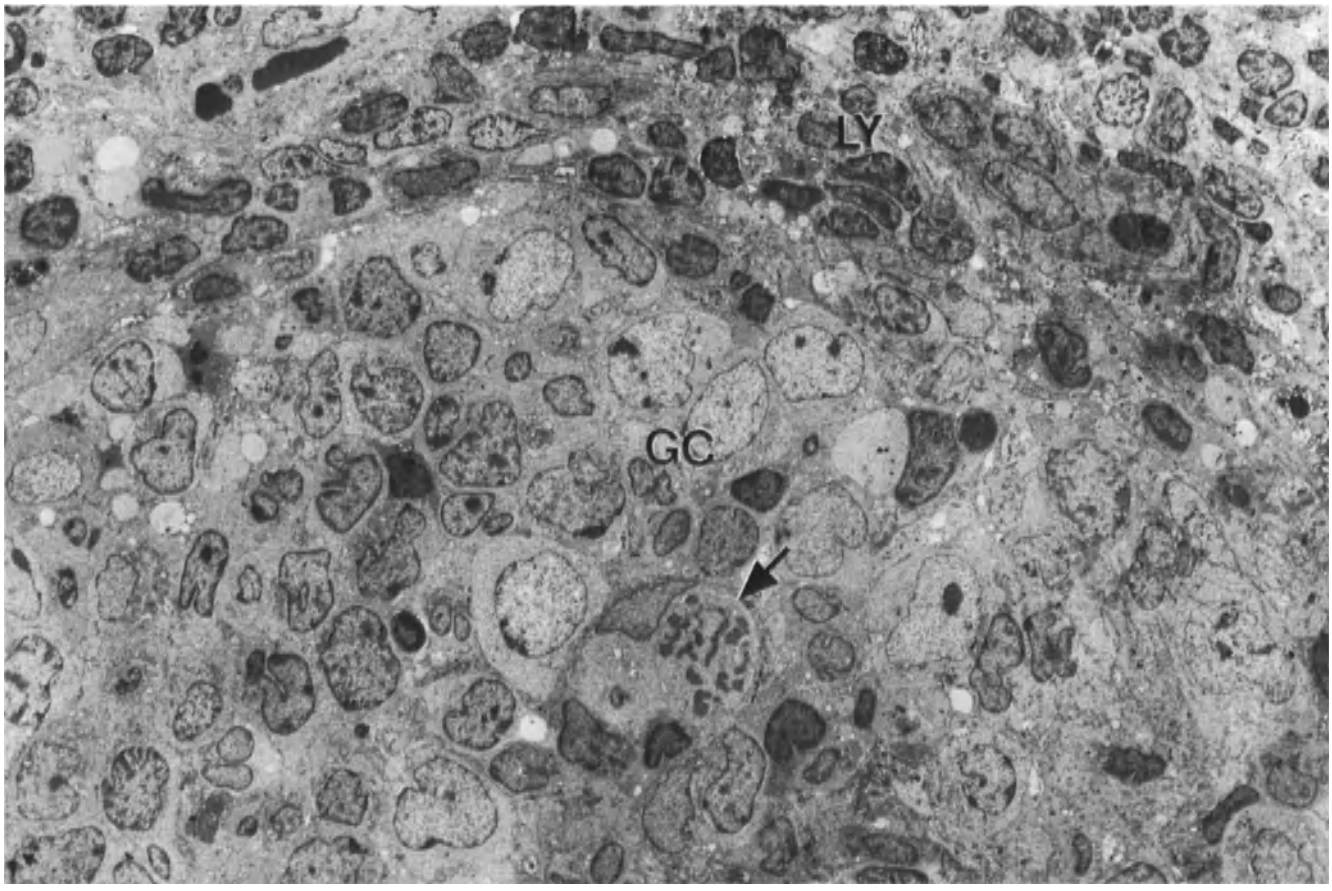


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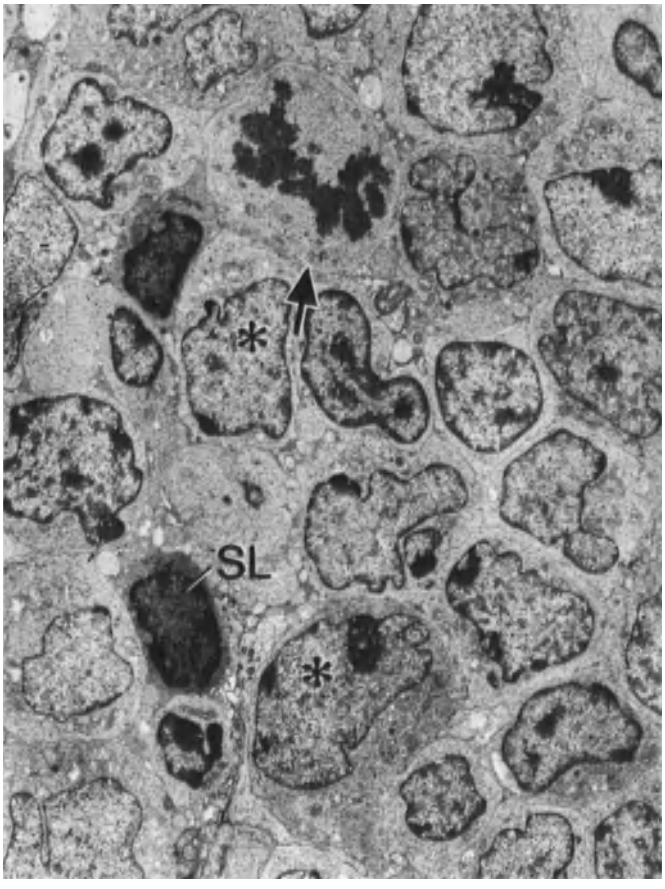



9.14

**Fig. 9.13.** Part of a lymph follicle in Figure 9.11. Germinal center (*GC*): germinocytes with cleaved electron-opaque nuclei and germinoblasts with noncleaved electron-lucent nuclei. Lymphatic tissue (*LY*); mitotic figure (→). Male, 13 years. EM (×1400)

**Fig. 9.14.** Part of a germinal center in Figure 9.11: predominance of germinocytes with cleaved nuclei and germinoblasts with noncleaved nuclei (*). Very few isolated small lymphocytes (*SL*); mitotic figure (→). Male, 13 years. EM (×2500)

# 10. Histopathology of the Renal Vessels

The diagnostic evaluation of vascular changes can prove to be extremely difficult, especially in relation to their causal significance, since the lesions may be primary and as such, the cause of other tissue changes; or secondary, i.e., the consequence of nonvascular tissue processes; or they may arise concomitantly with changes of the other tissue elements.

Very often these three possibilities overlap, and present the investigator with an almost insoluble problem. Only the most precise analysis and meticulous consideration of the changes in the vascular elements (e.g., study with van Gieson-elastin stain, EM, etc.) are suitable for solving the inherent difficulties posed by vascular changes.

In needle biopsies, usually only small arteries (the interlobulars) and arterioles are present for morphologic investigation. In case of the rare occurrence of parts or even cross-sections of the arcuate artery, the clinician should be informed immediately, since the probability of serious hemorrhage with subsequent shock is very great. In contrast to the previous chapters, EM changes of the vascular wall are discussed first, since the EM reaction pattern in the different specific vascular lesions is very similar.

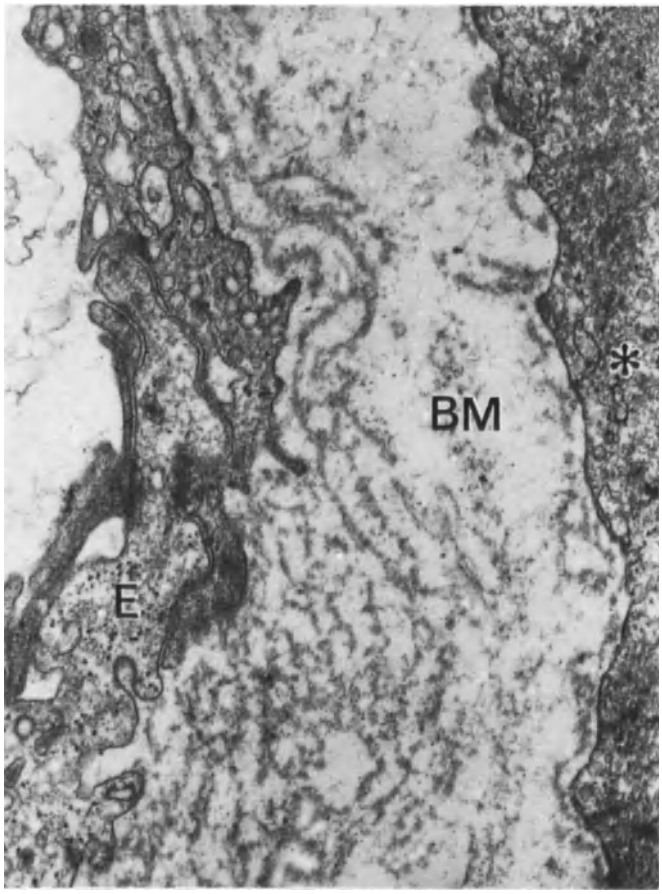



**Fig. 10.1.** Intima in adaptive intimal fibrosis. Endothelial cell (*E*), split, loosened and thickened basement membrane (*BM*), cytoplasmic projections of an undifferentiated cell which has migrated into the intima (*). Male, 62 years. EM (×29,300)

## Ultrastructural Elements in Vascular Changes

The essential endothelial cellular changes have been discussed on p. 90.

### Basement Membrane

The endothelial BM may be thickened either homogeneously or by lamellar stratification.

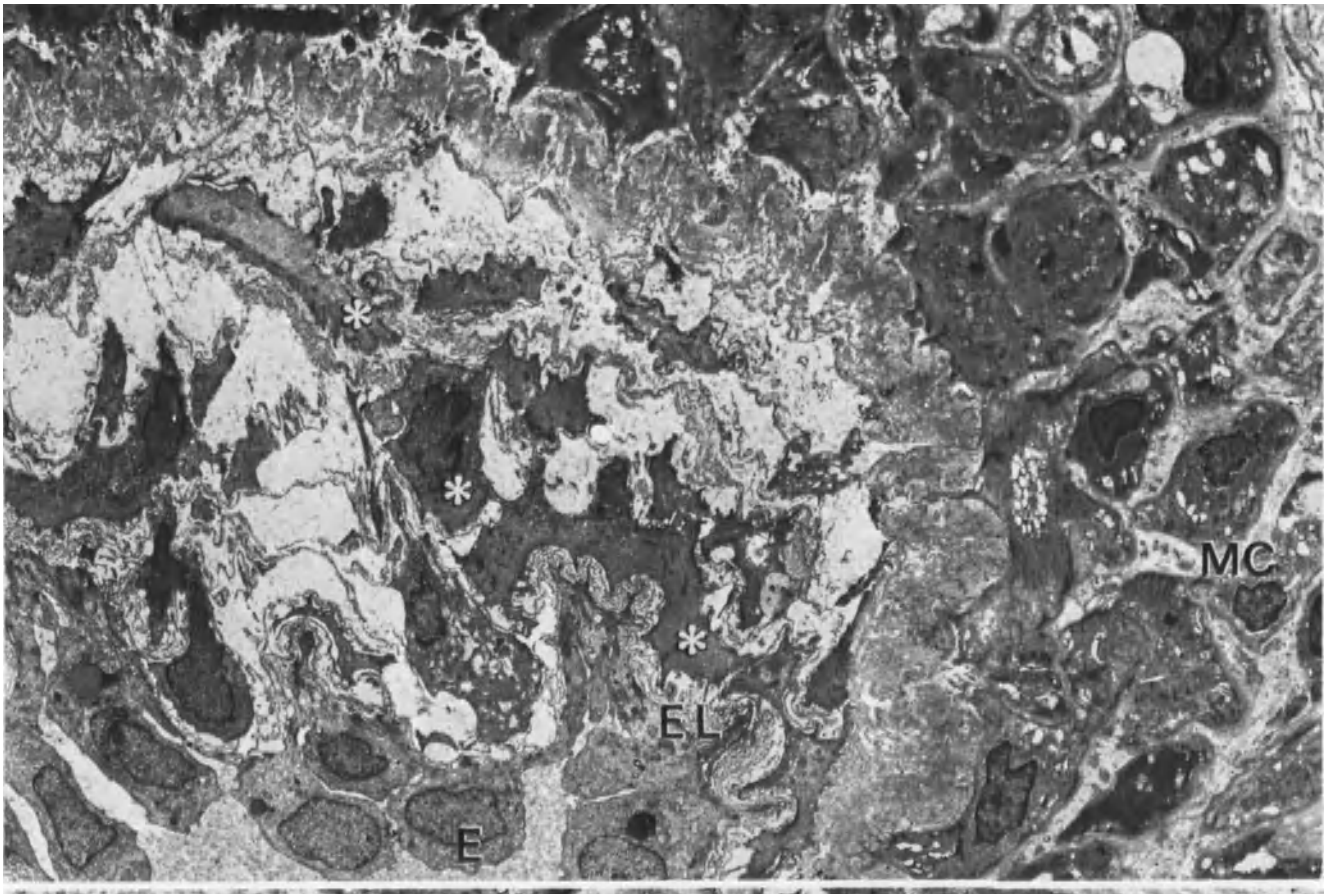
In homogeneous BM changes, the thickness of the BM is at most twice that of the normal value [1241, 1675].

It is observed in association with aging, but also occurs in the early stages of vascular diseases. It is not known whether the thickening is due to increased BM production from endothelial cells stimulated by noxious substances [1261] or to a swelling of the BM only [517a].

BM thickening by lamellar stratification (Fig. 10.1) is thought to be the morphologic result arising in conjunction with repeated or chronic endothelial (possibly lethal) injury. In this process, each new endothelial generation produces its own BM layer (reminiscent of the annual tree rings) between which vesiculo-granular debris is found [1675, 1675a]. This change, accordingly, is the morphologic correlate of persistent or repeated vascular injury and repair [1591a, 1675].

### Subendothelial Space

The subendothelial space may be viewed as a gully for the vessel. In young individuals, the subendothelial space

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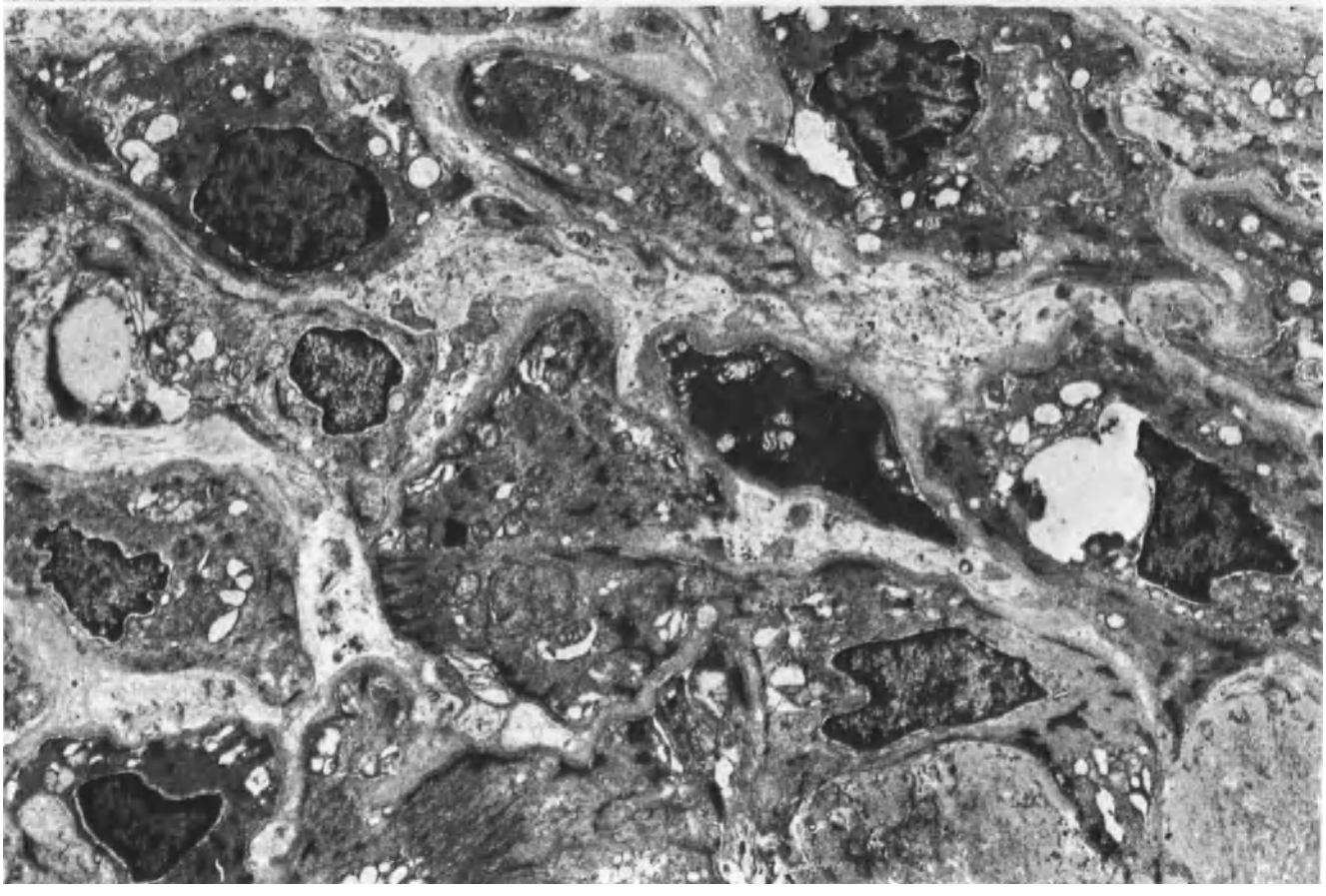

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is hardly discernible, but becomes more and more expanded with age and filled by a loose amorphous matrix and cellular debris [545a]. Blood plasma and cellular constituents appear in the subendothelial space in the presence of increased blood pressure and/or of increased endothelial permeability [723a, 873a, 1565a, 1568a]. These insudates manifest themselves either as osmiophilic, finely granular, rather massive deposits with map-like contours of plasma proteins and/or immunocomplexes [28a, 1287] or as strip-shaped fibrin derivatives [723a].

### Myocytes

The functional spectrum of the myocytes of the vascular wall is in harmony with their mesenchymal character [1752a]. They react in a monotonous way to the numerous vascular noxae, in that they become oval, develop many vacuoles and occassionally nuclear and cytoplasmic signs of necrobiosis (Figs. 10.2, 10.3). During this response, the organelles seem to disappear, the sarcoplasm becomes granular or homogenous [1336, 1591a] and the myocytes ultimately disintegrate, leaving behind vesiculo-tubular osmiophilic debris (Fig. 10.5).
Myocyte regeneration is still possible in the stage prior to condensation of the cytoplasm [1602b]. The regeneration of myocytes is characterized by their morphologic and functional transformation as shown by (1) the increase in volume of cellular organelles participating in synthesis and secretion (rough endoplasmatic reticulum, Golgi apparatus, mitochondria); (2) the displacement of sarcoplasm peripherally; (3) the disappearence of myofibrils, and (4) by the appearence of numerous, large cytoplasmic processes (Fig. 10.2). Finally, the myocytes come to look like fibrocytes (Figs. 10.4, 10.5).

◁ **Fig. 10.2.** Adaptive intimal fibrosis (early phase) in GN contracted kidney. Myocytes (*MC*) show vacuolar changes, lamina elastica interna (*EL*) and BM are severely split and, in subendothelial space, undifferentiated cells (*)—probably transformed myocytes—are present. Endothelium (*E*). Male, 22 years. EM (×2600)

**Fig. 10.3.** Part of the media seen in Figure 10.2. Numerous vacuoles are present in the myocytes. Between the myocytes, an increased amount of ground substance-like material is present. Male, 22 years. EM (×5600)

The factor triggering transformation appears to be either the decreased tension to which the elastic vascular structures are exposed by the reduced blood flow (see p. 151), during which an increased production of collagen fibers leads to a narrowing of the vascular lumen or the loss of vascular elasticity [1336] brought about by physicochemical, hypoxic, or inflammatory injury to the cells of the vascular wall [861a]. This gives rise to copious production of elastic lamellae, and leads to passive maintenance of elasticity otherwise actively assured by myocytic responses. The transformation of the myocytes—especially in the larger vessels—is initiated in the subintimal layer of myocytes (Fig. 10.2).

## Specific Vascular Lesions

### Idiopathic Fibroelastosis

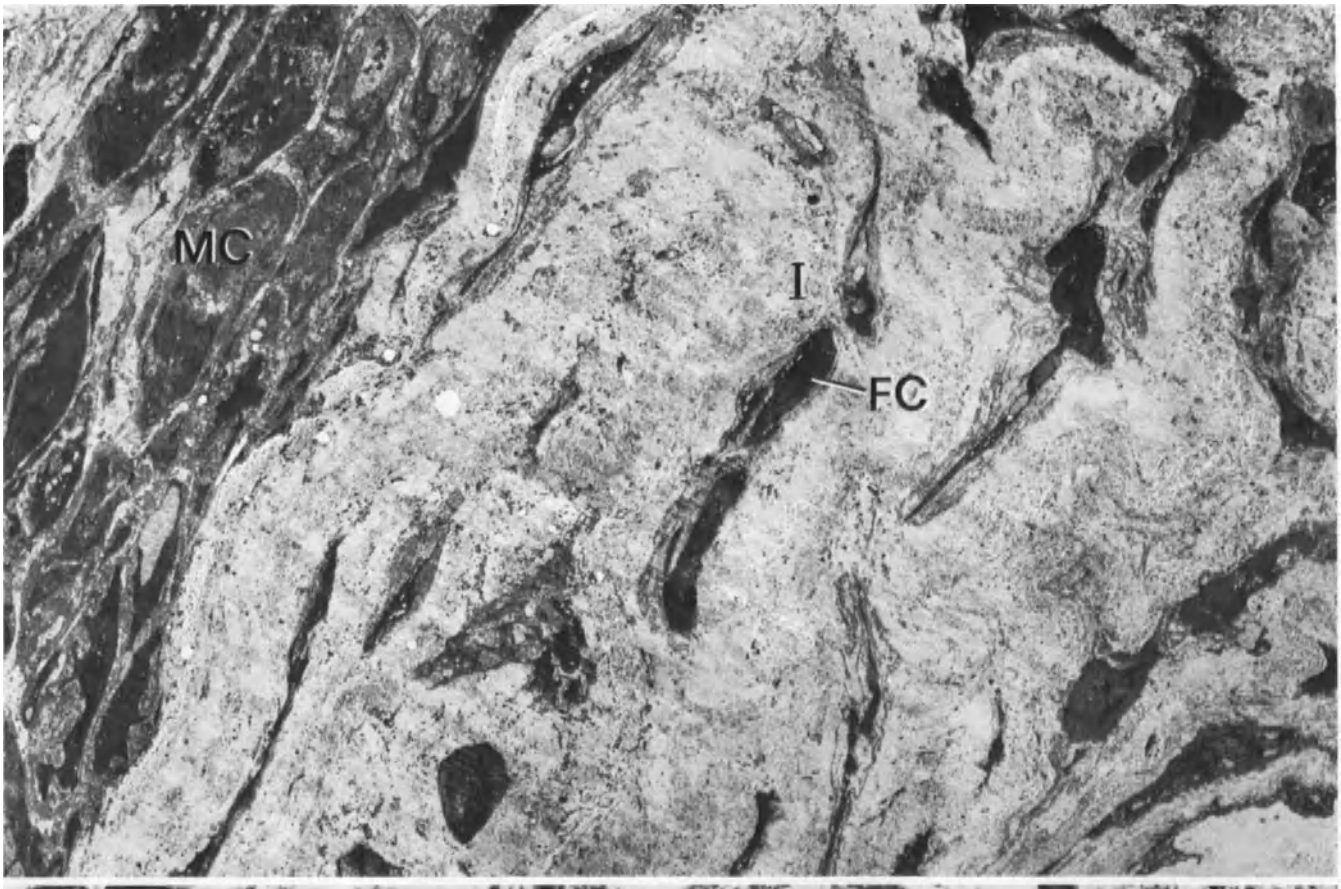
Apart from atrophy attendant on severe intimal thickening, media changes are infrequent. The finding of idiopathic fibroelastosis with patchy media thickening, spotty fibrosis and a dense elastin fiber network in needle biopsies is very rare [1336]. We have never observed it. Idiopathic fibroelastosis has no relationship to hypertension. It is encountered chiefly in the older age groups. Its cause is unknown. Pathogenetically, it is based on degeneration and functional change of the myocytes which are recognizable with EM (see above). Except for scattered cases with aneurysma disecans of a major artery, the change is completely insignificant.

### Arteriosclerosis

Coarse fibers, stained a bright red with van Gieson stain (Fig. 10.6), and a mild to severe fragmentation and lamellar new formation of the internal elastic membrane are observed in this condition. Our observations have shown that true atheromatous formation occurs mainly in diabetes mellitus with increased incidence in peripheral vessels. Hypertension may play a primary or secondary role in the genesis of arteriosclerosis, but it is not an absolute prerequisite.

### Arterial Elastosis

This change, also referred to as hyperplastic sclerosis [13] is most frequently—but not always—found in association with arteriosclerosis. It is characterized by thickening and increase of the elastic fibers (Fig. 10.7) between which only transformed myocytes and very scanty connective tissue are found in cases uncomplicated by other

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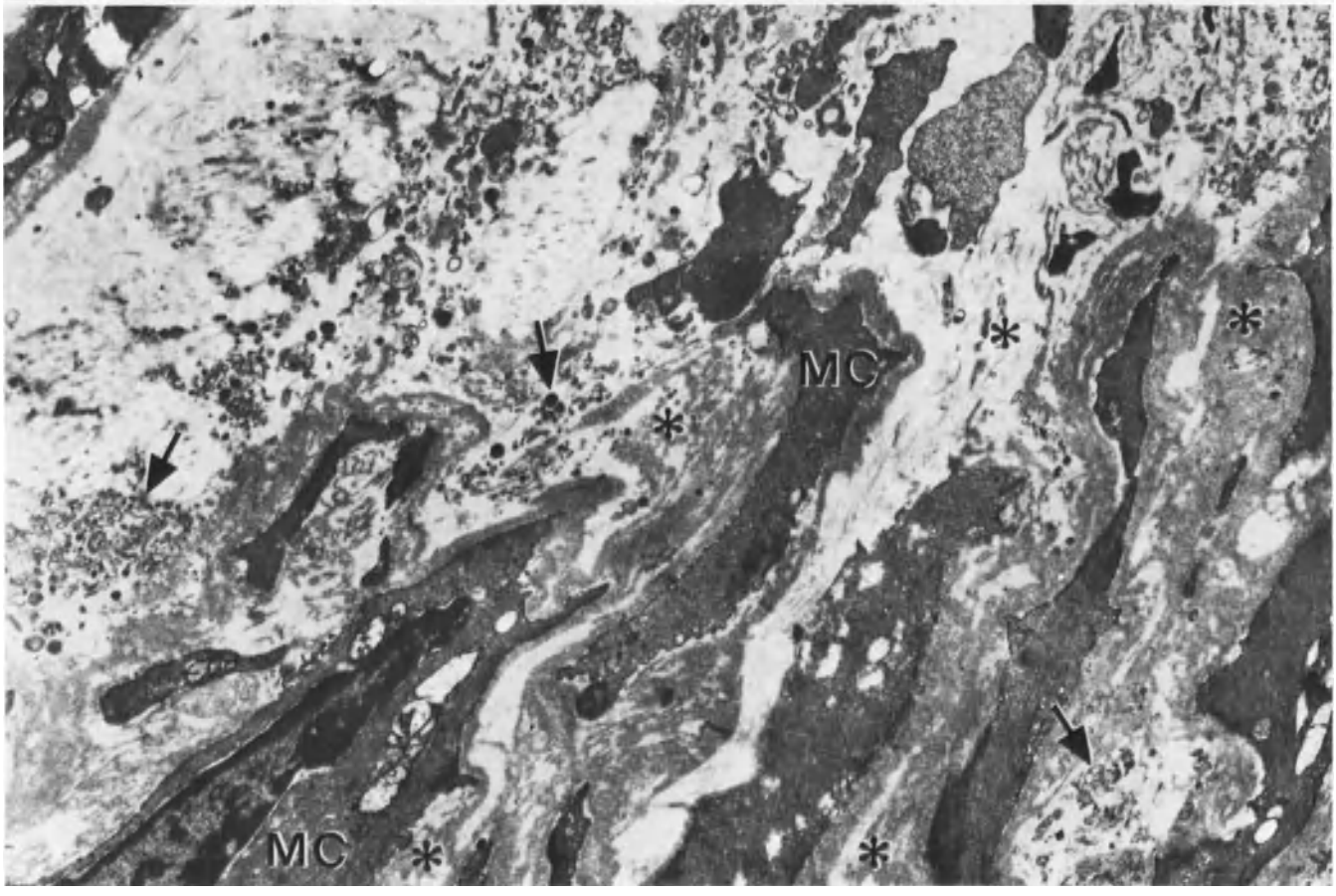



10.5

diseases (Fig. 10.8). We have observed this change exclusively in severe hypertension. The lesion apparently has no significant consequence for renal function.

### Adaptive Intimal Fibrosis

Adaptive intimal fibrosis (Figs. 10.9, 10.10; [1794]) features a dense, rather fine-fibered collagenous tissue in the intima which is relatively poor in cells. Myocytes are definitely present, whereas no significant increase of elastin is encountered.

The lesion arises as an adaptive response to decreased blood flow which may be due either to severe reduction of the peripheral vascular bed, as in contracted kidney of any etiology, or to proximal, usually arteriosclerotic artery stenosis, with or without thrombosis [1794]. Myocytes lying on the internal elastic membrane transform first and most vigorously. Experimental findings [494] indicate that endothelial injury may be involved in producing the lesion (see p. 149). Accordingly, adaptive intimal fibrosis, as the term itself indicates, is never the cause but always the consequence of parenchymal shrinkage or of proximal arterial stenosis. It is accordingly, absent in congenital renal hypoplasia and dysplasia.

As seen with EM, the change appears to be initiated by injury to the media-myocytes (Figs. 10.2, 10.3).

They pass through the elastic membrane into the subendothelial space, where they are characterized by their extensive cytoplasmic extensions. In this early stage of the lesion, the subendothelial space is considerably widened and edematous (Fig. 10.2). Later, the transformed myocytes assume the morphologic characteristics of fibrocytes and fibroblasts (Figs. 10.3, 10.4) and form a fine-fibered network filled occasionally with degradation granules (Fig. 10.5). It appears to us very unlikely that adventitial fibroblasts migrate into the endothelial space as has been proposed [8a].

In the late phase of the process, the media of the smaller arteries is frequently atrophic and in EM the myocytes reassume their original form (Fig. 10.4). Medial atrophy in larger arteries is scarcely apparent (Fig. 10.9).

◁ **Fig. 10.4.** Late phase of adaptive intimal fibrosis evidences numerous fibrocytes (*FC*) in the relatively loose intima. Media (*MC*), intima (*I*). Pyelonephritic contracted kidney. Male, 59 years. EM (× 1700)

**Fig. 10.5.** Part of the media seen in Figure 10.4. Increased newly formed ground substance (*) rich in degradation granules (→) is present between myocytes (*MC*) in adaptive intimal fibrosis. Male, 59 years. EM (× 12,000)

A change similar to that detailed above for arteries, can be observed in the arterioles (Fig. 10.10). In addition to obvious increase in elastic membrane material, the arterioles demonstrate a loosely organized increase of cells in the region of the intima resulting in partial or complete displacement of the lumen. The media is mostly atrophic, and inflammatory changes as well as necrosis are absent. This lesion is mainly found in severely contracted kidneys and is most pronounced after long-term dialysis.

### Arteritis

Lympho-plasmocytic infiltrates of the vascular wall, together with histiocytes and proliferation of mural cells, are encountered in acute transplant vasculopathy, periarteritis nodosa and other rarer forms of arteritis such as Horton's giant cell arteritis [1791], Takayasu's disease, etc. Periarteritis nodosa (macroform) (see p. 533) is characterized in the acute phase usually by the sector-like occurrence of medial necrosis, as seen especially in the arcuate and interlobular arteries. The necroses are often infiltrated with numerous eosinophilic leukocytes. Formation of a pronounced perivascular mantle of infiltrates is also a feature of the acute phase (it is noted parenthetically that in general, various stages of the disease are present simultaneously). Treatment with steroids leads to scar formation and the medial defects are replaced by scar tissue.

The hypersensitivity angitis (periarteritis nodosa, microform, see p. 536) runs its course in one attack, involves smaller arteries and arterioles, and can be scarcely differentiated histologically from the changes observed in the interlobular arteries as they occur in Wegener's granulomatosis and SLE. An unspecific chronic inflammatory constellation with secondary thrombosis and small medial and intimal fibrinoid necrosis indicates Winiwater-Buerger thrombangitis (see p. 540) and especially so when different stages of the process occur simultaneously, a finding hardly to be encountered in needle biopsy, however [1791].

### Thrombosis

Fresh, often hyaline (better: fibrinoid) thrombi with slight or no secondary inflammation indicate severe, generalized intravasal coagulation which occurs above all in gram-negative septicemia and also subsequent to shock (see p. 490). The same finding is present in the hemolytic-uremic syndrome (see p. 499), and in microangiopathy (see p. 499) for which the concomitant occurrence of thrombi of different ages is characteristic. Glomerular thrombi are always present in these three conditions for which they are diagnostically confirmatory.

### Onion Bulb-Like Arteries

Changes in scleroderma exhibit an onion bulb-like fragmentation and lamellation of intimal elements with loosely organized increase of reticulin and collagenous fibers (Fig. 10.11) as well as an increase of a mucoid, alcian-blue staining substance in the vessels wall. These findings are restricted to the small arteries and especially to the interlobular arteries. A nearly identical change in the interlobular arteries also occurs in severe malignant nephrosclerosis (see p. 520) and in older intravasal coagulation (see p. 499; [1068]). In both instances, however, the mucoid substance is somewhat less pronounced. Overlapping does occur since sclerodermic lesions tend to lead to renal hypertension, which in turn results in hypertensive vasculopathy. The morphologic similarities are interpreted as the expression of a common pathogenetic mechanism [1068].

### Transplantation Vasculopathy

The histopathology of this lesion is presented on p. 573 and 596.

## Arteriolar Lesions

### Arteriolitis

Arteriolitis—with or without fibrinoid necrosis—can be found, albeit exceptionally, in various immunopathologic conditions such as hypersensitivity angitis, purpura Schönlein-Henoch, SLE, Wegener's granulomatosis, Goodpasture's syndrome, cryoglobulinemia, and in acute transplant rejection.
Except in transplants, an accompanying glomerular inflammation is almost uniformly present, and its form is diagnostically decisive.
The formation of glomeruloid structures from endothelial and medial proliferation is, according to our findings, a rare change in diffuse GN. These structures may become as large as 200 μm [1641].

### Arteriolosclerosis

Arteriolosclerosis is characterized by bright red, starkly sudanophilic fibrinoid deposits (red with Masson trichrome/AFOG, yellow with van Gieson, and PAS-positive) which occur between the atrophic media and compressed intima without the presence of necrosis (Fig. 10.12, see also p. 520). The deposits are also not infrequently seen in normotensive subjects (Fig. 25.1) where, moreover, they are rather scanty and only encountered in a few vessels. Arteriolosclerosis occurs primarily and secondarily in the kidney, and is a frequent finding in the contracted kidney and more frequent in non-GN than in GN (for EM findings, see p. 517, for frequency in our material see Fig. 25.1). If many arterioles are severely involved, the change is usually the consequence of generalized hypertension or diabetes mellitus (Fig. 25.1). In the latter vasa efferentia are also afflicted.

### Arteriolonecrosis

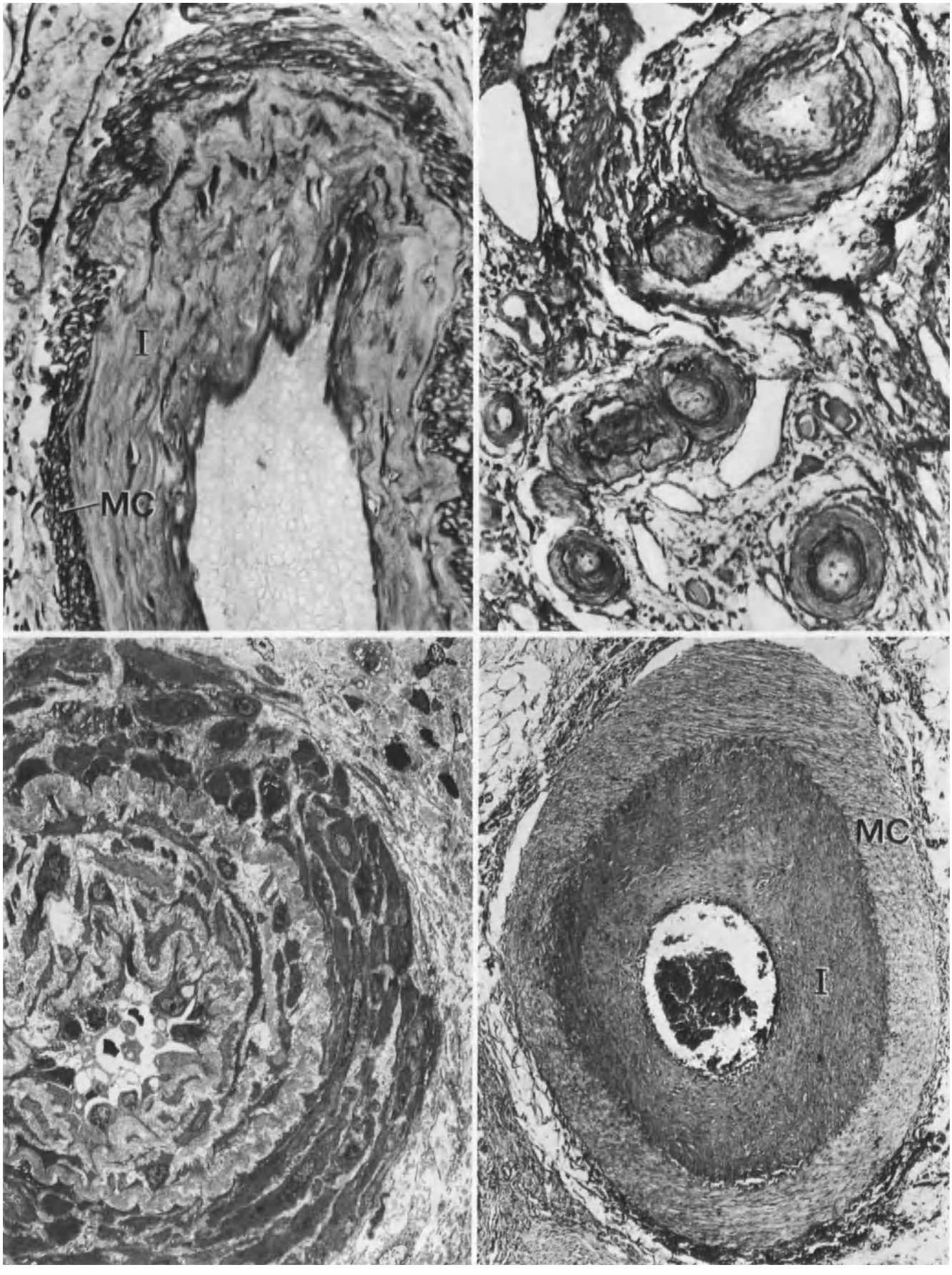
Arteriolonecrosis with fibrinoid deposits and slight or absent inflammatory reaction (Fig. 10.13) is characteristic for the severe form of hypertensive arteriolopathy [1790]. The deposits exhibit the same staining characteristics as in arteriolosclerosis. They are, however, more granular and less sudanophilic.
Arteriolonecrosis may occur primarily, i.e., independent of prior renal disease leading to hypertension. The primary form usually occurs in young individuals, and results in parenchymal injury in the form of small subinfarcts. The lesion may also be secondary to severe essential or renal hypertension in pyelonephritis, GN, etc.
Therefore, the differentiation between the primary and secondary form of arteriolonecrosis depends on parenchymal and not vascular findings.
The intertubular capillaries, veins and lymph vessles do not exhibit changes of diagnostic significance.

**Fig. 10.6.** Arteriosclerosis of a middle-sized renal artery. Severe coarse, bulky, cell-poor thickening of intima (*I*), media (*MC*). Male, 62 years. PAS (×270) ▷

**Fig. 10.7.** Severe elastosis with multilayered elastic lamellae in small and middle-sized arteries in association with hypertension. Male, 34 years. Van Giesson-elastin (× 133)

**Fig. 10.8.** Elastosis of a small artery. Same case as in Figure 10.7. Media is loosened, and severely thickened intima exhibits numerous elastic lamellae. Male, 34 years. EM (×850)

**Fig. 10.9.** Adaptive intimal fibrosis in pyelonephritic contracted kidney. Media (*MC*) is unchanged, intima (*I*) is very severely thickened with few nuclei and rather delicate fibers. Endothelium is unchanged. Male, 58 years. HE (×8)

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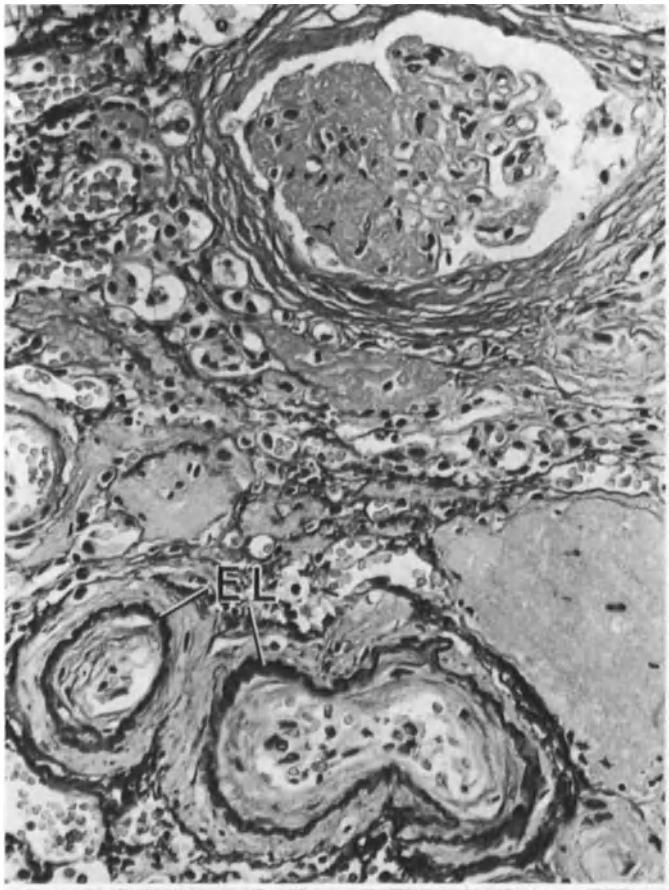


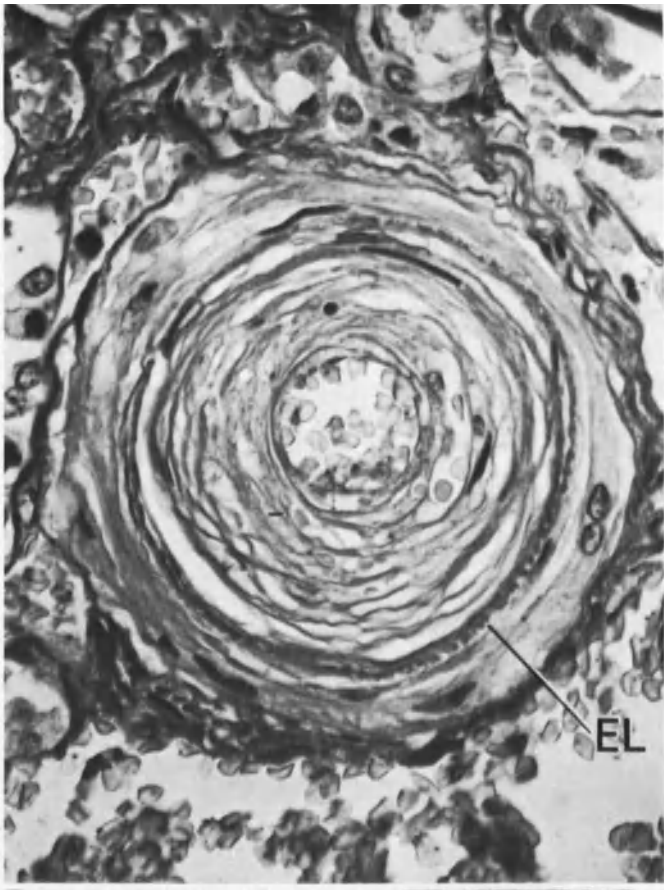


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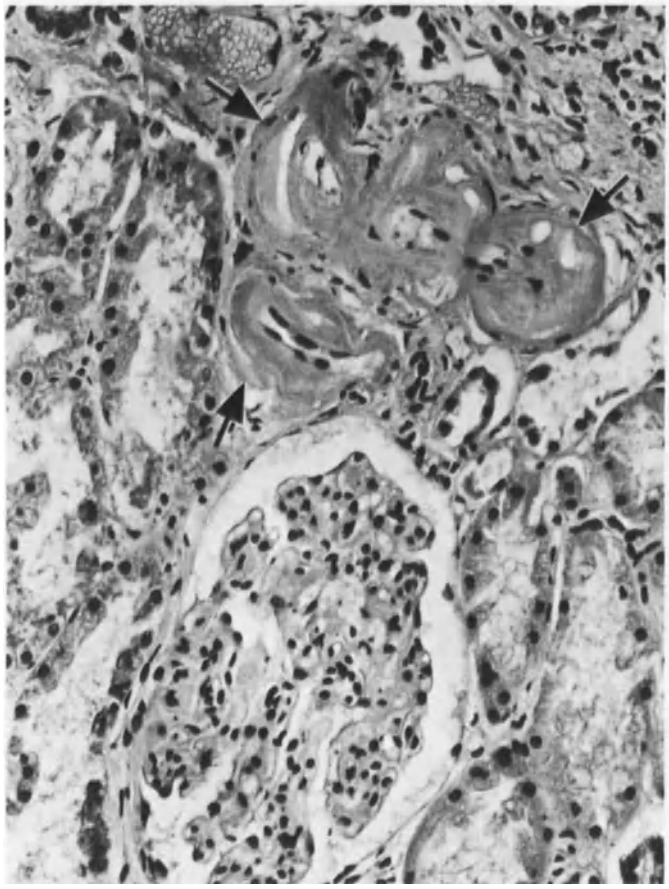

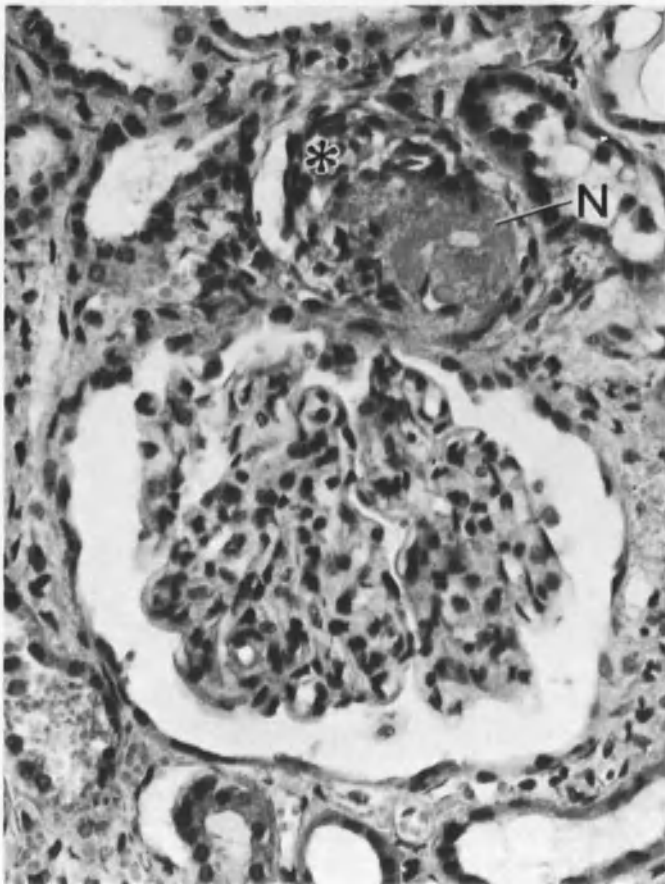


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# 11. Immunohistopathologic Parameters

## Definitions

1. Intrarenal distribution pattern
   This may be diffuse, focal, segmental or global (see p. 48).
2. Intraglomerular distribution pattern
   a) Purely peripheral (membranous) deposits = deposits along the glomerular BM
   b) Purely mesangial deposits = deposits exclusively within the mesangial matrix including mesangial BM
   c) Mesangial and peripheral deposits = combination of both depositional patterns (arbitrary subdivision according to predominant type possible).
3. IF Character
   a) Linear = deposits along the peripheral glomerular BM which evidence no granular structure even under high magnification
   b) Pseudolinear = coalescence of extremely fine granular or abnormally coarse deposits to form a pseudolinear pattern. Under high magnification, the granular character of the deposits is usually recognizable
   c) Granular = deposits which are sharply demarcated from each other (arbitrary subdivision into fine- and coarse-granular is possible).

◁ **Fig. 10.10.** Adaptive intimal fibrosis in small arteries in GN contracted kidney. Lumen severely narrowed by loose, fibrous tissue. Lamina elastica interna (*EL*) thickened but not split. Female, 62 years. Van Gieson-elastin (×276)

**Fig. 10.11.** Onion-bulb-like split and thickened intima of a small renal artery in scleroderma. Lamina elastica (*EL*). Male, 34 years. Van Gieson (×400)

**Fig. 10.12.** Arteriolosclerosis in hypertension. Arterioles have a homogeneous thick wall (→). Lumens are almost occluded, endothelial cells are well preserved and adventitia is sharply delimited. HE (×120)

**Fig. 10.13.** Arteriolonecrosis (malignant nephrosclerosis). Fibrinoid necrosis (*N*) in the vas afferens surrounded by an almost circular granuloma (*). Glomerular loops are slightly collapsed, and tubules are frankly atrophic. HE (×200)

## Diagnostic Significance of IF

IF processing of tissue permits specific staining of immunoglobulins and other proteins which is not necessarily tantamount to the demonstration of immunocomplexes (see also [128]). The interpretation of findings such as immunocomplexes or anti-BM antibodies is often possible only in conjunction with LM and EM studies.
The diagnostic domain of IF is GN. In most cases, it is used as a complementary investigation which, together with LM and EM studies, corroborates the diagnosis of GN and which, above all, allows conclusions regarding the composition and amount of immune deposits and their persistence in sequence biopsies.
EM has not proven to be a substitute for IF study of GN! In 250 of our own biopsies which were IF positive, no deposits were found in 42% with EM (only 0.6% of the cases positive under EM were falsely negative under IF). Additionally, EM does not provide informations as to the protein composition of the deposits unless the technically problematic immuno-EM is used (this does not imply that immuno-EM and LM-immunohistology are mutually interchangeable).
IF is of unequivocal diagnostic value with respect to the disease states given below.

1. Recognition of anti BM-type GN (Masugi-type GN) (e.g., Goodpasture's Syndrome, ALG-nephropathy in renal transplant recipients)
2. Mesangial IgA GN
3. Diagnosis of epimembranous GN, especially of stage I without LM changes
4. Differentiation of idiopathic glomerular minimal change from symptomatic forms
5. Differential diagnostic delineation between GN and eclampsia (eclampsia is IF negative except for fibrin)
6. The identification of AG, i.e.: DNA in SLE-GN (Fig. 11.1), hepatitits-B virus (Fig. 11.2; [1531, 1171, 307, 615]); plasmodium malaria antigen [1689], streptococcal antigens [28, 1766], staphylococcal antigens [813], measles antigens [359], thyroglobulin [1744, 1271a], and rubella antigen [Z].

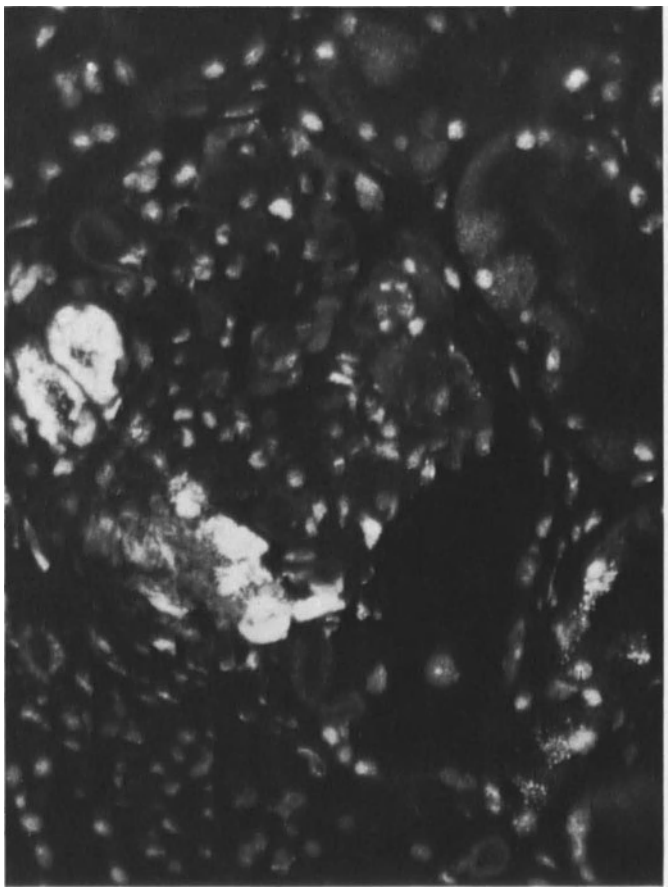


**Fig. 11.1.** DNA demonstration in proliferative FGN in SLE. Note also the normal staining of tubular nuclei. Female, 24 years. IF (×430)

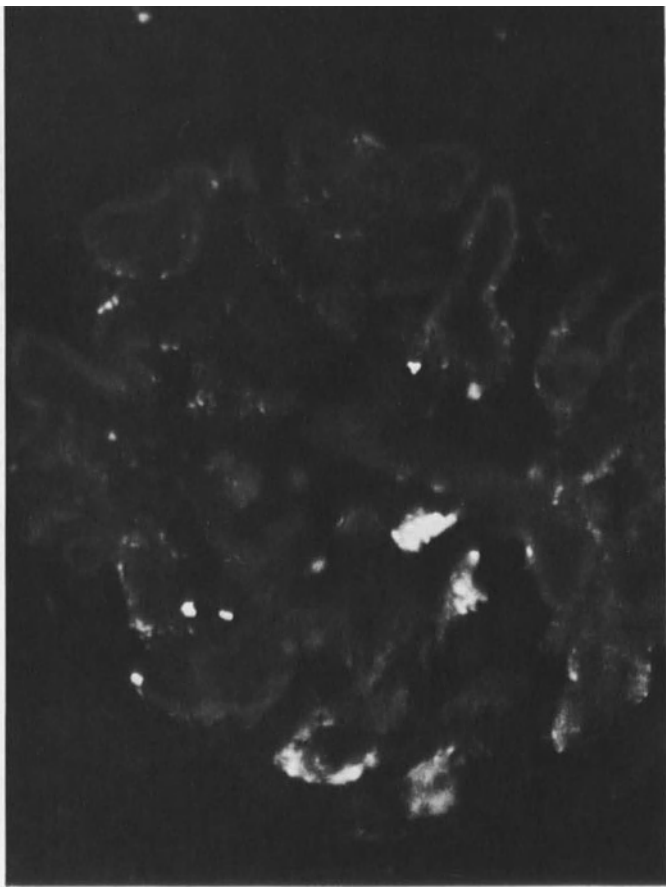


**Fig. 11.2.** Hepatitis B surface antigen in renal transplant in a patient with chronic persistant hepatitis. Male, 44 years. IF (×500)

## Quantification of IF Findings

The quantification of IF findings is extremely problematic as long as the factor(s) relevant to the functional impairment is (are) unknown [128]. Decisive factors in this respect include the extension of the process—(with corresponding functional impairment of the implicated glomeruli)—as well as the local concentration of deposited immunocomplexes—with resulting local structural lesions—which may be reflected in the labeling intensity unless there is no mutual blocking between the complex components.

Both type and concentration of the individual components of deposited complex may be subject to considerable variation. Thus, for example, in the late phase of GN, we have frequently observed only a weak patchy fluorescence for IgG, but a clear-cut and more extensive presence of complement. This may reflect the true relations within the immunocomplex, but it could be caused by steric or immunologic blockage of a given component by another. Finally, sensitivity of IF depends on so many various factors such as AG preservation, section thickness, quality of sera, illumination and filter systems of the microscope, etc., that quantitative data must be taken as very arbitrary if appropriate standardization procedures are not empolyed [786a].

In spite of all reservations, in our material investigated semiquantitatively, there is a statistically significant correlation between the amount of EM demonstrable deposits and the intensity of fluorescence if the AG with the strongest fluorescence is considered. One can, accordingly, conclude that IF examination of sequential biopsy permits measured judgement with respect to an increase or decrease in the amount of immunocomplex under investigation. IF is especially useful for prognostic deductions on material studied during the course of the disease, as well as on therapeutic efficacy, since LM and, conditionally, EM do not permit reliable conclusions relating to the persistence of the underlying immune reaction in a given case.

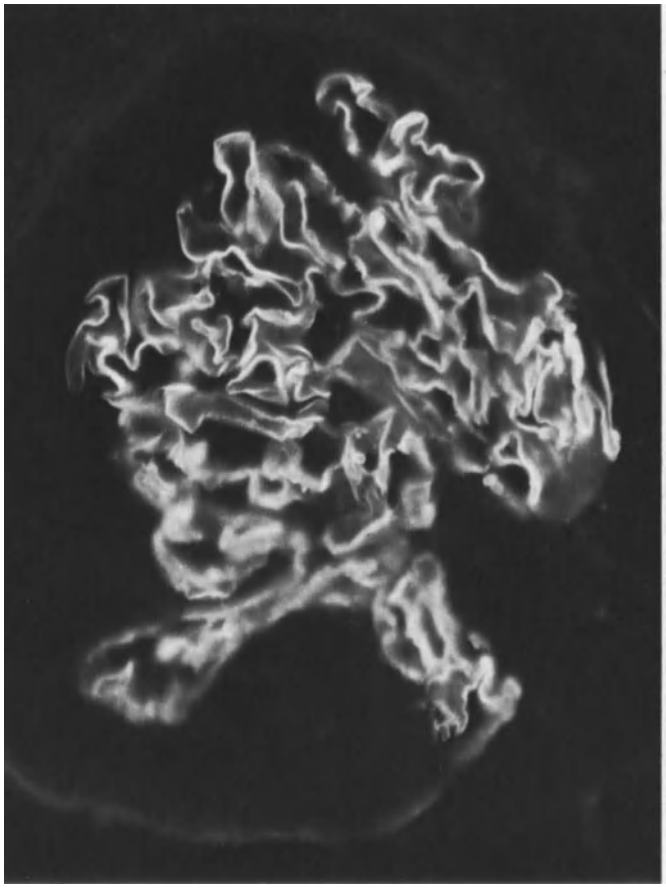


**Fig. 11.3.** Linear BM staining for IgG in Goodpasture's syndrome. Female, 62 years. IF (×500)

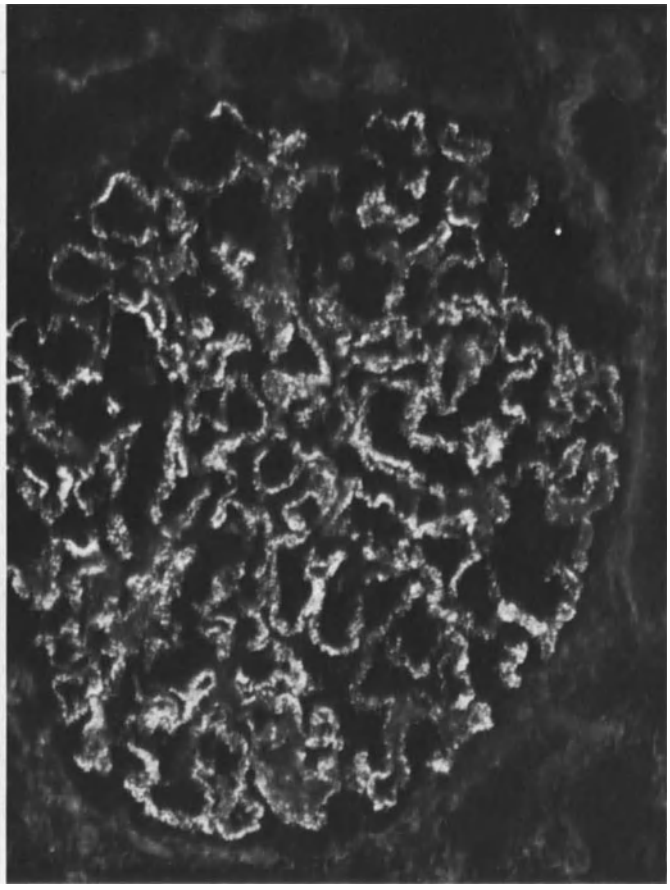


**Fig. 11.4.** Purely peripheral granular deposits positive for IgG in epimembranous GN. Female, 61 years. IF (×500)

## IF Deposition Character

### Linear Deposition

***Anti-BM-AB (Masugi, Specific) Type.*** In the clinical setting—analogously to the experimental Masugi-GN—a diffuse and global linear deposition of immunoglobulins and complement is present exclusively along the glomerular BM due to the fixing of anti-BM antibodies.

A condition most closely resembling Masugi-GN is the ALG nephropathy of renal transplant recipients which is generated by use of heterologous ALG preparations (usually from the horse) with cross-specificity against BM antigens [1132, 1805]. In this process, there occurs an immediate heterologous phase with binding of horse gamma globulin on the BM, which can be demonstrated with appropriate species-specific antibody.

According to the degree of immunosuppression, an autologous phase with binding of newly formed host AB against the BM-bound heterologous immunoglobulins can, facultatively, occur subsequently.

The spontaneous occurrence of linear deposits in GN (Fig. 11.3) as seen in Goodpasture's syndrome and extracapillary accentuated GN, for example, is related to primary autologous anti-BM antibodies of unknown origin, usually also with concomitant activity against pulmonary BM. In this condition, complement may be absent in one third of the cases [1744]. Cross-reactions between BM-antigens and bacterial and other exogens are currently being discussed [1377, 943, 1131].

We found anti-BM type GN in 2 of 227 cases of GN examined with IF. A frequency of 1–5% corresponds to that in the literature [1744, 544, 1136, 1035, 1747].

From the differential diagnostic standpoint, nonspecific linear depositions without GN of the anti-BM-AB-type and pseudolinear depositions in complex GN must be recognized.

***Non-GN (Nonspecific) Type.*** Linear IgG deposition without either complement participation or GN has been observed in SLE [869] and in diabetic glomerulosclerosis

Table 11.1. Nonspecific linear deposits of immunoglobulins, C3 and fibrin(-ogen)

| Diagnosis | Depositional character | |
|---|---|---|
| | Linear | Granular |
| Glomerular minimal change ($n=1$) | IgG, IgM, IgA | – |
| Endotheliomesangial GN without crescents ($n=1$) | IgA | – |
| Unspecific glomerulosclerosis ($n=1$) | IgG | IgM |
| Acute interstitial nephritis ($n=1$) | IgG | IgM, IgA, C3 |
| Acute transplant rejection ($n=7$) | C3 | Fi |
| | IgM, Fi | C3 |
| | IgG | – |
| | IgG | IgM, C3 |
| | Fi | – |
| | IgG, Fi | IgM, C3 |
| | IgG, IgA | IgM |
| Shock kidney in renal transplant ($n=1$) | IgG | IgM, C3 |

[1035, 525] without being able to demonstrate AB with anti-BM activity in eluates. Linear deposits in renal transplants treated with and without ALG were demonstrable subendothelially but not in the BM with immunoelectron microscopy [28].

In our own material, we found 12 cases with nonspecific linear immunofluorescence (7 in acute renal transplant rejection and five others in a variety of other nephropathies, see Table 11.1) which were not always diffuse. Rebiopsy was carried out in 3 of the cases: in 1 case after 19 days with identical IF findings; in the other 2 it was performed after 4–5 weeks with negative findings. These observations indicate that linear deposition may be a temporary phenomenon without nephritiogenic activity. It is conceivable—as in our cases—that anoxic or other endothelial damage may be significant pathogenetically.

## Granular Deposition

***GN (Specific) Type.*** Specific granular deposition (immunocomplex glomerulopathy) is chiefly characterized by granular deposition of immunoglobulins (especially IgG) and complement. The identical localization of these components is generally interpreted as the expression of immunocomplex formation.

The presence of immunocomplex is assured by microscopic demonstration of inflammation and above all in the rate cases in which AG is also demonstrable (e.g., DNA in SLE-GN, hepatitis B surface antigen in viral hepatitis B). The isolated demonstration of IgM and/or C3 may be the manifestation of an immunocomplex process. It also may occur, however, in nonglomerulonephritic lesions (see below).

The size of the complex varies between fine-granular and just resolvable to coalescing coarse-granular such that pseudolinear configurations not infrequently arise in BM. Three types of intraglomerular distributional patterns can be recognized:

1. Purely peripheral (membranous) type: involvement of BM exclusively, as in epimembranous GN (Fig. 11.4)
2. Purely mesangial type (Fig. 11.5): involvement exclusively of the mesangium, as in IgA mesangial GN
3. Mixed mesangial peripheral type (Fig. 11.6): involvement of both regions to the same or different degrees as in endotheliomesangial GN. A typical finding in mesangial component predominance is the encroachment of fine-granular deposits upon BM sectors near the mesangium.

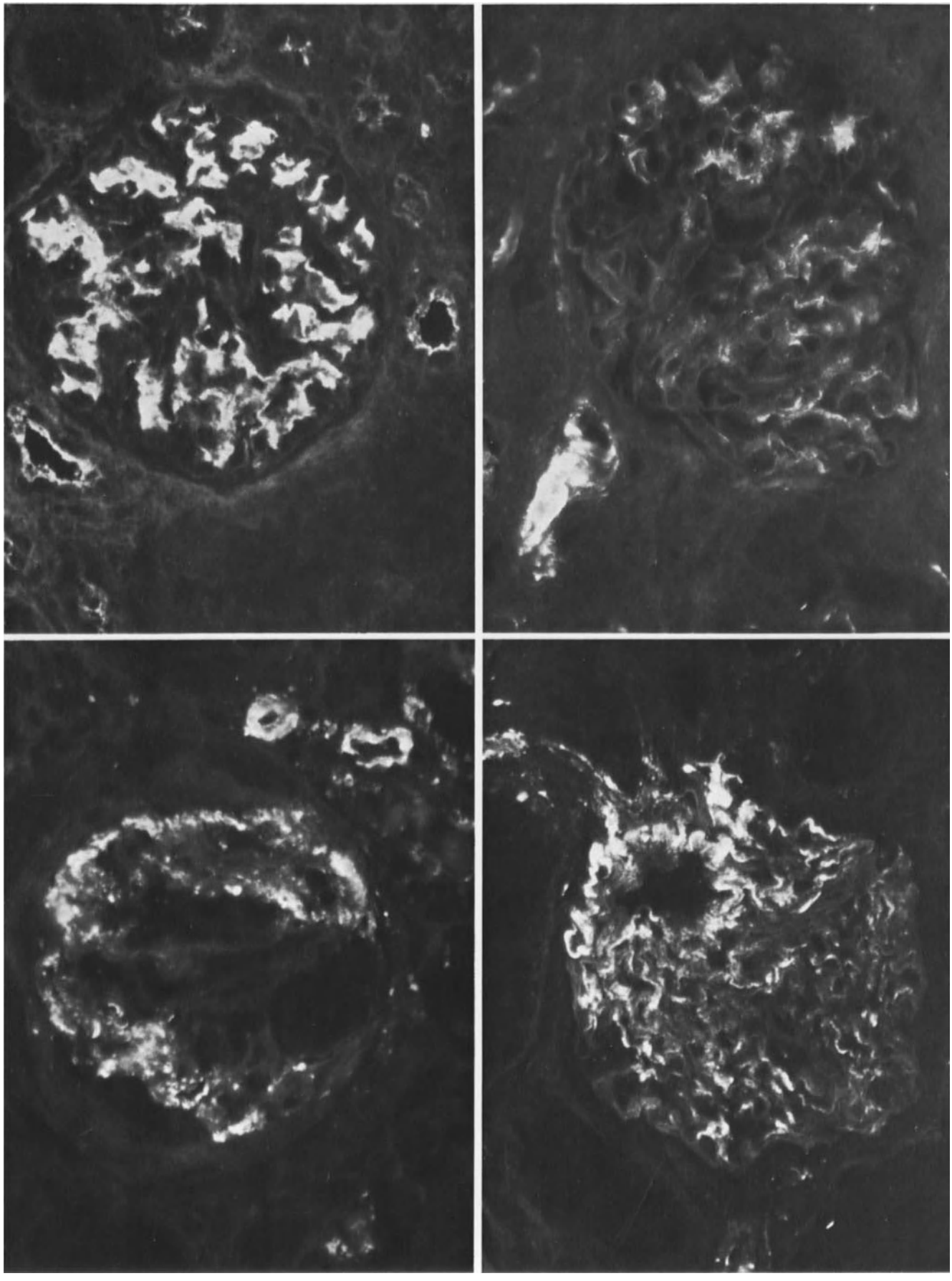
***Non-GN (Nonspecific) Type.*** Nonspecific granular depositions occur in non-GN lesions such as chronic pyelonephritis, hydronephrosis, etc. (Fig. 11.7) and they preferentially occur in the mesangium near the vascular pole (Fig. 11.8) and often with similar IF findings in the wall of the afferent arteriole. These deposits are usually focally or segmentally distributed in contrast to the deposits in GN, which are usually diffusely and globally distributed (Fig. 11.11) and are composed of IgM and/or C3 only. IgG is not present. They can, however, evidence the same intraglomerular and intrarenal distribution pattern as nephritogenic deposits so that in some cases, diffcrentiation from an immunocomplex glomerulopathy is practically impossible. In these cases, LM or EM findings are essential for deciding whether or not the demonstrated components have a nephritogenic effect.

**Fig. 11.5.** Pure mesangial deposits positive for IgA in a case of IgA mesangial GN. Note IgA positivity of tubular epithelial surface. Male, 4 years. IF (×350)

**Fig. 11.6.** Mesangial and peripheral C3 positive deposits in glomerulus of a 3.5-year-old transplant. There are heavy deposits in the vas afferens. Male, 41 years. IF (×700)

**Fig. 11.7.** C3-positive, coarse-granular deposits in the glomerular capillary loop periphery in pyelonephritic contracted kidney associated with so-called overload glomerulitis. Deposits in the vas afferens are also present. Male, 32 years. IF (×220)

**Fig. 11.8.** IgM deposits in a glomerulus which are especially evident at the vascular pole in arteriolosclerosis due to hypertension. Female, 42 years. IF (×400)



11.5
11.6

11.7
11.8

## Significance of Immunoglobulins and Other Proteins in Glomerulopathy

An overview of the relative frequency of occurrence of the various immunoglobulin classes and other proteins in a selection of nephropathies is given in Figure 11.9. A similar tabularization in relation to the basic disease: GN (including glomerular minimal change), non-GN and transplants is given in Figure 11.10.

***IgG*** (mol wt 160,000), with a serum concentration of $1143 \pm 235$ mg/100 ml, constitutes the predominant constituent of the immunoglobulins. It is formed as the AB of the anamnestic immune response and is chiefly directed against bacteria, viruses, toxins and most soluble proteins. The subclasses G1, G2 and G3—but not G4—can activate complement via the classical activation pathway. Thus, the lack of C3 in cases of anti-BM-type GN can be explained by the presence of IgG4 [954].
The physiologic half-life in serum is 25 days. This value, however, does not give information on the turnover of a specific AB during the immune response. In the human, nothing is known about the turnover of IgG in immunocomplexes. Experimental work has shown that AG size and the relative AG and AB concentration exert an influence on the size, solubility and persistence of immunodeposits [544].
It is conceivable that enzymatic degradation procedes differently in BM than elsewhere. In this connection, for example, we noted in one instance of ALG nephropathy persistence of horse gamma globulin in BM of up to 36 months after withdrawal of ALG therapy.

IgG is encountered—with varying frequency—in practically all forms of GN (see Table 11.2). Accordingly, IgG demonstration is one of the most certain immunohistologic indications of the presence of GN (Fig. 12.1). IgG is rarely found in non-GN lesions, and then usually with a focal-segmental distribution. The biological significance of this finding is unknown. IgG occurrence in transplants indicates a GN relapse (Fig. 12.2; [1058a]).

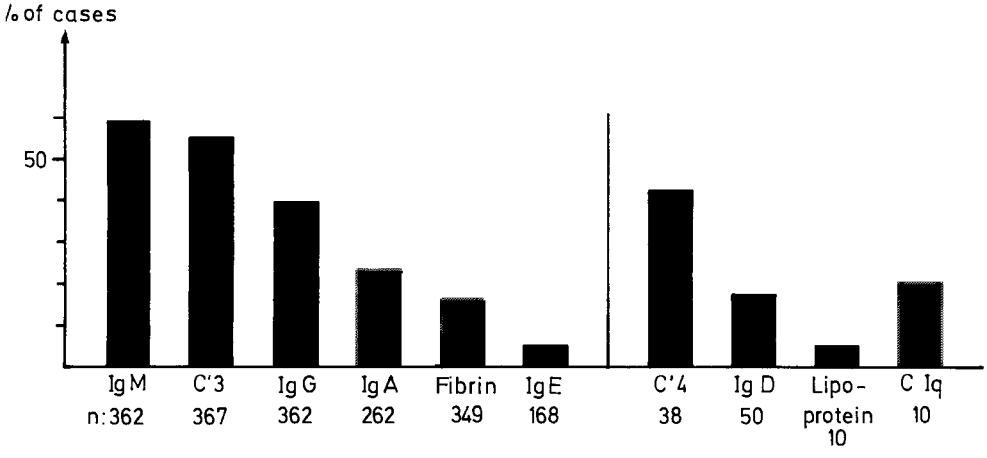



**Fig. 11.9.** Relative frequency of immunoglobulin and other protein findings in glomeruli of 367 unselected cases of different renal diseases. n = number of cases examined for the stated antigen

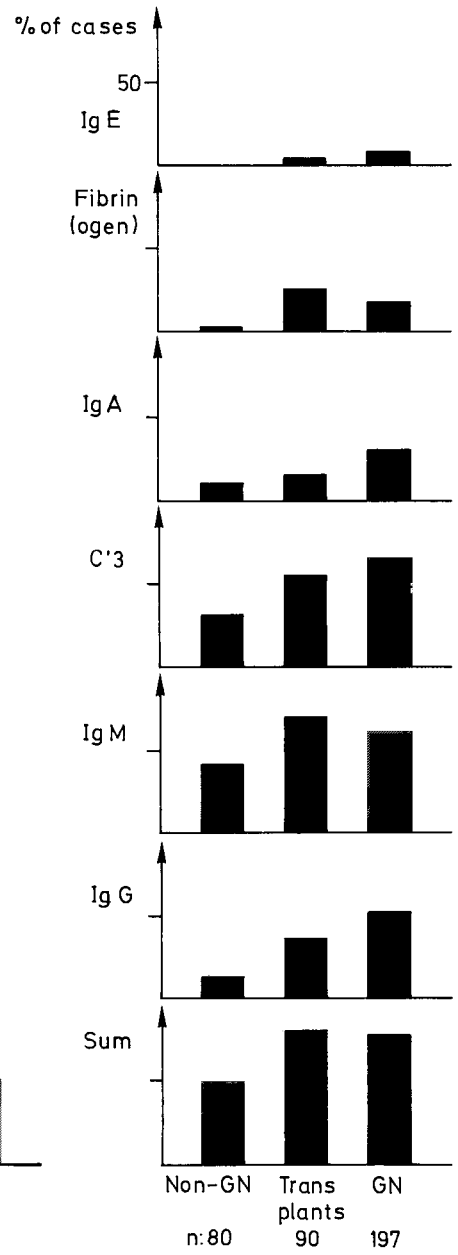



**Fig. 11.10.** Relative frequency of positive IF findings for different proteins in nonglomerulonephritic disease (*Non-GN*), glomerulonephritis including glomerular minimal change (*GN*) and in transplants. Sum = relative frequency of positive cases irrespective of the antigen

Table 11.2. Relative frequency of occurrence of various immunoglobulins, complement and fibrin(-ogen) (own and literature [1136, 1281, 1055, 231, 1092, 28, 1747] findings)

| GN | IgG | IgM | IgA | C3 | Fi |
|---|---|---|---|---|---|
| Endotheliomesangial GN (exudative, exudative proliferative stage) | +++ | (+) | (+) | ++++ | + |
| Endotheliomesangial GN (proliferative sclerosing stage) | ++ | ++ | + | ++ | + |
| Membranoproliferative GN | +++ | +++ | ++ | ++++ | ++ |
| Epimembranous GN | ++++ | ++ | ++ | +++ | + |
| IgA mesangial GN | ++++ | + | ++++ | ++++ | + |
| Segmental focal proliferative GN | +++ | ++++ | + | ++++ | ++ |
| Segmental focal sclerosing GN | (+) | +++ | − | ++ | (+) |
| Transplants | (+) | +++ | + | +++ | ++ |
| Non GN | (+) | ++ | + | ++ | (+) |

++++=75–100%, +++=50–75%, ++=25–50%, +=10–25%, (+)=<10% of cases.

***IgM.*** The serum concentration of IgM (mol wt 900,000) is between 72±23 mg/100 ml and its serum half-life is 5 days. IgM is the AB of the early immune response and it appears before adjustment to IgG synthesis. In the event of subthreshold immunization and with certain AG (pneumococcal polysaccharides, gram-negative bacteria) an IgM response may be the only humoral immune reaction.

Natural AB against bacteria, blood group substances and heterophilic AB belong to the IgM class. IgM is an effective complement activator via the classical pathway. But it appears that aggregated IgM has also the ability to unspecifically bind C3 [271, 752], a fact which would explain the frequent common occurrence of IgM and C3 in non-GN.

IgM is found in practically all forms of GN (Table 11.2). It favors the mesangial location but is also found in persisting BM immunocomplexes. It is especially characteristic for sclerosing FGN (see also [1136]) and—together with C3—for transplant glomerulopathy where it exhibits a global, diffuse distribution (Figs. 11.10, 11.11).

Due to the relatively frequent occurrence of IgM (alone or in combination with C3) in non-GN nephropathies, the discriminating value of a positive IgM finding with respect to GN and non-GN is limited (Fig. 11.10), so the segmental occurrence of IgM alone rather indicates non-GN (Fig. 12.1).

***IgA*** appears in the blood as a monomer, (mol wt 170,000) and has a blood concentration of 204±85 mg/100 ml. Its half-life is 7 days. In secretions it appears as a dimer which is bound via a secretory piece (mol wt 390,000).

IgA can frequently be demonstrated as a superficial coating on distal tubular epithelial cells which may represent extrusion of secretory IgA into the tubular lumen.

In the IgA class are found antiviral, antibacterial, and antitoxic AB. Monomeral IgA does not activate comple-

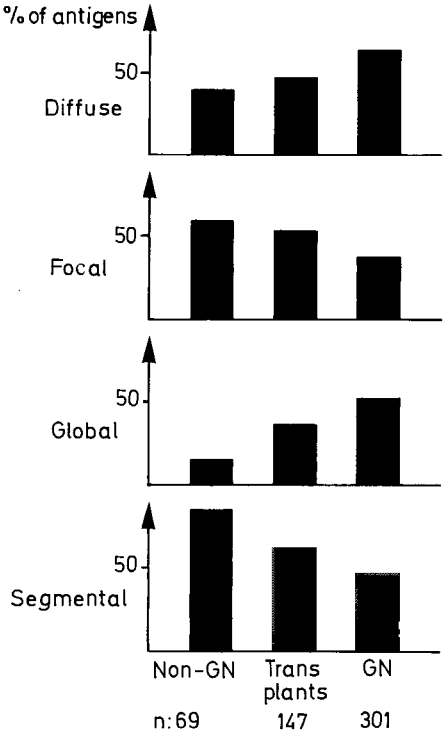



**Fig. 11.11.** Intrarenal and intraglomerular distribution of immunoglobulins (IgG, IgM, IgA) and C3 in nonglomerulonephritic disease (*Non-GN*), glomerulonephritis—including glomerular minimal change—(*GN*), and in transplants. n=number of times antigens demonstrated

ment, but aggregated IgA can activate C3 via the alternative pathway, a fact which may explain our demonstration of IgA in association with C3—but not with C4 or C1q [1052] in four out of four cases of IgA mesangial GN (Table 11.3).

Granular mesangial deposits of IgA together with IgG and C3 are typical but not pathognomonic for IgA mesangial GN [123, 951, 1002], since identical findings may be present in Schönlein-Henoch's purpura as well as more rarely in SLE. In IgA mesangial GN deposits are not always limited to the mesangium, but encroach frequently upon BM near the mesangium [951] as has been illustrated by several investigators [1052, 1136].

The diagnosis of IgA nephritis is only possible with IF, since the IF pattern of IgA nephritis has no constant LM equivalent [743, 1052, 1136]. In our own 15 cases under LM, we observed glomerular minimal change once, proliferative-sclerosing endotheliomesangial GN 10 times, and proliferative FGN 4 times.

Additionally, IgA can be demonstrated in practically all severe forms of GN, to be sure, in a small percent of the cases and with weak intensity (see Table 11.2).

The meaning of the rare occurrence of IgA in non-GN and in transplants is obscure. We have found no relationship to GN relapse in transplants (Fig. 11.10).

Table 11.3. Frequency of occurrence of complement factors in various nephropathies

| Diagnosis | No. of Cases (*n*) | C3 | C4 | C1q | Only C3 positive |
|---|---|---|---|---|---|
| Glomerular minimal change | 15 | $8^{+}/15^{0}$ | 5/15 | 1/9 | 3 |
| Exsudative stage of endotheliomesangial GN | 1 | 1/1 | 0/1 | – | 1 |
| Endotheliomesangial GN: proliferative sclerosing stage | 11 | 10/11 | 3/11 | 1/5 | 6 |
| Membranoproliferative GN | 3 | 3/3 | 1/3 | – | 2 |
| Epimembranous GN | 6 | 6/6 | 4/6 | 1/2 | 2 |
| Proliferative FGN | 11 | 11/11 | 8/11 | 1/1 | 2 |
| Sclerosing FGN | 4 | 1/4 | 0/4 | – | 1 |
| IgA-GN | 6 | 6/6 | 0/6 | 0/6 | 6 |
| Transplants | 10 | 6/10 | $2^{x}/10$ | – | 4 |
| Non-GN nephropathies[a] | 10 | 7/10 | 2/10[b] | – | 5 |

[a] Acute interstitial nephritis ($n=3$), Tubulopathy ($n=2$), Alport's disease ($n=2$), Arteriolosclerosis ($n=2$), Scleroderma ($n=1$).

[b] Acute interstitial nephrits in rubella (1 ×) and tubular disorder of unknown origin (1 ×).

$^{+}$ = No. of positive cases; $^{0}$ = No. of cases tested; $^{x}$ = GN-relapse.

***IgE*** antibodies (mol wt 200,000) are also designated as reagines or atopical AB. They have a very low serum concentration (0.3 mg/100 ml) and a half-life of 2.3 days. In predisposed patients with atopical disease, their concentration may be increased 10-fold. IgE mediates its main biological action by sensitizing mast cells with attendant histamine release in the presence of AG, but it may also activate complement via the alternative pathway.

We demonstrated IgE intraglomerularly in 9/195 of our cases: four times in epimembranous GN, twice in endotheliomesangial GN, twice in proliferative FGN, and once in a transplant with GN relapse. In another series of cases, positive IgE findings were obtained in 30 of a total of 146, and especially in SLE-GN, IgA mesangial GN, extracapillary accentuated GN, chronic sclerosing GN and in exudative and focal proliferative GN [1065a].

In 30 cases of glomerular minimal change (see also [245, 651]) we did not succeed in demonstrating IgE (contra: [542]).

It is unknown whether or not the usually small amounts of glomerular IgE are of importance and in some way of etiologic significance [1065a].

In three cases with positive glomerular IgE findings, IgE serum concentration was increased [1065a] without, however, concomitant atopic disease. In three such cases of our own, one evidenced marked blood eosinophilia, one developed epimembranous GN following gold therapy, and one suffered from atopic disease, including hay fever.

***IgD.*** The biological significance of IgD and its role in GN is unknown. No clear-cut AB activity can be attributed to this class of immunoglobulin at the time of writing. Its biological half-life in serum is 2.8 days and its serum concentration is 3 mg/100 ml. IgD probably does not have the ability to activate complement.

In our own material, we found IgD intraglomerularly in nine cases all of which had severe immunocomplex involvement. In these nine cases we found epimembranous GN, endotheliomesangial GN and proliferative FGN (three cases of each).

Other investigators have also reported on positive IgD deposits partly in granular, and partly in linear form [812, 797]. We have not, as also reported by other investigators [812], been able to get positive IgD findings in non-GN (contra: [1600]: diabetic glomerulosclerosis one in four, amyloidosis five in eight).

## Complement [141] and Properdin System

The extremely complex complement and properdin systems play a key role for the understanding of the various forms of GN, of their pathogenesis and possibly of their

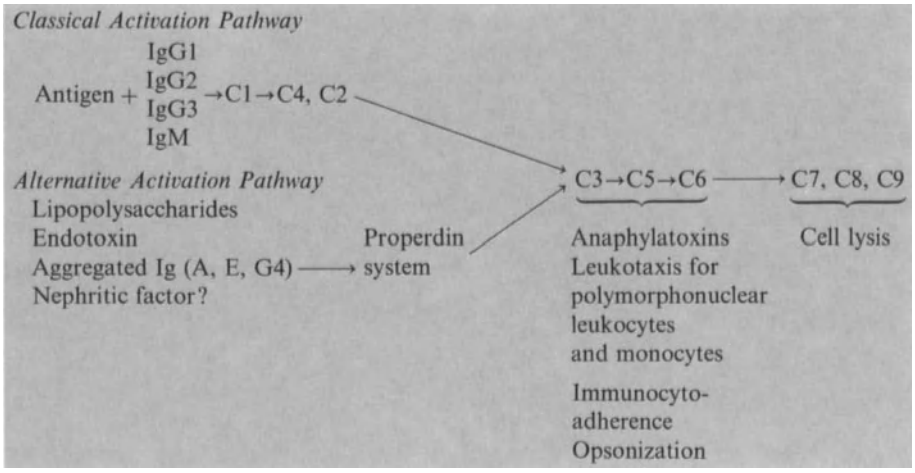



**Fig. 11.12.** Simplified scheme of activation and biological activities of the complement cascade

etiology. The complement system consists of nine enzymes designated as C1 to C9.

In classical complement activation (Fig. 11.12) activation of complement components—by immunocomplexes as well as other substances—occurs in the following sequence: C1, C4, C2, C3 and then C5–C9. Direct activation of C3 by an alternative pathway via the properdin system may occur independently of the presence of AG-AB complexes and with omission of the C1, C2 and C4 components [582].

Biologically important activators of the properdin system and, accordingly, of the alternative pathway, are aggregated immunoglobulins and endotoxin. The latter is also capable of producing a cytotoxic action on the RHS (endothelial and mesangial cells).

Activation of the complement system by the classical or alternative pathway leads to the generation of active complement components of inflammatory promoting potency, increased vascular permeability, chemotaxis, membrane and cell injury.

In most of the available IF studies, only the C3 component was determined which is present in almost all cases of GN but also in some non-GN lesions and in transplanted kidneys. From Figure 11.12 it is apparent that the pathway of complement activation is not determined by the simple demonstration of C3 but that the search for either C1q and C4 (classical pathway) or properdin (alternative pathway) is essential. But as is apparent in Table 11.3, there is no parallel positivity for C4 and C1q, therefore both complement factors must be tested in a given case to be sure which pathway is used for complement activation.

Currently available results from serologic and IF studies of individual complement components and of the properdin system [1379, 1724] have shown that membranoproliferative GN occupies a special position in the GN group of diseases. In this GN type, C3 and properdin are frequently demonstrable in the glomeruli, while the other components can only be shown so in a small percentage of the cases [1092, 1724] (see also Table 11.3). In serum, this finding corresponds to a decrease of C3 with maintenance of normal concentration of the first complement components (C1, C2 and C4).

It follows that in the majority of membranoproliferative GN cases the activation of complement is via the alternative pathway in which a so-called C3 nephritic factor [141, 1092, 1550, 1650] as well as other poorly defined serum factors are thought to play a significant role. In a minority of cases, complement activation follows primarily or in addition the classical pathway (Table 11.3).

The situation in exudative/proliferative endotheliomesangial GN (so-called acute poststreptococcal type of GN) is uncertain. In this form, immunologic study demonstrates only complement and properdin in some of the cases [1724] a finding which suggests that in some of these cases activation of complement possibly occurs via the alternative pathway. In our material C3 was in 6 out of 11 cases the only complement component demonstrated (Table 11.3).

It also appears very likely that alternative pathway activation of complement also plays the major role in IgA mesangial GN ([1052, 1668]; Table 11.3).

In all other forms of GN, the part played by the alternative pathway is obscure [1379, 1668].

IF demonstration of properdin and of the early and late—C1, C4, C2, C3—components in association with the determination of the respective components in blood (for blood concentrations see [245, 1397]) may be expected to provide increased insight into the various activation pathways in the various form of GN (Table 11.3) and other nephropathies. Such correlated studies may also contribute to refined differential diagnosis of membranoproliferative and the other forms of GN.

### Fibrin

In addition to the well established mechanism of activating blood coagulation by tissue thromboplastin (extrinsic

mechanism) and the Hageman factor via surface contact (intrinsic mechanism), other factors can lead to the formation of fibrin [1059]. Potentially the most important of these factors is the complement system which, subsequent to activation by AG-AB complexes [715, 800] or by the alternative pathway, e.g., via endotoxin, staphylococcoci, protein A or immunoaggregates, is capable of triggering the clotting system [1775].

IF study reveals four fibrin patterns—listed below—in the glomerulus (attention should be paid to artifacts which may arise by the squeezing of the cylinder or pinching of the renal vessels prior to biopsy):

1. In the capillary lumen in local or generalized intravasal coagulation as round or sausage-shaped forms.
2. As a diffuse insudation of the entire glomerular tuft or of individual lobules in capillary loop necroses or infarcts respectively (Fig. 11.13).
3. In the mesangium or along the peripheral BM in granular form in association with immunocomplexes (Fig. 11.10).
4. In non-GN disease (especially in hypertension, scleroderma, eclampsia, and transplants) as fine or coarse granules (Figs. 11.10, 11.14; see also p. 514).

It is difficult to determine the pathogenesis of a given pattern of fibrin deposits. Either systemic (intravasal coagulation) or local processes (necroses, endothelial injury, [1059]) may be involved. The significance of the coagulation-promoting action of AG-AB-complexes can hardly be proven in any given case. The demonstration of fibrin can, under certain circumstances, be indicative of an active inflammatory process. Thus, for example, extracapillary crescents (Fig. 11.13) are generally interpreted as a consequence of the activation of the fibrin system [282, 1068].

IF demonstration of glomerular fibrin is usually accompanied by urinary elimination of fibrin metabolites [986].

The frequent failure to detect fibrin by EM in biopsies positive by IF for glomerular fibrin may be explained by the fact that IF also detects fibrinogen and fibrin split products which have no periodicity with EM.

## Additional Glomerular IF Findings
(Fig. 11.15)

### Obsolescent Glomeruli

Completely obsolescent glomeruli are generally IF negative. In early or partially obsolescence, however, coarse clumps of IgM and/or C3 deposits are often encountered in GN, non-GN (Fig. 11.17) as well as in transplants (Fig. 11.17). Other immunoglobulins, e.g., IgA or IgG, are extremely seldom demonstrable (about 5% of all cases in obsolescence (Fig. 11.17). In all cases, the depositions appear to result from prolonged local circulatory disorder and/or membrane alterations. Only early infarction is occassionally distinguished by diffuse insudation of the entire capillary loop convolute with fibrin(-ogen). IF findings in either completely or partially obsolescent glomeruli do not permit conclusions relating to the basic disease.

### Capsular BM

In about 5% of cases, IgM and/or C3 can be demonstrated in capsular BM irrespective of the basic disease (Fig. 11.16). Involvement of the capillary loop in these cases may or may not be present.

### Podocytes

In about 20% of the cases of GN, podocytes demonstrate protein droplets (Fig. 11.17) which usually contain IgG and IgM. All other immunoglobulins as well as fibrin (-ogen) and complement are demonstrable in less than 5% of the cases. In segmental focal sclerosing GN (Fig. 11.18), protein droplets in podocytes are especially frequent. However, they are not specific, and are also found in non-GN diseases e.g. diabetes mellitus (6%) and in transplants (4%).

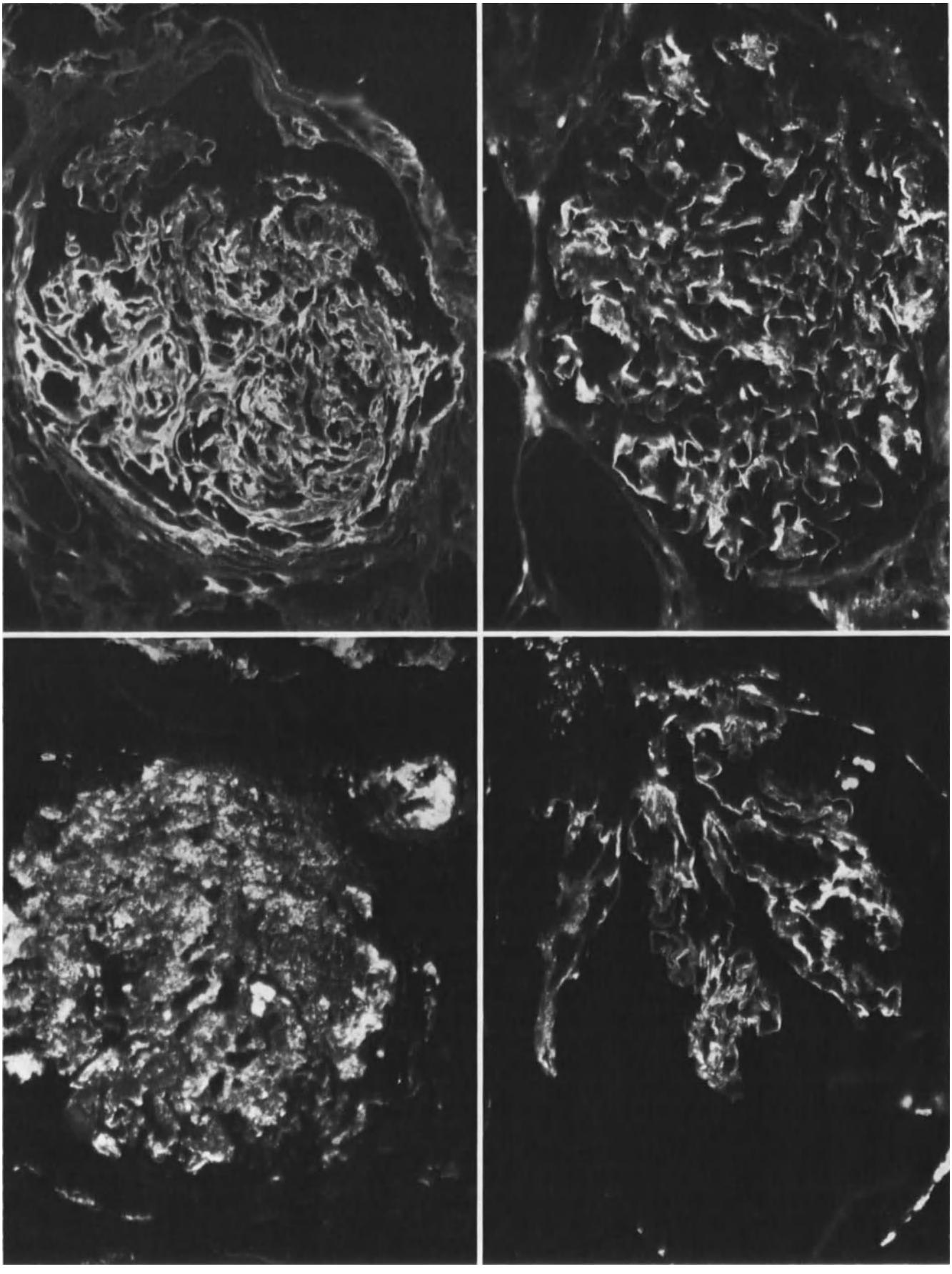
In all our cases with podocytic resorption droplets, a clinically significant proteinuria is present. Podocytic protein droplets are the expression of an increased resorption of podocytes covering severely injured capillary loop segments.

**Fig. 11.13.** Extracapillary accentuated GN with diffuse insudation of the glomerulus with fibrin(-ogen). Fibrin(-ogen) is also present in the extracapillary crescent. Female, 70 years. IF (×450) ▷

**Fig. 11.14.** Fine-granular peripheral and mesangial deposits of fibrin(-ogen) in glomerulus of 5-month-old transplant. Male, 56 years. IF (×450)

**Fig. 11.15.** IgM positive, by and large obsolescent glomerulus in a 2.5-year-old transplant. Male, 28 years. IF (×380)

**Fig. 11.16.** Fine-granular, confluent (pseudolinear) staining of the peripheral glomerular BM with C3 in extracapillary accentuated endotheliomesangial GN. Note the C3-positive granular deposits in the capsular BM. Same case as in Figure 11.13. Female, 70 years. IF (×380)



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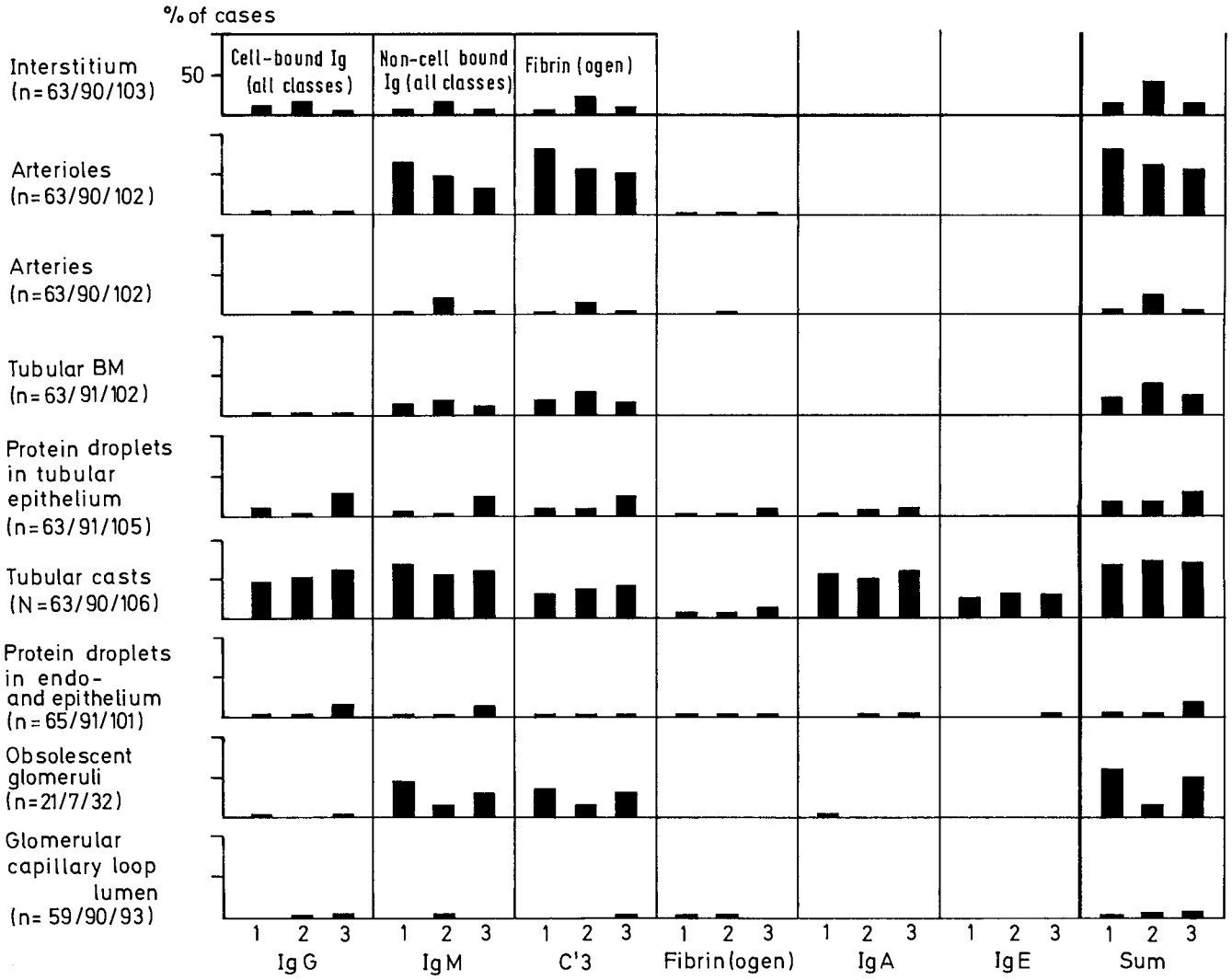



**Fig. 11.17.** Relative frequency of IF findings in various renal structures in nonglomerulonephritic disease (1), transplants (2), glomerulonephritis (3). Numbers in brackets underneath the various renal elements state number of examined cases. (n = nonglomerulonephritic disease, transplants and GN.) Sum = relative frequency of positive IF findings independent of the participating antigen. Protein droplets in endo- and epithelium refer to glomeruli only

### Capillary Lumens

Clumpy, coarse masses of immunoglobulins deposited within the capillary lumen are very rare (< 5% of cases); their significance in a given case is often unknown (Fig. 11.17). Coarse clumps of protein thrombi are characteristic for cryoglobuinemia and they also are observed as part of other hyperviscosity syndromes e.g. in Waldenström's disease (see [1135]). Therefore, in the presence of cases of the above mentioned finding, a clinical examination for cryoglobulinemia should be undertaken. For intravasal coagulation, see p. 493.

## IF Findings in Nonglomerular Structures

### Tubules

A reliable and statistically highly significant—although not absolute—indication of proteinuria are resorption droplets in the epithelium of the proximal tubules (Fig. 11.19). These are the IF equivalent of hyaline (fibrinoid) droplet protein storage, and they are generally positive for IgG, IgM, C3, and, infrequently, for IgA and fibrin(-ogen). From our material, we were not able to demonstrate a characteristic diagnostic pattern for

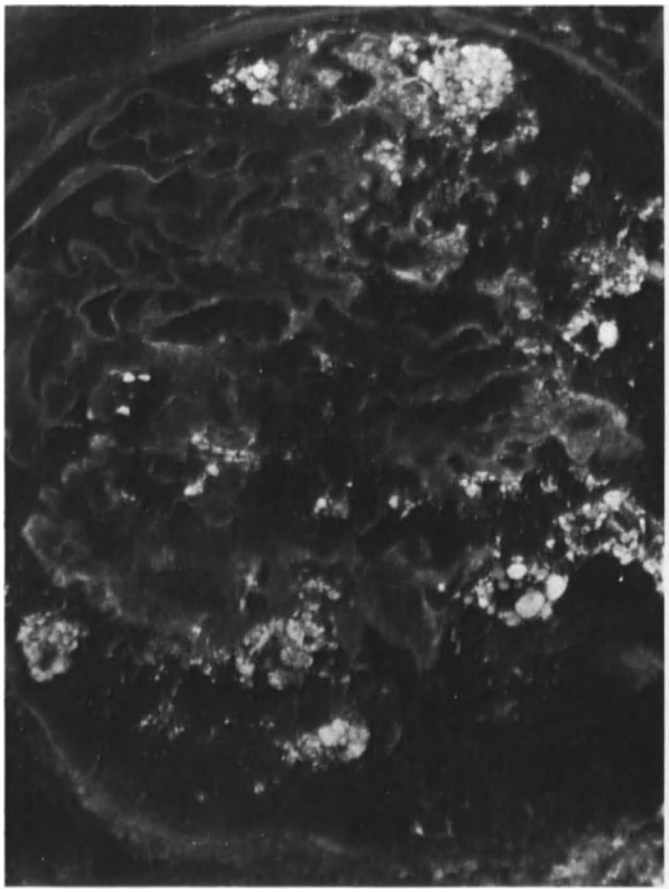


**Fig. 11.18.** Podocytic protein reabsorption droplets positive for IgG in pyelonephritic contracted kidney associated with overload glomerulitis. Same case as in Figure 11.7. Male, 32 years. IF (×600)

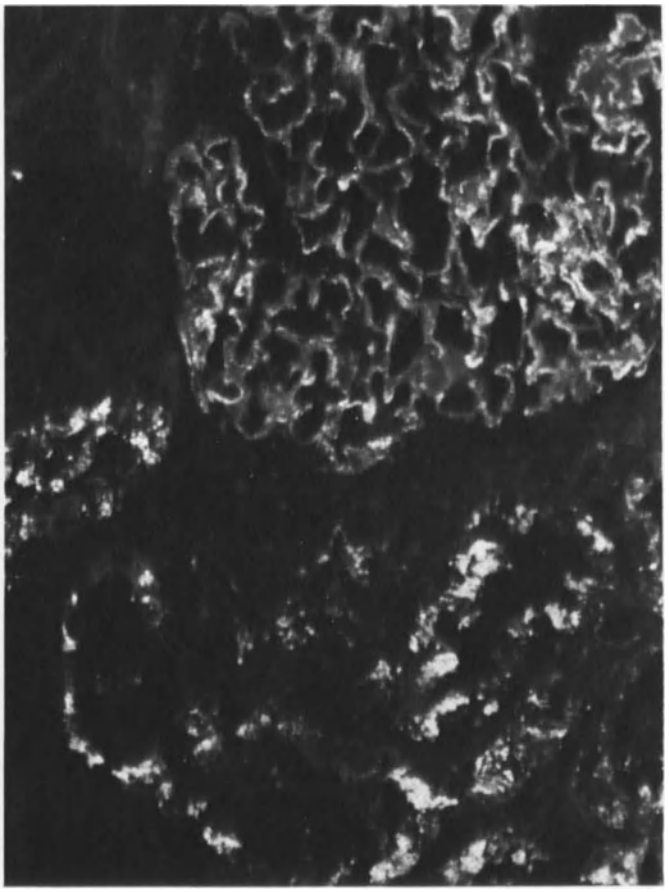


**Fig. 11.19.** Global finely granular IgG deposits in the glomerular capillary loops in epimembranous GN. Massive protein droplets of IgG in the tubules. Female, 28 years. IF (×480)

the various GN or for selective and nonselective proteinuria respectively (Fig. 11.17).

Tubular casts (Fig. 11.20) are a very frequent finding in all nephropathies. In contrast to tubular resorption droplets, they are not correlated with proteinuria. Neither does their qualitative composition bear any relation to the kind of nephropathy or proteinuria, viz. selective or nonselective. Tubular casts generally contain IgG, IgM, C3, IgA – often especially strongly positive – and IgE, as well as fibrin(-ogen). The less common occurrence of fibrin(-ogen) in tubular casts and resorption droplets (Fig. 11.17) deserves special attention since fibrin split products are demonstrable in the urine of such cases [986].

The epithelial surface of distal tubules rarely exhibits a finely granular IgA-positive coating which is an expression of tubular IgA secretion (Fig. 11.20). With one exception, we have observed this finding exclusively in GN and transplants. In transplants, there was no relationship to the presence of an acute rejection; but in five out of nine of such transplant cases, we did encounter viral infections (HB-Ag three times, herpes simplex and cytomegaly each once). Among 11 GN patients demonstrating IgA-positive tubular surfaces, SLE and Schönlein Henoch's purpura were each present once and four cases demonstrated an acute respiratory infection. The diagnostic significance of this tubular IgA finding is unclear.

In both non-GN and GN diseases, the tubular BM demonstrates coarse granular or short linear staining reactions for IgM and C3 in 22% and 24% respectively (Figs. 11.17, 11.21) of the cases and in 40% of transplants. In all nephropathies (GN and non-GN) a significant correlation between the presence of positive IF findings and tubular atrophy under LM is present; this is not the case for transplants, in which we ascribe positive tubular IF findings to repeated acute rejection episodes.

Predominance of IgM and/or C3 findings in obsolescent glomeruli, in degeneratively changed BM of Bowman's capsule, in tubular BM, and probably also in arteries and arterioles (Fig. 11.17) indicates a common underly-

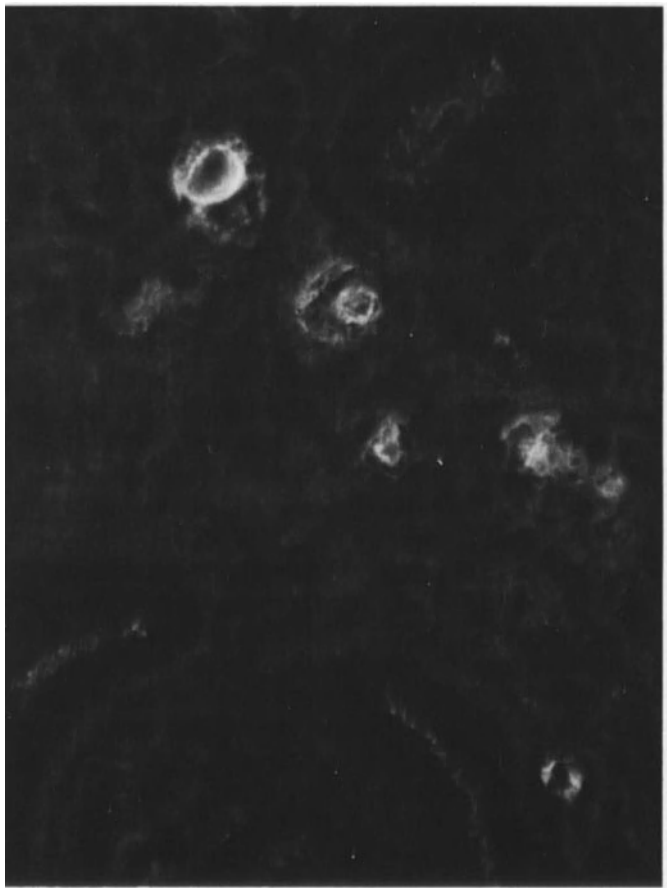


**Fig. 11.20.** IgA positive tubular cell surface in a renal transplant with cytomegalovirus infection. Male, 41 years. IF (×300)

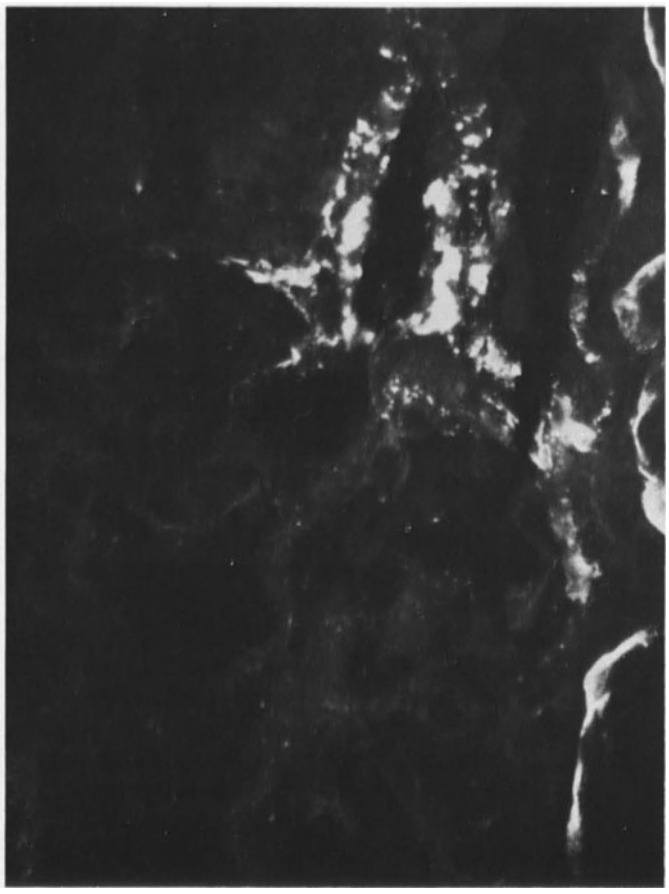


**Fig. 11.21.** C3 positive, coarse deposits in the vas afferens in arteriolosclerosis due to hypertension. The neighboring tubular BM also evidences deposits. Female, 42 years. IF (×380)

ing pathogenetic principle as being operative for the occurrence of these immunoglobulins. Degenerative BM changes (thickening and fragmentation) and the resulting impairment of permeability in association with other insudation-promoting factors (e.g., circulatory disturbance, pressure increase) are the most probable explanation for the trapping of especially high molecular weight proteins, such as IgM. The concomitant occurrence of complement (C3) is possibly an expression of the nonspecific binding of complement to aggregated IgM.

We were able to demonstrate IgG (in granular or linear form) along tubular BM in only four cases: twice in transplants and once each in Moschkowitz's syndrome and epimembranous GN. Similar findings in SLE-GN and idiopathic hematuria [1035] as well as in transplants [27] are interpreted as binding of auto-antibodies on tubular AG [1035, 1181].

### Blood Vessels

Arterioles are obviously structures of low resistance (Figs. 11.17, 11.21) [747] as evidenced by positive IF findings in 80% of non-GN and in 53% of GN in which IgM is present in 67% and 33% respectively and C3 in 81% and 50%. In contrast, presence of IgG was – with one exception of malignant nephrosclerosis – restricted to GN.

Hypertension (blood pressure ≧ 160/100 mm Hg) is present in 40–45% of mild cases of IF-positive arteriolopathy and in 65–70% of severe cases. In view of the fact that the procentual occurrence of hypertension is the same in GN and non-GN, it is a remarkable fact that there is an obvious difference in the frequency of IF arteriolopathy in the two kinds of lesions. The finding suggests that other insudation-promoting factors (e.g., ischemia, interstitial inflammation, diabetes mellitus, see p. 514) may also be involved in the evolution of circumscribed arteriolosclerosis. This is also suggested by the frequent positive IF findings of IgM and/or C3 in arterioles of transplants since in this group of patients, the percentage of hypertensives is very small.

The presence of fibrin(-ogen) in arterioles and small arteries is supposedly indicative of malignant hypertension in nontransplant patients and of an acute vascular rejection in patients with renal transplants.

The occurrence of IgM and/or C3 arteriopathy in non-GN (8% of our cases) and in GN (4%) is relatively insignificant (Fig. 11.17). Hypertension was present in all of these cases. The infrequent presence of IgG in arteries and arterioles—usually in conjunction with GN—arouses suspicion of vasculitis which, however, we were unable to verify in the above-cited cases.
The frequently positive IF findings in the arteries of transplants (24%) are sufficiently accounted for by the transplantation vasculopathy. It is questionable, however, as to whether or not the demonstrated arterial and arteriolar immunoglobulins are the expression of a binding of cytotoxically preformed AB or merely of an unspecific insudation of immunoglobulins. Although we have been able to demonstrate a slightly significant relationship between the presence of preformed cytotoxic AB and the severity of transplant vasculopathy, we do not believe that the immunohistologic findings represent in all cases the IF correlate of fixation of cytotoxic AB since in the arteries and arterioles, only 5% of the immunoglobulins involved were of the IgG class while cytotoxic AB are said to belong predominantly to this class [1181]. In this situation too, one is probably dealing in some cases with a consequence of an unspecific insudation of IgM and/or complement.

### Interstitium

In cellular infiltrates, immunoglobulin-producing plasma cells can be demonstrated. In 20 renal transplants of our own, IgM-producing plasma cells predominated in 75% of cases where IgG producing plasma cells were found only in 45%. Plasma cells with specificity for other Ig classes were absent. In contrast, in GN and in non-GN, IgG-, IgM-, IgA- and IgE-producing plasma cells were detected each in 5 of 10 cases.
Increased staining in the interstitium of immunoglobulins (especially IgG) and fibrin(-ogen) usually occurs during interstitial edema (Fig. 11.17). The higher incidence in transplants is explained on the basis of acute or chronic rejections. The presence of fibrin(-ogen) is usually associated with fibrin-split products in urine [986].

## Cryoglobulins and Kidney

Cryoglobulins (see [95, 201, 592]; for cryofibrinogenemia: [1524]), better defined as cryoimmunoglobulins, are complexes of immunoglobulins composed of one or different classes of immunoglobulins which, depending on their serum concentration, precipitate reversibly between 5° C and 30° C.

### Nosology

From the immunologic standpoint, three types of cryoglobulins can be differentiated [201]: (1) monoclonal cryoglobulins, (2) mixed cryoglobulins with a monoclonal component and (3) mixed polyclonal cryoglobulins.
Monoclonal cryoglobulins consist exclusively of one monoclonal immunoglobulin of which IgG and IgM cryoglobulin occur in about the same frequency and are much more frequent than IgA cryoglobulins [592].
In general, the serum concentration of monoclonal cryoglobulins is more than 1 mg/ml [201]. Mixed cryoglobulins with a monoclonal immunoglobulin component contain, beside the monoclonal immunoglobulin, a polyclonal immunoglobulin (usually IgG). These mixed cryoglobulins generally consist of IgG and IgM [201] or, less frequently, of IgG (polyclonal) and IgG (monoclonal) or IgG and IgA. Their serum concentration usual exceeds 1 mg/ml.
The mixed polyclonal cryoglobulins also consist predominantly of IgM and IgG, but their serum concentration is rarely more than 1 mg/ml [201]. These forms may also contain IgA, or lipoprotein, alpha-2-microglobulin and complement factors [15, 95, 956].
In addition to the frequent presence of rheumatic factor activity in mixed cryoglobulins [95, 592], they possess—rarely—AB activity against nuclear factors [95, 201]. In a few instances, DNA was demonstrated in the cryoglobulin fraction [95]. There is much controversy as to whether other AB activity (for example against cytomegalovirus, bacteria, erythrocytes and complement) can or cannot be enriched in cryoglobulin fractions [95, 201].
From the clinical viewpoint, two groups of cryoglobulinemia may be differentiated: (1) essential (monoclonal or mixed) cryoglobulinemia (no known basic disease) and (2) secondary (monoclonal or mixed) cryoglobulinemia (known basic disease) [95, 201, 592].
So-called "essential" monoclonal cryoglobulinemias may be the first symptom of a plasmocytoma or of Waldenström's disease, which become clinically manifest years later [201, 592]. The essential mixed cryoglobulinemias may be the initial indication of an autoimmune disease, which likewise may become apparent after many years (see below). In a large series of cases with follow-up over many years [201] 29 out of 86 cases had to be classified as essential cryoglobulinemia; 22 out of 29 cryoglobulins were of the mixed polyclonal variety.
Secondary monoclonal cryoglobulinemias are especially found in plasmocytoma and Waldenström's disease and, less frequently, in malignant lymphoma [201]. Secondary mixed cryoglobulinemia of the poly- or monoclonal type is found in a variety of conditions such as Waldenström's disease, plasmocytoma, malignant lymphoma, periarteritis nodosa, SLE, rheumatoid arthritis Sjögren's syndrome, syphilis, kala-azar, lymphogranuloma venerum,

infectious mononucleosis, cytomegaly, subacute bacterial endocarditis, sarcoidosis, chronic hepatitis and glomerulonephritis [201, 469, 592, 813, 1022, 1291].

Mixed cryoglobulins are found in considerable frequency, especially in proliferative (endotheliomesangial) glomerulonephritis (with or without crescents) as well as in post-streptococcal and membranoproliferative GN [6, 605, 1057, 1058]. Cryoglobulins appearing within the framework of infectious diseases, GN and in SLE are often transitory, and demonstrate low serum concentrations [201, 1057, 1058].

Although 50% of the monoclonal cryoglobulinemias and 15% of the mixed types can take an asymptomatical course [201], the clinical picture in the symptomatic cases is very similar. One encounters—in decreasing order of frequency—skin symptoms: especially purpura, acral necrosis, urticaria, acrocyanosis, Renaud's phenomenon, arthralgia, renal symptoms, polyneuropathy, lymphadenopathy and hepatosplenomegaly [201, 592, 1075].

## Renal Changes

Two types of renal change may be recognized in cryoglobulinemia: those characterized by protein thrombi alone and those characterized by GN.

***Protein Thrombi.*** In monoclonal and mixed cryoglobulinemias (with a monoclonal component), typically large protein thrombi, such as occur in plasmocytoma and Waldenström's disease, are present. The thrombi completely occlude the glomerular capillary loops and other renal vessels, show in IF the same immunoglobulin pattern as serum cryoglobulins [201, 1667], and can lead to acute renal failure. In later phases—and as a result of repeated episodes of intravasal protein thrombus formation—findings similar to chronic, nondestructive interstitial nephritis may develop, as illustrated by one of our cases of a 46-year-old female patient with a 10-year history of essential, mixed (IgG, IgA) cryoglobulinemia. In this case, no glomerular protein thrombi were present, but there were nonoccluding protein thrombi in the intertubular capillaries. A similar finding in two cases of mixed cryoglobulinemia (IgG, IgM, IgA) has been described by other investigators [1517].

***GN: LM and EM Findings.*** GN develops in about one-fifth to one-third of all cases of cryoglobulinemia [201, 501]. GN is especially frequent in mixed cryoglobulinemia with a monoclonal component, but may also develop in mixed polyclonal cryoglobulinemia. Since it is not always possible to determine whether or not cryoglobulinemia is a cause or effect of GN or merely an insignificant epiphenomenon, the following discussion will consider only those cases of GN in essential cryoglobulinemia. In the presently available literature, there are 26 reports of GN to which we add two of our own [53, 201, 311, 501, 577, 859, 1014, 1128, 1138, 1254, 1517, 1595, 1667].

A very characteristic picture of GN in cryoglobulinemia has emerged from the above-cited observations. In all cases, proliferative GN, partly diffuse and partly of focally accentuated character, is present and is accompanied in about one-half of the cases by crescents. A modern nosologic classification cannot, unfortunately, be formulated on the basis of the descriptions given in the quoted literature. Membranoproliferative GN (Fig. 11.23) was present in five cases, two of which were our own [1128, 1138, 1517]. There was one case of mixed epimembranous and membranoproliferative GN with irregular mesangial proliferation and extra-capillary crescents [1138]. Glomerular capillary loop necrosis was mentioned once [1075]. In about one-third of the cases [53, 75, 201, 1014, 1075, 1138, 1595] there occurs an arteritis of a few small and larger renal vessels characterized by fibrinoid necrosis of the vascular wall, extravasation of erythrocytes and a perivascular inflammation of lymphocytes, plasma cells or polymorphonuclear leukocytes [53, 75, 201].

Perivascular granuloma may rarely be present [1138]. The renal vasculitis is usually accompanied by a similar cutaneous vasculitis (see also [201]).

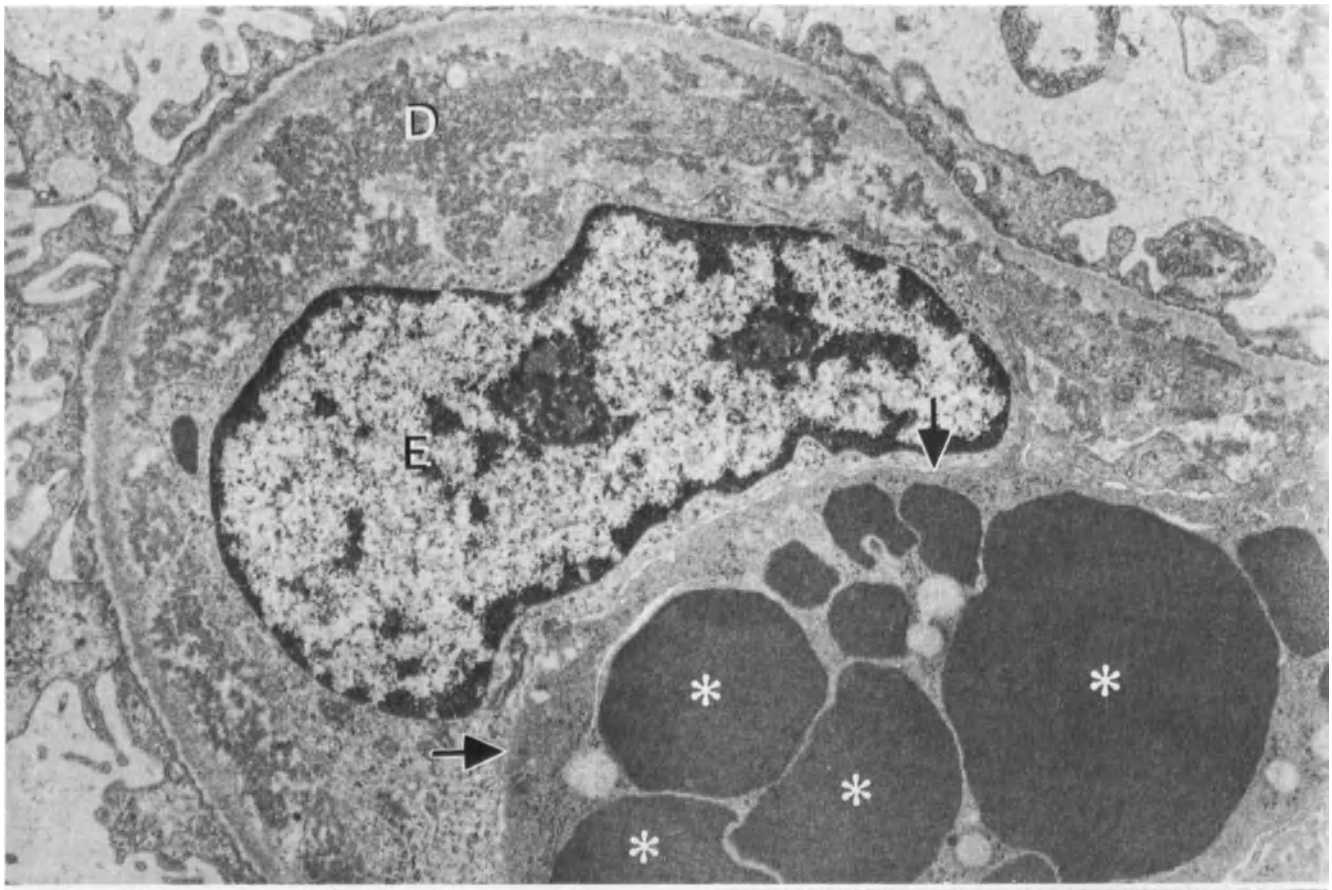
A further characteristic, likewise observed in about one-third of the cases, are voluminous partially occlusive intravasal/intraglomerular protein deposits ('thrombi') (Fig. 11.23; [53, 201, 1075, 1138]). Similar thrombi have also been observed extrarenally [207, 947].

**Fig. 11.22.** Same case as in Figure 11.23. Coarse-granular subendothelial deposits (*D*) and osmiophylic spheres (*) in intraluminal monocyte (cell border of monocyte: →), slight fusion of foot processes. Endothelial cell (*E*). Female, 64 years. EM (×9640) ▷

**Fig. 11.23.** Membranoproliferative GN with 'hyaline' thrombi (giant deposits →) in cryoglobulinemia. Female, 64 years. PAS (×600). Inset: 'hyaline' thrombus in peripheral glomerular loop, PAS (×1875)

**Fig. 11.24.** Slightly osmiophilic spheres (*) in the lumen of an intertubular vessel in a case of cryoglobulinemia. Female, 46 years. EM (×1740)

**Fig. 11.25.** Higher magnification of subendothelial deposit (seen in Fig. 11.22) with crystalloid (tubular) structure (*). Podocyte (*P*), lamina densa (*LD*). Female, 64 years. EM (×46,000)

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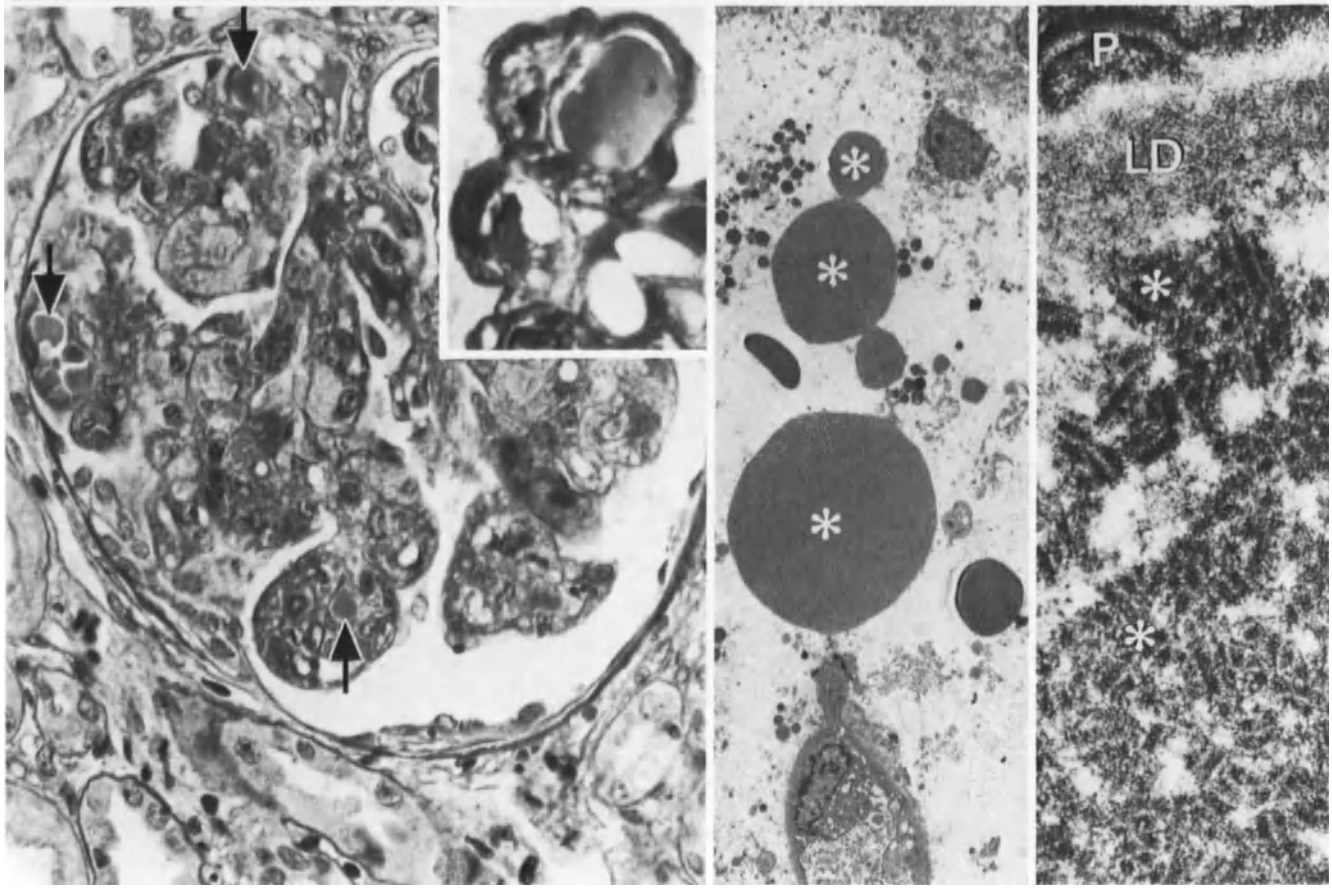


11.23
11.24
11.25

These intravasal/intraglomerular protein thrombi appear in LM to be fundamentally extracellular, a finding we have confirmed in EM study for the thrombi in the intertubular capillaries (Fig. 11.24). In our two cases of cryoglobulinemia with GN, we have demonstrated large monocytoid cells containing voluminous protein inclusions in glomerular capillary loops (Fig. 11.22, see also [1128]).
Additionally, with EM, peculiar crystalloid structures can occassionally be demonstrated in extracellular deposits (Figs. 11.22, 11.25); these crystalloid structures are similar to those found in the in vitro cryoprecipitates ([311]; see also [158]).

***IF Findings.*** Findings from 20 cases of essential cryoglobulinemia investigated with IF are available [53, 75, 201, 577, 1014, 1128, 1138, 1595] including one of our own cases. One case out of 20 was completely negative [311, 1014], i.e., no immunoglobulins were demonstrable, even in the renal eluate; while in the rest of the cases—with 2 exceptions [1138, 1595]—an immunoglobulin pattern identical to the cryoglobulin composition as well as complement (C3) was demonstrated. Only once was it possible on the basis of rheumatic factor activity [53] to establish the identity of immunoglobulins deposited in the glomeruli with the cryoglobulin isolated from the serum.

## Prognosis

The prognosis of GN in cryoglobulinemia appears, in general, to be extremely poor. Most afflicted patients die within a few weeks or months following diagnosis in uremia [53, 75, 577, 1014, 1075, 1517] (one case of our own). In our second case, the disease progressed with episodic attacks during a period of several years.

## Etiology and Pathogenesis

The etiologic significance of cryoglobulins in GN as well as in renal and nonrenal vasculitis is established by the fact that in essential cryoglobulinemia, immunoglobulin patterns of cryoglobulins in the serum, glomerulum and skin vessels are identical [872].
A further proof is high rheumatic factor activity in glomerular immunocomplexes [53] as in cryoglobulins isolated from the serum. With EM, identical crystalloid structures have been demonstrated in glomerular deposits and in cryoprecipitates [311].
It is generally recognized today that cryoglobulins represent AG-AB complexes, a concept repeatedly confirmed by the demonstration of the rheumatic factor activity of mixed cryoglobulins [592]. The simultaneous deposition of immunoglobulins and complement in the glomerulus and the decrease of serum complement in essential cryoglobulinemia [53, 201, 577, 1014, 1595] both indicate complement activation by cryoglobulins, a concept confirmable by in vitro tests [1378]. Additionally, passive transfer of mixed cryoglobulins to guinea pigs produces vasculitis and GN [95, 328].
Despite the evidence cited, the pathogenesis of GN has not been fully explained, since at body temperature (37° C) cryoglobulin precipitates in serum are extremely rarely encountered, and then only in scant amounts [859, 1075, 1254]. Perhaps cryoprecipitation sets in at higher temperatures with increasing serum concentrations [592]. A fact militating against this concept is the finding that all data relating to essential cryoglobulinemia with GN report, with one exception [53] serum concentrations scarcely exceeding 1 mg/ml.
On the other hand, the low cryoglobulin serum concentrations could simply be the consequence of the deposition of the cryoglobulins in the glomeruli and skin as well as of the elimination of cryoglobulin complexes by RHS.
The etiologic, pathogenetic and prognostic significance of cryoglobulins occurring within the framework of secondary cryoglobulinemia such as in post-streptococcal GN, idiopathic GN, etc. awaits elucidation.
As noted previously, this finding may be merely the reflection of an insignificant epiphenomenon. This concept is supported by the lack of concordance between the immunoglobulin pattern of serum cryoglobulins and the IF-demonstrable immunoglobulins in the glomeruli [6, 1057, 1058] and by the lack of correlation between cryoglobulinemia on the one hand and on the other morphology, clinical activity of GN, and the reduction of the serum complement level respectively [1057, 1058]. However, the persistence of cryoglobulins in cases of GN may be associated with a chronic course [6, 1057, 1058]. This leaves little doubt as to their possible pathogenetic and prognostic significance in a given case.
In contrast to post-streptococcal GN, cryoglobulins assume greater significance within the framework of SLE in which lupus patients with cryoglobulins develop GN considerably more frequently than those without, and in which the clinical activity of the disease and the reduction of the serum complement level correlate significantly with the presence of cryoglobulins [272, 657, 872, 1560]. The etiologic and pathogenetic significance of cryoglobulins in SLE is further emphasized by their demonstration in glomeruli [872] as was possible in essential cryoglobulinemia [53].

# 12. General Differential Diagnosis Between Non-Glomerulonephritic Nephropathies and Glomerulonephritis

In order to obtain objective parameters for differential diagnosis between GN and non-GN nephropathies, more than 650 semiquantitatively evaluated biopsies of our material studied with EM and 400 with IF were examined, using stepwise discrimination analysis. The individual glomerular parameters selected are presented in the histograms in the previous chapters. The most important of the EM parameters can be also judged with LM.
The IF parameters suitable for discrimination analysis encompass the presence of immunoglobulins (IgG, IgM, IgA) as well as complement (C3) and fibrin(-ogen) in general, their intraglomerular distribution (segmental/global) and their character (fine-granular/coarsely-granular). Discrimination analysis compared non-GN to GN (including glomerular minimal change) as well as GN (including glomerular minimal change) to transplants. The results are presented in Figs. 12.1, 12.2).
Extracapillary crescent formation as well as capillary loop necrosis were underestimated in the analysis of EM material insofar as their frequency of occurrence was small. The same is also true for IgA in IF-material since IgA was not tested in all cases.

Morphologic findings (the more pronounced, the more diagnostically substantiating) speaking for GN are listed below:

1. Mesangial change in general and mesangial cell increase in particular
2. Presence of deposits in general
3. Obsolescence of glomerular capillaries due to proliferation
4. Global fusion of foot processes
5. Presence of IgG and complement (C3).

Findings which speak against the presence of GN are:

1. Glomerular collapse
2. Lamellation of the lamina densa (this finding was overestimated since the material encompassed numerous cases of Alport's syndrome)
3. Presence of IgM in segmental distribution.

All the other morphologic EM and IF parameters examined are of lesser significance for the differential diagnosis between GN and non-GN. On the basis of discrimination analysis, i.e., from purely statistical data, it appears that idiopathic glomerular minimal change and sclerosing FGN do not belong to the group of GN.

The morphologic parameters which are significant for the diagnosis of GN also reflect inflammatory activity. In general, the following morphologic parameters speak for inflammatory activity, (i.e., inflammation has not regressed but is progressing):

1. Hypercellularity of the glomerulus, especially mesangial cell increase (as associated with proliferative glomerular capillary loop obsolescence)
2. Subepithelial as well as subendothelial and mesangial deposits
3. Capillary loop necroses
4. Proliferative (fresh) crescents
5. Accompanying interstitial nephritis with numerous polymorphonuclear leukocytes and/or plasma cells
6. Presence of IgG and C3 intraglomerularly.

The following changes are not conclusive evidence for inflammatory activity and speak against rapid progression:

1. Fibrotic crescents and synechiae
2. Few and small intramembranous deposits
3. BM thickening (of l. densa and l. rara interna)
4. Interstitial fibrosis.

The results of the comparison between GN and transplants are of special diagnostic importance since diagnosis of GN recurrence in transplants may prove to be very difficult (Fig. 12.2). The demonstration of mesangial cell increase followed by deposits in general, and in the subepithelial position in particular as well as capillary loop obsolescence due to proliferation has proven to be of value in identifying relapsing GN in transplants, as has the IF demonstration of complement (C3) and IgG generally. Thus, the main diagnostic parameters for GN relapse in renal transplants are the same as for the differentiation between GN and non-GN. Subendothelial new formation of densa lamellae and the presence of pathologic capillary loop contents (polymorphonuclear leukocytes, monocytes, fibrin(-ogen)) must not be taken as the expression of GN relapse.
The data cited above, however, are subject to the restriction that in the discrimination analysis, GN in nontransplant kidneys were compared to transplant kidneys, so that the possible deviating glomerular reaction pattern of GN in transplant kidneys due to immunosuppression did not receive consideration.

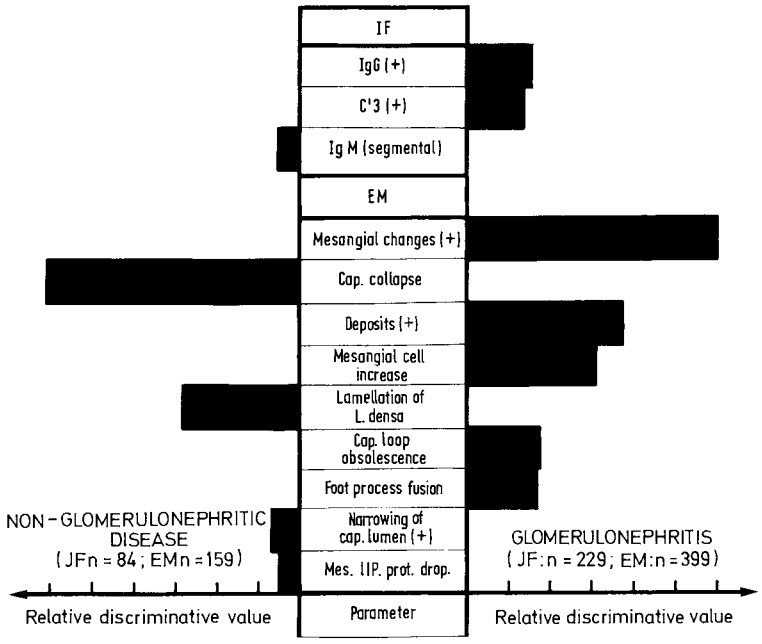


**Fig. 12.1.** Results from stepwise discrimination analysis: significant EM and IF parameters and the relative discrimination value for the comparative delineation between GN and non-GN (Wilcoxen U-test, $P \ll 0.05$). +, presence of EM or IF parameters independent of further specification. See also text

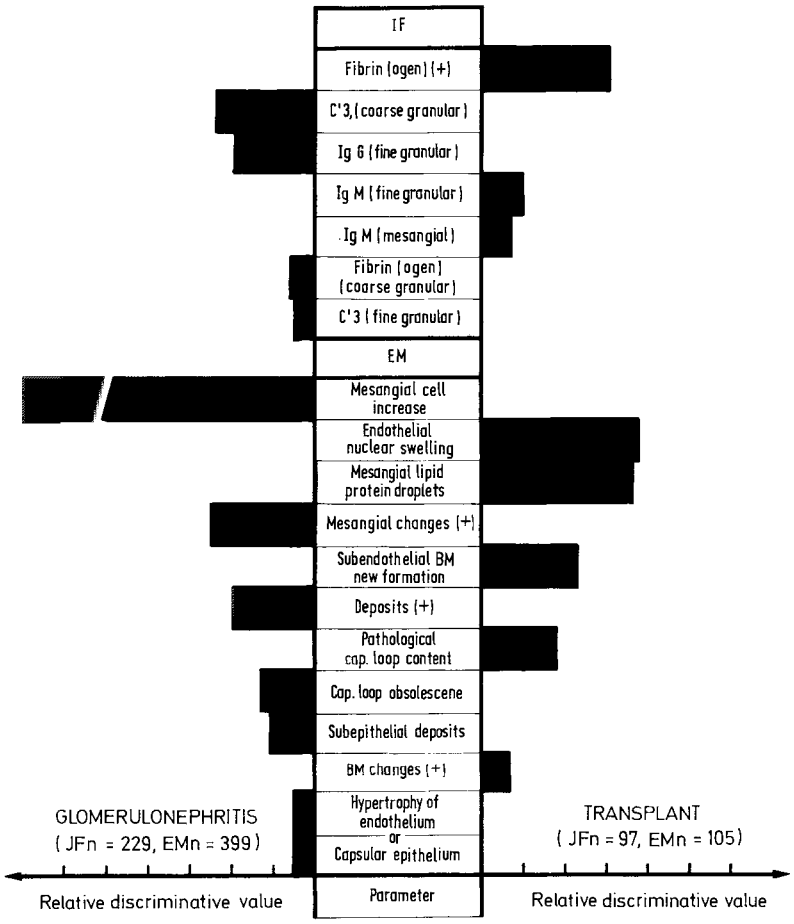


**Fig. 12.2.** Results from stepwise discrimination analysis: significant EM and IF parameters and the relative discrimination value for the comparative delineation between GN and transplants (Wilcoxen U-test, $P \ll 0.05$). +, presence of EM or IF parameters independent of further specification. See also text

Part II

# Histopathology of Specific Renal Disease States

# 13. General Aspects of Glomerulonephritis

Etiologic classification represents the culminating objective of all the efforts devoted to the morphologic study of a given disease entity. No such classification is currently possible for many diseases such as GN. A more attainable goal would be a classification of GN from the pathogenetic point of view, but even this approach remains generally unsuccessful (e.g., systemic diseases such as SLE, Schönlein Henoch's purpura, vasculitis, etc.).

Accordingly, the old system of classification based on malformations, nephroses (an anatomical concept), inflammatory glomerular, interstitial and vascular diseases, and tumors is still in use. But even this gross model of classification poses problems with complexe lesions; such as renal transplantation, radiation nephropathy, nephronophthisis etc.

The order of topics presented and the amount of attention given them in this presentation have been chosen in view of their significance in needle biopsy evaluation. The group of lesions encompassing glomerular inflammatory diseases is, with respect to the above-mentioned criteria, by far the most important; it also presents the greatest difficulties when the multiplicity of etiologic and pathogenetic factors involved in GN is considered.

## Nosology

In our nosology of GN (Table 13.1) we have formulated a broad classification based mainly on morphology (LM, EM, IF) completed by clinical information. This classification can be extended in a given case by including further morphologic parameters, e.g., severity of mesangial changes, stage of inflammation (exudative, proliferative, sclerosing), extent of crescent formation etc.

References to the time course (acute, subacute, chronic) of the disease formerly used by many investigators as a basis for classification were completely omitted.

The first part of our nosology (Table 13.1) comprises a systematic morphologic classification of all forms of diffuse and focally accentuated GN based mainly on LM (independent of but evolved from IF or EM findings) and independent of their possible association with systemic diseases. Morphologic guidelines for classification of GN are schematically summarized in Figure 13.1 taken from the histogram Figure 6.34. These parameters also parallel our pathogenetic concept outlined in Figure 13.7.

Table 13.1. Classification of glomerulonephritis (GN)

*A. Diffuse GN*
- I. Diffuse endotheliomesangial GN (so-called post-streptococcal type) Addendum: extracapillary accentuated GN
- II. Membranoproliferative GN
- III. Intramembranous GN
- IV. Epimembranous GN
- V. Mixed forms (A I–IV)

*B. Focally accentuated GN*
- I. Embolic, purulent focal glomerulitis
- II. Thrombotic GN
  - a) FGN in subacute bacterial endocarditis (Thrombocapillaritis Löhlein)
  - b) GN following generalized intravasal coagulation
- III. Segmental-focal (accentuated) proliferative GN
- IV. Segmental-focal (accentuated) sclerosing GN
- V. Secondary accompanying glomerulitis associated with non-GN diseases (amyloidosis, arteriolosclerosis and -necrosis, pyelonephritis)

*C. Non-classifiable GN*
(especially in relation to contracted kidney)

*D. Special forms*
- I. Diffuse and segmental-focal (accentuated) GN in systemic disease (Schönlein-Henoch's purpura, Wegener's and Goodpasture's syndrome, systemic lupus erythematosus)
- II. IgA mesangial GN (IgA-nephritis)
- III. Congenital and early infantile GN

*Glomerular Minimal Change*

A. Primary idiopathic form (=lipoid nephrosis =IF negative)

B. Secondary symptomatic forms
- I. Minimal endotheliomesangial GN
- II. Minimal change plus segmental-focal sclerosing GN
- III. Unspecific secondary reaction in non-GN renal disease such as Alport's disease, etc.

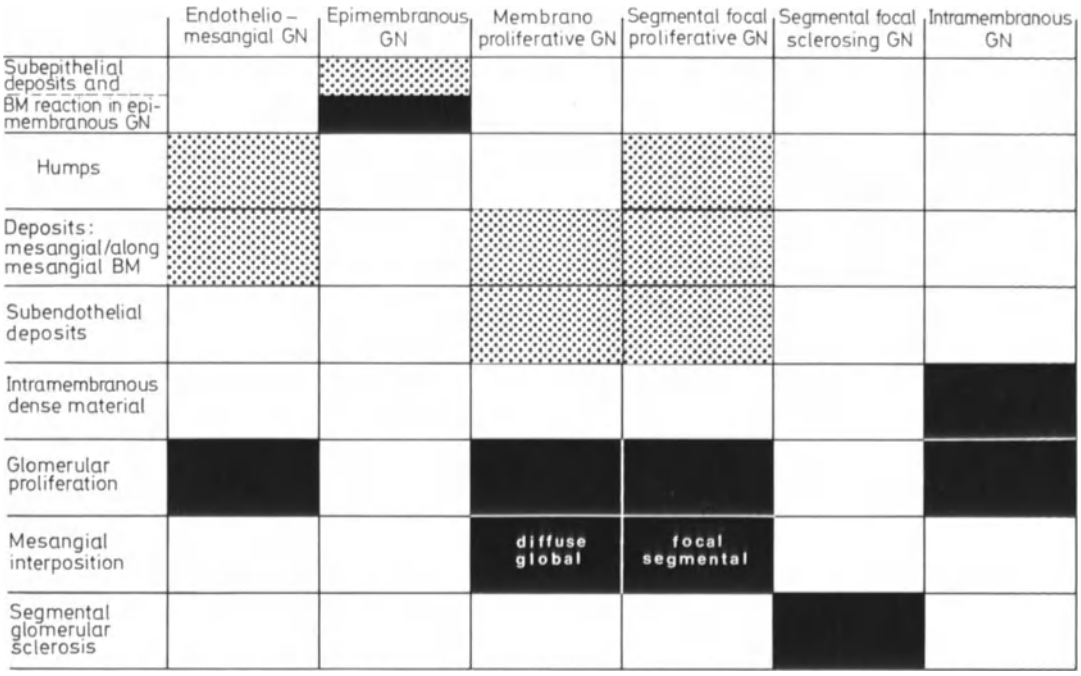


**Fig. 13.1.** Schematic presentation of the decisive morphologic guidelines for diagnosis of the different forms of GN. Black: LM parameters. Stippled: IF and EM parameters

The second part, "Special GN Forms" (Table 13.1) is devoted to disease entities—especially systemic diseases—which require, for diagnosis, more complete information, e.g., clinical and laboratory data, IF and EM results.

Glomerular minimal change constitutes a separate group due to the etiologic and pathogenetic problems involved in this disease, as well as to the multiplicity of methods required for exact classification. Since glomerular minimal change as seen by LM belongs partly to GN, they are considered along with GN.

An internationally accepted nosology of GN does not as yet exist and, accordingly, many classification systems have been proposed during the last decades which vary considerably from each other [13, 126, 161, 433, 620, 684, 846, 1325, 1395, 1713].

A detailed analysis of the most widely used classifications published since 1970 reveals, however, only minor semantic differences (Table 13.2). In diagnostic practice, there is said to be disagreement in 5–20% of cases (see discussion [277]) among pathologists; but, the more the number of investigation techniques used simultaneously (e.g., LM + IF + EM), the less the percentage of disagreement. If the relative frequencies of the different forms of GN are considered, the difference between lowest and highest incidence given in different published series varies by a factor of 2–3 in endotheliomesangial GN, extracapillary accentuated GN, intramembranous and epimembranous GN, and glomerular minimal change, increases to 5–15 in segmental-focal sclerosing GN, in membranoproliferative GN and in segmental-focal proliferative GN. The differences in frequency in the latter three forms of GN cannot, in our opinion, be explained only by regional or ethnic factors or from criteria used for selection of patients for biopsy. These data demonstrate which forms of GN require further discussion to achieve a semblance of uniformity.

## Basic Morphologic Parameters of Glomerulonephritis

In the following, some basic morphologic parameters are discussed which serve as guides to a definitive classification as well as permitting further specification of the diagnosis in a given case i.e. severity of involvement of the kidney (diffuse/focal see p. 48), of the glomeruli (global/segmental see p. 48), of the mesangium, stage of inflammation, capillary loop (BM) involvement and localization of deposits, and finally extent of crescent formation.

### Mesangial Changes

From the quantitative point of view, mesangial changes, as they are mainly to be judged in endotheliomesangial, membranoproliferative and intramembranous GN, can be grossly divided into three degrees of severity. We

Table 13.2. Comparison of classification of glomerulonephritis (for further synonymes see appropriate chapters)

| Zollinger/ Mihatsch | Bohle [159a, 163a] | Thoenes [1611] | Habib [620, 624] | Hamburger [654] | Cameron [242a] | Churg and Duffy [277] | Kincaid-Smith [840a] |
|---|---|---|---|---|---|---|---|
| Endotheliomesangial GN (For further subdivisions see text) | Exudative GN<br>–<br>Endocapillary (acute) GN (post-streptococcal type)<br>–<br>Mesangioproliferative GN<br>– without crescents<br>– with focal epithelial crescents<br>– | Exudative GN<br>–<br>Exudative or exudative and proliferative GN (acute)<br>–<br>Mesangial (endocapillary) proliferative GN<br>–<br>Proliferative sclerosing GN<br>–<br>Intra- and extracapillary proliferative GN<br>– | Pure mesangial proliferative GN with or without exudation (purely endocapillary GN)<br>–<br>Mesangial proliferative GN with focal crescents (endo- and extracapillary GN with focal crescents)<br>– | Proliferative GN (endo-/intercapillary proliferation)<br>– | Proliferative-exudative GN<br>–<br>Proliferative mesangial GN<br>– | –<br>Acute diffuse proliferative and exudative GN<br>–<br>Incompletely resolved ("latent") GN (chronic early GN) (with crescents)<br>– | Endocapillary proliferative/ exudative GN<br>–<br>Endocapillary GN<br>–<br>Mesangial proliferative GN<br>– |
| Membranoproliferative GN | Membranoproliferative GN<br>– simple form<br>– lobular variant | Membranoproliferative and lobular GN | Membranoproliferative GN<br>– pure<br>– lobular<br>– with crescents | Membranoproliferative/ lobular GN | Proliferative mesangiocapillary GN | Chronic early mesangiocapillary/ lobular GN | Mesangiocapillary (membranoproliferative) GN |
| Intramembranous GN | | | | Dense deposit disease | | | Mesangiocapillary GN with dense deposits in BM |
| Epimembranous GN | Peri- (extra-/ epi-) membranous GN | (Peri-) membranous GN | Extramembranous GN<br>Membranous GN (late stage) | Extramembranous deposit disease | Membranous (epimembranous) nephropathy | Membranous nephropathy | Membranous GN |
| Extracapillary accentuated GN<br>>50% crescents | Mesangioproliferative GN with diffuse epithelial crescents (rapid progress) | Intra- and extracapillary proliferative GN (rapidly progressing) | Mesangial proliferative GN with focal/diffuse crescents (endo- and extracapillary GN with focal/diffuse crescents) | Malignant GN | Proliferative GN with extensive crescents | Rapidly progressive (extracapillary) GN | Proliferative GN with epithelial crescents |

Table 13.2 (continued)

| Zollinger/ Mihatsch | Bohle [159a, 163a] | Thoenes [1611] | Habib [620, 624] | Hamburger [654] | Cameron [242a] | Churg and Duffy [277] | Kincaid-Smith [840a] |
|---|---|---|---|---|---|---|---|
| Segmental focal (accentuated) proliferative GN | Focal GN Mesangio-proliferative GN with focal and segmental scarring | Focal and segmental proliferative GN | Focal-segmental GN | Focal GN | Focal proliferative GN | Focal proliferative GN | Segmental focal proliferative GN<br>–<br>Diffuse proliferative GN with focal/ segmental mesangiocapillary changes |
| Segmental focal (accentuated) sclerosing GN | Minimal proliferative intercapillary GN and so-called focal sclerosis/ Focal sclerosing GN | Focal segmental sclerosing GN | Focal sclerosing GN<br>– segmental hyalinosis<br>– global fibrosis | | Focal glomerulosclerosis | Focal sclerosing GN | Segmental focal hyalinosis/ Segmental focal sclerosis |
| Glomerular minimal change<br>– primary<br>– secondary | Minimal proliferative intercapillary GN<br>– without/ with nephrotic syndrome | Minimal change Minimal glomerulitis | Minimal glomerular lesions (subtypes) | Minimal changes | Minimal change | Lipoid nephrosis (nil or minimal change disease) | No/minor/minimal lesions by LM (subtypes 1.1–1.5) |

designate the most severe change as panmesangial, the moderately severe as axial, and the mildest form as minimal.

In the panmesangial change (Figs. 13.2, 14.17; p. 181, 202) the entire glomerular mesangium is considerably widened as in membranoproliferative GN, in which it is often nodularly (lobularly) transformed. This form is always associated with narrowing of the capillary lumen in which mesangial and, presumedly, endothelial cells participate.

In the moderately severe axial form (Figs. 13.2, 14.12; p. 181, 199), the mesangium extends from the glomerular hilus in a finger-like fashion into the periphery. The capillary loops are – if at all – insignificantly narrowed.

The minimal change designates the mildest form (Figs. 13.2, 18.6, 18.7). It corresponds to "glomerular minimal change" and other analogous designations, which are encountered in the idiopathic nephrotic syndrome of childhood. Glomerular minimal change is characterized by a very discrete, insular, spotty and discontinuous mesangial enlargement usually seen as a singular mesangial field containing 3–5 nuclei per glomerulus.

**Inflammatory Stage**

Previous designations of acute and chronic have resulted in such great confusion between pathologists and clinicians that they had to be discarded in favor of the morphologically defined stages of inflammation, namely, exudative, proliferative, proliferative-sclerosing, and sclerosing (Fig. 13.3). An overview of the relative frequency of the morphologic stages and their correlation to disease duration is given in Figure 13.4.

The *exudative stage,* a designation also used by other investigators, provides the greatest difficulty, since it is characterized by a massive accumulation of neutrophilic leukocytes – and later, of monocytes – in the capillary loops. An actual cellular or fibrinous exudation as such is not a compulsory feature. Nevertheless, scattered erythrocytes are not infrequently found in the capsular space, whereas fibrin and leukocytes are rarely encountered. With reference to the designation of inflammatory stages used to describe changes in general pathology and in the absence of a better expression, we feel the term "exudative" to be appropriate. Alteration, i.e., capillary loop necrosis, can also be summarized under

the term exudative stage (see also [13, 161, 1068, 1713]). The exudative stage of GN is usually encountered in cases of less than 10 weeks' duration.

The *proliferative* stage is present in those cases which demonstrate an increase of in situ cells (i.e., mesangial and endothelial cells) and which show signs of cellular activity in EM (see p. 100) such as nuclear swelling or increase in rough endoplasmatic reticulum, etc. (contra: [1611]). Proliferative stages are most frequently encountered in cases of less than 25 weeks' duration, but they are also now and again observed in cases of up to 6 years' duration (Fig. 13.4). It is noted, however, that the retrospective determination of disease onset is fraught with possible error. It is also pointed out that post-streptococcal GN may show the proliferative stage for quite a long time after clinical healing and it may even persist for years. Finally, a proliferative stage may develop during a relapse (exacerbation) of a decade-old disease.

The *proliferative-sclerosing* stage is basically differentiated from the purely proliferative stage by an increase in mesangial matrix which is clearly demonstrated in PASM stain. The capillary lumen is not displaced by endothelial proliferation in this stage but the cells can

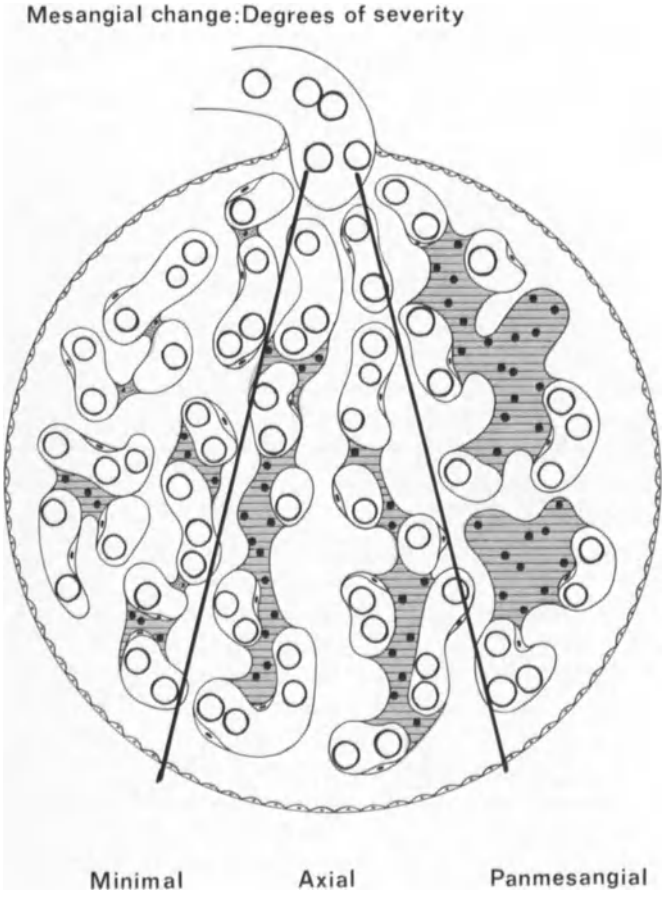


**Fig. 13.2.** Schematic presentation of the different degrees of severity of mesangial involvement

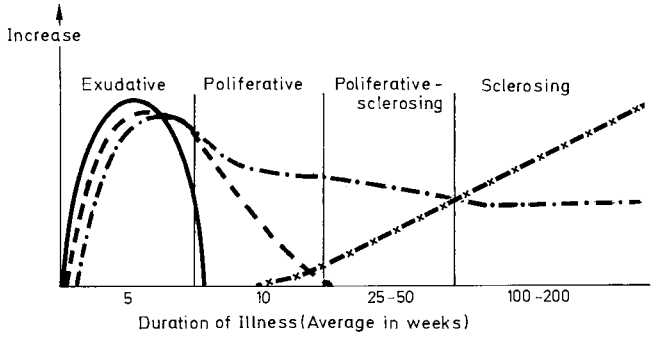


**Fig. 13.3.** Schematic presentation of the various inflammatory stages observed in the course of GN
— × — : Mesangial matrix; – – –: Endothelial cells; · – · –: Mesangial cells; ——: Polymorphonuclear leukocytes

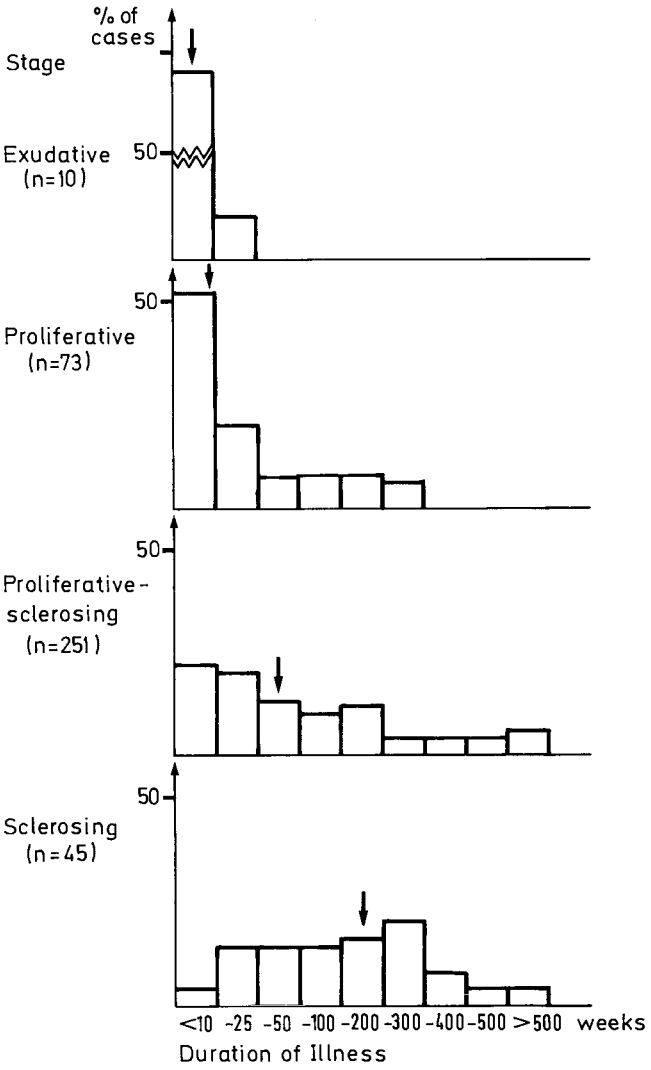


**Fig. 13.4.** Relationship between the morphologic inflammatory stages of GN and duration of illness (glomerular minimal change and epimembranous GN are excluded) (→ = median-value)

show signs of activity (see above). In general, the proliferative-sclerosing stage is encountered on average after a disease duration of about 50 weeks (Fig. 13.4) but, as with the proliferative stage, it may still be encountered many years after disease onset.

The *sclerosing* stage is, in part, difficult to differentiate from the proliferative-sclerosing stage. We always speak of a sclerosing stage, however, when the proportion of the mesangial matrix increase is greater than that of the cellular increase (Fig. 13.3). In segmental-focal sclerosing GN, however, the determination of stage is simple, since in this case, cellular increase is practically absent.

The sclerosing stage is usually observed in cases with a duration of disease between 2 and 4 years (Fig. 13.4).

The differentiation of these four inflammatory stages (exudative, proliferative, proliferative-sclerosing and sclerosing) does not imply that every case of GN necessary takes this morphogenetic course.

Indeed, the disease may heal—at least clinically—in any one of the four stages. It is also noted that the sclerosing stage in particular may develop without a prior exudative stage (sclerosing FGN, see p. 296). The practical value of the recognition of the four different stages of the inflammatory reaction (the same holds true for the different stages in epimembranous GN) is that especially in cases of GN representing chance findings—with appropriate reservation—indications as to real duration of the disease are possible. This permits, although rarely, the unmasking of possible etiologic factors.

### Changes of the Peripheral Capillary Loop Wall (BM Changes, Localization of Deposits)

Changes associated with the peripheral capillary loop wall (BM changes) have been described extensively on p. 62). Their detailed analysis, especially of the precise localization of deposits, as well as mesangial interposition are of decisive diagnostic significance. There is no generally accepted rating scale (for IF see p. 155).

### Extracapillary Crescents

Extracapillary crescents show segmental development (i.e., proliferation is restricted to a glomerular segment) or global development (the crescent surrounds the entire glomerular convolute). Since the presence of extracapillary crescents, which are found in 25% of all our GN excluding glomerular minimal change, has considerable prognostic significance independently of the basic type of GN involved, we feel that a differentiation of three groups is desirable: GN without crescents, GN with $<50\%$ crescents (*crescentic involvement*) and $>50\%$ crescents (*crescentic accentuation*) (Fig. 13.5). We formerly used a more extensive and subtle differentiation (no crescents, less than 10%, 10–25%, 25–50%, 50–75%, more than 75%) which proved to be unuseful (contra: [621]) since there was an excessive overlapping of survival rates within the groups with less or more than 50% crescents. This can be explained by the fact that biopsy is performed at different times of the disease course, so that early rebiopsy of a case initially showing only few extracapillary crescents will demonstrate their diffuse presence.

Based on the above discussion we formulate the diagnosis as follows, e.g., diffuse membranoproliferative GN, axial form, proliferative stage, 10% segmental crescents.

## Special Clinical Courses of Glomerulonephritis

Clinically, different terms such as progression, latency, persistence, protraction, and defective healing are used to characterize special clinical courses of GN; they pose great problems for the pathologist. Since these terms are of considerable significance for clinicians, pathologists should give them due consideration. It must be borne in mind that the above-mentioned terms should not be used by the pathologist, since even serial biopsies do not allow—when only LM is used—prediction of the course of GN with certainty [484a]: in a series of 189 cases (excluding glomerular minimal change and necrotizing GN) 35% improved clinically but only 15% morphologically and 26% worsened clinically and 48% morphologically. A better correlation between clinical course and morphology can only be expected in studies combining different techniques (LM, IF, EM).

*Progressive GN* is characterized by a slow but irrevocable progression of the disease [1325].

*Persistent GN* [544] identical to latent GN as described by other investigators [911, 1541] was found in 69 out of 625 cases of proliferative GN [277]. It is reported to procede without hematuria or proteinuria [911]. In the clinically acute phase, it cannot be differentiated from the usual endotheliomesangial GN. In the late form (1–3 years after acute onset) irregular parietal loop thickening, an increase in mesangial cells, and local loop obliteration—which may be accompanied by synechiae—are encountered. EM study in this stage reveals, on occasion, small osmiophilic intramembranous deposits and a few fresh humps. IF shows peripheral granular deposits of IgG and complement. Since a few mesangial and subendothelial deposits have been reported [544], it appears to us that the reports are more indicative of membranoproliferative or proliferative FGN since the lesion is reported to develop into contracted kidney.

Other investigators [1158, 1325] characterize the term

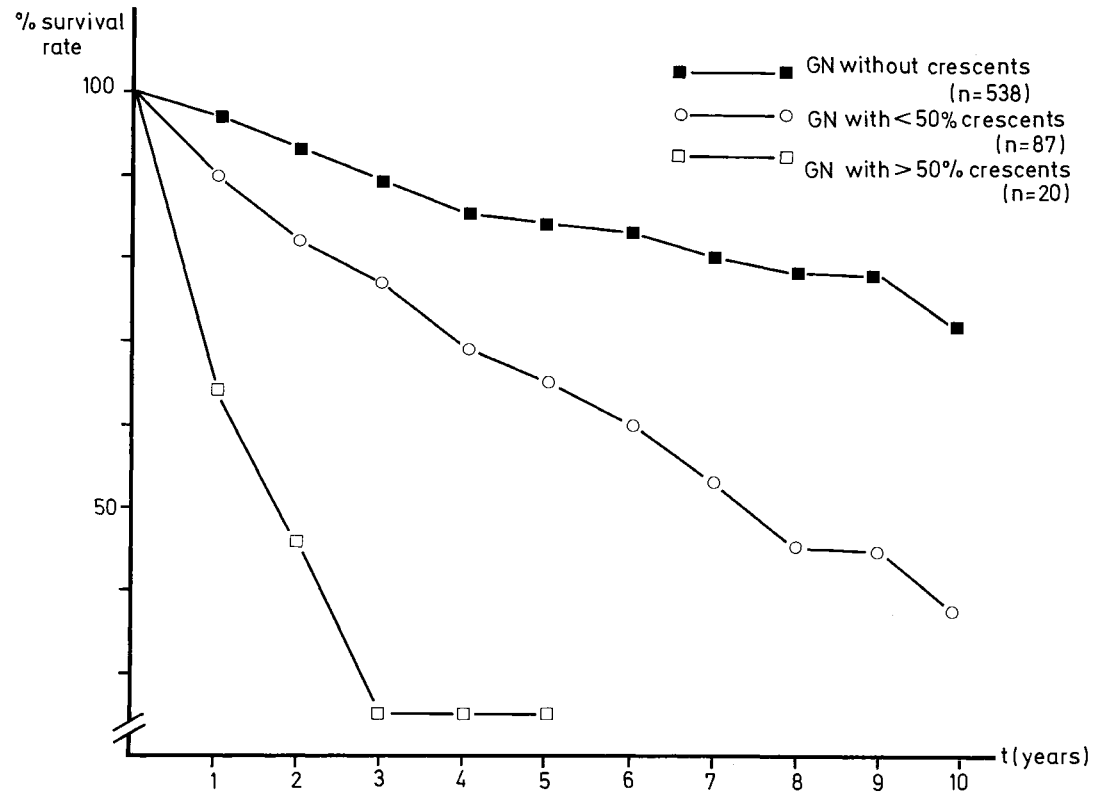


**Fig. 13.5.** Survival rate from biopsy onwards in all GN forms in relation to the degree of extracapillary crescents (for further details, see text)

"latent" as referring to a very long-lasting stationary finding such as pronounced mesangial hypercellularity still present at least 1 year after clinically acute onset of GN. This definition coincides with that of *"unresolved GN"* [1068]. Still other investigators define "latent" as lipoid nephrosis in general [1272] or as intracapillary (membranoproliferative) GN [772].

The diagnosis of *defective healing* is neither possible clinically nor morphologically. Thus, in persistent GN, it is impossible to determine whether these changes are indicative of a potential for disease progression or in fact do represent defective healing [1325].

The *protracted form* [1325] refers to those cases which show clinically a retarded healing tendency (up to 3 years) and a very slow recovery of the glomerular filtration rate.

## General Pathogenesis of Glomerulonephritis [544, 1083, 1200, 1257, 1643]

Corresponding to experimental animal models, two forms of GN can be differentiated: an immunocomplex type (serum nephritis type [384], Fig. 13.6) and an anti-BM type (nephrotoxic serum nephritis, Masugi nephritis). It is being recognized more and more, however, that this simple pathogenetic scheme does not sufficiently explain the wide variety of human GN [654]. Very problematic in this respect are intramembranous GN and sclerosing FGN. A further possibility has emerged in that it has been shown that mesangially bound AG can be the target of circulating humoral AB and, as such, give rise to mesangial inflammation and proliferation [1028]. In addition, the discovery of the alternative pathway of complement activation has opened up new possibilities for explaining the origination of glomerular inflammatory changes [931, 1257]. Finally, it must always be borne in mind that not every IF demonstration of immunoglobulin—and especially of IgM and complement—represents immunocomplexes exclusively as it may indicate the probable presence of secondarily deposited biologically inert material (see p. 158). It is further noted that obviously genuine immunocomplexes are not irrevocably associated with inflammatory changes.

There is, however, general agreement that the nephritogenic action—in most cases—is due to antigen-antibody (AG-AB) reaction in the glomerulus either by binding of circulatory auto-AB (anti-BM type) or by immunocomplex deposits in the broadest sense. In both cases,

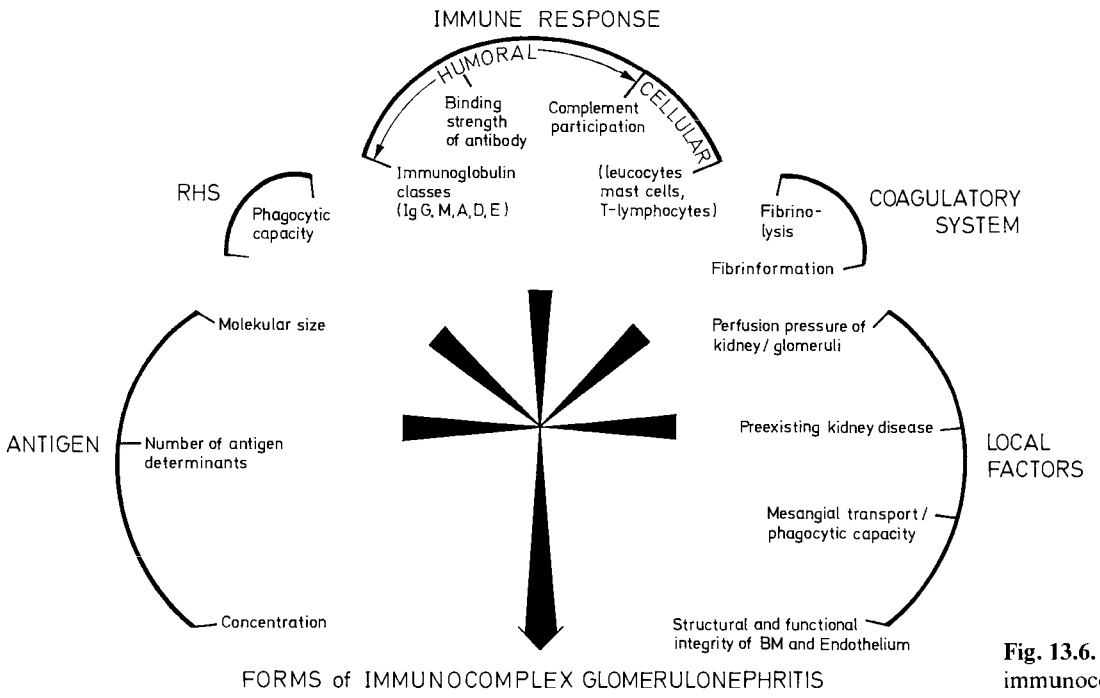


**Fig. 13.6.** Pathogenic factors in immunocomplex GN

the morphologically recognizable inflammatory reaction is due to secondary mechanisms to which belong, above all, activation of the complement system with the release of vasoactive and chemotactic substances (surveys: [309, 931, 1396], and of the coagulation system: [1059, 1060, 1396, 1653, 1690]) which is chiefly associated with fibrosclerotic changes. Leukocytes do not appear to play a significant role in GN, since in cases of agranulocytosis, the same glomerular lesions occur [544]. It is noted, however, that following destruction of the endothelium there occurs a direct contact of polymorphonuclear leukocytes with the BM, a degranulation of leukocytic lysosomes and, in EM, dissolution of the BM [229, 683]; these changes are not found in the presence of agranulocytosis [668].

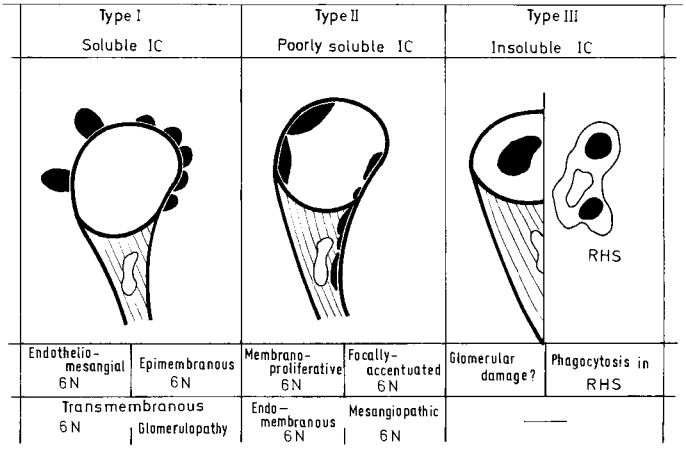


**Fig. 13.7.** Significance of solubility of immunocomplexes (*IC*) in the pathogenesis of GN (modified from [544])

## Immunocomplex Glomerulonephritis

This form of GN is due to deposition of circulating AG-AB complexes in the glomeruli. The various depositional patterns—and the thereby correlatable forms of nephritis—are determined by at least three groups of factors (Fig. 13.6).

1. AG-AB properties (Fig. 13.7)
2. RHS function, including the mesangial clearance function
3. Glomerular function.

***AG-AB Properties.*** The size, solubility, and glomerular localization of the complex is considerably dependent upon the AG-AB relationship. Three classes of immunocomplexes demonstrating different degrees of pathogenicity can be distinguished [544]. These are:

*Class I.* Small, soluble complexes (as a rule, under 1,000,000 Daltons) which form in the presence of a relative excess of AG. These complexes can pass through the BM and have been referred to as causing "transmembranous immunocomplex GN" [544]. Accordingly, these complexes are found subepithelially (epimembranous GN) and, typically, also in post-streptococcal type GN with formation of subepithelial humps as a self-limiting form [382].

There are, however, also rapidly progressive and persistent forms [544] whose pathogenesis must be affected by other factors. According to experimental findings following administration of a single dose of bovine serum albumin (acute serum sickness), the antigen is only demonstrable for a few days in the deposits while IgG and C3 remain and increase [1745], i.e., the AB accumulates more and more on the sessile complexes. Although complement and leukocytes are also present, the disease can heal without defect. In the persistent forms – and analogously to the experimental chronic serum sickness – persistency of the AG must be assumed.

*Class II.* Complexes of this class arise in the presence of AG-AB equivalence, they are of intermediate size (over 1,000,000 Daltons) and are poorly soluble. Since complexes of this size cannot pass through normal BM, they are preferentially deposited in the subendothelial-mesangial space [544, 819, 1377] as, for example, in membranoproliferative and focally accentuated GN. Immunocomplexes deposited along the BM can, indeed, change the BM permeability in such a way as to permit entrance of high molecular weight substances such as ferritin and catalase [1442] and, accordingly, presumably also of larger immunocomplexes.

*Class III.* These complexes are large, insoluble and arise in the presence of AB excess. They are generally phagocytized by the RHS and are said to be not pathogenic for glomeruli. It has, however, been recently shown [520] that immunocomplexes of this size may possibly evoke inflammatory glomerular changes.

It can be assumed that the qualitative properties of the involved AG and AB may result in modification of the above formulated scheme. The AB class can influence the localization of deposits and especially so when high molecular weight IgM and polymers (IgA) participate.
Slight AB avidity [1532] and nonprecipitating AB [1270] probably enhance pathologic immunocomplex deposition (contra: [1746]). Molecular properties of the AG, e.g., molecular weight, number of AG determinants, also appear to influence immunocomplex deposition [544]. It is noted, however, that only a few nephritogenic AG have been identified up to now, and little is known of their properties (DNA, AG in streptococcal, malarial, syphilitic and virus hepatitis B infections). Experimental work on GN in chronic viral infection shows additionally that, as a rule, several AG-AB complex systems can affect the glomeruli simultaneously and may act additively or protectively [383].

***RHS Function.*** The importance of the clearance funtion of the mesangium as part of the RHS is generally recognized [1476]. The elimination of potentially pathogenic immunocomplexes is, accordingly, dependent on the function of the RHS in general and on that of the mesangium in particular [1026, 1027, 1028].
Normally, both high and low molecular weight substances (e.g., ferritin: [461]; peroxidase: [588]; catalase: [1660]), India ink: (own observation) are removed by way of the subendothelial space and via the mesangium, partly by phagocytosis and partly by drainage to the glomerular pole [1026, 1027, 1028]. Immunocomplexes use the same route chiefly when their size exceeds the permeability of the BM. The efficiency of mesangial clearance function is a factor determining whether, when, and to what extent accumulation of immunocomplexes occurs. It is to be expected, accordingly, that pre-existing mesangial injury can lead to an aggravation of immunocomplex glomerulopathy.

***Glomerular Function.*** Glomerular excretion of immunocomplexes appears to be assured by the glomerular hydrostatic pressure which is four times greater than in other capillaries.
Accordingly, increased pressure in the afferent vessels (hypertension) or narrowing of the efferent vessels (interstitial processes) would enhance an increase of deposition. If the hydrostatic pressure is absent or significantly reduced such as in arterial stenosis [452] or hydronephrosis, no immunocomplex deposition occurs [544, 1237].
With the functional significance of the mesangial transport system in mind, it is seen that blockade by excess of circulating substances (overload glomerulitis, see p. 308), scar formation or other injury resulting in impaired drainage can lead to an accumulation of immunocomplexes in the subendothelio-mesangial space. This can cause secondary inflammatory reactions insofar as the immunocomplexes trigger complement activation.
IF demonstrable IgM and/or C3 deposits without inflammatory changes, which are observable in the most diverse kinds of renal disease [128, 193, 506, 651] arise, according to our opinion, in the same way, i.e., through impairment of mesangial clearance [1745].
Finally, it appears that injuries to the capillary loop enhance the deposition of the complexes. The role of vasoactive substances – chiefly of histamine – in facilitating the deposition of high molecular weight complexes has been reported [293]. Further factors which can alter permeability include hypoxia, toxic substances (endotoxins?) and structural defects, e.g., as occurring in Alport's syndrome (see p. 466).

## Anti-BM Glomerulonephritis

This second form of GN is far more rare than the first type. It has been reported to occur in 1–5% of all IF-positive GN biopsies ([1035, 1512, 1744, 1747]; 2 out of 227 cases of GN: Z).

Circulating AG-AB complexes are absent. Animal experiments permit differentiation of a passive form (Masugi nephritis) and of an active or heterologous GN as demonstrated in sheep and goats [544]. In experimental animals (Rhesus monkeys) given ALG containing anti-BM-antibodies, linear deposition of horse immunoglobulin and complement as well as severe extracapillary accentuated endotheliomesangial GN could be produced. The same deposits are encountered in humans with renal transplants following ALG therapy but, however, without any signs of GN [1132].

The AG in this kind of GN is the capillary BM and especially that of the glomeruli themselves. AB and complement are presumed to be deposited diffusely on and in the lamina rara interna, i.e., subendothelially. Corresponding IF study demonstrates a nongranular (ultra-)linear subendothelial deposition which can also be occasionally seen with EM. In human serum of such cases, AB can often first be demonstrated after the AB-binding kidney has been removed [544, 955], and AB can persist in the serum for 6 months or longer [1747]. This condition must be differentiated from subendothelial immunocomplex deposition which can lead to the finding of pseudolinear immunofluorescence [128]. Anti-BM GN is chiefly associated with extracapillary accentuated GN as in Goodpasture's syndrome and the idiopathic form. Anti-BM GN has very rarely been described in malignant lymphomas [609], in penicillamin-induced GN [680, 1566a], as well as in SLE-GN [1408a]. It is interesting to note that only 2 out of 32 patients with linear BM-AB staining showed under LM extracapillary accentuated GN whereas in the majority a wide variety of GN forms were present including glomerular minimal change, focal proliferative or necrotizing GN and chronic GN [1814] (see also: [1512]).

The reason for the antigenic transformation of BM is obscure. A possible explanation is indicated by the cross-reaction with streptococcal membranes which are said to contain the same low molecular weight glucoproteins as the BM [934, 1377, 1766], but also viral infections (influenza $A_2$) may be involved [1748]. A second hypothesis suggests a chemical alteration of the BM [934] as a cause for anti-BM-AB formation. In fact, hydrocarbon solvents are reported to lead to an anti-BM type GN by injury to pulmonary BM [107].

On the other hand, damage of the glomerular BM in a variety of nonimmunologic renal diseases and insufficient excretion of antigenic BM material may result in anti-BM-AB formation [1349]. Anti-BM-AB can also be demonstrated in the serum of patients with chronic aggressive hepatitis [954] who have circulating AB against smooth muscle cells but who do not necessarily have GN.

Table 13.3. Etiology of glomerulonephritis. Diseases present within 1 month prior to onset of GN in 673 patients

| Prior disease | Frequency (in %) |
|---|---|
| In tonsils, pharynx, oral cavity | 20.8 |
| General infection including Schönlein-Henoch's disease | 6.6 |
| SLE | 3.9 |
| In bronchi, lungs | 2.4 |
| In skin | 2.4 |
| Malignant tumors | 0.9 |
| In nose, ethmoid sinuses | 0.7 |
| In ear | 0.7 |
| In heart | 0.7 |
| In gastrointestinal tract | 0.6 |
| In bones, joints | 0.4 |
| In other structures | 0.3 |
| No prior disease | 60.7 |

Table 13.4. Etiology of glomerulonephritis. Assumed/assured antigens and systemic diseases in 265 patients with diseases within 1 month before onset of glomerulonephritis

| Noxae | Frequency (in %) |
|---|---|
| Bacteria | 9.9 |
| Streptococci | 7.5 |
| (in scarlet fever) | (2.6) |
| Staphylococcus albus | 0.8 |
| Staphylococcus aureus, Pneumococci, C. diphtheria | 0.4 each |
| (N.B. AST was increased in 19.9% of 517 patients) | |
| Virus | 5.8 |
| Hepatitis B | 2.6 |
| Mononucleosis | 0.8 |
| Mumps, influenza, measles, rubella, cytomegalovirus | 0.4 each |
| Protozoa, parasites | 0.8 |
| Malaria | 0.4 |
| Helminthiasis | 0.4 |
| Drugs | 1.5 |
| Gold | 1.1 |
| Penicillamine | 0.4 |
| Malignant tumors | 2.3 |
| Lymphoma | 1.1 |
| Cervix, stomach, tongue carcinoma | 0.4 each |
| Systemic Disease | 10.9 |
| SLE | 9.8 |
| Goodpasture's syndrome | 1.1 |
| No incriminable antigen or systemic disease found | 68.8 |

## General Etiology of Glomerulonephritis

Etiologically, GN does not represent a sharply delineated entity but rather a reaction to a wide variety of antigens, a minor part of which have been unequivocally identified within immunocomplexes in the kidney as of now [1217a]; see p. 155.

We will discuss etiologic details when dealing with the various forms of GN. At this point, only the following facts, evaluated from our own material, should be stressed: in 60% of our patients, no disease within 1 month prior to GN manifestation/detection was noted, and only half of the preceding diseases affected the oropharynx (Table 13.3). In 68% of patients with diseases within 1 month prior to GN, the antigen probably involved could not be determined, and streptococci represented the possible offending agent in only 7.5% (Table 13.4). Thus, in only 12% of all patients was a possible association with known antigens detected. This underlines how distant we still are from an etiologic classification of GN and, accordingly, from a causal therapy.

# 14. The Diffuse Forms of Glomerulonephritis

## Diffuse Endotheliomesangial Glomerulonephritis

### Definition

Endotheliomesangial GN is characterized initially by an endothelial and subsequently by a mesangial reaction. Additionally, the periphery of the capillary loop is neither thickened by diffuse subendothelial or subepithelial deposits nor by mesangial interposition.

***Synonyms:*** Transmembranous GN [544], endothelial GN [1541].
Other synonyms are summarized in Table 13.2.

### Nosology

From the purely morphologic point of view, four different inflammatory stages of the disease can be recognized:
1. Exudative
2. Proliferative
3. Proliferative-sclerosing
4. Sclerosing

In stages 3 and 4, mesangial changes can be differentiated into three degrees of severity: panmesangial, axial, and minimal (discussed on p. 180) and crescents may be absent or present (in 0%–50% of glomeruli).

### Incidence

The following incidence has been reported in total renal biopsy material: 1.8% [544], 3% [1312], 3.9% [655], 7.3% [163], 8.5% [277], and in pediatric material: 17% [620].
In clinical diagnosis of acute GN, 90% of the biopsies from these cases were diagnosed as endotheliomesangial GN (in children [1630]) and in 10–34% of patients with nephrotic syndrome [1484, 616, 621, 661, 671]. For relative frequency among all GN, see Table 14.1.
The pediatric age group is significantly more frequently affected than the adult (Table 14.2, Fig. 14.1). In all age groups, males are affected about twice as frequently as females (Z:1.84:1, see also [72, 163, 1730]). Female children however, have about twice as many exacerbations [387]. In the second Red Lake Indian Reservation Epidemic (streptococcal pyoderma), all afflicted individuals were less than 10 years of age, and boys and girls were equally afflicted [803].
The frequency of the four stages in needle biopsy material of other investigators is difficult to evaluate, since most of them do not differentiate between them. Our own frequency distribution is given in Table 14.2. It is

Table 14.1. Relative frequency (%) of endotheliomesangial glomerulonephritis (EM-GN) and of extracapillary accentuated glomerulonephritis

| Investigator | Total GN (without glomerular minimal change) | EM-GN | | Extracapillary accentuated GN[a] |
|---|---|---|---|---|
| | | without crescents | with crescents < 50% | |
| Hamburger et al. (1971) [654] | 725 (573) | 5.4 (6.8) | | 4.3 (5.4) |
| Cameron (1973) [242b] | 526 (373) | 11.6 (18.1) | | 3.6 (5.6) |
| Morel-Maroger et al. (1973) [1137a] | 476 (380) | 12.8 (16.0) | | 6.5 (8.2) |
| Habib (1973) [621] | 1193 (607) | 7.2 (14.1) | 10.1 (19.9) | 2.3 (4.4) |
| Zollinger and Mihatsch | 900 (689) | 20.6 (26.8) | 3.0 (3.9) | 4.2 (5.5) |
| Bohle (1976) [163a] | 2450 (1376) | 23.8 (45.6) | 2.2 (4.0) | 2.0 (3.6) |
| Germuth and Rodriguez (1973) [544] | 208 (141) | 27.8 (41.1) | | 3.3 (4.9) |
| Churg and Duffy (1973) [277] | 1042 (862) | 39.4 (47.7) | | 4.9 (5.9) |

[a] More than 50% of glomeruli afflicted.

certain, however, that the purely exudative stage of endotheliomesangial GN is, in general, rarely observed in needle biopsy, since biopsy today is rarely undertaken early enough in clinically acute GN; the stage is occasionally found fortuitously in autopsy material.

### Clinical Findings

(Tables 14.3, 14.4, 14.5, 14.6; Fig. 14.1)

Endotheliomesangial GN can begin either with typical symptoms of acute GN with hematuria, proteinuria and hypertension (with or without oligo-anuria, Table 14.5), or with only very mild symptoms. Clinically acute GN (Table 14.5) need not necessarily be associated with endotheliomesangial GN as it does occur in the presence of other morphologic forms of GN. In a typical case, the disease becomes symptomatic 1 to 2 weeks (range: a few days to 4 weeks, and within 1 to 2 days in case of relapse) after acute infection which is usually located in the upper respiratory tract with, for example, beta-hemolytic streptococci. In our material, prior disease was present in 44% of the patients (Fig. 14.1) in whom, however, streptococcal infection could only rarely be demonstrated (Table 14.3). Manifestation of this GN in the course of systemic disease, e.g., SLE, Schönlein-Henoch's syndrome etc., is also possible. The most striking—but in no way obligatory—clinical symptoms we encountered at disease onset are macrohematuria (36%), edema (36%), and oligoanuria (22%) (Fig. 14.1). Oligoanuria was found to be considerably more frequent in a series restricted to pediatric cases (55 out of 86 children: [621]). Examination of the urine reveals proteinuria in over 50% of the cases and microhematuria (24%) and typically erythrocytic casts (Table 14.3, Fig. 14.1). These findings, however, may occasionally be completely missing or only demonstrable for a few days [879]. Initial hypertension is also characteristic, but it was only mentioned in 15% of our cases (Fig. 14.1). Rarely, hypertension may dominate the clinical findings due to the presence of hypertensive encephalopathy with tonic, clonic cramps, and disorientation [415].

Table 14.2. Frequency of the various disease stages in endotheliomesangial glomerulonephritis

| Stage | Total | Pan-mesangial | Axial | Average duration of illness in weeks (range) |
|---|---|---|---|---|
| Exudative | 7 | – | – | 5 (3–8) |
| Proliferative | 43 | 7 | | 9 (1–208) |
| Proliferative-sclerosing | 128 | 6 | 122 | 50 (1–1750) |
| Sclerosing | 10 | 1 | 9 | 100 (6–270) |

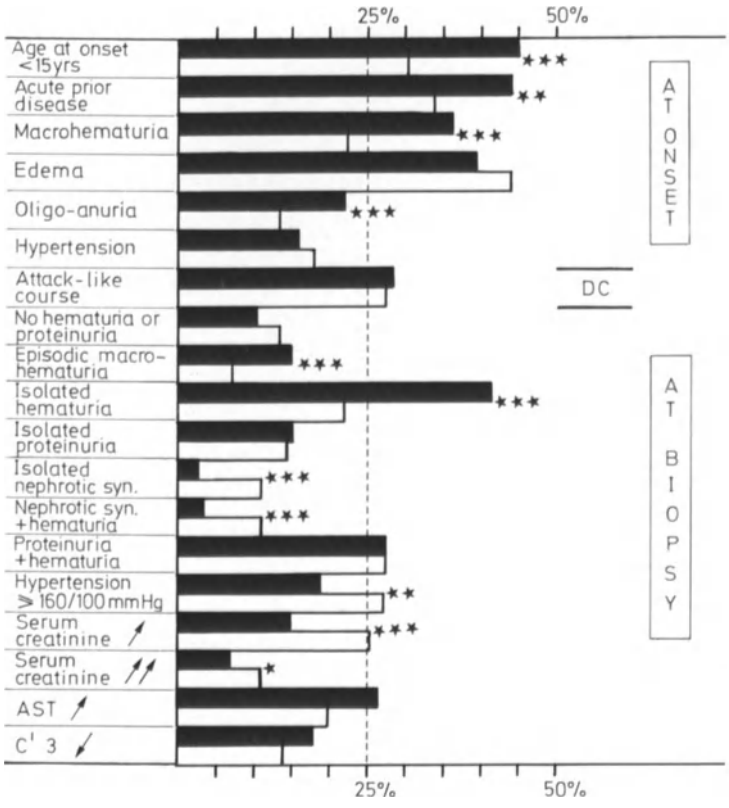


**Fig. 14.1.** Profile of symptoms and clinical findings in endotheliomesangial GN
*White columns:* Relative frequency of symptom/finding in all GN
*Black columns:* Relative frequency in endotheliomesangial GN
Asterisks indicate characteristic findings for endotheliomesangial GN:
*: characteristic
**: very characteristic
***: highly characteristic; DC: disease course (see also Tables 14.3 and 14.4)

Table 14.3. Clinical findings in glomerulonephritis (own cases)

| No. | Clinical findings in GN as such and in systemic diseases | Relative frequency (%) in GN | No. of cases ($n$)[4] | Age (years) distribution at biopsy (at disease onset) in % of cases | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | <5 | <10 | <15 | <20 | <30 | <40 | <50 | <60 | >60 |
| 1 | Endotheliomesangial GN Exudative stage | ↑ | 8 | 0 (0) | 12.5 (12.5) | 0 (0) | 0 (0) | 0 (0) | 12.5 (12.5) | 12.5 (12.5) | 50 (50) | 12.5 (12.5) |
| 2 | Proliferative sclerosing stage without crescents | 23.6 | 177 | 14.7 (17.5) | 19.8 (19.2) | 9.0 (9.0) | 10.7 (13.5) | 16.4 (15.3) | 14.7 (11.3) | 10.7 (10.2) | 3.4 (3.4) | 0.6 (0.6) |
| 3 | Proliferative sclerosing stage Crescents <50% | ↓ | 27 | 14.8 (18.5) | 14.8 (11.1) | 14.8 (18.5) | 7.4 (7.4) | 11.1 (11.1) | 11.1 (7.4) | 7.4 (11.1) | 11.1 (7.4) | 7.4 (7.4) |
| 4 | Extracapillary accentuated GN | 4.2 | 38 | 0 (0) | 10.5 (10.5) | 5.3 (5.3) | 18.5 (21.0) | 18.5 (15.8) | 13.2 (13.2) | 10.5 (10.5) | 10.5 (10.5) | 13.2 (13.2) |
| 5 | Membranoproliferative GN | 5.2 | 47 | 0 (2.5) | 10 (12.5) | 7.5 (5.0) | 2.5 (10.0) | 25 (25.0) | 35 (27.5) | 7.5 (5.0) | 5.0 (10.0) | 7.5 (2.5) |
| 6 | Intramembranous GN | 0.6 | 5 | 0 (0) | 0 (0) | 20 (20) | 0 (0) | 20 (20) | 40 (40) | 0 (0) | 0 (0) | 20 (20) |
| 7 | Epimembranous GN | 8.0 | 72 | 1.4 (2.8) | 8.3 (8.3) | 2.8 (1.4) | 4.2 (6.9) | 13.8 (12.5) | 22.1 (20.8) | 16.6 (18.1) | 12.4 (15.3) | 17.9 (13.9) |
| 8 | Segmental-focal proliferative GN, no crescents | ↑ | 74 | 8.1 (9.5) | 18.9 (21.6) | 9.5 (5.4) | 8.1 (12.2) | 17.6 (17.6) | 16.2 (12.2) | 6.8 (8.1) | 5.4 (4.0) | 9.5 (9.5) |
| 9 | Segmental focal proliferative GN, crescents <50% | 17.3 ↓ | 82 | 2.4 (2.4) | 8.5 (9.8) | 7.3 (7.3) | 8.5 (14.6) | 26.9 (24.4) | 13.4 (9.8) | 13.4 (14.6) | 12.2 (12.2) | 7.3 (4.9) |
| 10 | Segmental-focal sclerosing GN | 14.4 | 130 | 1.5 (8.5) | 3.1 (2.3) | 7.7 (6.2) | 1.5 (10.0) | 30.8 (26.8) | 23.1 (18.5) | 14.6 (13.0) | 8.5 (8.5) | 9.2 (6.2) |
| 11 | Glomerular minimal change | 23.5 | 211 | 17.5 (30.8) | 24.6 (16.6) | 10.0 (7.6) | 6.6 (8.5) | 15.2 (12.3) | 7.1 (7.6) | 7.1 (6.6) | 7.1 (5.7) | 4.7 (4.3) |
| 12 | Schönlein-Henoch's syndrome | 2.4[1] | 22 | 13.6 (13.6) | 45.5 (50) | 9.1 (4.5) | 4.5 (9.1) | 9.1 (4.5) | 0 (0) | 4.5 (4.5) | 9.1 (9.1) | 0 (0) |
| 13 | Systemic lupus erythematosus | 2.9[1] | 26 | 0 (0) | 11.5 (11.5) | 7.7 (7.7) | 11.5 (19.2) | 42.3 (42.3) | 15.4 (3.8) | 3.8 (3.8) | 7.7 (7.7) | 0 (0) |
| 14 | Wegner's syndrome | 0.8 | 7 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 14.3 (14.3) | 14.3 (14.3) | 0 (0) | 14.3 (14.3) | 57.1 (57.1) |
| 15 | IgA-nephritis | | 15 | 6.6 (6.6) | 19.9 (39.9) | 46.6 (26.7) | 6.6 (6.6) | 0 (13.2) | 13.2 (6.6) | 0 (0) | 6.6 (0) | 0 (0) |
| | | 0.4[2] 2.0[3] | | | | | | | | | | |

[1] Already considered in the systematics of GN.
[2] Mixed forms of GN.
[3] Unclassifiable GN.
[4] Note the occasional small case number when comparing the relative frequencies in %.
[5] No hematuria = < 3 erythrocytes/HPF (high power field). No proteinuria: < 0.3 g/day/1.73 $m^2$ body surface area.
[6] Proteinuria ≧ 3.5 g/day/1.73 $m^2$ body surface area.
[7] < 500 ml/day for adults; for children, depending on age.
[8] > 3000 ml/day for adults, for children, depending on age.
[9] Leukocyturia = > 5 leukocytes/HPF. Bacteriuria not quantitative.
[10] Hypoproteinemia 6 g %, Hypalbuminemia 2.5 g %.
[11] $\beta$-lipoprotein > 600 mg %, cholesterol 250 mg %.
[12] All cases exceeding values given below: Serum-creatinine > 1.3 mg %, Serum-urea > 45 mg %, Serum-urea-N > 25 mg %, Creatinine clearance ≦ 60 ml/min.
[13] All cases exceeding values given below: Serum-creatinine ≧ 2 mg %, Serum-urea > 70 mg %, Serum-urea-N > 40 mg %, Creatinine-clearance < 35 ml/min.

Table 14.3 (continued)

| Sex ratio ♂:♀ | Familial renal disease in % of cases {n} | Latency between disease onset and biopsy in weeks, average (range) | Acute prior disease in % of cases {n} | In % of cases with prior disease[24] | | | | Systemic diseases (n) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Unspecific URTI | Streptococcal infections | Other bacterial infections | Viral infections | Schönlein-Henoch's purpura | SLE | IgA-GN | Goodpasture's syndrome |
| 1.6:1 | ↑ | 5 (3–8) | 100 {8} | 100 | 0 | 0 | 0 | ↑ | ↑ | ↑ | ↑ |
| 1.78:1 | 3.5{170} | 120 (3–1750) | 40 {140} | 71.5 | 14.2 | 0 | 3.6 | 8 | 3 | 10 | 0 |
| 2.37:1 | ↓ | 154 (4–1100) | 47.6 {21} | 60.0 | 20.0 | 0 | 0 | ↓ | ↓ | ↓ | ↓ |
| 1.23:1 | 0 {26} | 13 (3–52) | 61.5 {26} | 75 | 0 | 6.3 | 6.3 | 1 | 0 | 0 | 2 |
| 1.22:1 | 0 {35} | 161 (3–450) | 21.4 {28} | 83.4 | 0 | 16.6 | 0 | 0 | 5 | 0 | 0 |
| 1:1.5 | 0 {5} | 60 (16–150) | 40 {5} | 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2.4:1 | 1.7 {57} | 82 (3–350) | 13.8 {58} | 62.5 | 0 | 0 | 0 | 0 | 4 | 0 | 0 |
| 1.76:1 | ↑ 2.5{120} | 73 (4–425) | 43.1 {58} | 84 | 8 | 0 | 8 | ↑ | ↑ | ↑ | ↑ |
| 2.9:1 | ↓ | 213 (2–800) | 41 {61} | 72 | 4 | 12 | 12 | 11 | 11 | 4 | 0 |
| 1.5:1 | 0 {90} | 228 (3–1400) | 31.6 {95} | 76.7 | 3.3 | 3.3 | 6.6 | ↓ 1 | ↓ 2 | ↓ 0 | ↓ 0 |
| 1.5:1 | 4.7{192} | 131 (2–2000) | 23.2{185} | 65.1 | 14.0 | 0 | 9.3 | 1 | 0 | 1 | 0 |
| 1.33:1 | 4.5 {22} | 37 (3–250) | 55.5 {18} | 66.6 | 33.3 | 0 | 0 | – | – | – | – |
| 1:4 | 4 {25} | 66 (4–350) | 0 {20} | 0 | 0 | 0 | 0 | – | – | – | – |
| 1:1.3 | 0 {7} | 16 (9–40) | 0 {6} | 0 | 0 | 0 | 0 | – | – | – | – |
| 4:1 | 6.5 {15} | 194 (4–1100) | 20 {15} | 100 | 0 | 0 | 0 | – | – | – | – |

[14] ≧160/100 mm Hg.
[15] ≧250 Todd units.
[16] Variable, dependent on the different normal values of various laboratories.
[17] Blood eosinophilia ≧8%.
[18] [335a].
[19] Results from a polling of attending physicians in Germany, Switzerland, and Italy and information from the death register.
[20] Survival rates of a normal population (Switzerland) from 900 age- and sex-matched individuals as with the GN pool: 5 years=98%; 10 years=96%; 15 years=94% (SE<1%).
[21] Cure=complete remission=no proteinuria, no hematuria, normal blood pressure.
[22] For children <15 years.
[23] For adults >15 years.
[24] In the remaining unspecified cases, there was a wide variety of prior diseases (see Tables 13.4 and 13.5).

URTI Upper respiratory tract infection.
nd No reliable data of our own.
SE Standard error (in %) calculated according to [335a].

Table 14.3 (continued)

| No. | Symptoms at disease onset in % of cases {n}. Data from case histories | | | | | | | | Disease course up to biopsy in % of cases {n}. Data from case histories | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Macrohematuria | Microhematuria | Proteinuria | Edema | Dysuria Bacteriuria Leukocyturia | Oliguria Anuria | Hypertension | | <12 weeks | No change | Progressive deterioration | | Attack-like course | No of attacks average (range) |
| | | | | | | | | | | | No attacks | With attacks | | |
| 1 | 0 {8} | 37.5 | 50.0 | 100 | 12.5 | 37.5 | 37.5 | | 100 {8} | 0 | 0 | 0 | 0 | 0 |
| 2 | 34.7 {144} | 24.3 | 61.8 | 37.5 | 7.6 | 21.5 | 15.3 | | 28.0 {143} | 44.0 | 2.1 | 0.7 | 25.2 | 3.4 (1–>9) |
| 3 | 60.0 {20} | 15.0 | 65.0 | 30.0 | 5.0 | 20.0 | 10.0 | | 36.3 {22} | 18.2 | 4.5 | 9.1 | 31.8 | 3.7 (1–>9) |
| 4 | 32 {25} | 24 | 52 | 60 | 12 | 40 | 24 | | 50 {26} | 0 | 50 | 0 | 0 | 0 |
| 5 | 8.1 {37} | 29.7 | 67.6 | 45.9 | 8.1 | 13.5 | 29.7 | | 0 {24} | 16.7 | 24.9 | 41.7 | 16.7 | 1.6 (1–3) |
| 6 | 0 {5} | 60.0 | 80.0 | 40.0 | 0 | 0 | 20.0 | | 0 {4} | 50 | 25 | 25 | 0 | (5) |
| 7 | 5.2 {57} | 22.8 | 89.5 | 68.4 | 7.0 | 15.8 | 17.5 | | 14.9 {47} | 40.4 | 23.4 | 4.3 | 17.0 | 1.5 (1–3) |
| 8 | 31.6 {60} | 25.0 | 68.3 | 33.3 | 5.0 | 1.7 | 26.7 | | 36.1 {61} | 41.0 | 9.8 | 3.3 | 9.8 | 1.7 (1–5) |
| 9 | 33.3 {60} | 26.7 | 88.3 | 46.7 | 3.3 | 10.0 | 23.3 | | 19.0 {60} | 34.9 | 20.7 | 11.1 | 14.3 | 3.0 (1–>9) |
| 10 | 13.7 {95} | 16.8 | 68.4 | 31.6 | 2.1 | 1.1 | 22.1 | | 8.3 {84} | 39.3 | 14.3 | 9.5 | 28.6 | 3.9 (1–>9) |
| 11 | 15.7 {198} | 22.2 | 62.6 | 42.9 | 0.5 | ? | 10.1 | | 25.0 {196} | 38.8 | 5.6 | 0 | 30.6 | 4.0 (1–>9) |
| 12 | 23.5 {17} | 64.7 | 64.7 | 29.4 | 5.9 | 0 | 5.9 | | 35.3 {17} | 47.1 | 0 | 0 | 17.6 | 5.0 (2–>9) |
| 13 | 5.2 {19} | 42.1 | 68.4 | 42.1 | 5.2 | 0 | 17.1 | | 0 {12} | 33.3 | 0 | 66.7 | 0 | 3.0 (1–5) |
| 14 | 0 {6} | 0 | 0 | 16.6 | 0 | 83.4 | 0 | | 83.4 {6} | 0 | 16.6 | 0 | 0 | 0 |
| 15 | 80 {15} | 6.6 | 46.6 | 40.0 | 0 | 0 | 26.6 | | 13.3 {15} | 33.3 | 0 | 0 | 53.3 | 4.0 (2–>9) |

| No. | Urinary findings at the time of biopsy in % of cases {n} | | | | | Further urinary findings in % of cases {n} | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | No hematuria or proteinuria[5] | Isolated hematuria (macro-) | Isolated proteinuria | Isolated nephrotic syndrome[6] | Nephrotic syndrome and hematuria (macro-) | Proteinuria and hematuria (macro-) | Erythrocytic casts | Leukocytic casts | Oliguria Anuria[7] | Polyuria[8] | Episodic macrohematuria | Leukocyturia Bacteriuria[9] |
| 1 | 0 {8} | 12.5 (0) | 0 | 0 | 0 | 87.5 | 12.5 {8} | 0 {8} | 0 {3} | 0 {3} | 0 {8} | 12.5 {8} |
| 2 | 10.5 {143} | 41.3 (3.5) | 17.5 | 2.8 | 3.5 (0.7) | 24.5 (2.1) | 9.7 {133} | 2.2 {133} | 4.4 {67} | 2.9 {67} | 12.6 {143} | 7.4 {149} |
| 3 | 13.0 {23} | 52.2 (17.4) | 4.3 | 0 | 4.3 (0) | 26.0 (4.3) | 35 {20} | 5 {20} | 9.1 {11} | 0 {11} | 34.8 {23} | 19.0 {21} |
| 4 | 0 {24} | 4.2 (0) | 0 | 0 | 41.6 (0) | 54.2 (0) | 30 {20} | 15 {20} | 62.5 {24} | 4.2 {24} | 20.8 {24} | 25 {24} |
| 5 | 0 {36} | 2.8 (0) | 2.8 | 2.8 | 50.0 (0) | 41.7 (0) | 13.8 {29} | 10.3 {29} | 19.9 {15} | 6.6 {15} | 0 {36} | 3.3 {33} |
| 6 | 0 {5} | 0 | 0 | 0 | 40 (0) | 60 (0) | 25.0 {4} | 25.0 {4} | 0 {4} | 0 {4} | 0 {4} | 0 {5} |
| 7 | 10.9 {55} | 3.6 (1.8) | 14.5 | 47.3 | 10.9 (0) | 12.7 (0) | 1.9 {51} | 1.9 {51} | 0 {20} | 0 {20} | 1.9 {55} | 1.9 {55} |
| 8 | 8.2 {61} | 13.1 (4.9) | 8.2 | 4.9 | 13.1 (0) | 52.5 (8.2) | 13.7 {51} | 2.0 {51} | 0 {28} | 0 {28} | 11.5 {61} | 9.8 {61} |
| 9 | 1.6 {64} | 12.5 (1.6) | 6.3 | 3.1 | 26.6 (0) | 50.0 (3.1) | 12.5 {56} | 5.4 {56} | 8 {25} | 8 {25} | 9.3 {64} | 15.6 {64} |
| 10 | 11.0 {100} | 14.0 (2.0) | 28.0 | 11.0 | 12.0 (0) | 24.0 (2.0) | 8.3 {84} | 1.2 {84} | 4 {25} | 0 {25} | 4 {100} | 12.4 {89} |
| 11 | 27.5 {193} | 23.8 (0.5) | 14.5 | 17.1 | 4.1 (0.5) | 13.0 (0.5) | 2.7 {181} | 0.5 {181} | nd | nd | 2.6 {193} | 3.6 {193} |
| 12 | 0 {18} | 33.3 (5.6) | 0 | 0 | 22.2 (5.6) | 44.4 (0) | 6.3 {16} | 0 {16} | 0 {16} | 0 {16} | 5.5 {18} | 14.3 {14} |
| 13 | 19.0 {21} | 9.5 (0) | 4.8 | 4.8 | 38.1 (0) | 23.8 (0) | 30 {20} | 5 {20} | 0 {5} | 0 {5} | 0 {21} | 9.5 {21} |
| 14 | 0 {6} | 33.3 (16.6) | 0 | 0 | 0 | 66.6 (16.6) | 0 {5} | 0 {5} | 66.6 {6} | 0 {6} | 0 {6} | 16.6 {6} |
| 15 | 6.6 {15} | 46.6 (6.6) | 0 | 0 | 13.2 (13.2) | 33.3 (6.6) | 6.6 {15} | 0 {15} | 0 {15} | 0 {15} | 33.3 {15} | 6.6 {15} |

Table 14.3 (continued)

| No. | Serum/blood findings at the time of biopsy in % of cases {*n*} | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hypo-albumin-emia[10] | Hyper-lipemia[11] | Urea/ creati-nin ↗[12] | Urea/ creati-nin ↗ ↗[13] | Hyper-tension[14] | AST[15] | C3[16] | Rheu-matic factor | Anti-nuclear AB | LE-cells | Eosino-philia[17] |
| 1 | 12.5 {8} | 0 {8} | 75 {8} | 37.5 {8} | 50 {8} | 66.6 {6} | 100 {1} | 25 {4} | 0 {6} | 0 {6} | 0 {8} |
| 2 | 9.8{142} | 35.2{108} | 7.0{158} | 2.5{158} | 18.1{149} | 26.0{100} | 12.2{49} | 13.2{53} | 4.3{46} | 1.6{62} | 7.2{153} |
| 3 | 15 {20} | 42.9 {14} | 39.1 {23} | 21.7 {23} | 13.0 {23} | 13.3 {15} | 50 {6} | 18.2{11} | 20 {10} | 7.7{13} | 4.3 {23} |
| 4 | 51.9 {27} | 50 {18} | 100 {28} | 78.6 {28} | 44.4 {27} | 35.3 {17} | 0 {5} | 7.1{14} | 0 {13} | 0 {14} | 14.8 {27} |
| 5 | 60 {35} | 64 {25} | 56.3 {32} | 28.1 {32} | 71.4 {35} | 10.0 {33} | 60.0{10} | 20 {25} | 20 {25} | 4 {25} | 17.2 {29} |
| 6 | 60 {5} | 40 {5} | 40 {5} | 40 {5} | 60 {5} | 0 {5} | 50 {2} | 66.6 {3} | 0 {4} | 0 {4} | 50 {4} |
| 7 | 67.3 {55} | 67.3 {55} | 12.7 {55} | 3.6 {55} | 38.2 {55} | 8.9 {45} | 0 {10} | 25 {32} | 13.3{30} | 15 {33} | 10.9 {55} |
| 8 | 27.6 {58} | 30 {39} | 45.9 {61} | 19.7 {61} | 16.4 {61} | 35.4 {48} | 11.1{27} | 17.1{35} | 20.7{29} | 12.5{32} | 13.1 {61} |
| 9 | 36.6 {60} | 53.2 {47} | 51.6 {62} | 24.2 {62} | 44.6 {65} | 15.6 {45} | 14.3{14} | 21.2{33} | 18.8{32} | 15.2{33} | 12.3 {65} |
| 10 | 23.8 {80} | 55.0 {60} | 32.7 {98} | 15.3 {98} | 36.6{101} | 13.6 {59} | 0 {10} | 9.4{53} | 2.2{46} | 2.0{49} | 10.0{100} |
| 11 | 21.5{177} | 40.3{149} | 5.2{193} | 1.0{193} | 8.8{193} | 15.4{123} | nd | 6.8{59} | 1.7{58} | 0 {72} | 11.4{193} |
| 12 | 22.2 {18} | 33.3 {12} | 22.7 {22} | 4.5 {22} | 21.0 {19} | 64.3 {14} | 11.1 {9} | 0 {7} | 0 {7} | 0 {8} | 5.5 {18} |
| 13 | 52.4 {21} | 27.3 {11} | 47.6 {21} | 14.3 {21} | 33.3 {21} | 6.6 {15} | 83.3 {6} | 52.9{17} | 84.2{19} | 82.6{23} | 4.7 {21} |
| 14 | 16.6 {6} | 0 {4} | 83.3 {6} | 66.6 {6} | 16.6 {6} | 0 {6} | 0 {3} | 50 {6} | 0 {6} | 0 {6} | 16.6 {6} |
| 15 | 13.2 {15} | 60.0 {5} | 13.2 {15} | 6.6 {15} | 13.2 {15} | 9.1 {11} | 10 {10} | 0 {7} | 0 {7} | 0 {7} | 0 {15} |

| No. | Survival rate in % (SE)[18, 19, 20] | | | | | | Follow-up (> 12 months)[19] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | From disease onset | | | From biopsy | | | Died | Died from uremia | Complete remis-sion[19, 21] | Im-prov-ed |
| | 5 years | 10 years | 15 years | 5 years | 10 years | 15 years | | | | |
| 1 | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ |
| 2 | 95 (1.8) | 88 (3.0) | 81 (5.1) | 95 (1.9) | 84 (4.7) | 84 (4.7) | 8.6{139} | 3.6 | 29.5 | 13.7 |
| 3 | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
| 4 | 25 (10.6) | nd | nd | 25 (10.6) | nd | nd | 76.2 {21} | 76.2 | 4.8 | 14.3 |
| 5 | 70 (9.2) | 40 (9.5) | nd | 40 (11) | 30 (12) | nd | 46.6 {30} | 40.0 | 3.0 | 20.0 |
| 6 | 3/5 Dead after 0.5, 1, 2 years<br>2/5 Alive after 3 and 5 years | | | | | | | | | |
| 7 | 75 (5.7) | 60 (7.3) | 37 (9.6) | 76 (6.9) | 57 (7.2) | 28 (15.2) | 42.2 {45} | 26.6 | 17.4 | 2.2 |
| 8 | 84 (5.3) | 58 (9.6) | nd | 75 (6.9) | 56 (10.5) | nd | 29.2 {48} | 20.8 | 18.7 | 14.6 |
| 9 | 67 (6.3) | 36 (9.6) | 33 (9.3) | 54 (6.6) | 31 (7.3) | nd | 56.6 {60} | 41.6 | 8.3 | 11.7 |
| 10 | 77 (4.3) | 57 (5.7) | 52 (6.0) | 64 (5.5) | 42 (6.9) | 37 (7.3) | 39.3 {89} | 29.2 | 8.9 | 6.7 |
| 11 | 100[22]<br>94[23] (2.4) | nd<br>88 (4.1) | nd<br>82 (5.5) | 100<br>88 (3.7) | nd<br>80 (5.1) | nd<br>77 (6.1) | 0 {44}<br>16.6 {78} | 0<br>2.5 | 15.9<br>26.9 | 15.9<br>14.1 |
| 12 | 100 | nd | nd | 100 | nd | nd | 0 {10} | 0 | 40 | 60 |
| 13 | 66 (11.8) | nd | nd | 62 (12) | nd | nd | 46.6 {15} | 26.6 | nd | nd |
| 14 | nd | nd | nd | nd | nd | nd | 66.6 {6} | 66.6 | – | 33.3 |
| 15 | 100 | nd | nd | 100 | nd | nd | 0 {15} | 0 | nd | nd |

Table 14.4. Relative frequency of clinical findings in glomerulonephritis and their differential diagnostic significance

| Clinical findings / Glomerulonephritis | Disease onset < 15 years | Acute prior disease | Symptoms at disease onset | | | | Symptoms at biopsy[e] | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Macro-hematuria | Edema | Oligo-anuria | Hyper-tension | Attack-like course | No hematuria or proteinuria | Episodic macro-hematuria |
| All GN (own material) | 30.2%<br>261[a]/864[b] | 34.2%<br>244/713 | 22.4%<br>159/709 | 42.9%<br>304/709 | 13.7%<br>70/511 | 17.8%<br>126/709 | 27.4%<br>186/678 | 13.7%<br>103/752 | 7.2%<br>54/752 |
| Endotheliomesangial GN (including crescents < 50%) | ↗↗↗<br>95/212 | ↗↗<br>74/169 | ↗↗↗<br>62/172 | 68/172 | ↗↗↗<br>38/172 | 27/172 | 46/165 | 18/174 | ↗↗↗<br>26/174 |
| Extracapillary accentuated GN | ↙<br>6/38 | ↗↗<br>16/26 | 8/25 | 15/25 | ↗↗↗<br>10/25 | 6/25 | ↙↙<br>0/27 | ↙<br>0/24 | ↗↗<br>5/24 |
| Membranoproliferative GN | 7/40 | 6/28 | ↙<br>3/37 | 17/37 | 5/37 | 11/37 | ↗↗↗<br>14/24 | ↙<br>0/36 | 0/36 |
| Intramembranous GN[c] | ↗↗↗<br>94/152 | ↗↗↗<br>79/162 | 39/188 | nd | nd | 34/142 | nd | ↙↙↙<br>0/145 | ↗↗↗<br>50/148 |
| Epimembranous GN | ↙↙↙<br>9/72 | ↙↙↙<br>8/58 | ↙↙<br>3/57 | ↗↗↗<br>39/57 | 9/57 | 10/57 | 10/47 | 6/55 | 1/55 |
| Segmental-focal proliferative GN (including crescents < 50%) | 42/156 | ↗<br>50/119 | ↗<br>39/130 | 48/120 | ↙↙<br>7/120 | ↗<br>30/120 | ↙<br>24/124 | ↙↙↙<br>6/125 | 13/125 |
| Segmental-focal sclerosing GN | ↙↙↙<br>16/130 | 30/95 | ↙<br>13/95 | 30/95 | ↙↙↙<br>1/95 | 21/95 | ↗<br>32/84 | 11/100 | 4/100 |
| Glomerular minimal change | ↗↗↗<br>110/211 | ↙↙↙<br>43/185 | ↙↙<br>31/198 | 85/198 | nd | ↙↙↙<br>20/198 | 60/196 | ↗↗↗<br>53/193 | ↙↙<br>5/193 |
| IgA mesangial GN[d] | (↗↗↗)[b] | ↗<br>99/131 | (↗↗↗) | nd | nd | nd | (↗) | nd | ↗↗↗<br>129/268 |

[a] Parameter present.
[b] Parameter stated. Based on (own) cases only (see Table 14.3).
[c] Based on data from [35, 165, 231, 524, 631, 987, 1652].
[d] Based on data from [354, 393, 950, 1043, 1513, 1720, 1778a].
[e] For definition see Table 14.3.
nd = No data.

Increase of the antistreptolysin titer and decrease of complement (C3) are very dependent on the stage of the disease. During the first month of the disease, serum complement is usually (always: [911]) decreased. In our own material, there was a decrease of only 18% when all stages of the disease were considered (Fig. 14.1).

In the exudative stage, the antistreptolysin is increased in about 60% of the cases (23 out of 39: [1332]; 4 out of 6: Z) but in the later stages only in about 25% (5 out of 23: [1332]; 28 out of 115: Z).

Not too infrequently, the disease courses with very few symptoms (see also [410]). In fact, during the second Red Lake Indian Reservation Epidemic, 50% of patients were subjectively and clinically asymptomatic in whom only routine urine examination revealed the presence of hematuria [803]. This explains why acute GN was only mentioned in some of the case histories of patients with proliferative, proliferative-sclerosing and sclerosing stages of the disease (8 out of 21: [620]; 2 out of 10: [1414]).

If the disease does not heal during the acute stage, it assumes either a stationary course, or one characterized by attacks with recurrent macrohematuria (Fig. 14.1).

At the time of bioptic diagnosis, the clinical picture of endotheliomesangial GN – with inclusion of all stages – was generally characterized by isolated hematuria (Fig. 14.1) which can, as is known, remain the only symptom for years and even decades [816]. Proteinuria and hematuria were present in about 25% of our cases (Fig. 14.1). Isolated nephrotic syndrome, nephrotic syndrome assocaited with hematuria or hypertension, and an increase in serum urea or creatinine do occur, but they are not characteristic (Fig. 14.1). Pathologic urine findings at the time of biopsy were absent in 10% of our cases (Fig. 14.1) even though GN was certainly present in the case histories. This is explained by sequence biopsies obtained after diffuse GN which have shown that precisely the later stages of endotheliomesangial GN can persist for a long time in the absence of clinical symptoms [1414]. Relapses of endotheliomesangial GN

Table 14.4 (continued)

| Isolated hematuria | Isolated proteinuria | Isolated nephrotic syndrome | Nephrotic syndrome and hematuria | Proteinuria and hematuria | Oligo-anuria | Serum-creatinine/urea increase | | Hypertension | AST | C3 |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ↗ | ↗↗ | | ↗ | ↙ |
| 22.2% | 14.6% | 11.2% | 11% | 27.3% | 7.7% | 25.4% | 11.1% | 27.2% | 19.9% | 13.8% |
| 167/752 | 110/752 | 84/752 | 83/752 | 205/752 | 25/322 | 201/792 | 89/792 | 206/756 | 103/517 | 28/203 |
| ↗↗↗ | | ↙↙↙ | ↙↙↙ | | | ↙↙↙ | ↙ | ↙↙ | | |
| 72/174 | 26/174 | 4/174 | 6/174 | 48/174 | 3/81 | 26/175 | 12/175 | 34/180 | 32/121 | 10/56 |
| ↙ | ↙ | | ↗↗↗ | ↗↗ | ↗↗↗ | ↗↗↗ | ↗↗↗ | ↗ | | |
| 1/24 | 0/24 | 0/24 | 10/24 | 13/24 | 15/24 | 28/28 | 22/28 | 12/27 | 6/17 | 0/15 |
| ↙↙ | ↙ | | ↗↗↗ | ↗ | | ↗↗↗ | ↗↗ | ↗↗↗ | | ↗↗↗ |
| 1/36 | 1/36 | 1/36 | 18/36 | 15/36 | 3/15 | 18/32 | 9/32 | 25/35 | 3/33 | 6/10 |
| ↙↙↙ | | ↙ | ↗↗↗ | | | ↗↗↗ | | ↗↗↗ | | ↗↗↗ |
| 0/131 | 11/131 | 5/131 | 90/131 | 26/131 | nd | 67/173 | nd | 70/118 | 12/87 | 42/54 |
| ↙↙↙ | | ↗↗↗ | | ↙ | | ↙ | | | | |
| 2/55 | 8/55 | 26/55 | 6/55 | 7/55 | 0/20 | 7/55 | 2/55 | 21/55 | 4/45 | 0/10 |
| ↙↙ | ↙ | ↙↙ | ↗↗↗ | ↗↗↗ | | ↗↗↗ | ↗↗↗ | | | |
| 16/125 | 9/125 | 5/125 | 25/125 | 64/125 | 2/53 | 60/123 | 27/123 | 39/126 | 24/93 | 5/41 |
| ↙ | ↗↗↗ | | | | | | | ↗ | | |
| 14/100 | 28/100 | 11/100 | 12/100 | 24/100 | 1/25 | 32/98 | 15/98 | 37/101 | 8/59 | 0/10 |
| | | ↗↗ | ↙↙↙ | ↙↙↙ | ↙↙ | ↙↙↙ | ↙↙↙ | ↙↙↙ | | |
| 46/193 | 28/193 | 33/193 | 8/193 | 25/193 | 1/100 | 10/193 | 2/193 | 17/193 | 19/123 | nd |
| | ↙↙↙ | ↙↙↙ | | ↗↗↗ | | ↙↙↙ | | ↙↙ | | |
| 69/268 | 12/268 | 0/268 | 20/268 | 152/268 | nd | 30/268 | nd | 37/207 | 1/17 | 26/175 |

Table 14.5. Morphologic forms of GN in clinical (anamnestic) acute glomerulonephritis

| GN form | Number of patients | |
|---|---|---|
| | without oligo-anuria | with oligo-anuria |
| All GN | 35 | 45 |
| Endotheliomesangial (including crescents: <50%) | 5 | 13 |
| Extracapillary accentuated | – | 9 |
| Membranoproliferative | 3 | 3 |
| Epimembranous | – | 1 |
| Segmental focal proliferative (including crescents: <50%) | 16 | 13 |
| Segmental-focal sclerosing | 3 | 1 |
| Glomerular minimal change | 8 | 1 |
| Biopsy: average weeks after onset of disease (range) | 102 (3–350) | 24 (1–400) |
| Prognosis from disease onset | | |
| 5 year survival rate | 92% | 82% |
| 10 year survival rate | 87% | 62% |

*(Footnote to Table 14.4)* Based on chi-square test:
$p < 0.05$ more frequent (↗), rare (↙) than in the sum of all other GN i.e. characteristic for this GN
$p < 0.01$ more frequent (↗↗), rare (↙↙) than in the sum of all other GN i.e. very characteristic for this GN
$p < 0.001$ more frequent (↗↗↗), rare (↙↙↙) than in the sum of all other GN i.e. highly characteristic for this GN

Table 14.6. IF findings in endotheliomesangial glomerulonephritis (all stages except exudative stage) ($n = 62$, neg. 15 times)

| | IgG | IgM | IgA | C3 | Fibrin(-ogen) |
|---|---|---|---|---|---|
| Cases tested | 37 | 37 | 27 | 37 | 34 |
| Positive | 20 | 27 | 10 | 28 | 8 |
| Focal | 11 | 16 | 7 | 10 | 2 |
| Diffuse | 9 | 11 | 3 | 18 | 6 |
| Segmental | 11 | 16 | 10 | 15 | 5 |
| Global | 9 | 11 | – | 13 | 3 |
| Peripheral | 11 | 10 | 3 | 5 | 2 |
| Mesangial and peripheral | 7 | 14 | 6 | 17 | 4 |
| Mesangial | 2 | 3 | 1 | 6 | 2 |

Combinations see p. 201.

are apparently very rare (5 out of 23: [72]; 4 out of 38: [408]) and afflicts girls far more frequently than boys [387].

## LM Findings

The earliest stage i.e. the *exudative stage* is dominated by overwhelming leukocytosis of the capillary loops (Figs. 14.2, 14.3, 14.4; see also [1312]) as well as by incipient hematuria which is recognizable by the presence of erythrocytes in the capsular space and by the occurrence of erythrocytic casts. In many cases, the designation, "capillary loop leukocytosis" would be more apt since fibrin exudation is often not demonstrable. Capillary loop thrombi (Fig. 14.5) and indications of loop necrosis are, according to our findings, extremely rare. Cases of this kind are usually limited to infants [1791]. Additionally, great caution must be used to avoid including cases of hemolytic-uremic syndrome in this category of disease.

Capillary loop leukocytosis is usually clearly evident up to 3 weeks after commencement of clinical symptoms and, 6 weeks thereafter, it has almost disappeared [1791], but may persist up to 8 weeks (Table 14.2). Besides polymorphonuclear leukocytes, an increasing number of mononuclear cellular elements with large oval nuclei—which EM study has shown to be monocytes—are found. Their differentiation from proliferating endothelial and mesangial cells is impossible with LM.

Masson's trichrome/AFOG stain or stained semithin sections may demonstrate fibrinoid deposits (Fig. 14.6) on the outer aspect of the BM which are clearly recognizable as humps with EM. With LM, these humps are rarely found, since they are often present in only small numbers and are randomly distributed over the glomeruli.

*The proliferative stage* emerges progressively from the purely exudative stage (Table 14.2, Fig. 14.7) and is present averagely after 9 weeks. In this stage, the number of polymorphonuclear leukocytes in the capillary lumens has clearly decreased and is hardly greater than that found under normal conditions (Figs. 14.8, 14.9). Due to the extensive proliferation and swelling of endothelial and mesangial cells there is nearly no blood in the capillary loops. The mesangial space is now considerably widened due to massive proliferation of mesangial cells (Figs. 14.11, 14.12). As evidenced in PASM stain, there is no increase of mesangial matrix (Fig. 14.10) as occurs in the subsequent proliferative-sclerosing phase. With decreasing endothelial and mesangial proliferation and swelling, the mesangial changes of various severity (axial and panmesangial) appear (Fig. 14.12).

A lessening of nuclear and matrix increase (Figs. 14.13, 14.14) as well as a few persisting deposits—chiefly intramembranous—are found at the resolution of this stage.

**Fig. 14.2.** Exudative endotheliomesangial GN. All glomerular capillary loops are full of polymorphonuclear leukocytes. Proliferative changes are not yet present. Autopsy specimen. Female, 51 years. HE (×400) ▷

**Fig. 14.3.** Exudative endotheliomesangial GN. Even under high-power magnification, the polymorphonuclear leukocytic nature of the cells is only recognizable in a few instances. In general, the number of cells is considerably increased. Female, 54 years. PAS (×700)

**Fig. 14.4.** Peroxidase stain of exudative endotheliomesangial GN. In the glomeruli, multiple peroxidase-positive polymorphonuclear leukocytes can be seen. Male, 36 years. Frozen section (×150)

**Fig. 14.5.** Exudative endotheliomesangial GN (more advanced than in Fig. 14.3). Numerous polymorphonuclear leukocytes are present in the capsular space. Glomerular capillary loops are practically bloodless. Two loops contain fibrin clumps (→). Note a leukocytic cast in a proximal tubule. The interstitium is edematous. Female, 3 months. PAS (×180)

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**Fig. 14.6.** Exudative endotheliomesangial GN (same case as in Fig. 14.3). A moderate number of polymorphonuclear leukocytes (*PL*) fill the glomerular capillary loops. Numerous humps are present subepithelially (→). Otherwise, the BM appears unchanged. Female, 54 years. Semi-thin section, toluidine blue (×1000)

**Fig. 14.7.** Endotheliomesangial GN in the exudative-proliferative stage. The mesangial space has already increased; the glomerular capillary loops are generally severely narrowed. Male, 55 years. PAS (×350)

**Fig. 14.8.** Proliferative stage of endotheliomesangial GN. There is considerable glomerular hypercellularity; mesangial matrix seems to be increased (compare with Fig. 14.10). Male, 28 years. PAS (×220)

**Fig. 14.9.** Proliferative endotheliomesangial GN with synechia (*SY*). Severe hypercellularity. The nature of the cells cannot be determined but, in any case, polymorphonuclear leukocytes have disappeared. HE (×480)

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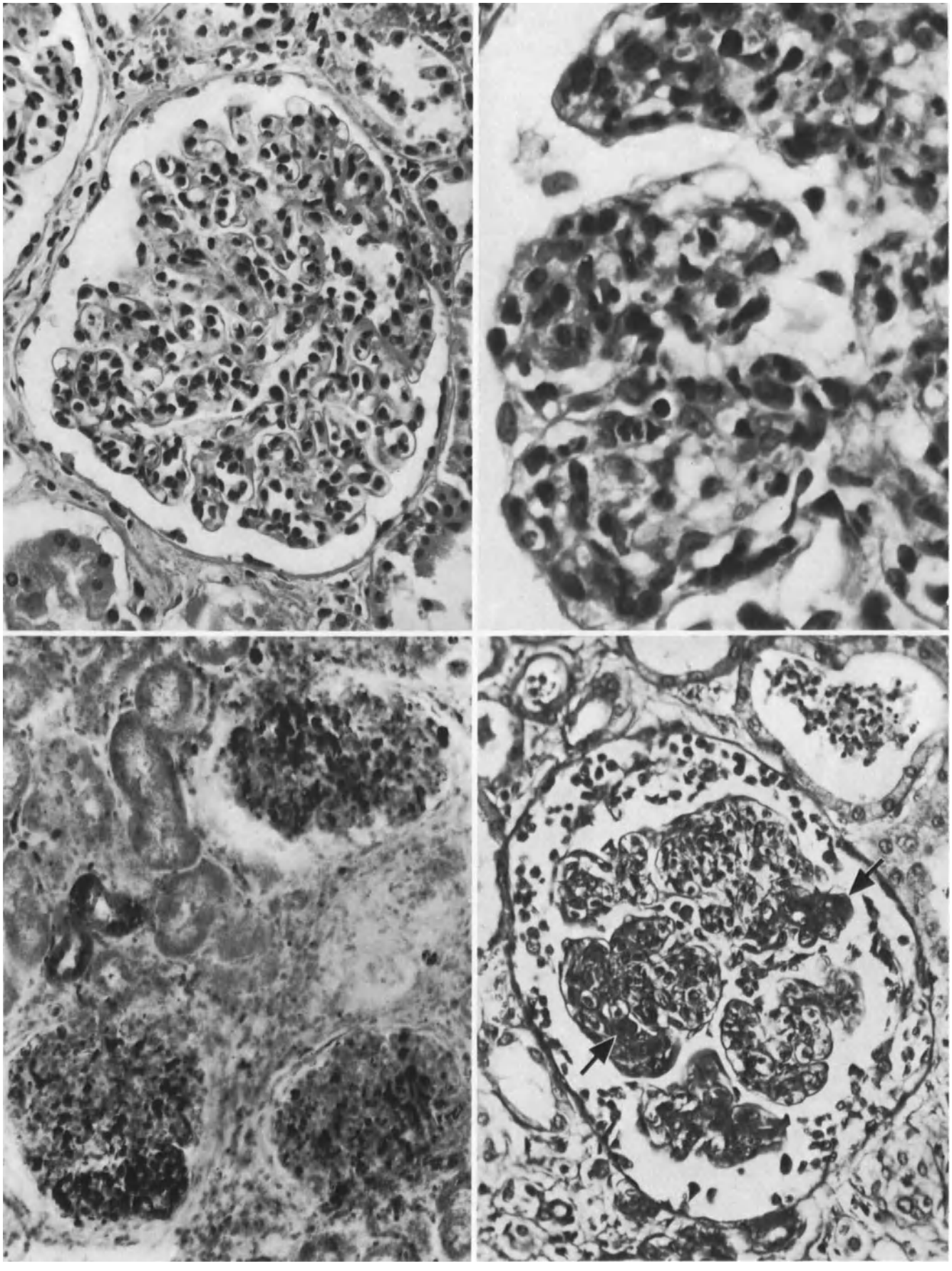
**Fig. 14.10.** Same case as in Figure 14.8. PASM stain shows that no significant mesangial matrix increase is present. (×380)

**Fig. 14.11.** Proliferative stage of endotheliomesangial GN. Slight extracapillary proliferation: note the multilayered capsular epithelial cells. Male, 13 years. PAS (×500)

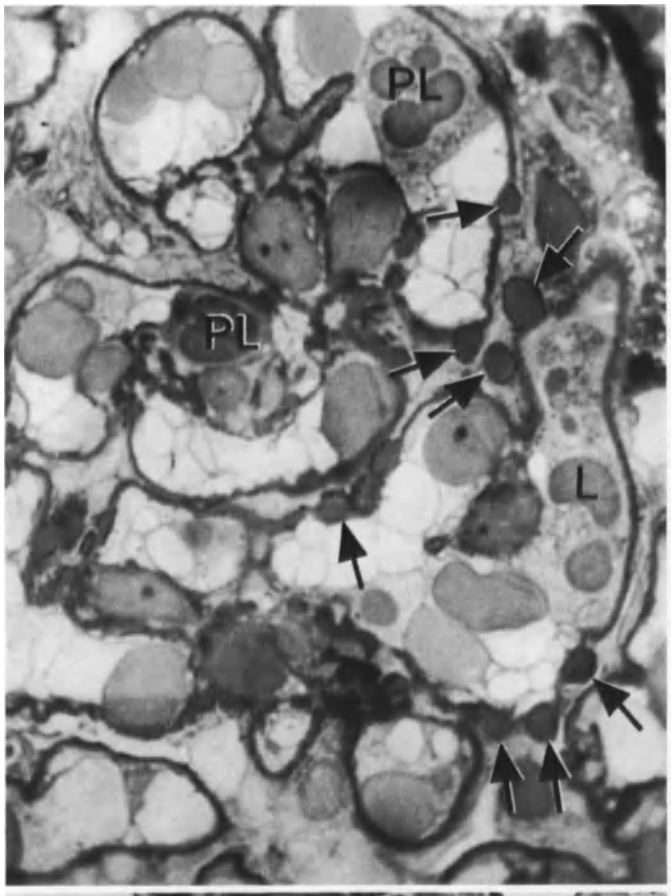
**Fig. 14.12.** Proliferative stage of endotheliomesangial GN with axial mesangial involvement. Cell proliferation is evident in enlarged mesangial areas as well as a beginning increase of mesangial matrix. Male, 14 years. Semi-thin section azure-eosin (×520)

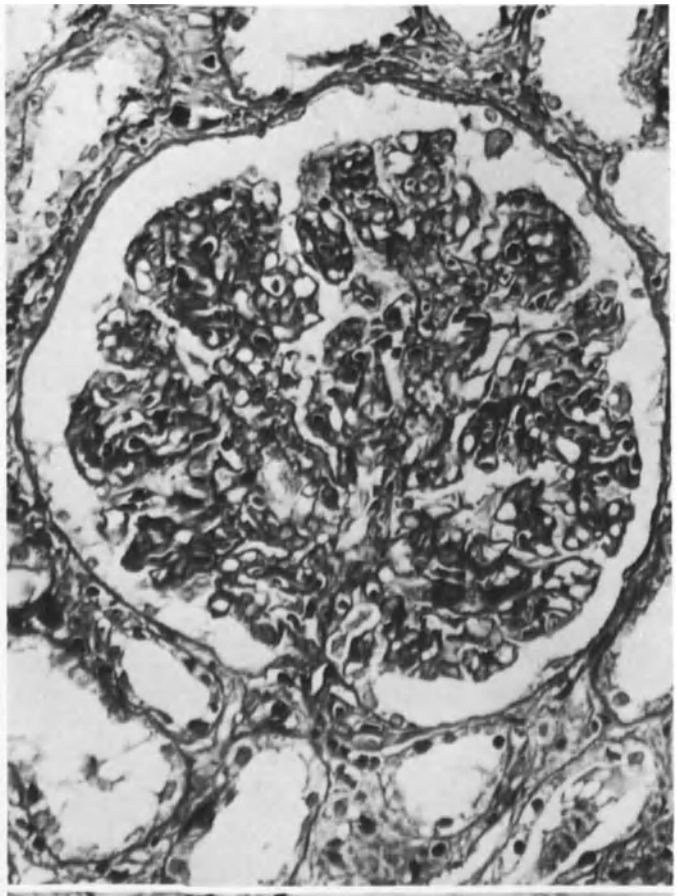
**Fig. 14.13.** Endotheliomesangial GN 20 days after an acute attack in a 2-year-old girl. There is slight enlargement of the mesangium which extends into the periphery of the glomerular capillary loops. Erythrocytes in the capsular space (→). Small partial crescent (*CR*) is present. PAS (×150)



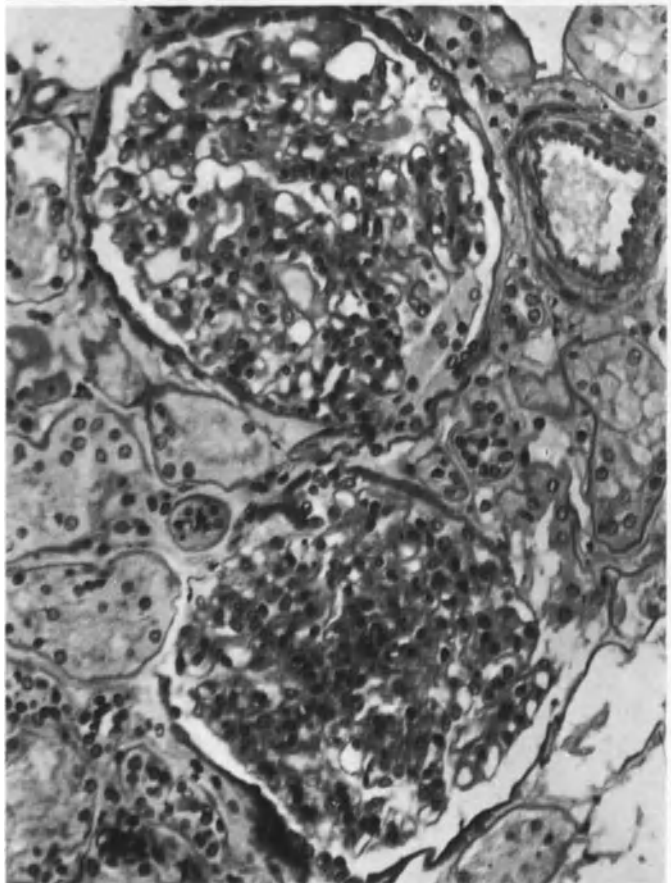
14.2
14.3

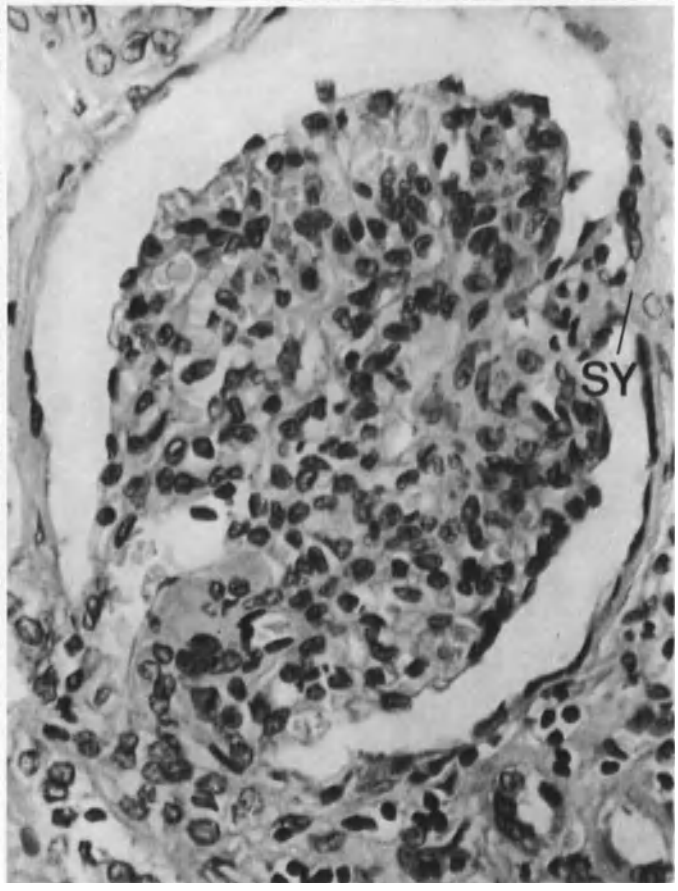
14.4
14.5



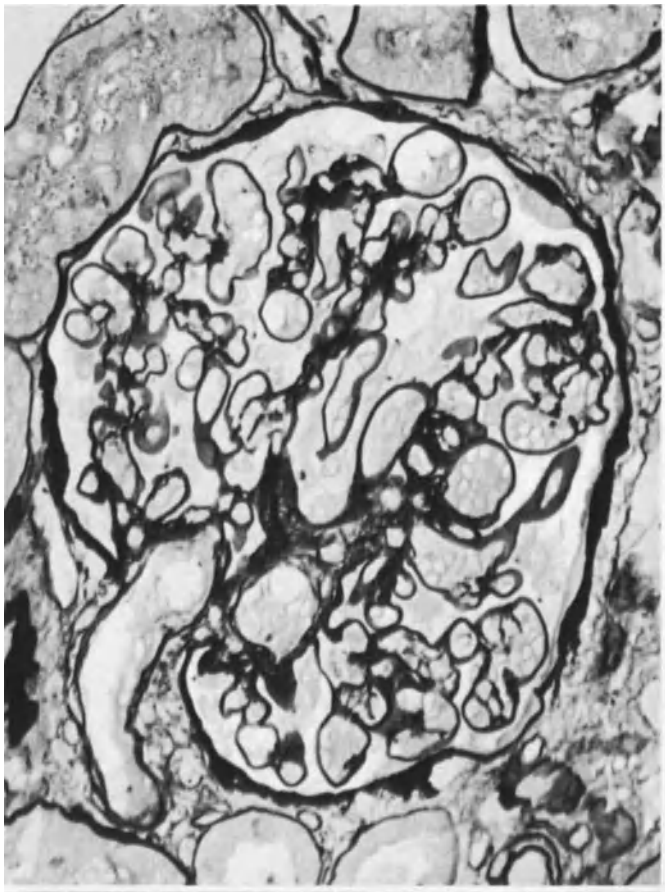



14.6
14.7

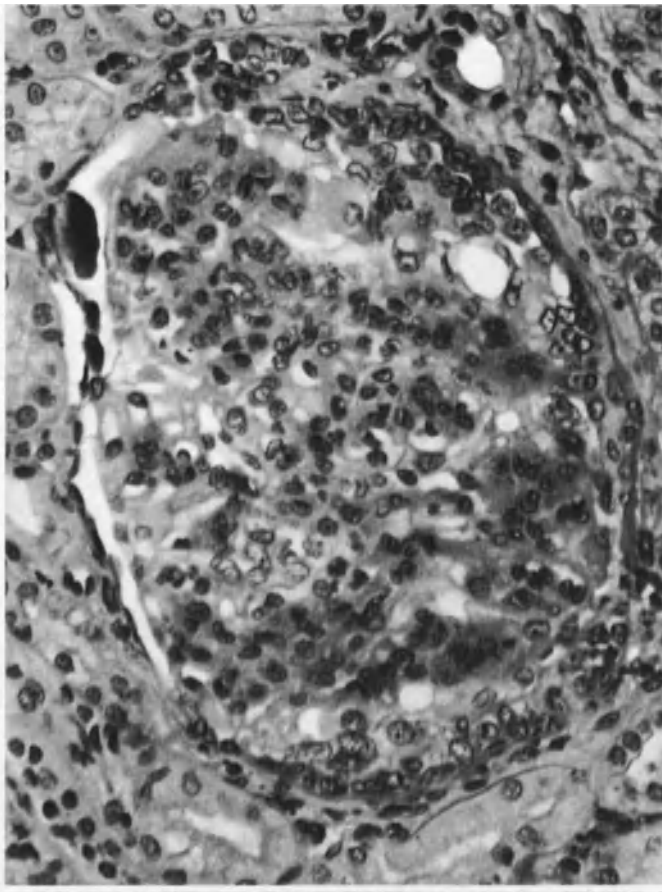


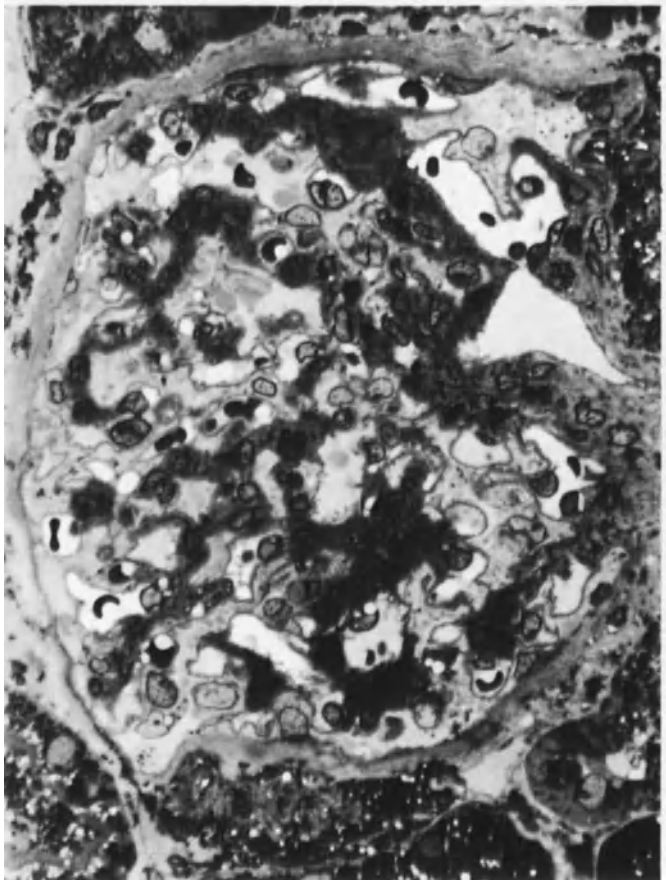



14.8
14.9



14.10
14.11





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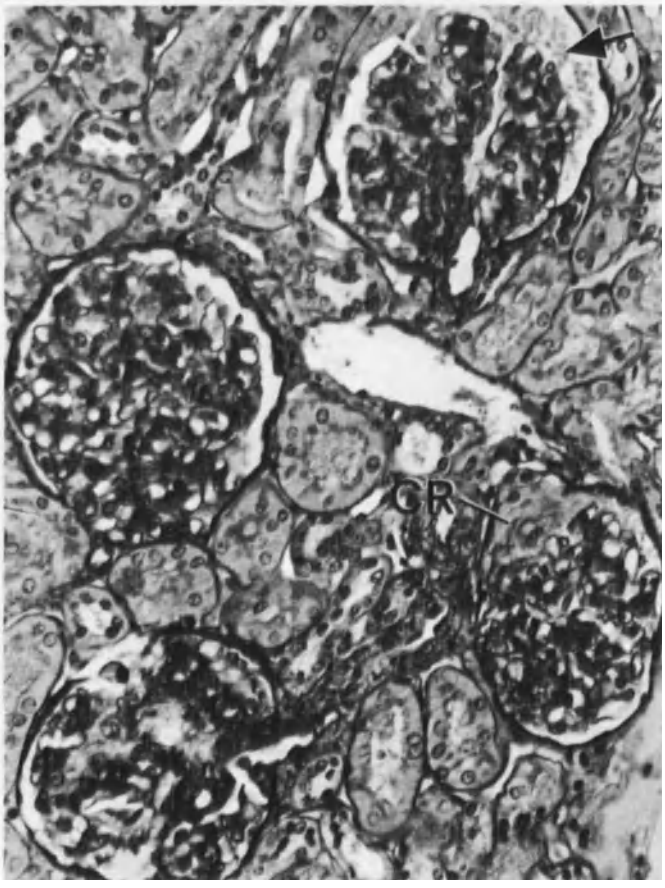
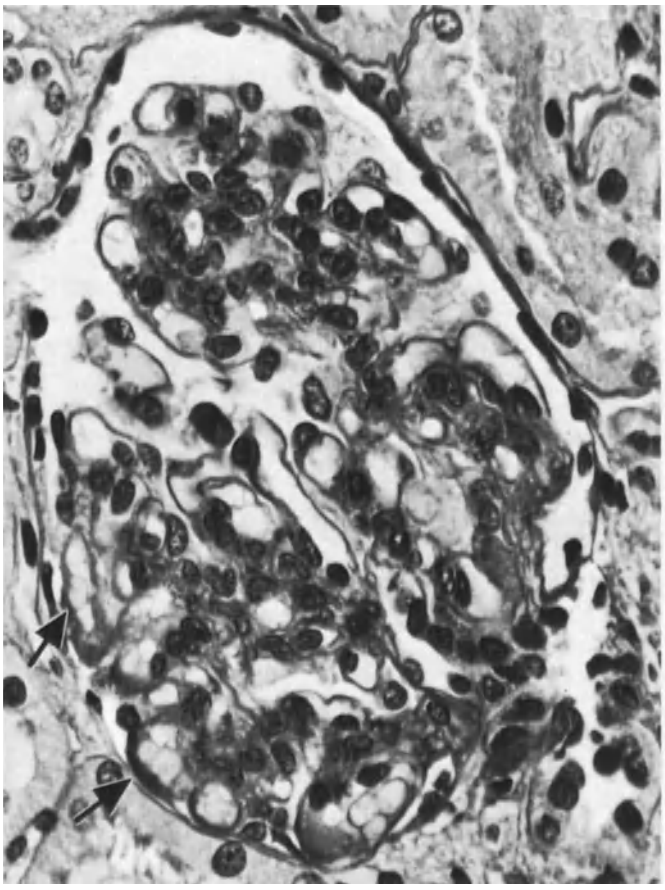
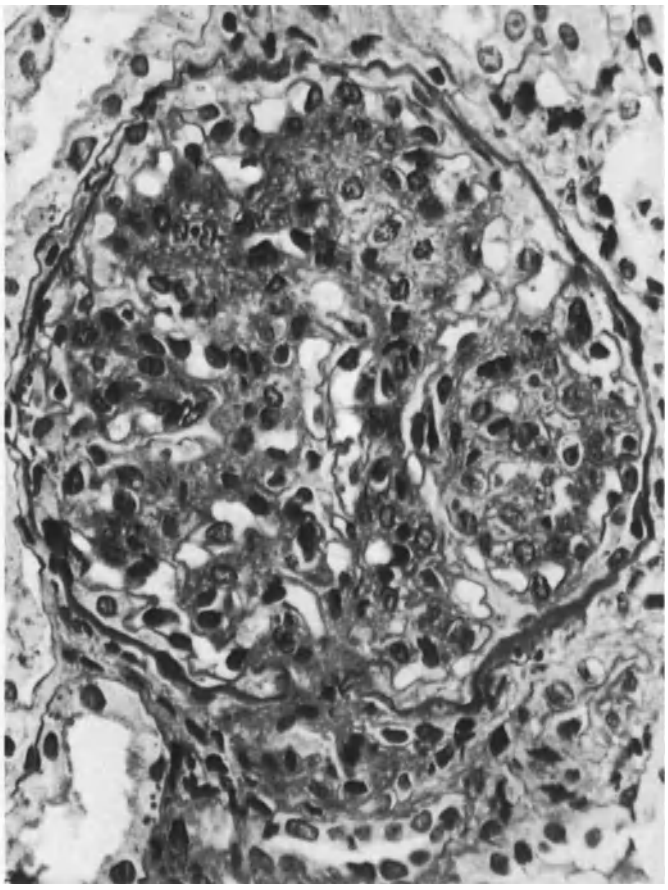
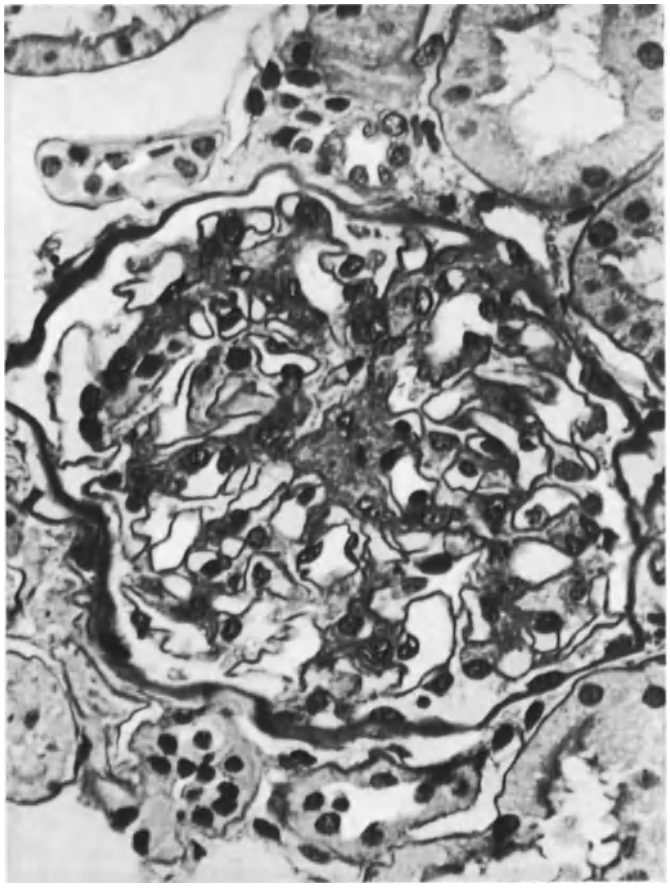
14.13







14.14
14.15



14.16

**Fig. 14.14.** Similar to Figure 14.13 but in a case of a 3.5-year-old boy without clinically acute GN. There is obvious cell proliferation and slight matrix increase in the enlarged mesangium. Isolated thickening of the peripheral glomerular capillary BM may be suspected (→). PAS (×380)

**Fig. 14.15.** Clinically acute poststreptococcal GN 3.5 months previously: proliferative sclerosing stage of endotheliomesangial GN with panmesangial involvement, pronounced matrix and moderate cell increase. Male, 13 years. PAS (×620)

**Fig. 14.16.** Proliferative-sclerosing stage of endotheliomesangial GN with axial mesangial involvement. Cell increase in the mesangium is relatively slight. Male, 33 years. PAS (×400)

In surgical biopsy material, occasionally a more severe involvement of juxtamedullary glomeruli—in comparison with those of the outer cortical region—can be seen [1797]. The glomerular capsular space usually contains only a scanty amount of PAS-positive fluid as well as a few erythrocytes.

In the *proliferative-sclerosing* stage which develops slowly from the proliferative stage (Fig. 14.11), the changes are limited almost exclusively to the mesangium. We have seen this stage on average after 50 weeks of illness, but it may persist for a very long time. The capillary lumen is no longer displaced by proliferating endothelial cells but occasionally by those of the mesangium (Fig. 14.15). The peripheral BM is unchanged and humps are no longer seen with LM. In addition to mesangial cell proliferation, an increase and coarsening of varying severity of the mesangial matrix bars ensue (Fig. 14.16), best demonstrated in PASM stain.

In general, two degrees of severity can usually be recognized. The entire glomerular mesangium may be afflicted (panmesangial change, Fig. 14.15) which, as clearly seen in EM, is accompanied by obsolescence of the capillary loops; or the increase of the mesangial matrix and cells may be restricted to a few thin, finger-like mesangial axes (axial change).

*The sclerosing stage* (PASM-stain) is different from the previous one essentially in that it demonstrates a predominance of mesangial matrix increase in comparison to that of cellular proliferation (Figs. 14.17, 14.18). The mesangial cell nuclei are now often small and exhibit dense chromatin.

Segmental or global crescents in up to 50% of glomeruli may be seen from the proliferative stage onwards (see p. 100). In the sclerosing stage only occasional synechiae are usually encountered.

Tubular changes—if present at all—are usually very discrete and are limited to only focal hyaline protein droplet storage and to a few foam cells which are usually found in the proliferative-sclerosing stage. Numerous hyaline and granular casts are almost always present.

No constant vascular changes are present in any of the stages.

In the exudative stage, the interstitium shows edema of varying intensity. In the proliferative stage, there is a usually moderate interstitial nephritis [1791] which demonstrates perivascularly accentuated infiltrates composed of lymphocytes, histiocytes, and plasma cells. Infiltrates occurring in the proliferative-sclerosing and sclerosing stages are usually scanty and consist predominantly of small lymphocytes.

**IF Findings**

Phasic disease development corresponding to that observed with LM is also seen in IF. In the exudative stage, a mixture of fine and coarsely granular deposits—which occur almost exclusively along the peripheral glomerular BM—is the dominating finding. These deposits correspond to EM-demonstrable humps and they are rich in complement and, in lesser concentration, in IgG (see Fig. 6.38) or other immunoglobulins [544, 1139]. In three of our own cases, C3 alone was present in the first, C3 and IgG in the second, and in the third case IgG, IgM and IgA were present as well. If healing occurs in this stage, the humps disappear and all the IF findings can become negative [51, 128, 730].

The IF findings in the later stages (proliferative, proliferative-sclerosing, and sclerosing) are not uniform. At times, findings similar to those of the exudative stage with irregularly distributed deposits of various sizes are encountered (14 out of 33: [1139]) and at other times the IF findings are completely negative (14 out of 33: [1139]; see also Table 14.6). The negative cases in our material were found in equal frequency in the proliferative, proliferative-sclerosing and sclerosing stage.

In these later stages the mesangium stains positively more often for various immunoglobulins (IgG, IgM, IgA) as well as for C3 and fibrin(-ogen) (see also [544]; Table 14.6). Comparison between the proliferative and sclerosing stage in our own material shows that IgM in focal-segmental distribution is uncommon in the proliferative stage (2 out of 9: Z), whereas in the sclerosing stage it occurs in focal-segmental or global and diffuse distribution mesangially and peripherally in all cases (5 out of 5: Z). For the other immunoglobulins, no difference was encountered.

It is important to note that in our material comprising 62 cases, 10 evidenced findings typical of IgA nephritis, and in the remaining 27 cases in which IgA was tested, 10 demonstrated IgA in focal or diffuse but always segmental distribution (see Table 14.6). Other investigators have reported IgA to be present in 33% of their cases [743]. Since only C3 may be present in GN caused by staphylococci the possibility of complement activation by staphylotoxin has been suggested [1256].

Without consideration of IgA and fibrin(-ogen) the following immunoglobulin combinations were found:

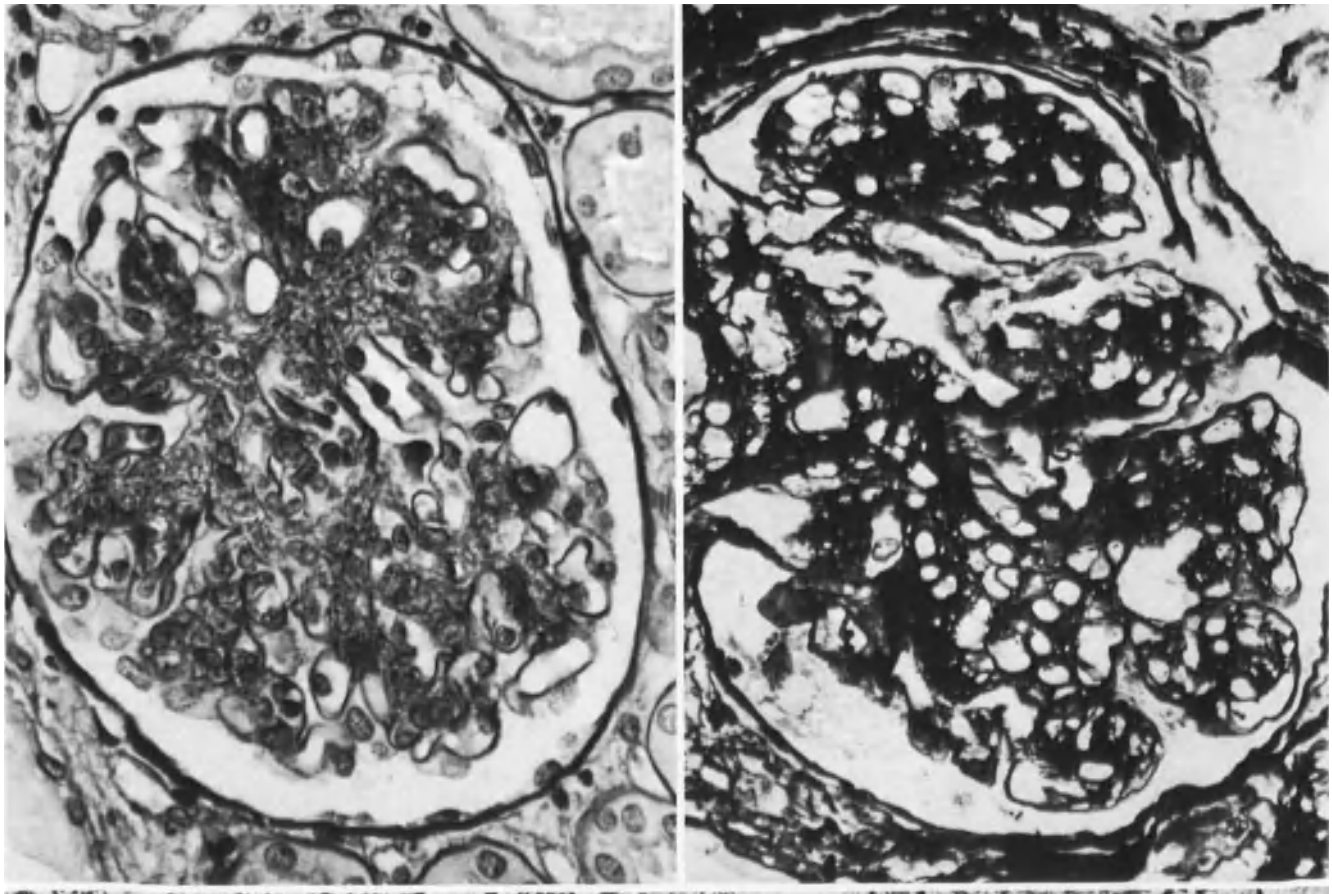
Combinations: Ig(G, M)+C3: 13 times, IgM+C3: 8 times, IgG+C3: 3 times; Ig(G, M): 4 times, C3: 4 times, IgM: twice

Including: IgA: Ig(G, M, A)+C3 4 times, IgA+C3: 3 times; Ig(G, A)+C3: twice; Ig(G, M, A): once.

Ten cases of IgA-nephritis and 15 IF-negative cases are not considered in Table 14.6.

**EM Findings**

The dominating finding in the exudative stage (Figs. 14.19, 14.22) is that of numerous polymorphonuclear leukocytes present in the capillary loops. Additionally, many typical humps are seen on the outer aspect



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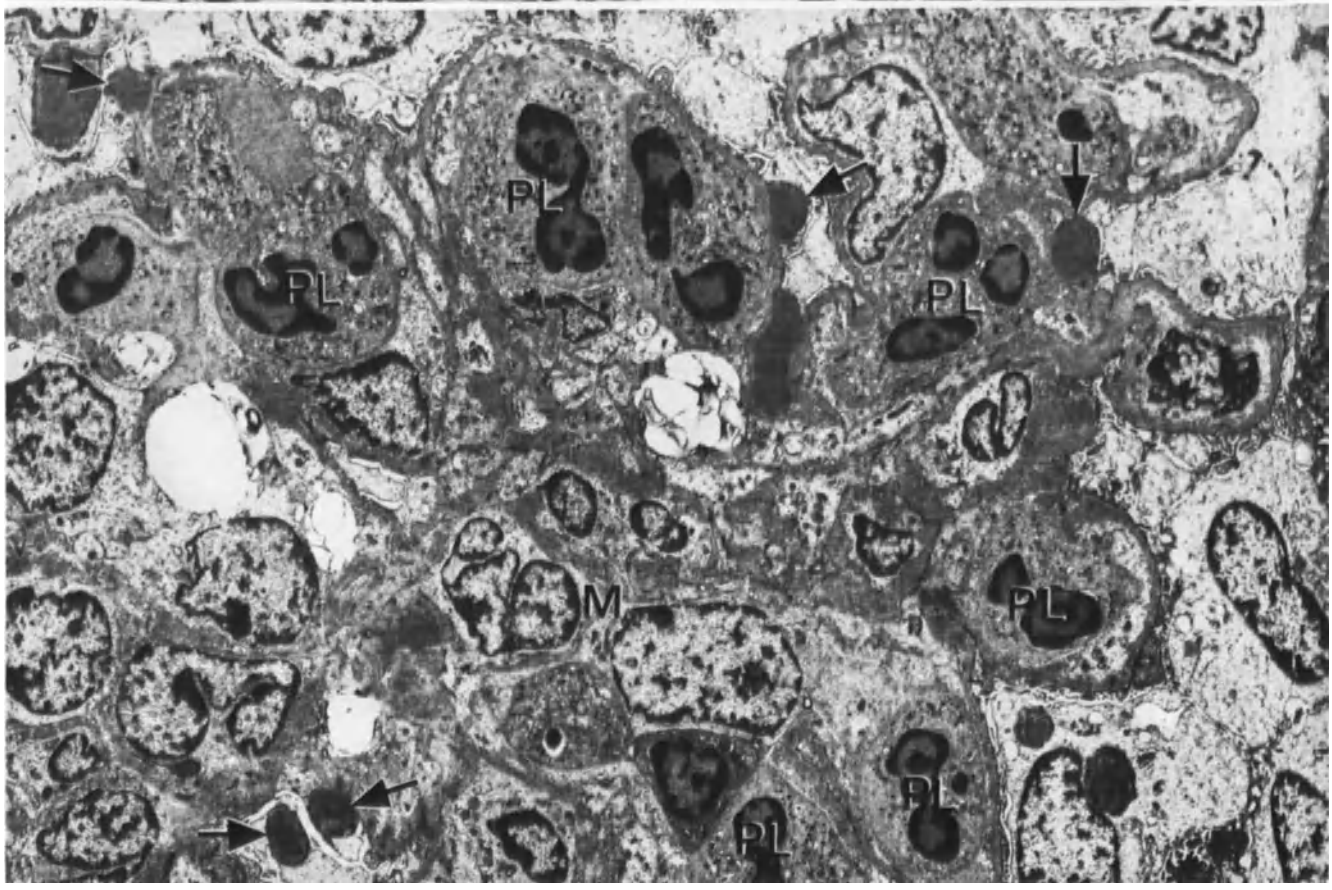


14.19

of the BM (Figs. 14.21, 14.22). Not too in frequently, humps are also encountered on the mesangial BM which bridges adjacent capillary loops (mesengial taille). Leukocytes are reported to be frequently present in the region of the smaller subendothelial osmiophilic deposits [771] which is considered as an indication of the leukocytotaxic property of these deposits; we have not been able to find these leukocytes. Exit of leukocytes through the loops is taken as an expression of leukocytic enzymatic BM injury [229] (compare p. 60).

Monocytes (already recognizable in LM) are also seen (Fig. 14.20); their involvement was often underestimated [382, 1499] even though their presence has been demonstrated with EM for almost 10 years [1582]. Recently, their extensive participation in experimental Masugi nephritis [875] has been demonstrated. These cells have the ability to migrate into the mesangium and thereby to contribute to the widening of the mesangial space.

In addition to the cellular changes, large (up to 5 μm) subepithelial humps are a striking feature of the exudative stage which, in its terminal period, also occasionally evidences small intramembranous deposits (Figs. 14.19, 14.22). The podocytes, which cover the humps in a dome-like manner, frequently demonstrate an increase of osmiophilic substance under the cell membrane (Fig. 14.22); the significance of this substance is not yet fully understood (see p. 78).

In contrast to the relatively frequent positive IF findings, fibrin is very rarely seen in EM.

The reactions of the other local cellular elements are certainly apparent in the exudative stage, but they become more clearly evident in the *proliferative stage*. For EM findings see also Figures 6.9, 6.21, 6.34, 6.57, 6.64, 6.80, 6.88. In this stage, the glomerular capillary lumens are filled with large mononuclear cells (Figs. 14.23, 14.24) whose histogenetic analysis often presents difficulties. In general, these elements are thought to be swollen and proliferated endothelial and mesangial cells [454].

In any event, endothelial cells are involved, since endothelial mitoses can occasionally be seen [1797]. Extensive hypertrophy of endothelial cells with nuclear enlargement and formation of numerous arcades is also present (Fig. 14.23; see also [349]). We have observed endothelial detachment with necrobiosis only once on the seventh day after disease onset.

The mesangial space is now widened by mesangial cell proliferation, which may be very pronounced (Fig. 14.25). The mesangial cells are hypertrophic (Figs. 14.23, 14.25) exhibiting an increased number of organelles, and their nuclei are usually enlarged and sometimes polymorphic.

The increase in the strikingly loosened mesangial matrix (Fig. 14.26) which is said to commence 12 days after disease onset [772] is generally only slight. In addition to the previously mentioned increase of osmiophilic substance over the subepithelial humps, the podocytes also demonstrate edema or hypertrophy with nuclear swelling and notching, and frequently with proliferation of microvilli (Fig. 14.26).

◁ **Fig. 14.17.** A 5-year-old boy presenting with isolated hematuria during the last 5 months. Sclerosing stage of endotheliomesangial GN with panmesangial involvement (compare with Fig. 14.18). PAS (×450)

**Fig. 14.18.** Same case as in Figure 14.17 but in PASM stain: note massive mesangial matrix increase. Male, 5 years. (×500)

**Fig. 14.19.** Exudative stage of endotheliomesangial GN (same case as in Fig. 14.3). Numerous polymorphonuclear leukocytes (*PL*) are present in the capillary loops. Numerous humps (→) between the edematous podocytes and the peripheral BM. Mesangial cells (*M*) are swollen and their nuclei activated. Female, 54 years. EM (×3370)

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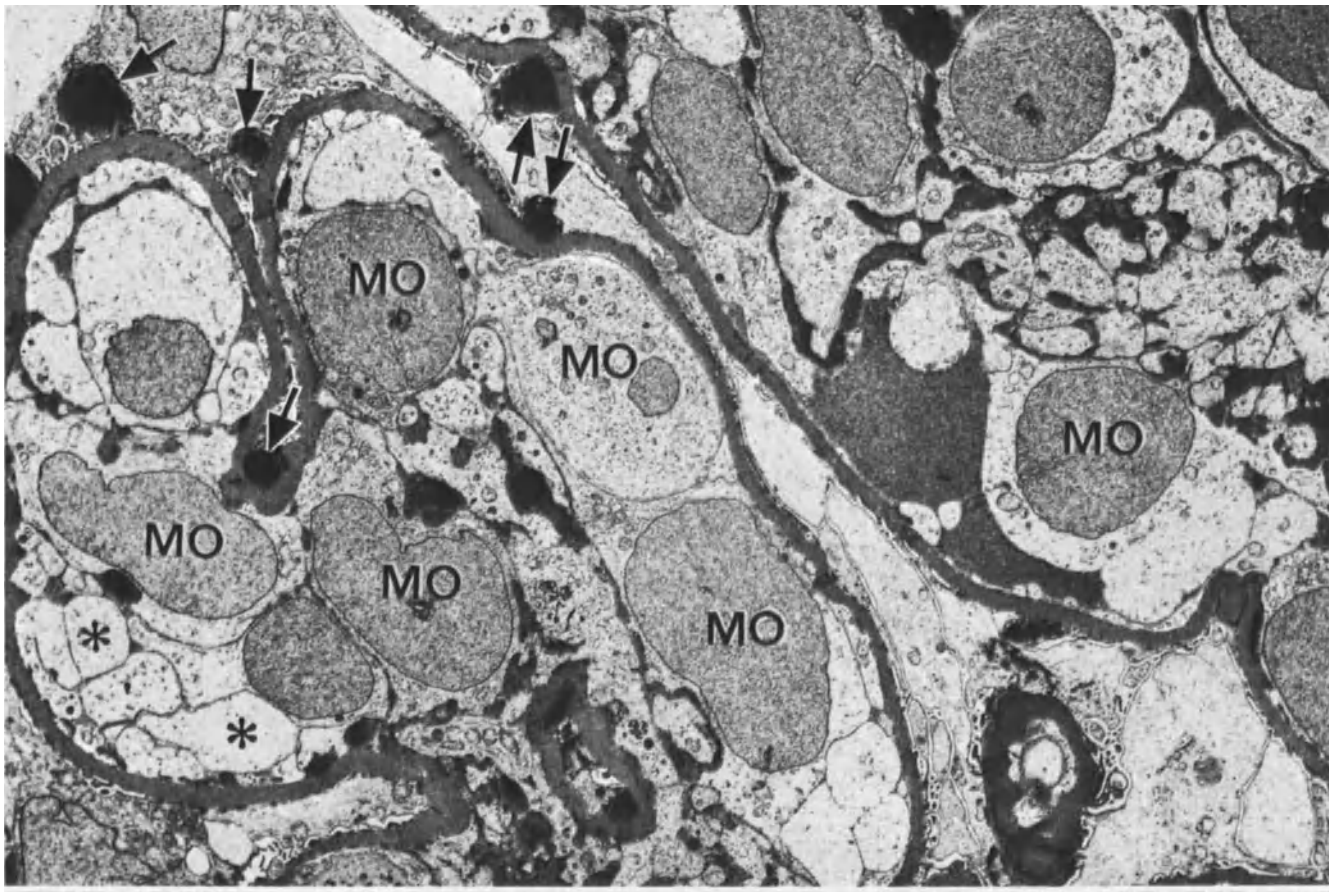
**Fig. 14.20.** Same case as in Figure 14.3. In addition to humps (→), the glomerular capillary loops contain numerous monocytoid cells (*MO*). Ballooned cell processes (*). Female, 54 years. EM (×3500)

**Fig. 14.21.** Same case as in Figure 14.3. Two humps (*H*) partially very sharply delimited by a membrane towards the covering podocyte containing increased osmiophilic substance. The boundaries towards the lamina densa are rather sharp. A subendothelial osmiophilic deposit is recognizable (→). Podocyte (*P*), nucleus of an endothelial cell (*E*). Female, 54 years. EM (×19,700)

Page 205

**Fig. 14.22.** Exudative stage of endotheliomesangial GN. A hump (*H*) has been sectioned tangentially and therefore appears to have no contact with the BM. Marked accumulation of osmiophilic substance in the podocytes and their foot processes—which have more or less fused—is present in the vicinity of the hump. A few subendothelial and intramembranous deposits (→) are recognizable, some of which show strong penetration of the lamina densa. Hypertrophied endothelium in the capillary lumen (*CL*). Male, 5 years. EM (×15,180)

**Fig. 14.23.** Proliferative stage of endotheliomesangial GN. Endothelial cells (*E*) are severely swollen and hypertrophied leading to almost complete occlusion of the glomerular capillary loop lumen. A nucleus of a mesangial cell (*M*) is enlarged and lobulated. Foot processes and peripheral BM are unchanged. Female, 6 years. EM (×4170)

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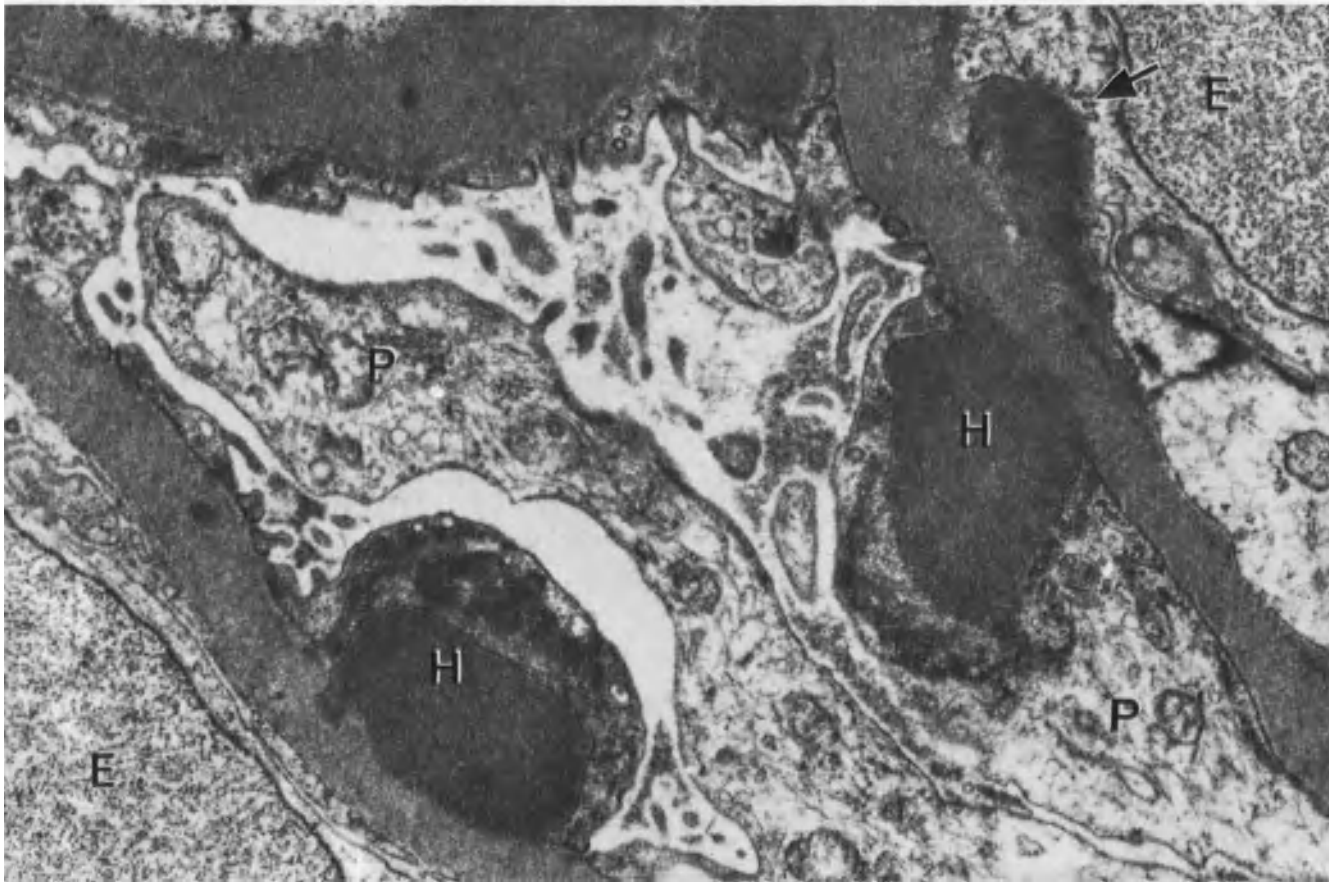


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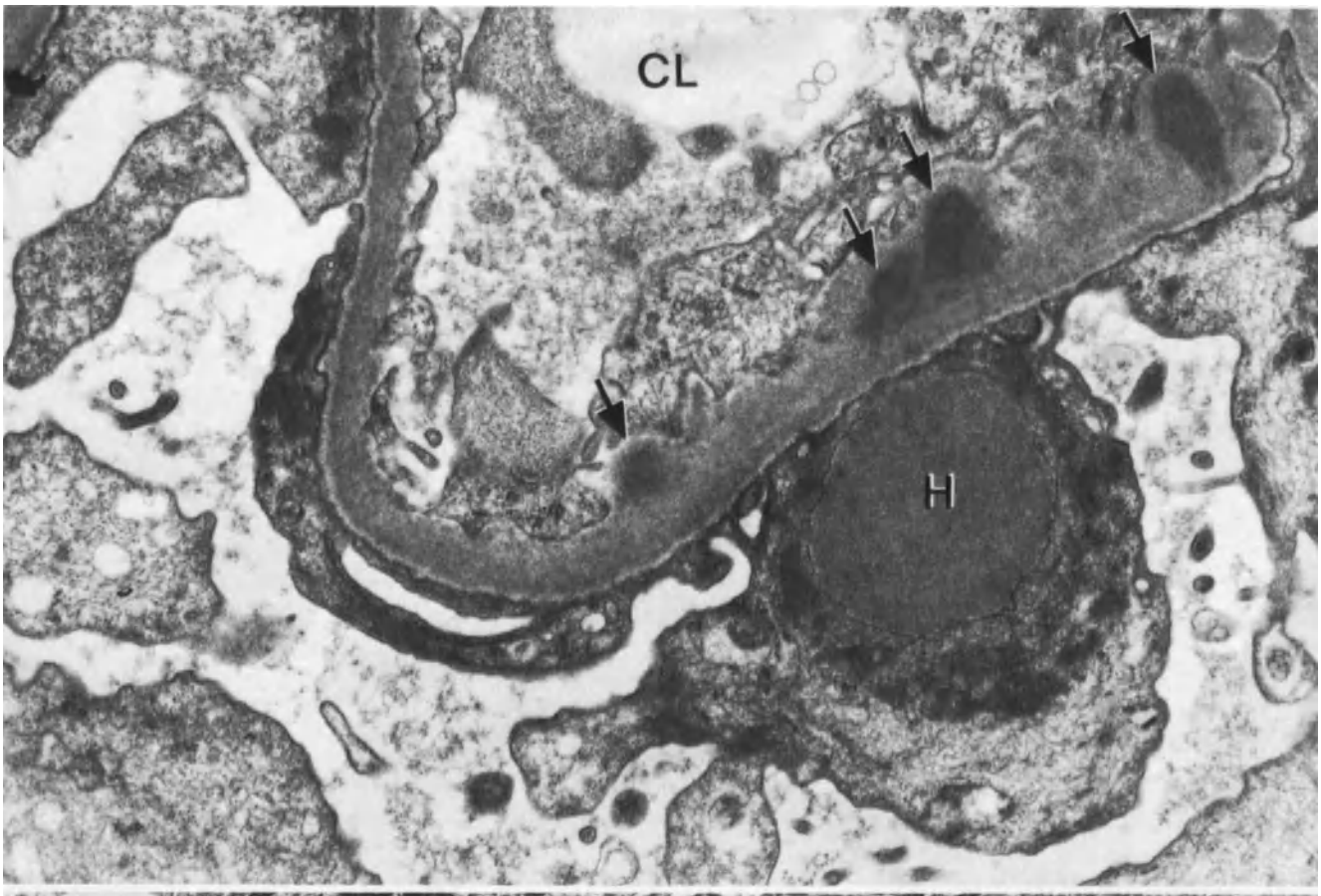


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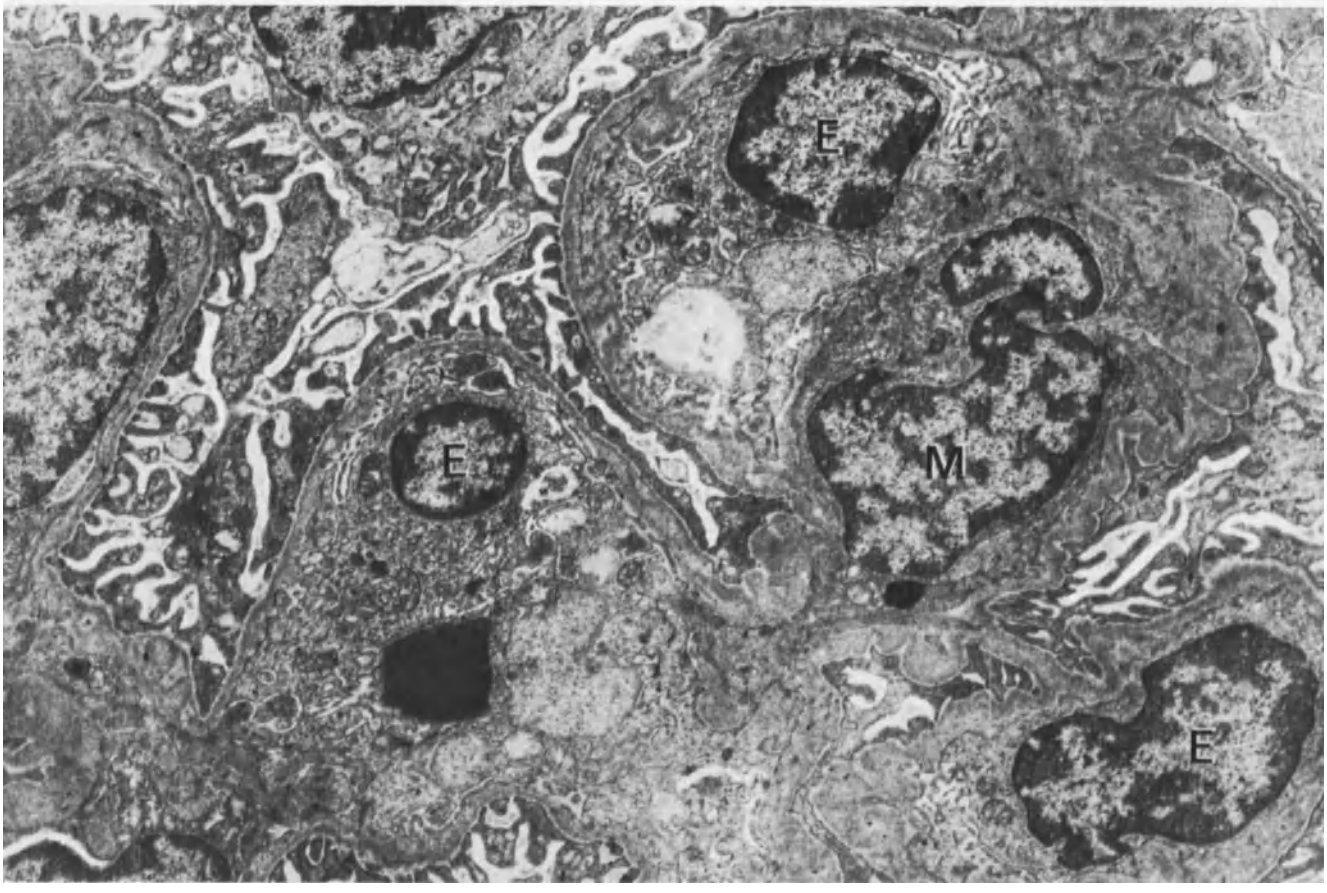


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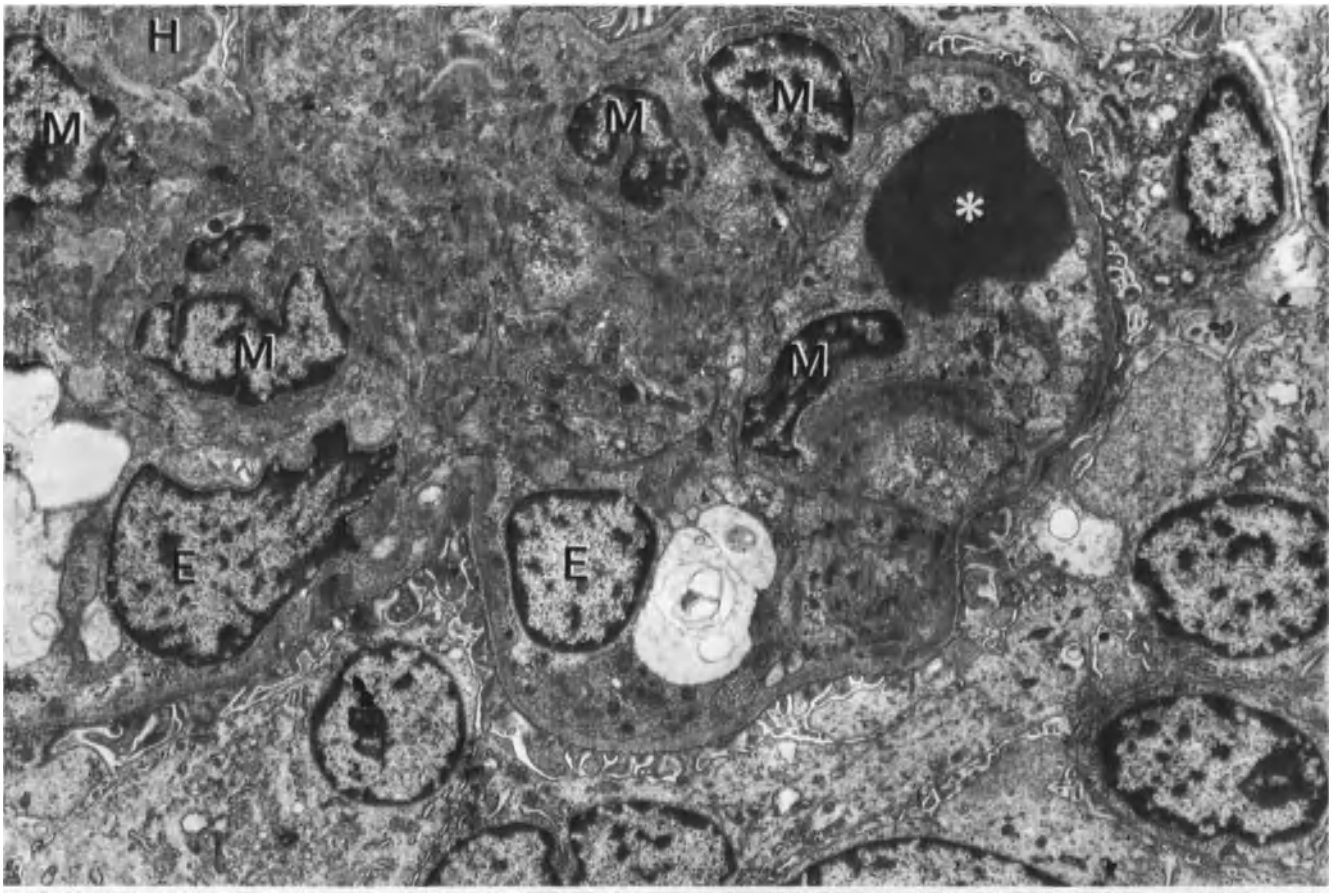


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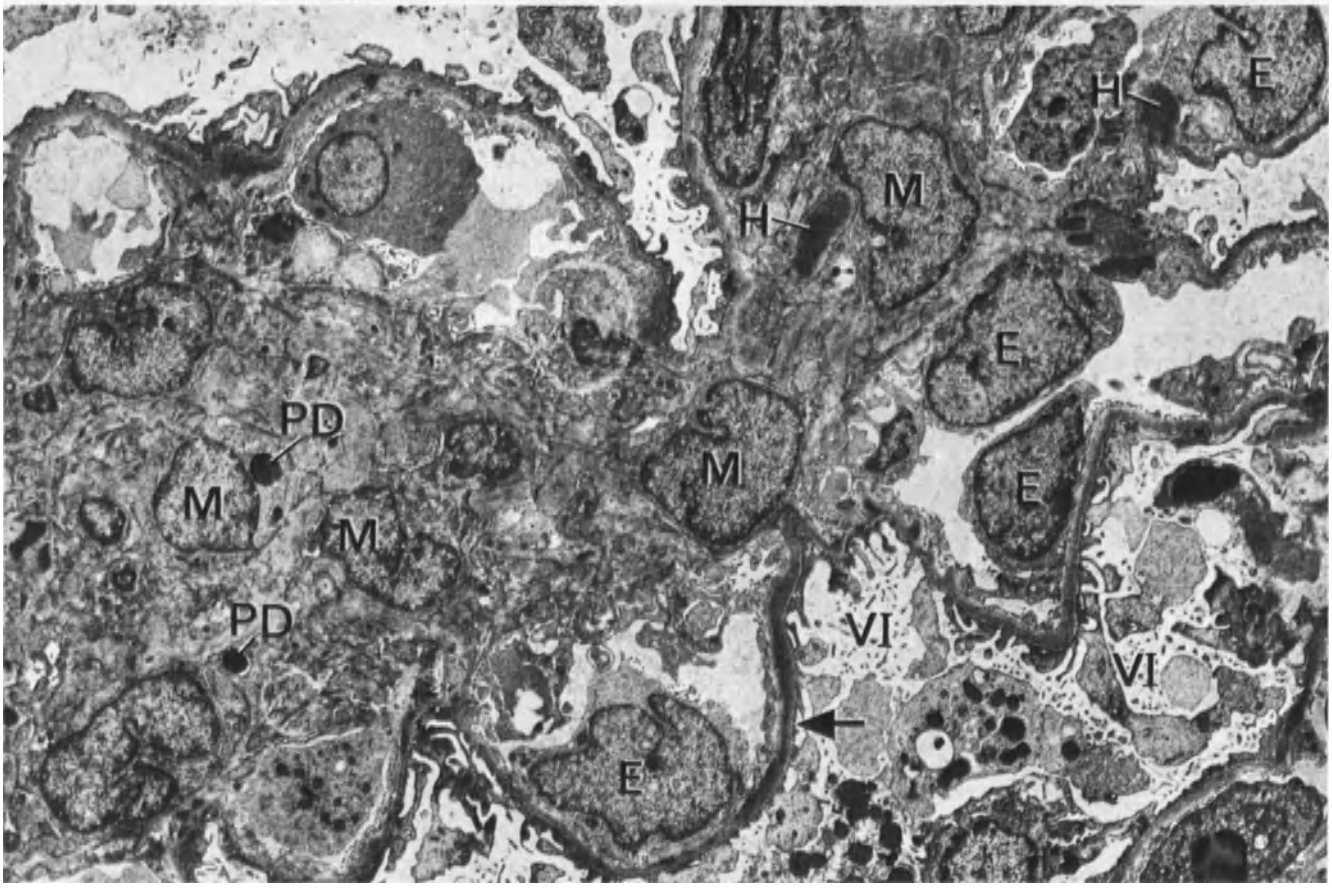


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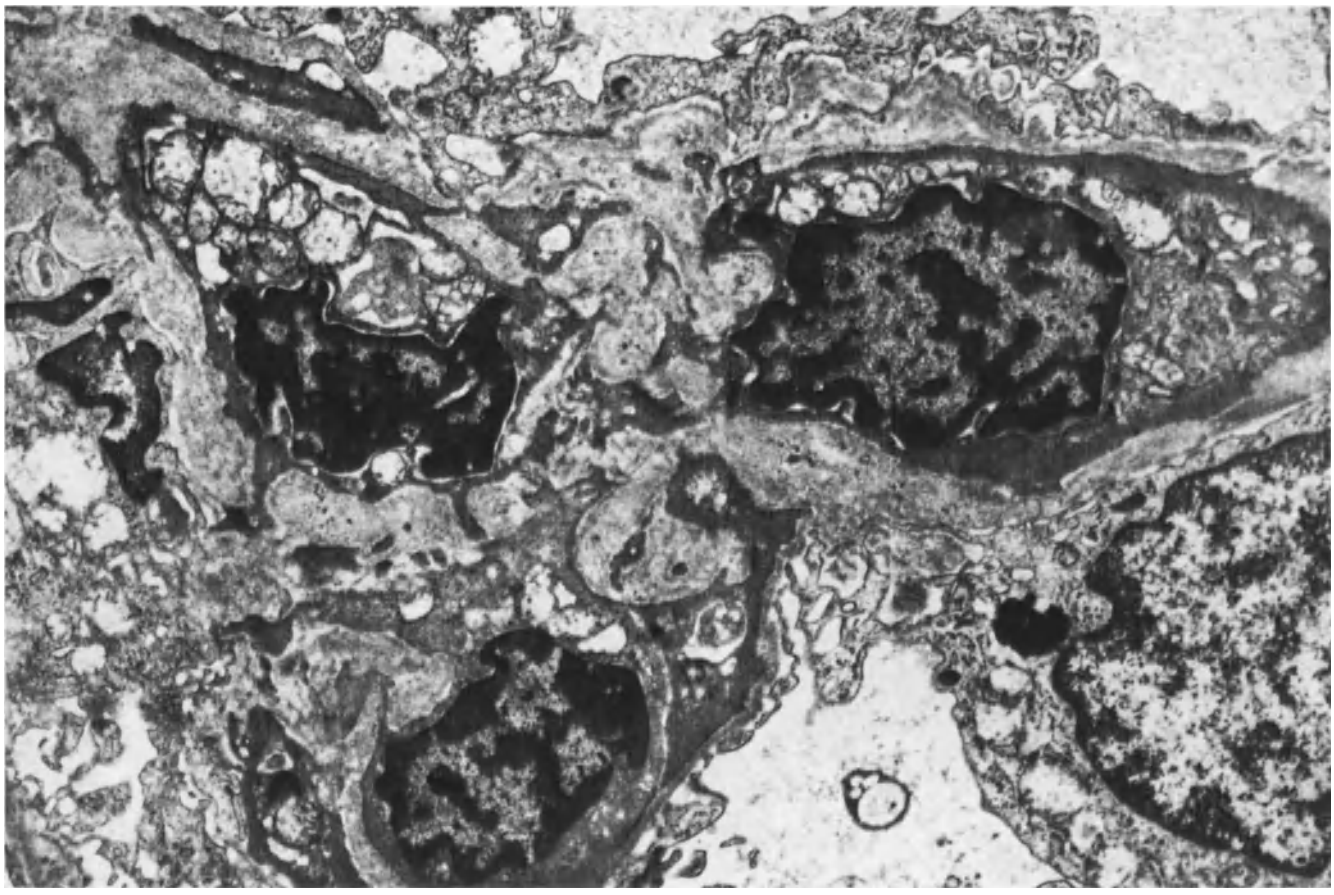


**Fig. 14.26.** Proliferative-sclerosing stage of endotheliomesangial GN with axial mesangial involvement. Mesangial matrix bars are loosely arranged, thickened and increased. Mesangial cell nuclei are slightly enlarged and polymorphic. Male, 13.5 years. EM (×11,600)

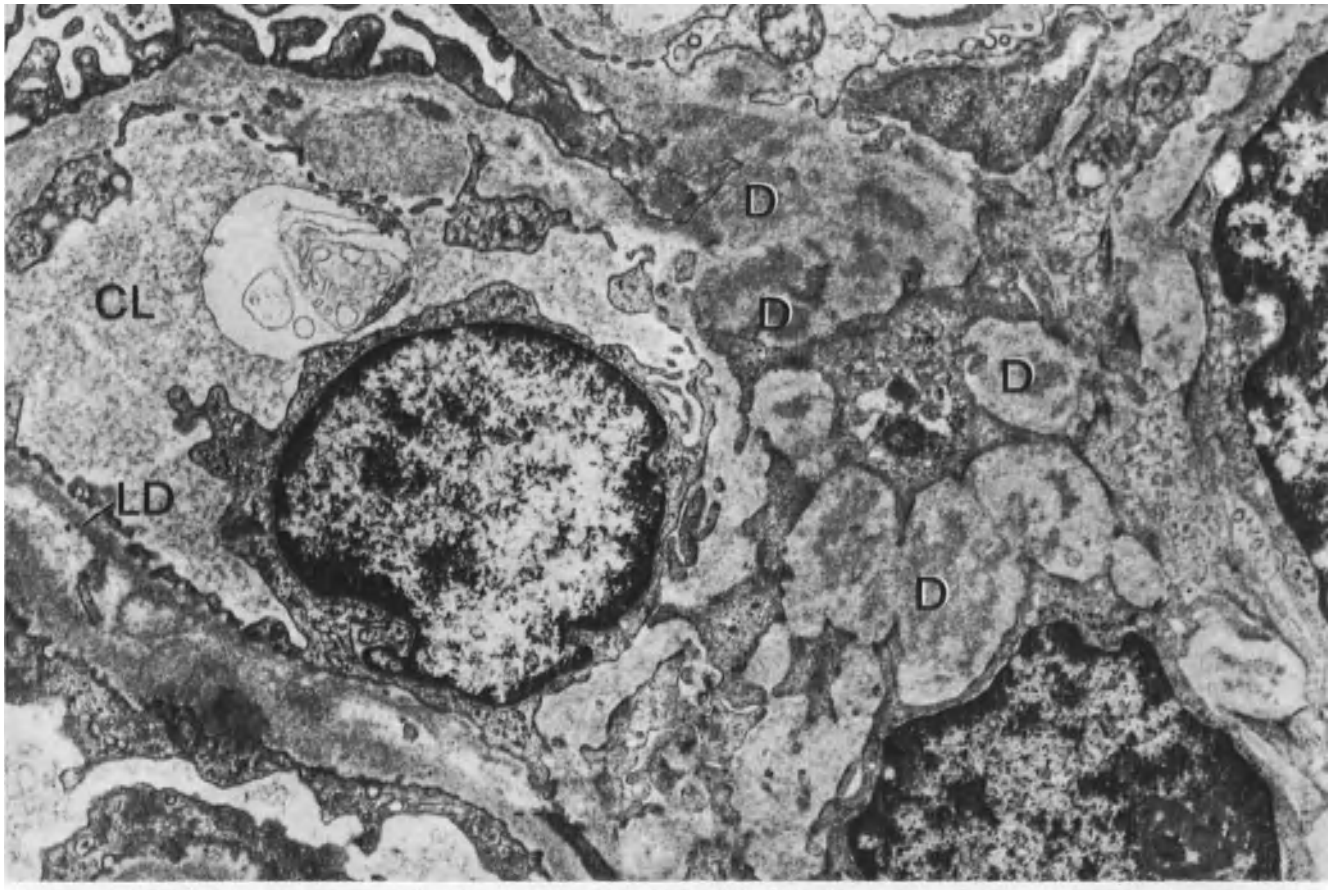
◁ **Fig. 14.24.** Same case as Figure 14.13, reportedly 20 days after an acute attack illustrates the proliferative phase of endotheliomesangial GN. One hump (*H*) is still present. The most striking feature, however, is the proliferation of mesangial cells (*M*) which show polymorphic nuclei. Mesangial matrix has already increased. Endothelial cells are still severely hypertrophied. Glomerular capillary loops are poor in blood, only one erythrocyte is seen (*). Female, 2 years. EM (×5000)

**Fig. 14.25.** Endotheliomesangial GN of about 7 weeks clinical duration. Some humps (*H*) are present beside a circumscript intramembranous osmiophilic deposit (→). Glomerular capillary loop lumens are patent. Endothelial cells (*E*), however, are still frankly swollen and exhibit nuclear polymorphy. Mesangium is severely enlarged and the mesangial cell nuclei (*M*) are enlarged and polymorphic. Mesangial matrix is already increased and accumulation of protein droplets (*PD*) within mesangial cells is present. Podocytes also evidence protein droplets, severe swelling, mild foot process fusion and microvilli (*VI*) formation. Male, 5.5 years. EM (×3530)

In addition to humps which we have found in 6 out of 18 cases of the proliferative stage with generally less than 8 weeks duration of disease (Figs. 14.26, 6.35, 6.38), we have also encountered intramembranous deposits (5 out of 18 cases Figs. 14.22, 14.32, 6.36) and subendothelial deposits (3 out of 18) and deposits along the mesangial BM (5 out of 18 cases). Mesangial matrix deposits (Fig. 14.27) have been observed in 4 out of 18 cases.

The glomerular BM is often focally thickened and especially so by a loose electron-translucent thickening of the lamina rara interna (Figs. 14.28, 14.29; see also [1582, 1797]) as has been demonstrated in animal experimentation [875]. At resolution, dissolved osmiophilic intramembranous deposits and focal BM thickening are occasionally observed (Fig. 14.29, 14.30).

The differences between the proliferative and the subsequent proliferative-sclerosing stage are not as evident in EM as they are in LM. In the *proliferative-sclerosing stage,* the increase in mesangial matrix becomes more apparent (Fig. 14.31) in addition to the signs of cellular (podocytic, endothelial and mesangial) hypertrophy or edema. The matrix bars are obviously thickened, increased and arranged irregularly; these changes may per-

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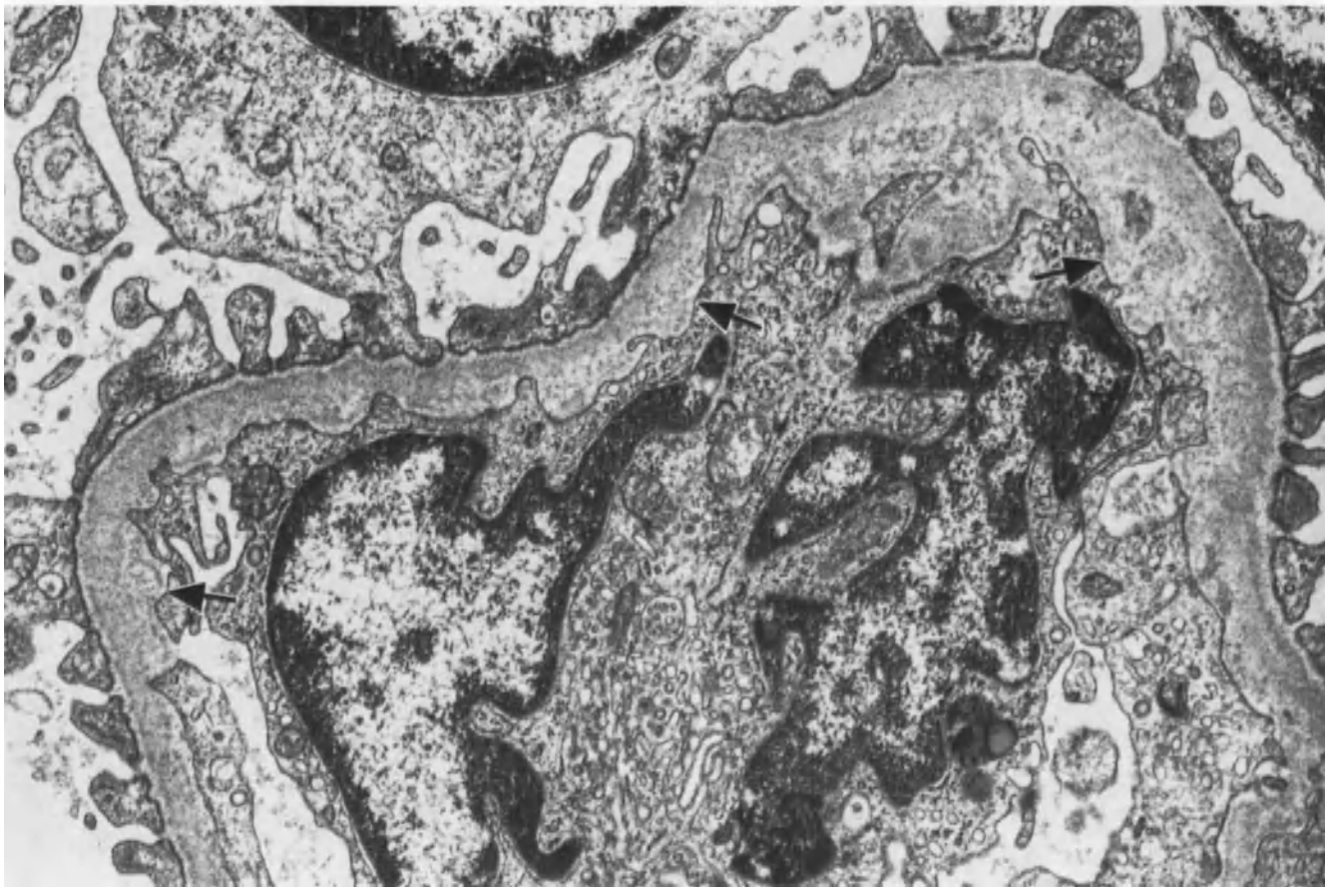

14.28

sist for years [1272, 1582, 1801]. This increase in mesangial matrix is demonstrable in LM by PASM stain.
Humps are found in scarcely 10% of the cases (4 out of 48: Z) but deposits along the mesangial BM or matrix (9 out of 48: Z; Fig. 14.31) and occasional intramembranous (5 out of 48; Fig. 14.32) and subendothelial deposits (6 out of 48: Z) without accompanying mesangial interposition are observed more frequently. In addition to the humps, a few small subepithelial deposits (3 out of 48: Z) which are unsharply demarcated from the lamina densa are demonstrable. Varyingly severe focal thickening of the BM is present in three-fourths of the cases (36 out of 48: Z) while diffuse thickening is rare (4 out of 48: Z). A loosely electron-translucent thickening of the lamina rara interna is present in two-thirds of our cases.
Cases with extracapillary crescents (for EM see p. 224) differ mainly in one respect, i.e., there are slightly more frequent subendothelial deposits encountered (4 out of 13) but humps are not present.
In the *sclerosing stage*, the matrix is considerably increased (Fig. 6.83) but the nuclear increase is not as pronounced as in the previous stages. The nuclei show no signs of activation (Fig. 14.33), e.g., lobulation or notching. In all cases, we find peripheral BM damage in this stage in which the BM is irregular (Fig. 14.35) and, occasionally, very roughly split (Fig. 14.36). Remnants of deposits are now and again demonstrable (Figs. 14.37, 14.38). The BM is at times considerably thickened and shows translucent areas arising from dissolution of osmiophilic deposits (Fig. 14.39).
In disease relapses, concomitant occurrence of very old sclerosing mesangial changes and old BM lesions as well as fresh osmiophilic deposits are usually clearly demonstrable (Fig. 14.40). A clear-cut proof of relapse is the presence of humps (Fig. 14.34, 14.40).

## Differential Diagnosis

The differential diagnostic spectrum of GN forms which should be considered is dictated by the inflammatory stage of the endotheliomesangial GN encountered.
Generalized leukocytosis and myeloid leukemia exhibiting massive capillary loop leukocytosis can be mistaken for exudative endotheliomesangial GN. In these cases, demonstration of subepithelial humps (Masson's trichrome/AFOG stain) as well as appropriate evaluation of clinical findings will usually suffice for correct differentiation. The presence of capillary loop necroses and thrombi—which are very rare—requires exclusion of the hemolytic-uremic syndrome (see p. 499).

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**Fig. 14.29.** Acute poststreptococcal GN 3 weeks before biopsy: lamina rara interna is severely loosened and contains unclearly delimited subendothelial deposits (*D*) which appear to be undergoing dissolution. A likewise unclearly demarcated clear area (*X*) is to be seen in the outer lamina densa. Female, 9 years. (×27,800)

**Fig. 14.30.** Clinically, acute GN 4 years before biopsy: there is obvious thickening of the mesangium which contains numerous, osmiophilic deposits (*D*). No IgA was demonstrable by IF. There is extensive fusion of foot processes and loosening and thickening of the lamina rara interna (→). Male, 10 years. EM (×10,400)

**Fig. 14.31.** Proliferative-sclerosing stage of endotheliomesangial GN with axial mesangial involvement. There is severe increase in the number of lobulated mesangial nuclei (*M*) and mesangial matrix. The endothelial nuclei are enlarged (*E*) as are the podocytes (*P*). Pronounced fusion of foot processes. Female, 3 years. EM (×3560)

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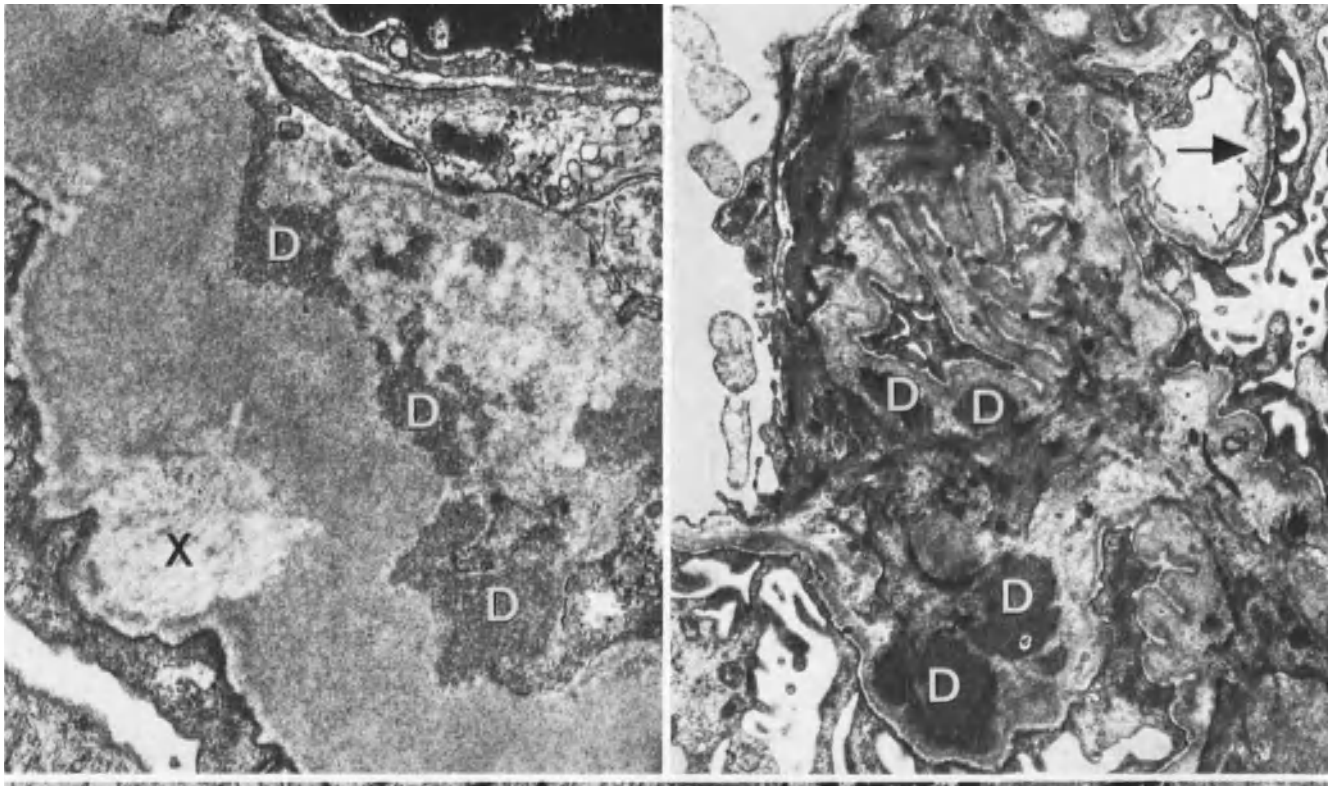
◁ **Fig. 14.27.** Proliferative-sclerosing stage endotheliomesangial GN after streptococcal angina and clinically acute GN 3.5 months prior to biopsy. Numerous osmiophilic deposits (*D*) are recognizable in the increased mesangial matrix. Subendothelially, the peripheral BM is severely loosened and sometimes evidences new formation of a thin densa layer (*LD*), glomerular capillary loop lumen (*CL*). Male, 16 years. EM (×13,800)

**Fig. 14.28.** Same case as in Figure 14.27. Thickening of lamina rara interna (→) is clearly recognizable. Endothelial cells are severely hypertrophied and evidence swollen, polymorphic nuclei, e.g., activated. There is mild foot process fusion. Male, 16 years. EM (×17,500)

**Fig. 14.32.** Endotheliomesangial GN as seen 3.5 months after clinically acute poststreptococcal GN (same case as in Fig. 14.27). Extensive osmiophilic intramembranous deposits (*D*) along the mesangium are present. There is very slight focal thickening of the lamina rara interna (→). Male, 16 years. EM (×14,200)

**Fig. 14.33.** Sclerosing stage of endotheliomesangial GN with panmesangial involvement. Massive increase of the mesangial matrix with disproportionately slight increase of mesangial cells (*M*). Numerous protein droplets (→) are seen in the cytoplasm of the mesangial cells. Foot process fusion is slight. Male, 65 years. EM (×3000)

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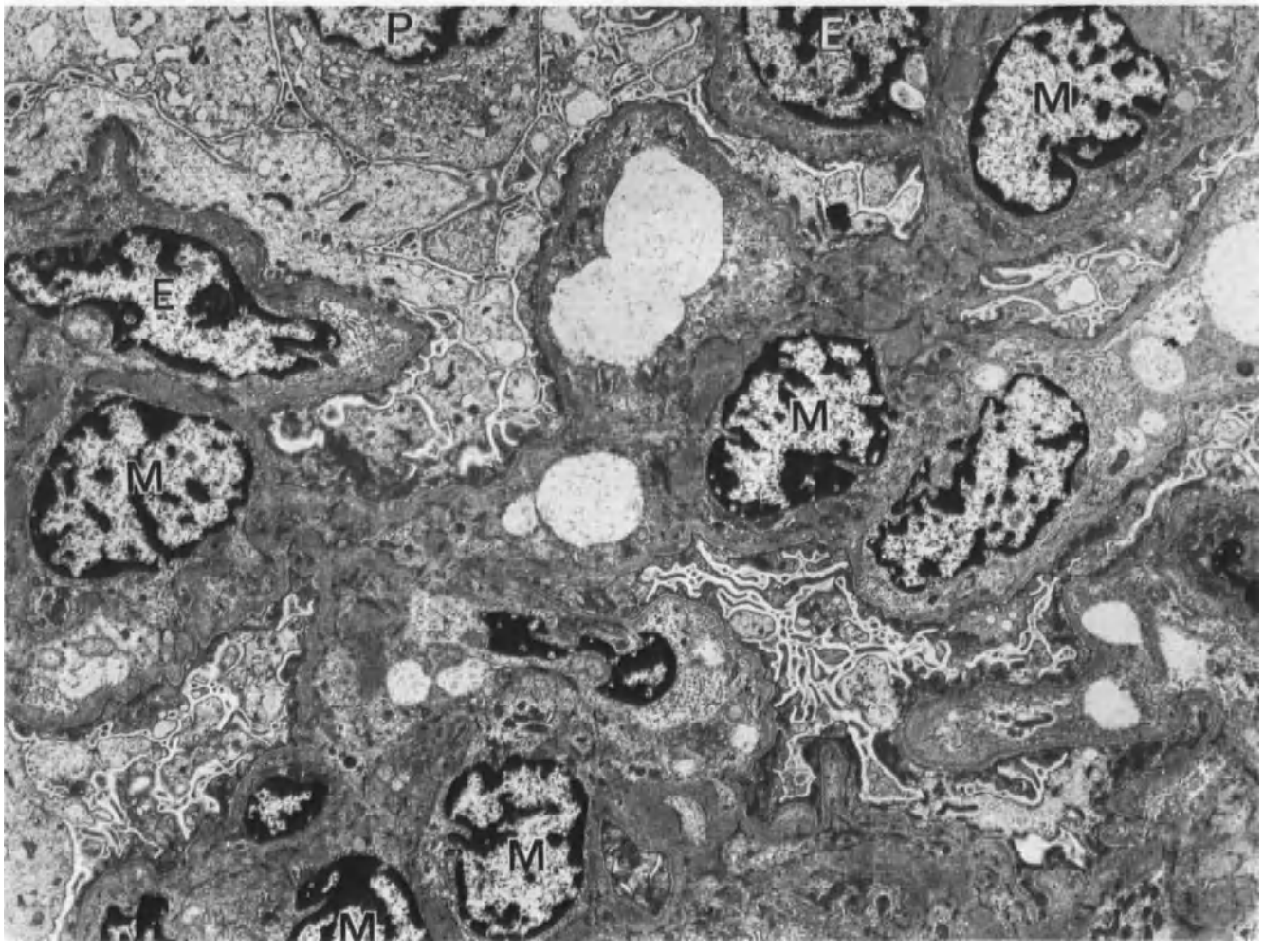


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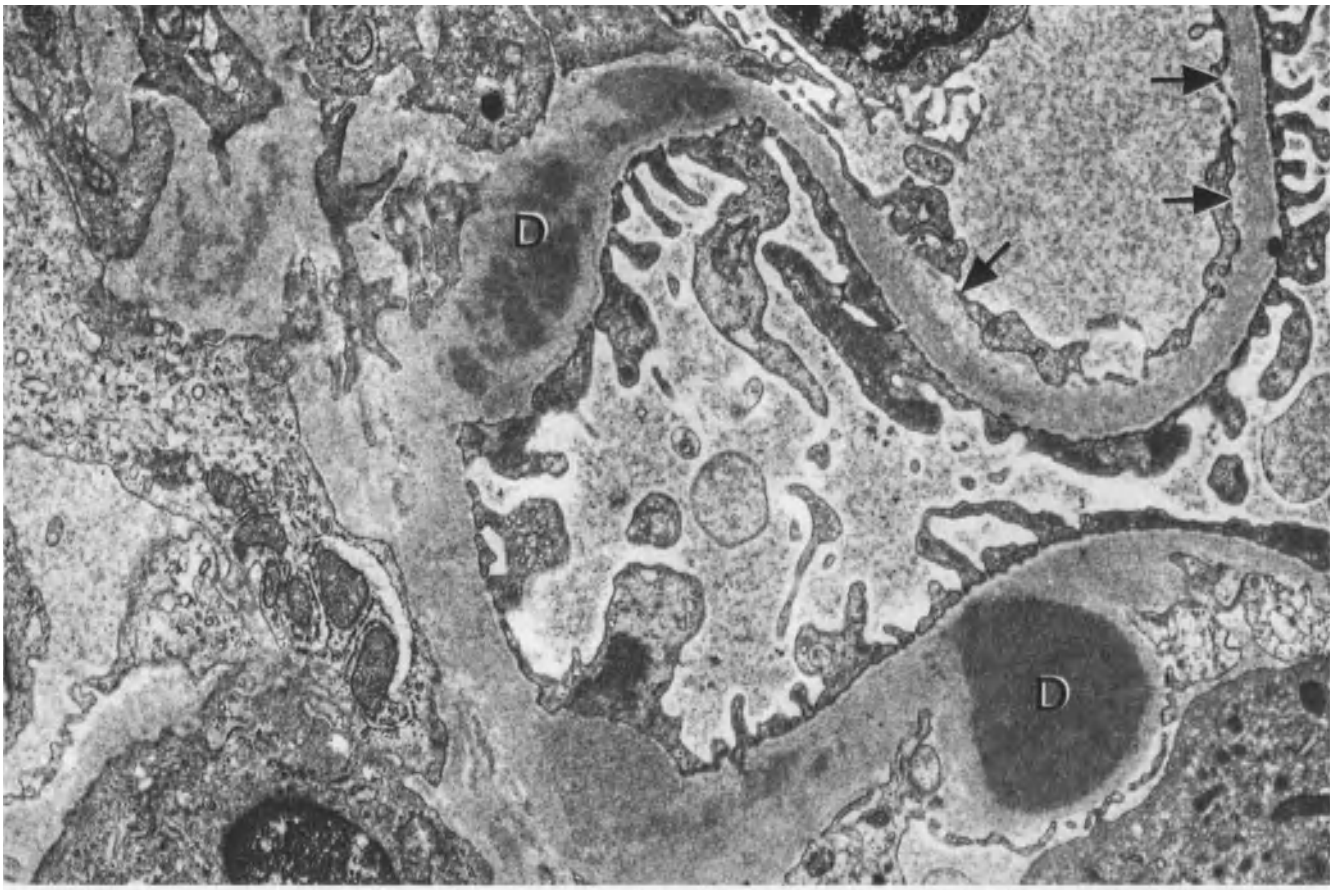


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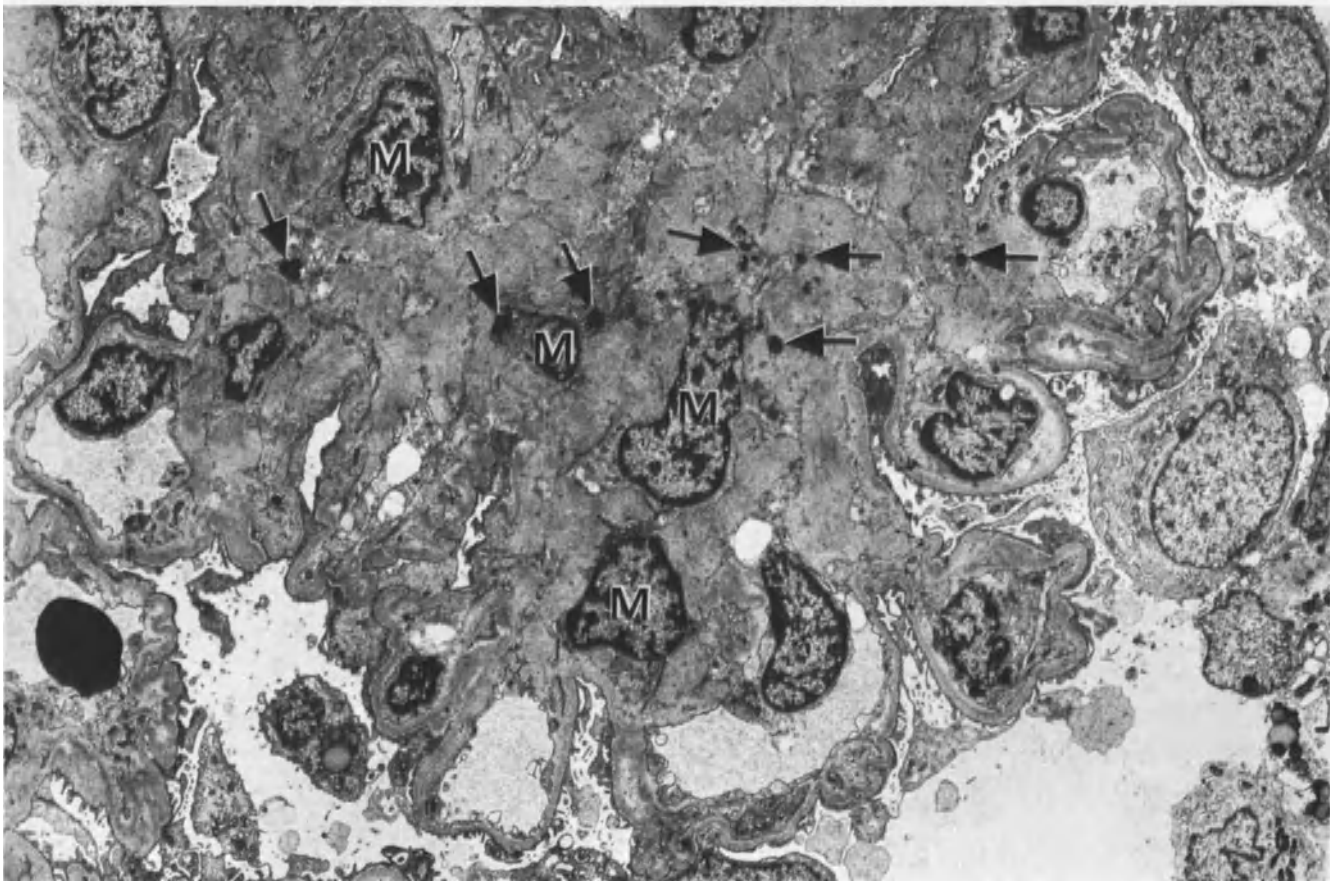


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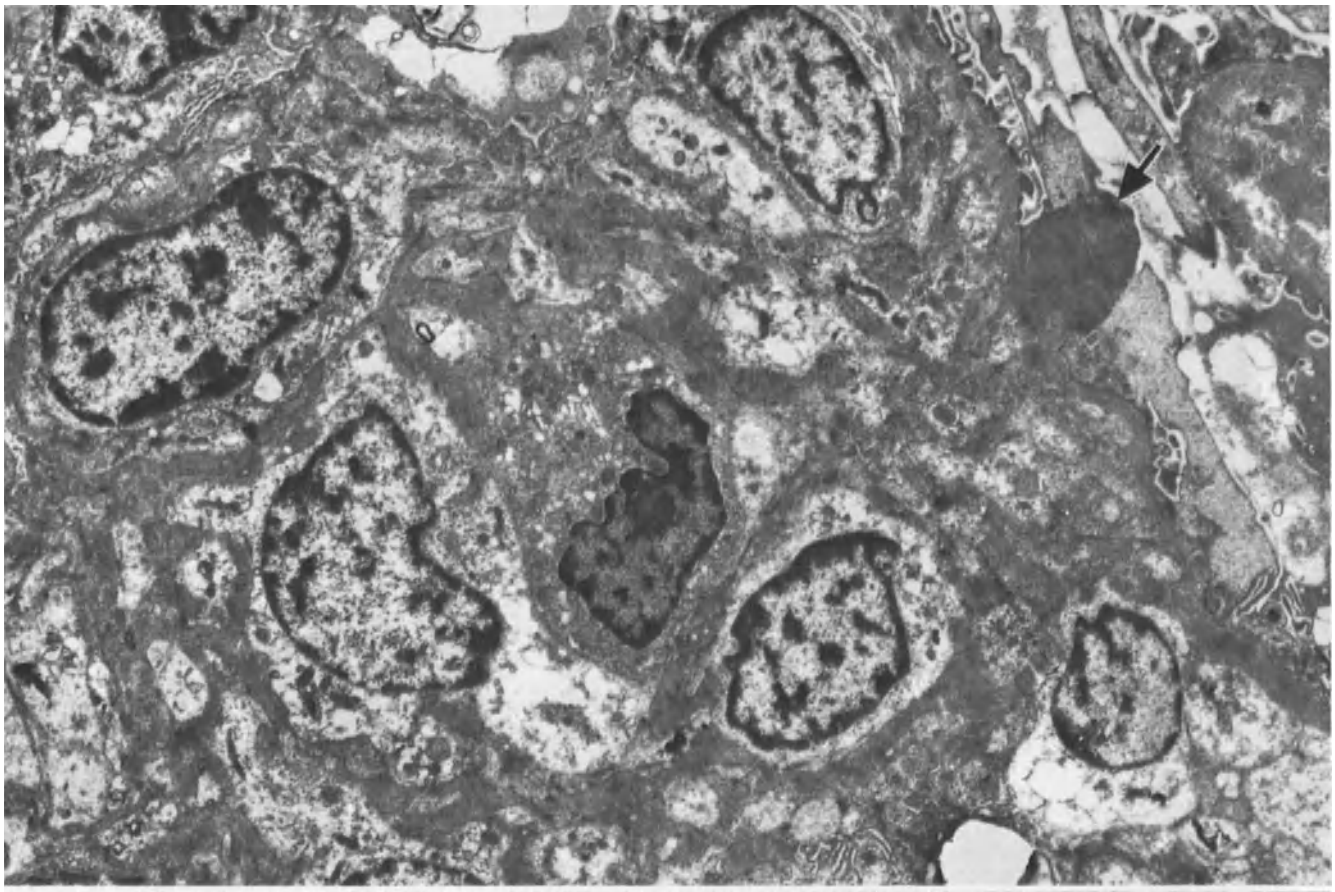

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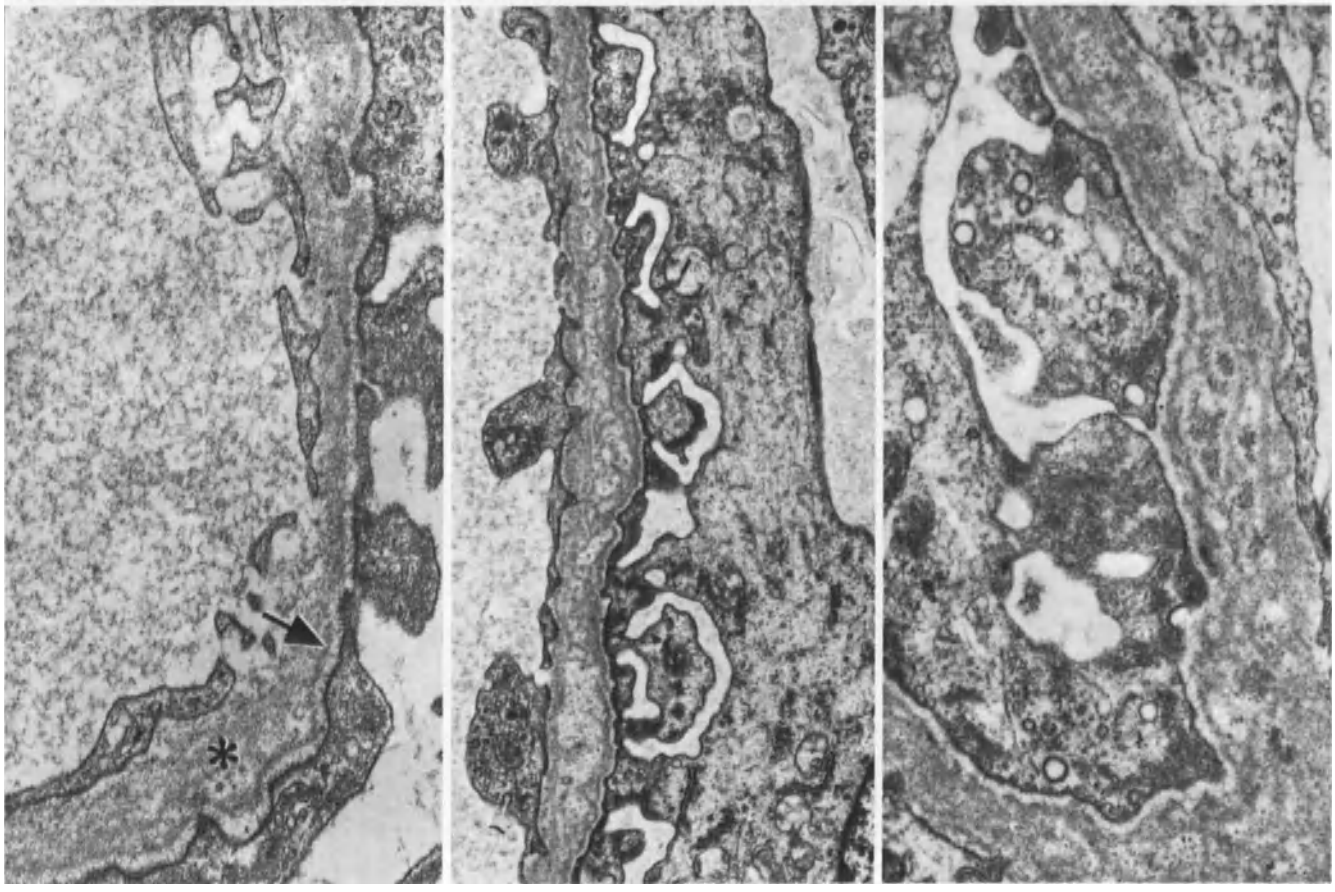

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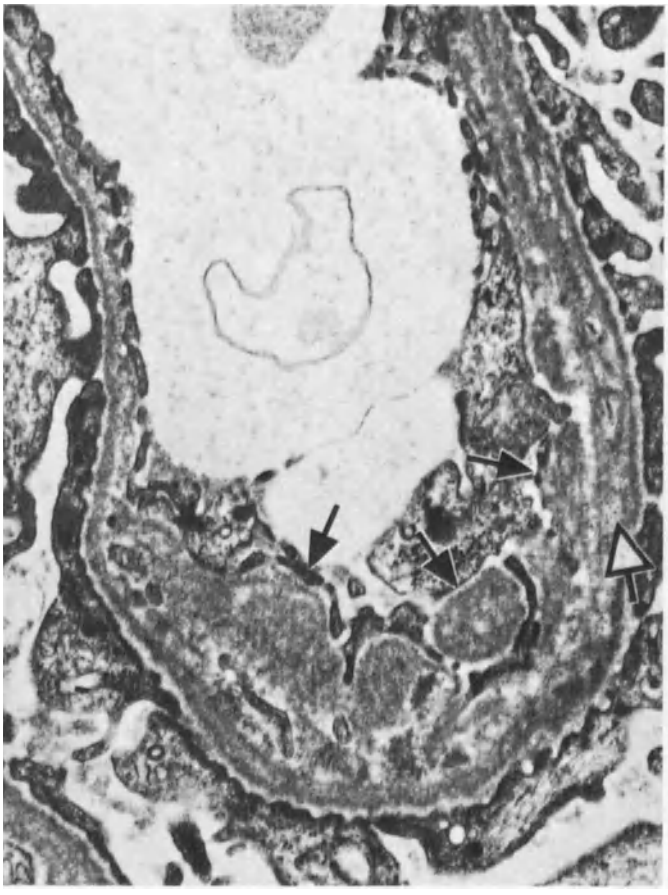


**Fig. 14.38.** Damage of glomerular capillary loop BM in the proliferating-sclerosing stage of endotheliomesangial GN with isolated hematuria for 5 months. Nodular thickening of lamina rara interna (→), and focal loosening of lamina densa subendothelially (⇾) are present. Severe foot process fusion is evident. Male, 5 years. EM (×21,700)

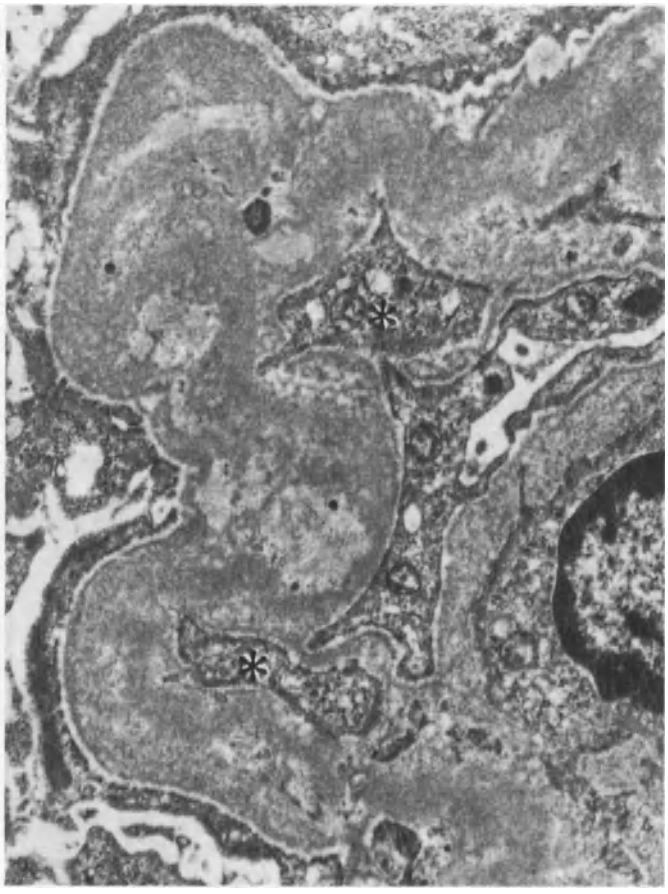


**Fig. 14.39.** Large translucent areas in the thickened peripheral BM where degradation products are occasionally seen. Questionable interposition of mesangial cell process (*). Female, 25 years. EM (×12,800)

◁ **Fig. 14.34.** Sclerosing stage of endotheliomesangial GN. Very extensive thickening and increase of the mesangial matrix and pronounced swelling of mesangial cells. Isolated subepithelial hump (→) indicates an acute relapse (clinically, 4 weeks prior to biopsy). Male, 13 years. EM (×6020)

**Fig. 14.35.** Damage of glomerular capillary loop BM in endotheliomesangial GN. BM is varyingly thick. Lamina densa is partly thinned to a narrow residual strip (→) lying directly under the lamina rara externa. Degradation granules (*). Female, 4 years. EM (×27,500)

**Fig. 14.36.** Same case as Figure 14.35, showing BM damage with longitudinal splitting of the BM as well as irregularity of the outer and inner aspect. Female, 4 years. EM (×12,400)

**Fig. 14.37.** Longitudinal lamellar splitting of peripheral glomerular capillary loop BM 1.5 years after clinically acute GN. Material seen between lamellae possibly represents deposit residues and degradation granules. Female, 12.5 years. EM (×24,700)

Differentiation of endotheliomesangial GN from the membranoproliferative form – which can exhibit clinical findings of acute GN (Table 14.5; 5 out of 14: [1312]) – is especially important. In the exudative stage, this differentiation is greatly facilitated by staining the extensive subendothelial deposits (Masson's trichrome/AFOG stain) which are present in membranoproliferative but never (with LM) in endotheliomesangial GN. Distinction between these two forms may also be difficult in the proliferative stage in which, in addition to the above-mentioned subendothelial deposits, the usually very extensive BM doubling by mesangial interposition will be helpful. It is also noted that mesangial change is seldom as massive, and is practically never lobular in the endotheliomesangial form as it is in membranoproliferative GN. Despite the differences cited, distinction between the two forms in some instances may prove impossible, and especially so in the presence of an acute relapse in membranoproliferative GN. If IF and EM findings

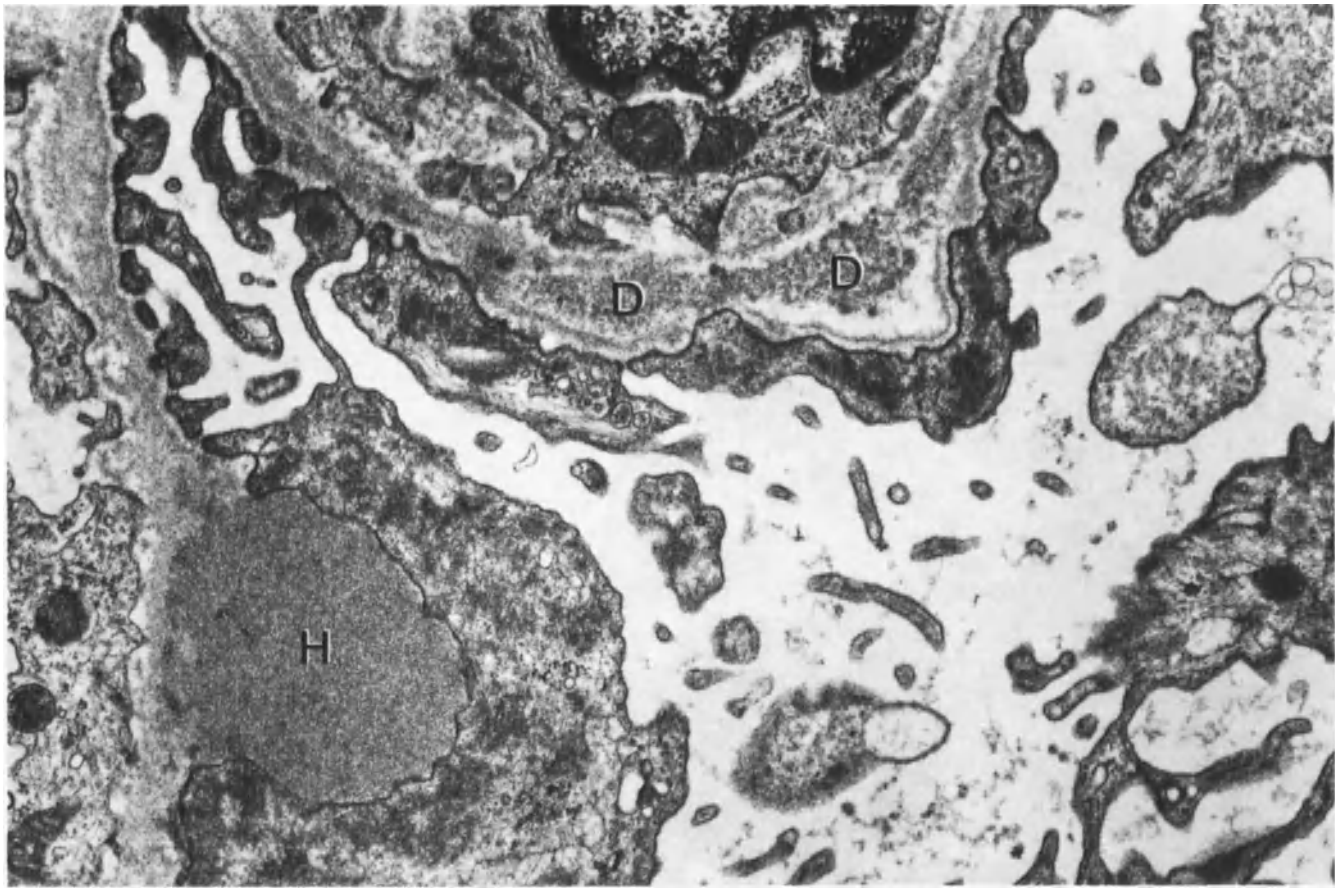



**Fig. 14.40.** Same case as in Figure 14.27, 3.5 months after clinically acute poststreptococcal GN. An acute attack is apparent by the presence of a hump (*H*) covered by a podocyte rich in osmiophilic substance. Lamina densa is split and contains osmiophilic deposits (*D*) in dissolution. Male, 16 years. EM ( × 20,300)

are available, however, the differentiation is usually easy.

The differentiation of endotheliomesangial GN from proliferative FGN is usually easy due to the different glomerular (segmental) and renal (focal) involvement as well as the presence of segmental focal mesangial interpositions (see p. 289). Findings from IF study permit unambiguous differentiation of IgA nephritis from endotheliomesangial GN. IgA nephritis can be suspected but not be proven when EM study reveals especially massive mesangial deposits or when such deposits are shown in Masson's trichrome/AFOG stain.

Differentiation of Alport's syndrome which, in LM, can yield the same findings as endotheliomesangial GN, is impossible. Indisputable diagnosis is only possible by the EM demonstration of the BM changes which are specific for Alport's syndrome (see p. 466).

## Prognosis

The prognosis of all stages of endotheliomesangial GN is better in childhood than it is later. In relation to cure, most data in the literature vary from 81% to 97% [410, 455, 512, 621, 1661]. Healing can, however, require 2 or even more years (see also p. 215; [262, 388, 1272, 1414]).

The prognosis of the disease is said to be poorer in adults with cure rates ranging from 20%–80% [407, 1630, 1661]. These statistics are not based in all cases on exact differentiation of the various forms of GN (i.e., membranoproliferative GN is often included) but if this is done, the prognosis of adult endotheliomesangial GN is also reported to be good [1272] (contra: [71a, 1429b]).

One group of authors reported less favorable results in a series of cases comprising adults and children in which 8% died during the first 6 months of the disease and 50% of the remaining cases later evidenced a reduction of glomerular filtration to less than 100 ml/min. Complete clinical healing was reported in 30–40% of the cases [72], (see also [772]).

Data of our own patients (belonging in 45% to the pediatric age group) confirm the generally favorable prognosis of this disease (Table 14.3, 14.7) especially if compared with an age-matched control population (see Table 14.3).

Table 14.7. Prognosis and outcome of endotheliomesangial glomerulonephritis (including cases with crescents of <50%)

| Prognosis | Survival rate in % | | |
|---|---|---|---|
| | 5 years | 10 years | 15 years |
| From disease onset | 95 | 88 | 81 |
| SE[a] | 1.8 | 3.0 | 5.1 |
| From biopsy | 95 | 84 | 84 |
| SE[a] | 1.9 | 4.7 | 4.7 |

[a] SE: standard error in %.

*Outcome* (after minimal follow-up of 1 year)

| | |
|---|---|
| Number of patients | 139 |
| Total mortality | 8.6% |
| Death in uremia | 3.6% |
| Complete remission | 29.5% |

The 10-year survival rate from onset or biopsy in our material is 88/84%, respectively. Only 29.5% were considered as cured after a follow-up time of 1 to 20 years (Table 14.7).

From a total of 12 deaths (none of which in the pediatric age group) only 5 were due to uremia (the others died from nonrenal causes). The 5- and 10-year survival rates of clinical acute GN corresponds to that of endotheliomesangial GN (Table 14.5) but if an initial oligo-anuria is present the prognosis is considerably worse.

Therapy has been reported as being more successful in the presence of strong IF findings then when the findings are weak or absent [1091].

Sequencial biopsy has shown that severe cases of the exudative-proliferative stage of endotheliomesangial GN can heal [1582] a finding which is also valid in endotheliomesangial GN with crescents ([621]; see also p. 227). Non-healing (unresolved GN: [1068]; latent GN: [107a]) can lead to the axial sclerosing form, which can remain stationary for years and whose frequency is unknown.

After clinical cure, mesangial thickening can persist. It was observed in a considerable percentage of cases 1–3 years after acute GN (2 out of 10: [1414]; 19 out of 23: [1632]). This finding results in down-grading of the favorable prognosis for acute GN in childhood. Subsequent examination of 19 cases showed normalization in 16 and unambiguous progression in 3 in which IF positive findings remained constant ([1632]; 3 out of 21 of such cases evidenced uremia: [636]). The frequency of late renal disturbances in cases of asymptomatic morphologic residues following acute GN is unknown. Transition of endotheliomesangial GN into a sclerosing stage is said to occur in 0.9% of children [64] and in 2%–6% of adults [1047, 1630] (see also: [71a, 1429b]).

Relapses of the disease are associated with a poorer prognosis [45, 388, 1068]. Cure in these cases has been reported in 3 out of 6 cases after 2 to 5 years [1630].

In all these prognostic data, there is a considerable amount of uncertainty in that they rely upon clinically or bioptically demonstrated disease and do not include the unknown quantities of primarily very mild cases of acute GN—especially in childhood—which never receive medical scrutiny. However, since chronic GN and other nephropathies of later life may develop or be aggravated from these symptomless forms, the very good prognosis of acute GN in childhood is possibly reduced.

Recurrence after transplantation has been described [1478a] but seems to be an exception.

## Pathogenesis and Etiology

Pathogenetically, endotheliomesangial GN is an immunocomplex GN brought about by small, highly soluble immunocomplexes which are formed in the presence of antigen excess and which can traverse the BM (transmembranous GN, class I immunocomplexes: [544]). Pathogenesis of IgA mesangial GN which cannot be differentiated in certain stages from the so-called poststreptococcal type is discussed on p. 353.

In recent years, understanding of the etiology of diffuse endotheliomesangial GN has been considerably expanded.

Streptococci (group A, types 4, *12*, 25, 49) are still considered the predominant etiologic factor [1661]. Streptococcal infection has been demonstrated in half of the children with diffuse endotheliomesangial GN with acute onset [621]. Some investigators have claimed streptococci to be responsible for the disease in as many as 90% of all cases [909, 911, 1408]. In acute rheumatic fever 3 out of 22 cases developed a mild and 1 out of 22 severe endotheliomesangial GN without humps [598].

The occurrence of GN following scarlet fever (2.3%: Z) and with streptococcal infection of the upper respiratory tract, which is often unequivocally demonstrable anamnestically as well as in epidemic outbreaks of the disease in which streptococci have been demonstrated, e.g., the Red Lake Indian Reservation Epidemic [803], cannot be dismissed. In patients with endotheliomesangial GN, bacterial plasma membrane AG from hemolytic streptococci have been demonstrated [909, 911].

With EM and using ferritin labeled AG, the antigen of A-12 streptococci has been identified in pinocytotic vacuoles and in mesangial and endothelial hyaline droplets of patients afflicted with the disease [28], a finding which has not been confirmed by other investigators. A further argument strongly in favor of a streptococcal etiology is the demonstration of streptolysin-0, streptococcal hyaluronidase and streptokinase in the serum of 85–90% of patients with acute GN [1661].

The route of entry for the streptococci is usually the upper respiratory tract and far less frequently the middle ear; occasionally, skin infections may also be implicated,

Table 14.8. Glomerulonephritis in malignancies in our own autopsy cases[a], biopsy material and from the literature [521 a]

| GN | Malignancies | | |
|---|---|---|---|
| | Own cases ($n=36$) | Galiano et al. [521 a] ($n=53$) | |
| Glomerular minimal change | $n=7$ | $n=19$ | |
| | Malignant lymphoma 6 × | Non-Hodgkin lymphoma | 10.5% |
| | Carcinoma of the cervix 1 × | Hodgkin's disease | 84.2% |
| | | Leukemia | 0% |
| | | Carcinoma | 5.3% |
| Epimembranous GN | $n=6$ | $n=24$ | |
| | Malignant lymphoma 1 × | Non-Hodgkin lymphoma | 8.3% |
| | Lymphatic leukemia 2 × | Hodgkin's disease | 16.6% |
| | Squamous carcinoma of tongue 1 × | Leukemia | 4.2% |
| | Liver cell carcinoma 1 × [c] | Carcinoma | 70.9% |
| | Colonic carcinoma 1 × [d] | | |
| Membranoproliferative GN | $n=3$ | $n=4$ | |
| | Colonic, gastric carcinoma 1 × each | Non-Hodgkin lymphoma | 50% |
| | Liver cell carcinoma 1 × | Hodgkin's disease | 25% |
| | | Leukemia | 25% |
| | | Carcinoma | 0% |
| Other proliferative GN[b] | $n=20$ | $n=6$ | |
| | Myeloic leukemia 1 × | Non-Hodgkin lymphoma | 0% |
| | Squamous cell carcinoma | Hodgkin's disease | 50% |
| | (tongue, bronchus, esophagus) 8 × | Leukemia | 16.6% |
| | Gastric carcinoma 4 × | Carcinoma | 33.4% |
| | Colonic, pancreatic, mammary | | |
| | supraadrenal carcinoma 1 × each | | |
| | Renal cell carcinoma 2 × | | |
| | Melanoma 1 × | | |
| | Astrocytoma 1 × | | |
| | Rhabdomyosarcoma 1 × | | |

[a] 26 malignancies with GN (0.3–5%) among 7300 autopsies with malignoma. Incidence of GN in our autopsies 0.65%.
[b] 3 cases with multiple malignancies.
[c] Hepatitis B surface antigen positive.
[d] CEA (carcino-embryonic antigen) increased in serum.

as indicated by reports of epidemics from the southern U.S. and from South America. In retrospective studies, such as ours, the incidence of streptococcal infections is considerably lower (9.5%).

The above evidence must be weighed against the fact that no primary streptococcal infection is present in many cases of the disease which are often especially characterized by insidious onset. In these patients, staphylococci are occasionally found as in infected ventriculoatrial shunt [1561, 1700] and staphylococcal endocarditis [612, 1661] which apparently occurs with increased frequency among heroin addicts [1425].

The bulk of knowledge about viruses acting as antigens has considerably expanded [221, 222, 774, 1522, 1531]. We observed one peculiar autopsy case of diffuse endotheliomesangial GN in an infant with a severe, generalized cytomegalovirus infection and in another similar case, focal, necrotizing GN [326] was observed.

Furthermore, one of our cases of endotheliomesangial GN developed in association with viral hepatitis. Hepatitis B virus is a generally recognized antigen in GN [304, 424, 615, 1531] although usually associated with epimembranous or membranoproliferative GN and only rarely with endotheliomesangial GN (2 out of 9: [609]; [1233c], see p. 250).

In this respect, more or less reliable observations have implicated varicella [1107], influenza [1096], and Epstein-Barr [1531] viruses.

Further indication of the etiologic role of virus has been provided by experimental findings of choriomenengitis

virus in newborn mice [221, 717], of encephalomyocarditis virus [717], of Coxsackie $B_4$-virus in mice [221, 222, 1521] and of reovirus III [1238] which is usually related to immunocomplex GN [1760].

GN of endotheliomesangial type has also been noted in malaria [16, 28, 1689, 1730] as well as in the following conditions: secondary syphilis [148], congenital syphilis [801, 1589], toxoplasmosis [553], and sarcoidosis [1045]. The GN in sarcoidosis was reported as proliferative in 3 out of 6 of the cases, epimembranous in 1 out of 6 and sclerosing in 2 out of 6 and, as sarcoidosis itself, can be considered as an immunologic response to an unknown AG [1045].

Diffuse endotheliomesangial GN has also been reported in sickle cell disease [1387a]; see also [1233b] and following antilymphocytic globulin therapy in liver transplantats [334] but not in kidney transplants (see p. 610).

GN due to malignoma-associated antigens is well known [345, 972, 521a]. The published cases belong mainly to epimembranous and less often to membranoproliferative GN (see p. 277) but also other proliferative GN (endotheliomesangial GN or proliferative FGN) may be present as we saw in a nephrectomy specimen from a patient suffering from a triple malignoma: squamous cell carcinoma of the tongue, rhabdomyosarcoma of the lung, and renal cell carcinoma. A survey of GN in malignancies is presented in Table 14.8; it shows the majority of malignancy to be associated with the group of proliferative GN in our material. Since we never attempted identification of tumor-associated antigens in the kidney, the possibility of a nonrelated fortuitous finding of GN together with the tumor cannot be excluded. But it can be supposed—as based on findings of other investigators—that a causal relationship between endotheliomesangial GN and malignancies is also present in some cases [521a, 1812].

The occurrence of endotheliomesangial GN associated with systemic disease was rarely encountered in our material: 1.7% in SLE, 4.7% in Schönlein-Henoch's purpura (in children in one-third of the cases: [1730]) and 16% of IgA-nephritis in IF investigated cases. This topic is discussed in greater detail in chapter 16.

## Extracapillary Accentuated Glomerulonephritis

### Definition

Extracapillary crescents may be present in any form of GN. From the prognostic point of view, we distinguish between two grades of severity, namely, cases with less than 50% crescents (crescentic involvement) and more than 50% crescents (crescentic accentuation).
Under the term "extracapillary accentuated GN", only endotheliomesangial GN and segmental-focal proliferative GN are discussed. Proliferative FGN is included since it cannot, in the advanced stages, readily be differentiated from endotheliomesangial GN. Special consideration of extracapillary accentuated GN is also merited since it can be associated with different pathogenetic mechanisms, i.e., immunocomplex GN or anti-BM GN. All other GN forms, e.g., membranoproliferative, intramembranous, epimembranous GN with crescents are not included nor are systemic diseases with a pathognomonic morphologic picture, e.g., Wegner's syndrome or hypersensitivity angitis which will be discussed in separate sections (survey: [1815]).

***Synonyms:*** Subacute GN, rapidly progressive GN [684], peracute extracapillary GN [161], oliguric GN [1451] and malignant GN [654]. For other synonyms see Table 13.2.

### Incidence

The severe form of the lesion (> 50% crescents) amounts to 4.2% of all our cases of GN. It is difficult to compare our statistics with those of the literature which often do not state the percentage of afflicted glomeruli or indicate the basic form of GN involved, e.g., endotheliomesangial, membranoproliferative, proliferative FGN, intramembranous GN, etc., as well as those associated with systemic diseases, e.g., Wegner's syndrome, etc. The relative frequency in GN-biopsy, which varies between 0.9% [134] and 6.5% is summarized in Table 14.1.
Most investigators report a considerable predominance of males [1019, 163, 344, 1574] (male:female as 2.3:1.0 [1209]) and some of females [636]. In our own material, the male:female ratio is 1.23:1. Fundamentally, all age groups are afflicted [621, 1019] including the very aged [1797]. The pediatric age group comprises only 15.8% of these cases (Fig. 14.41). In one large series of cases [1209, 1211] the lesion was noted in the following conditions: 35 out of 59 cases in endotheliomesangial GN, 11 out of 59 in Goodpasture's syndrome, 8 out of 59 in hypersensitivity angitis (microform of periarteritis nodosa) and 5 out of 59 in SLE or Wegner's syndrome.

### Clinical Findings

(Tables 14.3, 14.4, 14.5, Fig. 14.41)

Extracapillary accentuated GN usually exhibits a dramatic course. In more than 60% of the patients (Fig. 14.41) symptoms typical of acute GN usually set in after an acute febrile illness usually associated with upper respiratory tract infection (Table 14.3, Fig. 14.41; see also [1574]). In 40% of our cases, oliguria or, more rarely, anuria, was initially present, and macrohematuria in 30%, edema in 60%, and hypertension in 24% of the cases. Additionally, we encountered microhematuria, proteinuria and erythrocytic casts in the urine of 24% of our cases.
The disease usually shows a rapidly progressive course accompanied by repeated episodes of macrohematuria. Patients with oliguria usually develop complete anuria averagely after 40 days (range 5–100 days [344]). In our patients at the time of biopsy, oligo-anuria was present in 11 out of 24 cases and polyuria was noted in 2 out of 24 (Table 14.3).
At the time of biopsy (about 3 months after disease onset) the clinical picture (Fig. 14.41) was characterized in all cases by elevated serum urea and creatinine values which were accompanied by hypertension in 40% of our patients. The antstreptolysin titer was raised in one-third of the patients. Complement (C3) was always in the normal range (5 out of 5: Z; see also [243, 1574]).
Proteinuria and hematuria are almost always demonstrable. Fairly frequently, proteinuria may exceed 3.5 gm/day. Since leukocyturia, bacteruria, and leukocytic casts can also now and again be shown (Table 14.3) doubt can arise with respect to the diagnosis of GN. This is also true with sudden oligo-anuria subsequent to febrile disease which poses differential diagnostic problems with respect to acute interstitial nephritis.

### LM Findings

The predominant finding in the proliferative stage is the massive cellular proliferation occurring in the capsular space, i.e., so-called crescent formation (Fig. 14.42, see p. 100). Global crescents extend from the glomerular vascular pole to encompass the entire convolute (Fig. 6.90), while in segmental crescents only those segments over damaged, often necrotic loops (Fig. 6.91), are implicated.
These crescents consist of fibroblast-like cells with oval, moderately chromatin-rich nuclei in between which an occasional polymorphonuclear leukocyte is observed (Figs. 14.43, 14.44; [780]). Fibrin stains reveal fibrin fibrils between the individual crescent cells in more than 50% of the cases whereas with IF, fibrin(-ogen) can be demonstrated in the proliferative stage in almost 100% of the cases. It has been reported that crescents can develop in a few days [833, 1484].

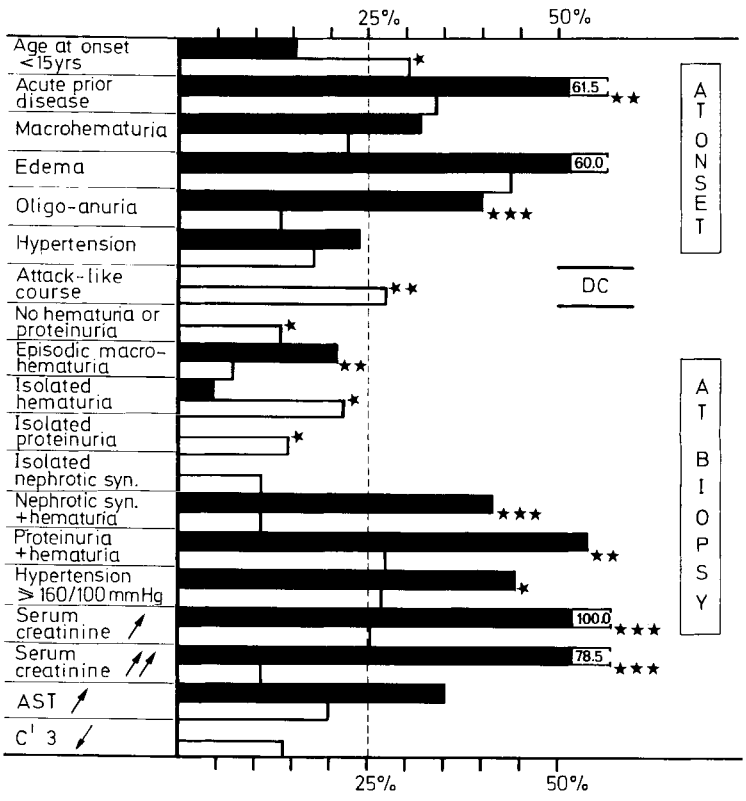



**Fig. 14.41.** Profile of symptoms and clinical findings in extracapillary accentuated GN
*White columns:* Relative frequency of symptom/finding in all GN
*Black columns:* Relative frequency in extracapillary accentuated GN
Asterisks indicate characteristic findings for extracapillary accentuated GN:
*: characteristic
**: very characteristic
***: highly characteristic; DC: disease course (see also Tables 14.3 and 14.4)

With longer duration and nonresolution, the crescent cells flatten out more and more and assume the form of fibrocytes (sclerosing phase). Soon thereafter, fine PAS- and PASM-positive fibrillar material grows out of the capsular BM and insinuates itself between the crescent cells (Figs. 14.46, 14,47; [279]). Later, the so-called adenomatoid structures may arise (Fig. 14.56, p. 103) from the confluence of intercellular spaces. Capsular BM is not sharply delimited from the crescents, but it is clearly marked off from the surrounding fibrotically transformed periglomerular interstitium for a long time (Fig. 14.45). Later, it is splintered and replaced by connective tissue (Fig. 14.46). Ultimately, it partly disappears (see also [1069]).

Foreign body-type giant cells can occasionally be found in the capsular space [1069] (in all cases: [1209]). We have observed them only rarely, and then in the presence of loop necroses and in Goodpasture's syndrome (Fig. 17.36, see p. 337; Table 8.1).

Isolated capillary loop necroses (Figs. 14.44, 14.45) are present in about half of the cases [62, 149, 1069, 1209, 1302, 1451]; contra: [282]. These necroses have been reported to be particularly frequent in cases caused by streptococci [1489]. A few instances have been cited in which these necroses have been found in all cases of extracapillary accentuated GN [344]; the same is true for capillary loop defects [1209]. We have not been able to verify these findings but to be sure serial sections were not done.

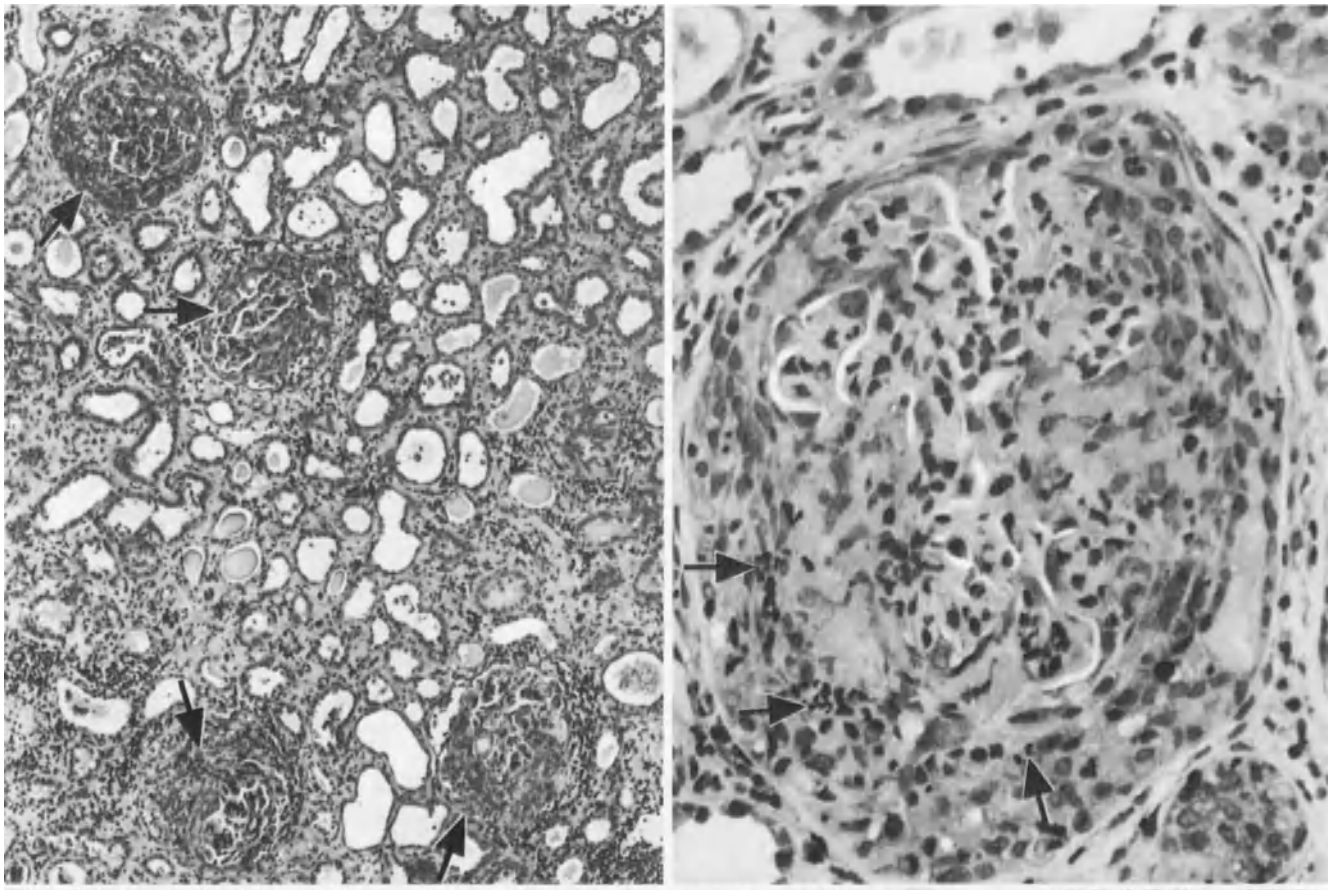
In general, mesangial proliferation is much less striking than it is in the absence of crescents: the more extensive the crescent formation, the less pronounced the proliferation. In fact, it has been reported that mesangial proliferation may be completely absent (44 out of 63: [1574], morphometry: [429]), especially so in those cases in which a streptococcal etiology can be excluded [654]. We have never encountered total absence of proliferation.

The simultaneous occurrence of very old sclerotic capillary changes and relatively fresh proliferative crescents—as encountered, for example, in contracted kidneys—is often striking.

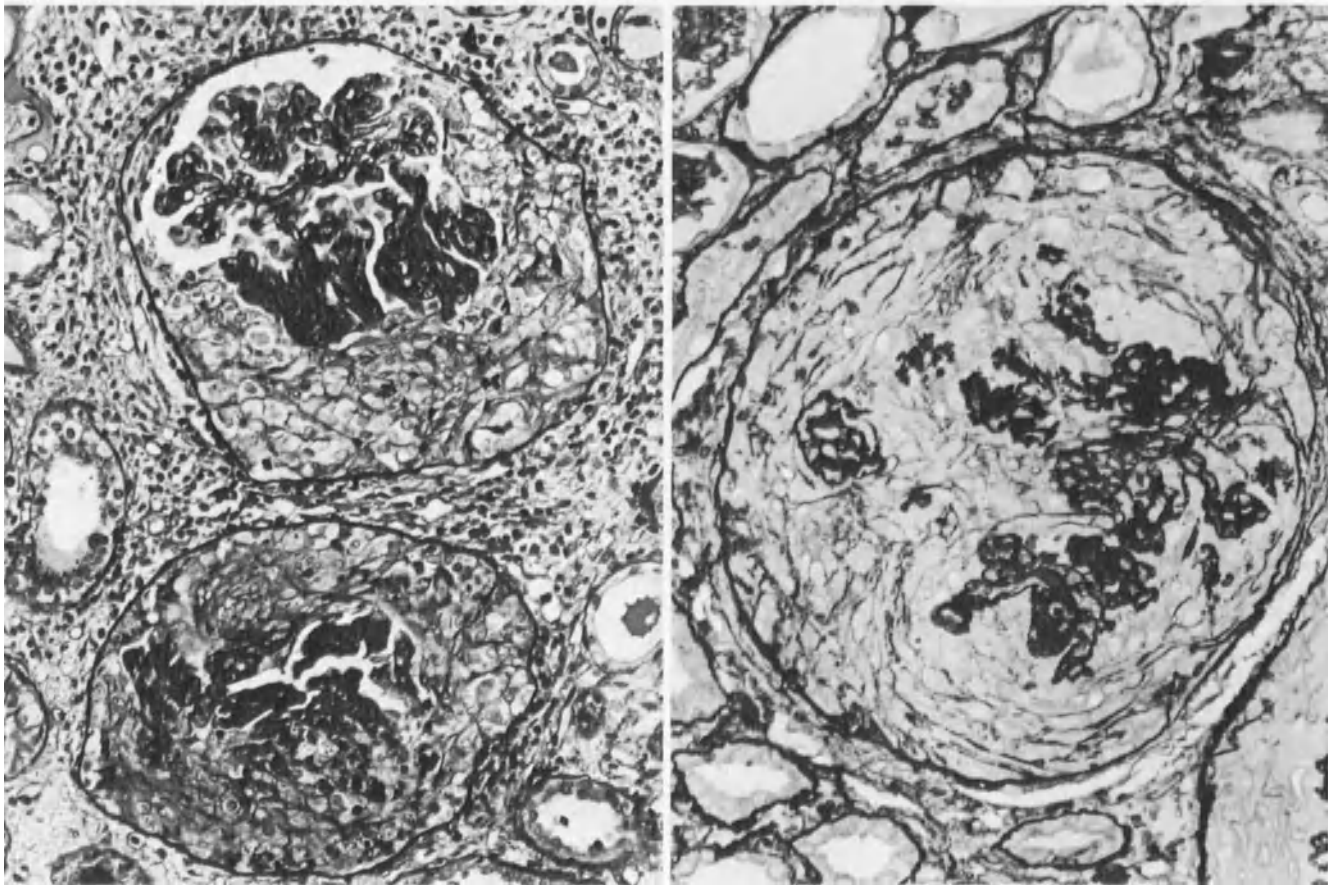
Tubular changes do not deviate qualitatively from those encountered in the other forms of GN except—as seen in our cases—for the presence of more intratubular debris and occasional leukocytic casts. The accompanying interstitial nephritis has almost always been very pronounced (Fig. 14.42). Changes in the arteries and the arterioles are not present except in cases of systemic disease (e.g., in hypersensitivity angitis [620]; see also p. 536).

### IF Findings

Fundamentally, two types of responses can be distinguished: a complex type (Fig. 14.48) and an anti-BM type with linear deposits (see also p. 157; Fig. 14.49).



14.42
14.43



14.44
14.45

The anti-BM type, which may be either idiopathic or associated with the Goodpasture's syndrome, comprises about 1%–5% of all GN ([1035, 1744, 1747]; see p. 337). In extracapillary accentuated GN, the results reported in the literature and summarized in Table 14.9, show that about 30% exhibit a linear pattern usually positive for IgG and in about two-thirds for C3 [1744, 1747] whereas the presence of other immunoglobulin is inconstant (see also [525, 1302, 1484, 1666, 1766]).

The immunocomplex-type comprises about 50% of the cases (Table 14.9). The predominating IF findings are C3 [525, 1136, 1212, 1302], IgG [134, 955, 1136, 1212] as well as fibrin(-ogen) in the damaged glomerular loops (27 out of 32: [1136]; 9 out of 15: [134]). Other immunoglobulins, e.g., IgA, IgM, etc., are far less frequently found [134, 1136, 1212].

It is also noteworthy that in a considerable percentage of cases (Table 14.9) the IF findings are entirely negative. This does not, in our opinion, suggest a nonimmunologic cause of injury but rather that the injury may more likely be the result of a rapid intraglomerular immunocomplex turnover.

In more than 70% of cases, glomerular crescents contain fibrin(-ogen) [128, 1103, 1136, 1212, 1747]. In fresh proliferative crescents this is nearly always the case, whereas in old crescents it may be lacking. Immunoglobulins are never found in crescents [128, 1103, 1136, 1212, 1747].

Table 14.9. IF findings in extracapillary accentuated glomerulonephritis (cases positive/tested)

| Author | Deposition Character | | |
|---|---|---|---|
| | Linear | Granular | Negative |
| Bernard et al. (1974) [134] | 0/15 | 13/15 | 2/15 |
| Dart et al. (1972) [344] | 7/17 | 8/17 | 2/17 |
| Lewis et al. (1971) [955] | 6/7 | 1/7 | 0/7 |
| Min et al. (1974) [1103] | 4/8 | 3/8 | 1/8 |
| Morel-Maroger et al. (1973) [1137a] | 3/33 | 18/33 | 12/33 (?) |
| Olson et al. (1974) [1212] | 6/26 | 14/26 | 6/26 |
| Striker et al. (1973) [1574] | 2/10 | 0/10 | 8/10 |
| Thoenes (1976) [1607a] | 11/16 | 5/16 | 0/16 |
| Zollinger and Mihatsch | 2/7 | 5/7 | 0/7 |
| Total | 41/139 =29,5% | 67/139 =48.2% | 31/139 =22,3% |

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**Fig. 14.46.** Extracapillary accentuated GN. Crescent has been considerably replaced by connective tissue and capsular BM has been largely destroyed. Glomerular capillary loops are completely collapsed. Autopsy specimen. PAS (×400)

**Fig. 14.47.** Same case as in Figure 14.46. Aging crescent with dense argyrophilic fibrils. Note focal interruption of the capsular BM. PASM (×400)

**Fig. 14.48.** Granular fibrin(-ogen) deposits in the mesangium and the capillary loop periphery as well as focally in (nonrecognizable) crescent (→). Isolated podocytic resorption droplets are discernible. Female, 60 years. IF (×530)

**Fig. 14.49.** Typical IF findings in the anti-BM type of extracapillary accentuated GN. There is sharp linear global staining of IgG. Note: no fluorescence in the capsular space. Female, 70 years. IF (×420)

◁ **Fig. 14.42.** Endotheliomesangial GN with severe extracapillary involvement (90%). All four glomeruli depicted evidence global crescents (→). Interstitium is edematous and rather heavily infiltrated with inflammatory cells. Proximal tubules show severe flattening of the epithelium as in shock and isolated casts. Male, 25 years. HE (×90)

**Fig. 14.43.** Endotheliomesangial GN with 100% extracapillary involvement. Between proliferated capsular epithelium nests of polymorphonuclear leukocytes (→). Highly collapsed glomerular capillary loops contain numerous polymorphonuclear leukocytes as well. Female, 70 years. HE (×420)

**Fig. 14.44.** Same case as in Figure 14.43. Glomerular capillary loop collapse is even more evident in the PAS stain as is the scanty—PAS positive—matrix between the cells of the crescent. Note severe interstitial inflammation. Female, 70 years. (×250)

**Fig. 14.45.** Same case as in Figure 14.43. In PASM stain, new formation of argyrophilic material within the crescent is clearly evident, as is glomerular capillary loop collapse. (×390)

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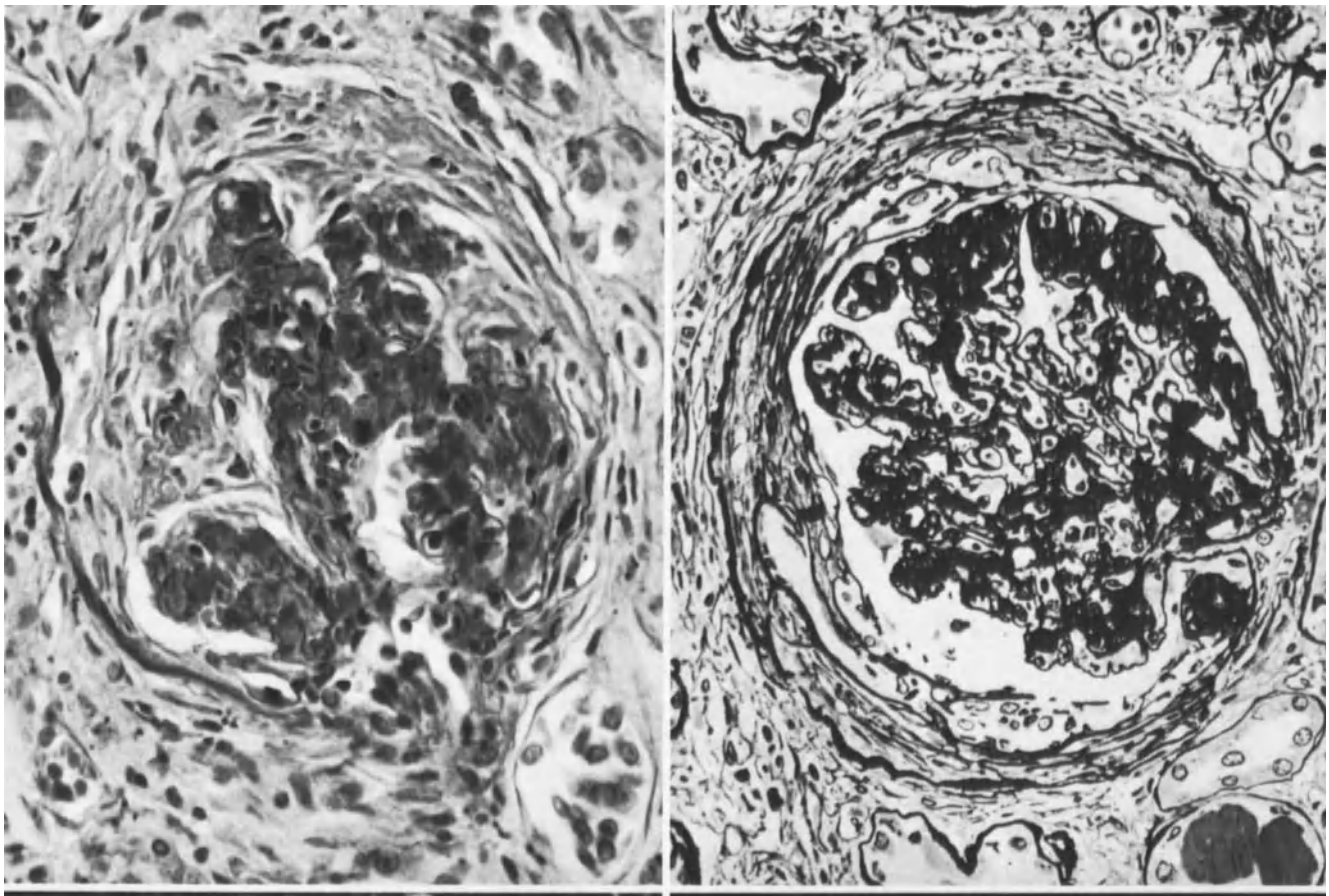
**Fig. 14.50.** Survey of an extracapillary crescent. Glomerular capillary loops (→) are completely collapsed. Capsular space is filled with proliferated capsular cells which are occasionally rich in protein droplets (*PD*). Isolated podocytes evidencing very pronounced cystoid widened organelles (*P*). Fibrin strands are found between capsular cells (→). Capsular BM (*CBM*). Female, 60 years. EM (×744)

**Fig. 14.51.** Crescent in extracapillary accentuated GN following Schönlein-Henoch's purpura. Predominantly large and swollen capsular epithelial cells with varying increase in cell organelles and enlarged nuclei. Scattered podocytes (*P*) with cystoid organelles and very osmiophilic cytoplasm are interspersed. Scanty thin strands of BM-like material (→) are already recognizable between capsular epithelial cells. Glomerular capillary loops (*G*) are largely obsolescent. Male, 7 years. EM (×3260)



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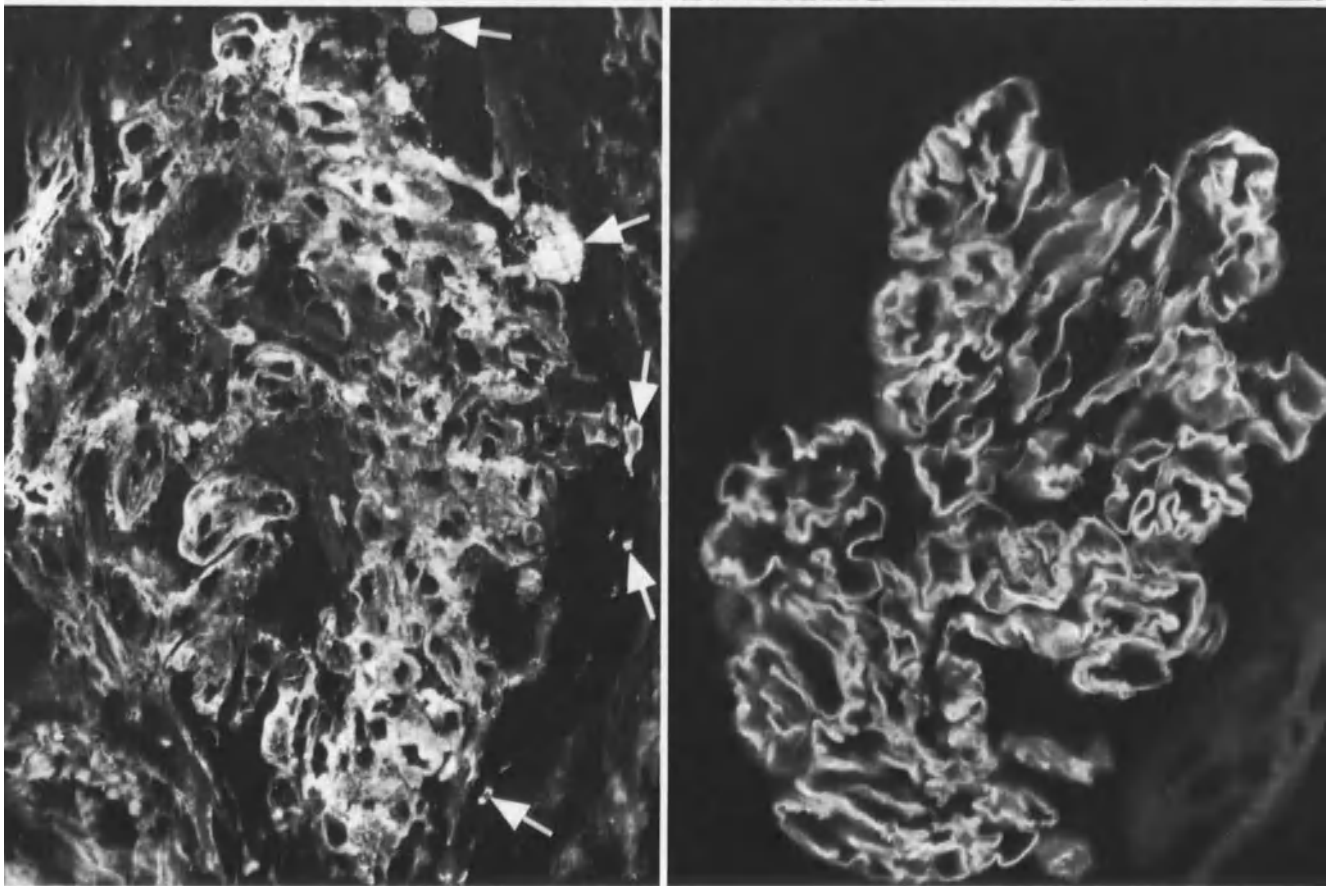

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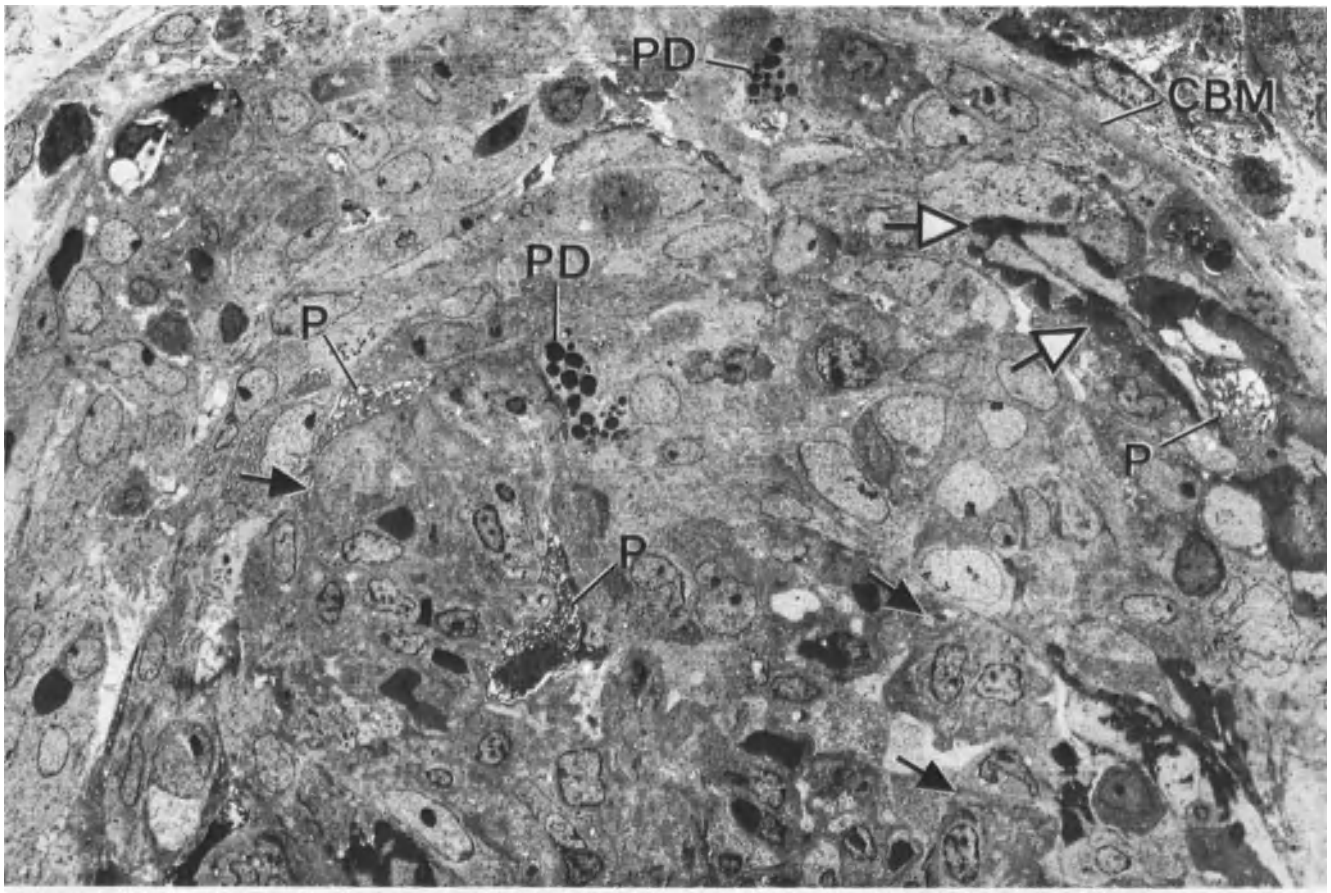


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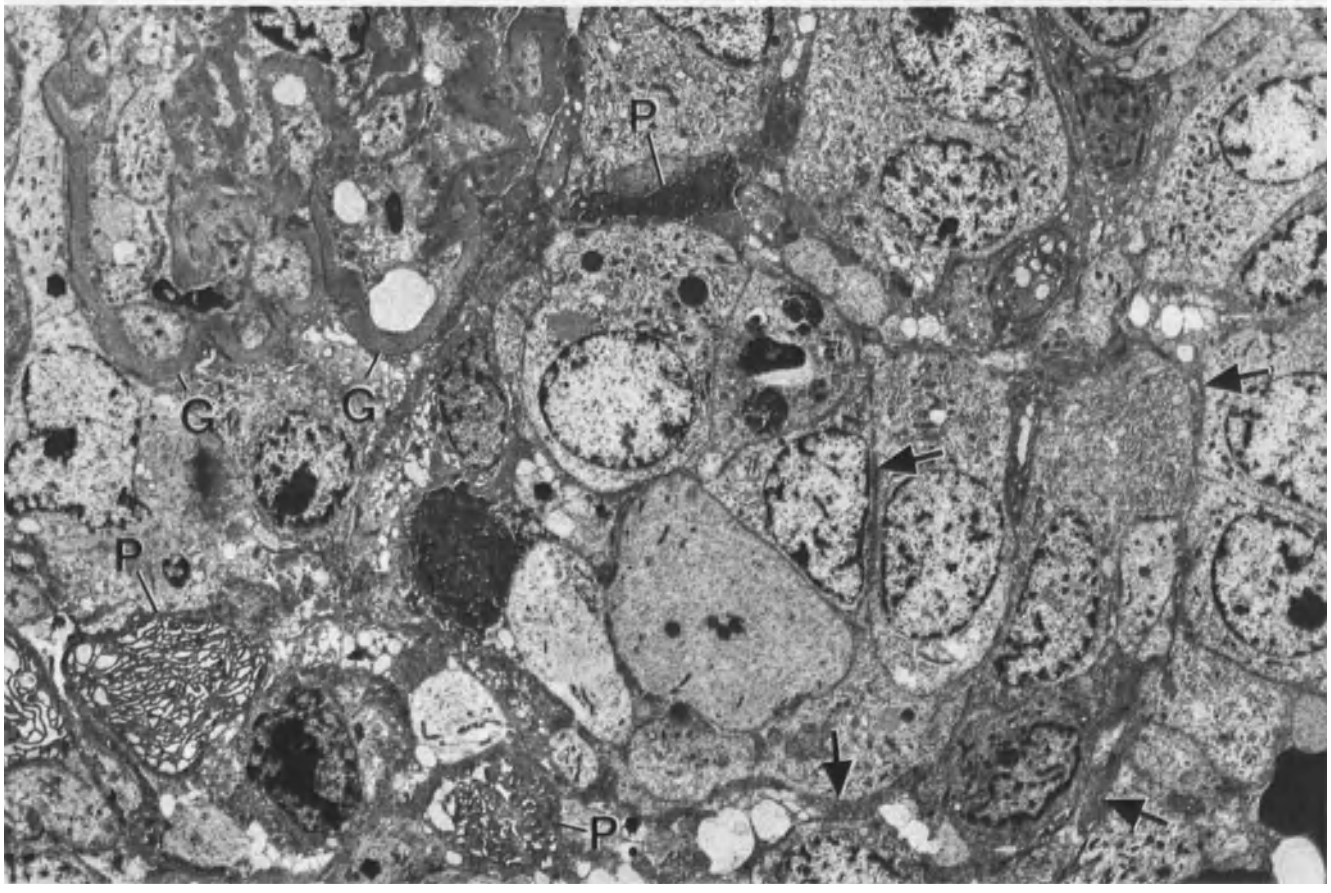



14.51

### EM Findings

Fresh crescents consist of highly swollen capsular epithelial cells of up to 32 μm in size (Fig. 14.50) which are rich in tonofibrils, glycogen and often phagolysosomes, but poor in other organelles (Fig. 14.51). Only the endoplasmatic reticulum is clearly visible. Mitoses and binucleated cells are also found and have been reported to arise from podocytes [780], a finding which we could not confirm (see p. 100). Between the proliferated capsular epithelial cells, at first only a few other cells are found which become somewhat larger and subsequently triangular; they have dark cytoplasm and usually a pronounced widening of the endoplasmatic reticulum (Figs. 14.51, 14.52, 6.92). Podocytes in situ evidence the same changes, so that the cells in question probably represent displaced and degenerated podocytes (see also [205, 780]). A third type of crescent cell is supposed to be a monocyte which, in any case, has been found in experimental Masugi nephritis [875]. We were not able to distinguish these cells in our own cases. Between these cells, fibrin strands (Figs. 14.53, 6.94) or at least fibrin-like material [134, 955, 1037, 1484, 1797] are found in very fresh cases and especially so in anti-BM type [1103].

A granular substance (Fig. 14.54) which presumably corresponds to the exudate in the capsular space in glomerular obsolescence (see p. 107) is found in later stages. It is also viewed as BM material [134]. Appearance of collagen fibers in the extracellular material (in LM: [279]) is demonstrable with EM [172] (Fig. 14.55). The BM-like strands sometimes appear to be in contact with the capsular BM, although we feel that they are formed in loco from both capsular epithelium and podocytes (Figs. 14.51; 6.95; p. 105).

The well-known adenomatoid formations arise from confluent openings between the proliferated capsular epithelium (Figs. 14.56, 14.60, 6.97). Later, the capsular BM is splintered and permeated by connective tissue elements (Fig. 14.57).

Ultrastructurally, the glomeruli evidence changes typical of endotheliomesangial GN which are, however, surprisingly little pronounced. In the relatively uncommon anti-BM type, diffuse thickening of the BM (2 out of 2: Z) and, very rarely, focal and tiny subendothelial (1 out of 2: Z) and/or intramembranous (1 out of 2: Z) (Fig. 14.59) as well as mesangial deposits (1 out of 2: Z) can be demonstrated.

In our patients, we encountered loop necrosis only once (Figs. 14.58, 6.14) but we repeatedly found interruptions of loop BM as also reported by other investigators: (8 out of 8 cases: [1103]; 12 out of 40 cases: [282]; see also [1144, 172]). Interruptions of the capsular BM are also characteristic and frequent [172].

In 7 other cases of our own, 5 with proven granular IF pattern, deposits in the following locations were encountered: subendothelial 5 out of 7; intramembranous 4 out of 7, along the mesangial BM 1 out of 7, mesangial matrix 4 out of 7 (10 out of 15: [282]). Subepithelial deposits were present in 2 out of 7 and humps only once (Fig. 14.61) (2 out of 8: [172]; see also [131, 1068]). Other investigators found no humps in any of their eases [62].

Unfortunately, in most EM descriptions of extracapillary accentuated GN, no differentiation is made between those with granular deposits with IF and those with linear ones, so that a reliable differentiation on the basis of EM findings is not yet possible.

### Differential Diagnosis

Of primary importance is establishment of the basic type of GN. All cases of membranoproliferative, intramembranous, and epimembranous GN must be excluded. Although the exclusion of the GN mentioned above may be difficult in advanced forms using LM alone, it should usually be possible using the combined methods of LM, EM, and IF. If differentiation proves to be impossible—especially after long term dialysis—we include such cases in the group of unclassified GN. The occurrence of crescents of various ages and, above all, the presence of relatively numerous partial crescents is strongly indicative of proliferative FGN, which suggests the presence of a systemic disease (see also: [1815]) (see p. 317).

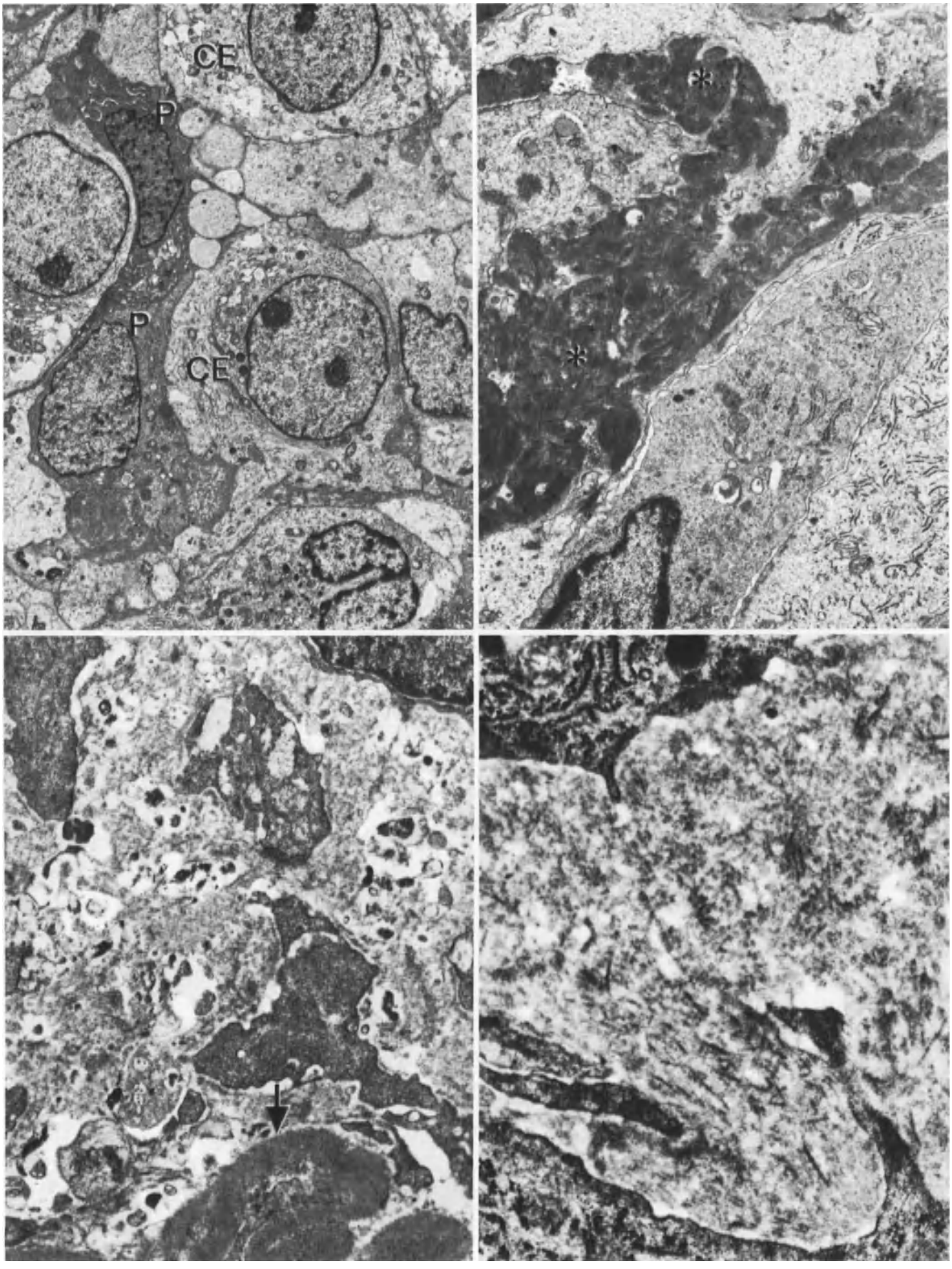
In the sclerotic stage, recognition of reactive crescents, as they are encountered, for example, in chronic pyelonephritis, ischemic loop damage, amyloidosis, malignant nephrosclerosis, etc. is not easy, but in these diseases, extracapillary involvement of 20% or more is extremely unusual.

**Fig. 14.52.** Part of a glomerular crescent: the swollen capsular epithelial cells (*CE*) are easily recognizable, as agtes (*P*) which in this case evidence only slight cystoid organelle transformation. Male, 70 years. EM (×4080) ▷

**Fig. 14.53.** Massive fibrin strands (*) are seen between the proliferated capsular epithelial cell. Same case as in Figure 14.50. Female, 60 years. EM (×8300)

**Fig. 14.54.** Exudate between obsolescent glomerular capillary loops (→) and capsular epithelial cells in extracapillary accentuated GN. Note the bulky degradation granules in the otherwise amorphous exudate. Same case as in Figure 14.43. Female, 70 years. EM (×12,8000)

**Fig. 14.55.** Same case as in Figure 14.54. In the exudate, collagen fibrils are clearly discernible. Female, 70 years. EM (×27,340)

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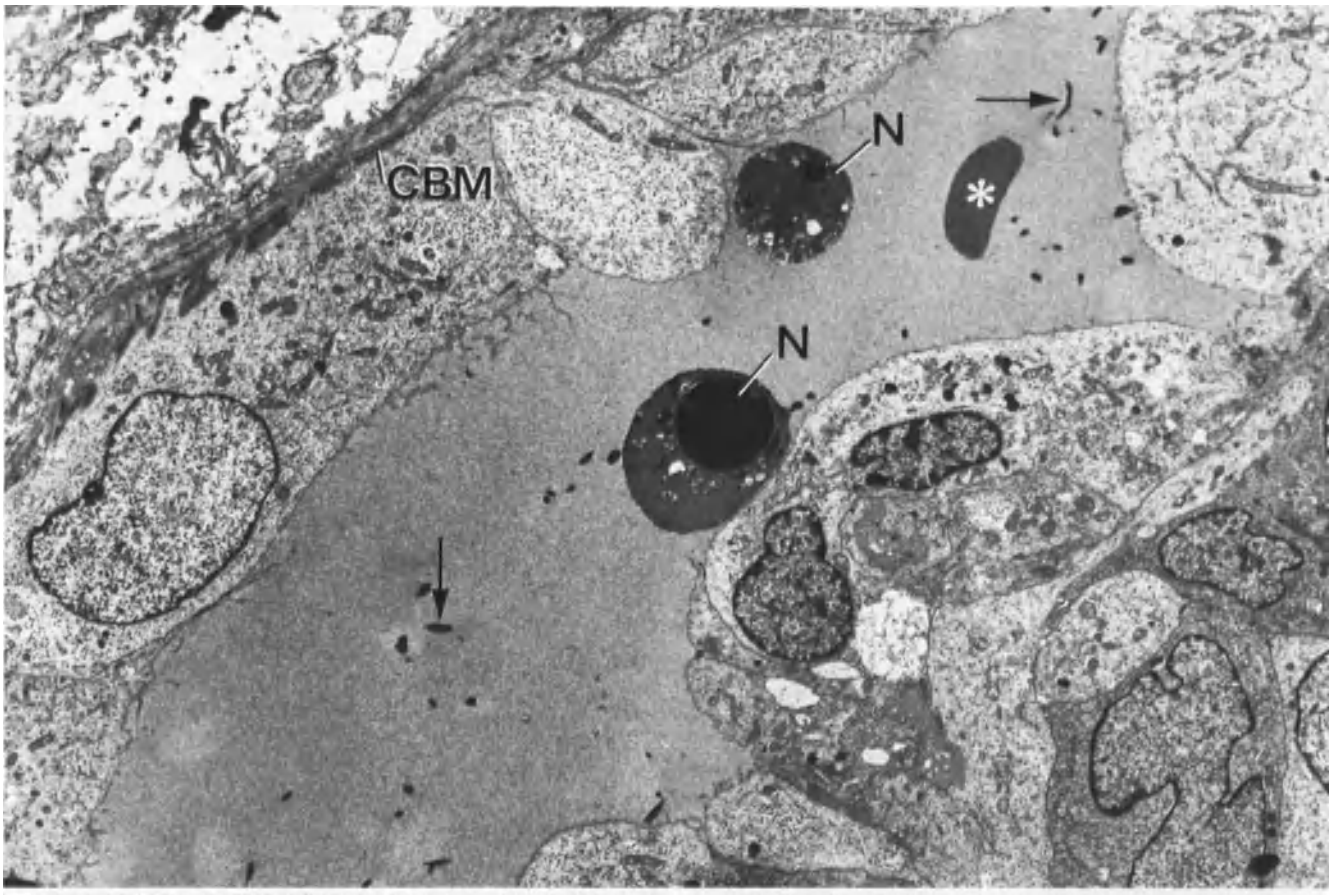


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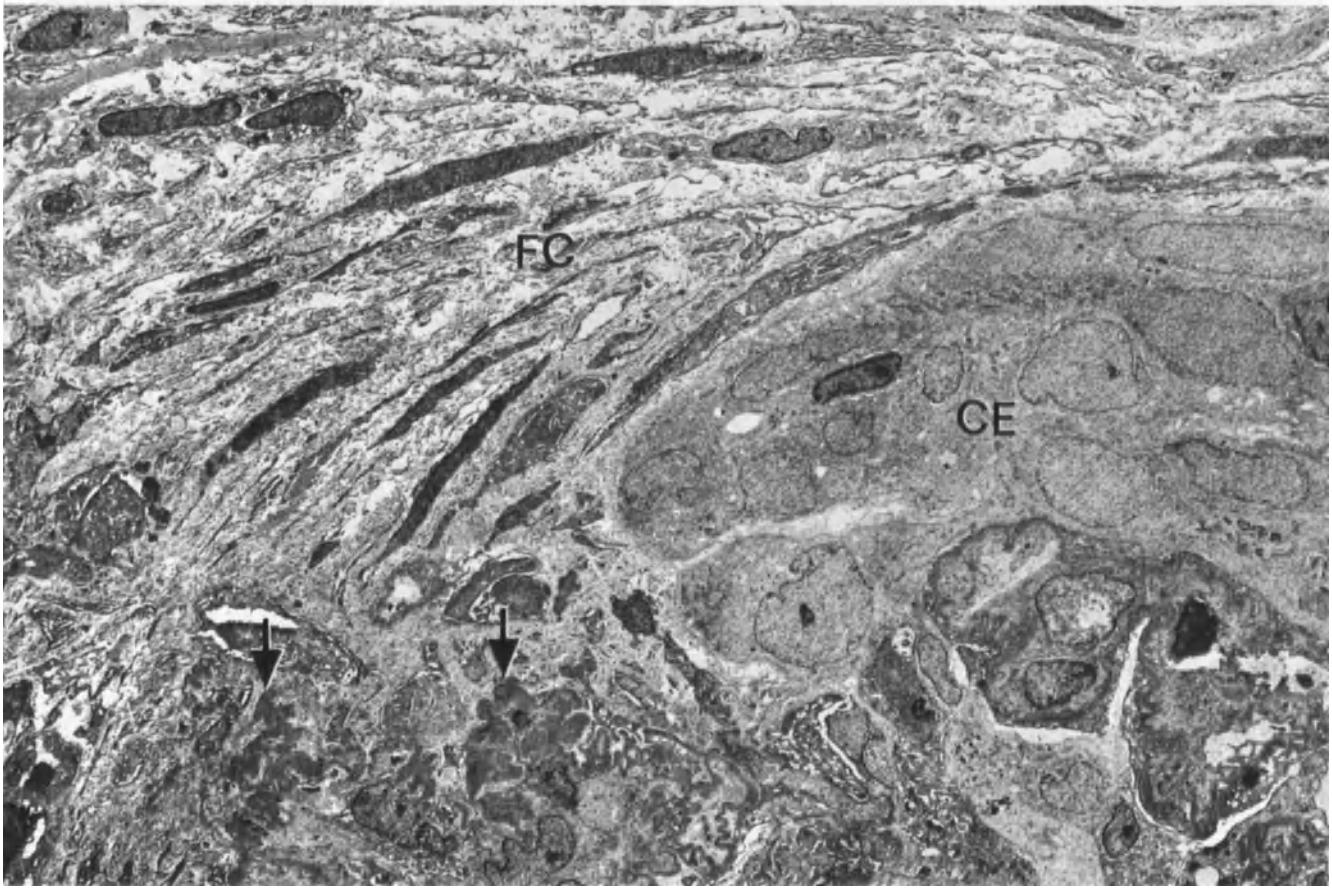



14.57

Extension of BM-like material and collagen into the capsular BM, and the presence of a few fibrocytes in old crescent masses [282] may be helpful in the diagnosis of GN, since both findings are chiefly observed in GN-caused crescent formation.

The form of GN which has been described as "apparently rapidly progressive" [544] is supposedly characterized by the slight presence of IgG and complement; it is not thought to be caused by streptococci. This form of GN has been proposed on the basis of two cases only [544] which is not sufficient to permit its clear differentiation at the present time.

## Prognosis

The extracapillary accentuated GN with involvement of more than 50% of glomeruli (see also [840a, 1212]) has an extremely bad prognosis. Prognostic data in our patients (Table 14.10) show a 5-year survival rate of 25% from disease onset/biopsy. More than 75% died from uremia. Five patients were still alive: one was considered to be healed (see below), three had improved, and one was in terminal renal insufficiency. The data from the literature confirm these results, although exact data about the percentage of glomeruli evidencing crescents are often lacking: 41 out of 63 cases died or were on dialysis [1103, 1484, 1574], 11 out of 15 had terminal renal insufficiency [134].

In children, mortality is around 90–100% when more than 80% of the glomeruli demonstrate crescents [620, 621]. If 50–80% of glomeruli demonstrate crescents, cure [620, 1484, 1791] or considerable improvement [1801] are possible. In mild cases (< 50% crescent formation) cure has been reported in half of the patients [1489] although morphologic or functional defects do persist.

Table 14.10. Prognosis and outcome of extracapillary accentuated glomerulonephritis (with crescents of > 50%)

| Prognosis | Survival rate in % | |
|---|---|---|
| | 3 years | 5 years |
| From disease onset | 40 | 25 |
| SE[a] | 11.2 | 10.6 |
| From biopsy | 34 | 25 |
| SE[a] | 10.6 | 10.6 |

[a] SE: standard error in %.

*Outcome* (after minimal follow-up of 1 year)

| | |
|---|---|
| Number of patients | 21 |
| Total mortality | 76.2% |
| Death in uremia | 76.2% |
| Complete remission | 4.8% |
| Improved | 14.3% |
| Terminal renal insufficiency | 4.8% |

In contrast to our former opinion, it is now thought that crescents are by and large reversible [1211, 1489]. In one of our own cases with originally more than 75% crescents (Figs. 14.60, 14.61) only an axial change with BM injury and no crescents were present 1.5 years later (14.63); 10% of the glomeruli, however, were obsolescent (Figs. 14.62,). We recently experienced a similar case with a time interval of 13 months.

The presence or absence of capillary loop necrosis is of great prognostic significance. Thus, in 41 patients without necroses, 12 survived, but in 54 with the lesion, only 4 remained alive [1302].

There is a general consensus among investigators in the field that the complex type of the disease with humps and a significant mesangial cell proliferation caused by streptococci has a better prognosis than that type without these features or than the anti-BM type [1019, 1330, 1489]. Initial serum creatinine values of more than 5 mg % are reported to herald a hopeless prognosis [1019]. The extent to which exacerbations impair the prognosis is not fully known [1661] (see also: [1815]).

The damaging effect of permanent injury in the anti-BM type is self-evident since the BM-AB continue to act on their target structure, the glomerular BM. In these cases, relapse is especially frequent after transplantation [955]. In 13 patients with anti-BM-type GN, the transplant was LM unchanged in 9 cases although IF demonstrated linear immunoglobulin deposits sometimes without C3 and showed relapses of GN in 4 patients [323, 1330, 1574, 1209]. Therefore, bilateral nephrectomy is recommended and transplantation must not be undertaken until serum BM-antibodies have disappeared [1302]. Even after bilateral nephrectomy, pulmonary bleeding, and anti-BM-AB in serum can persist for quite

◁ **Fig. 14.56.** Adenomatoid structure in a glomerular crescent. Isolated fibrin fragments (→), and necrotic cells (*N*) as well as an erythrocyte (*) are present in the lumen. Capsular BM (*CBM*) is unchanged. Same case as in Figure 14.43. Female, 70 years. EM (×3260)

**Fig. 14.57.** Endotheliomesangial GN with 100% crescents. Same case as in Figure 14.43. Completely collapsed glomerular capillary loops (→) with a synechia between the obsolescent loops and the periglomerular fibrous tissue are present. Capsule epithelial proliferation (*CE*); proliferated periglomerular fibrous tissue (*FC*). Female, 70 years. EM (×2850)

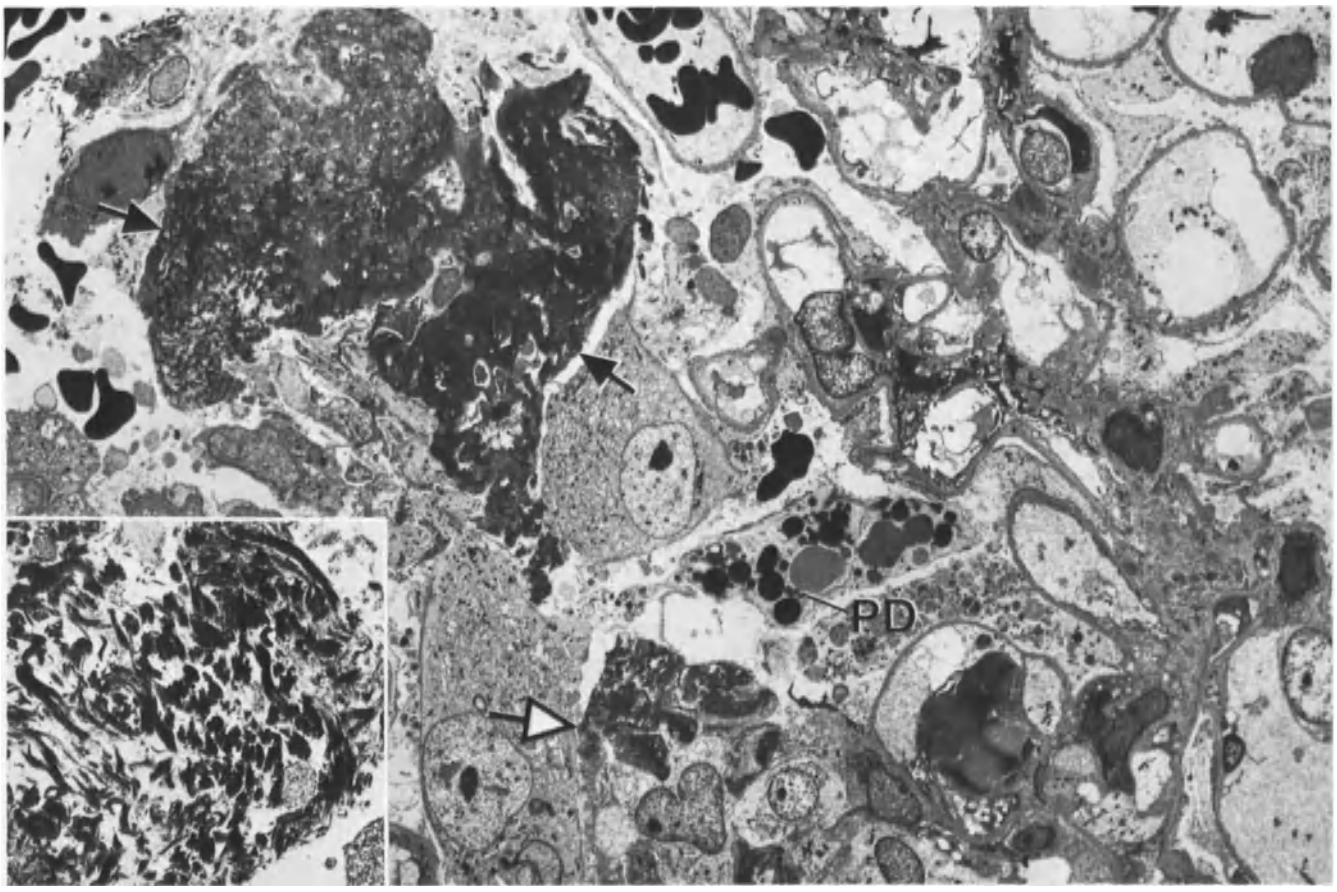



**Fig. 14.58.** Extensive capillary loop necroses in extracapillary accentuated GN. Loops are permeated with fibrin (→). Fibrin is also found in the capsular space (⇨, see inset). Numerous protin droplets (*PD*) are present in podocytes. Male, 47 years. EM (×1290)

some time [1512]. Extracapillary accentuated endotheliomesangial GN with linear immunodeposits had developed de novo in a transplant of a patient suffering primarily from sclerosing GN without immunodeposits [573].

## Pathogenesis and Etiology

The pathogenesis of crescent formation is identical whenever it occurs. Very severe injury to the capillary loops, e.g., necroses, BM defects is necessary for fibrin exudation into the capsular space [1209, 1497a]. In this process, the immunocomplexes must also attain the capsular space, but immunoglobulins themselves have not been observed with IF therein. Therefore, they may be deposited transitorily and/or quickly removed possibly via phagocytosis and/or with the glomerular filtrate, if any.

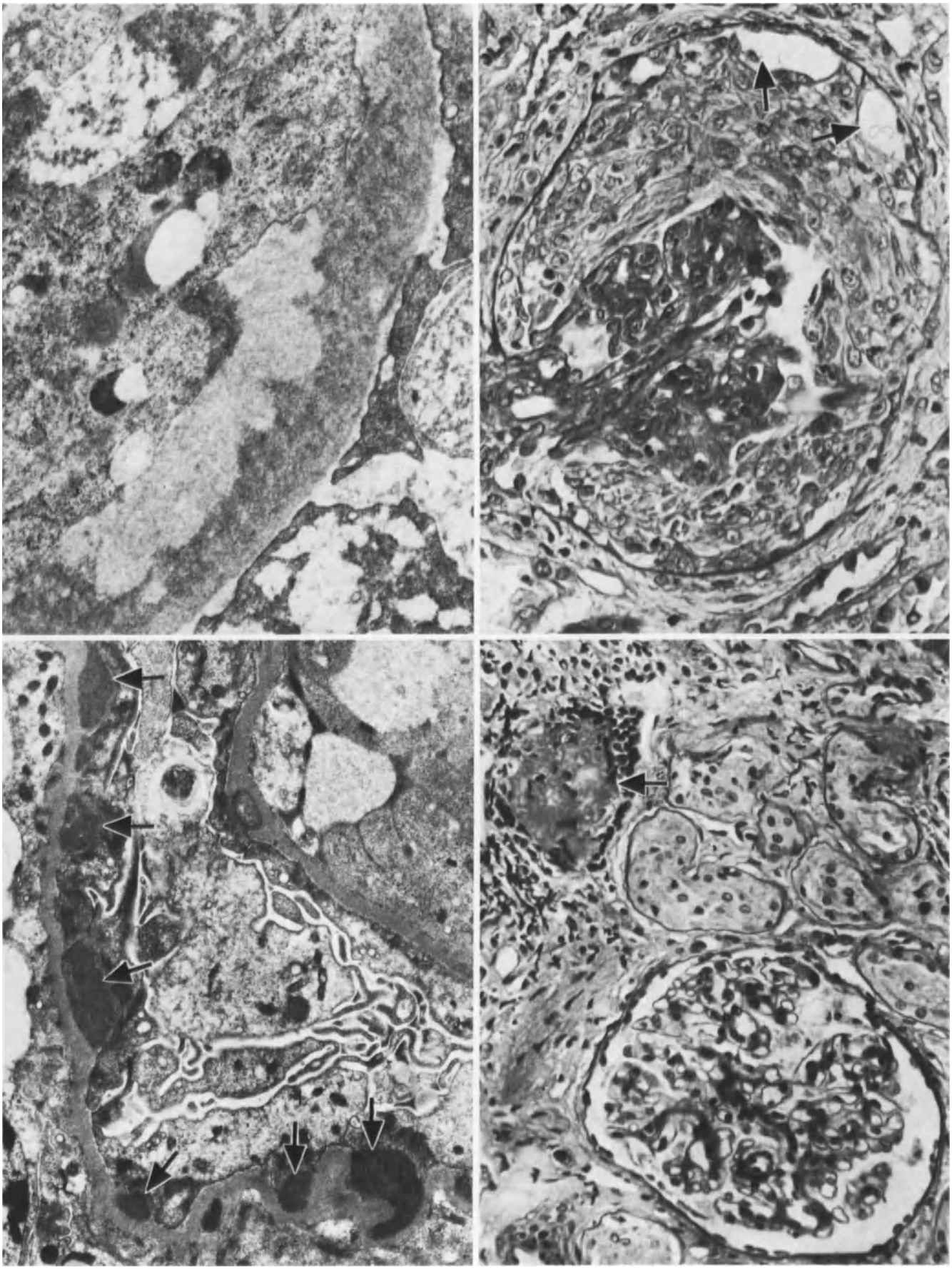
Since, however, crescents arise in many glomerular diseases not associated with immunologic processes, fibrin assumes the main role in triggering the proliferation of the capsular epithelium [282, 1069] (see also p. 100).

**Fig. 14.59.** Circumscribed, translucent subendothelial area with ⊳ osmiophilic fringes in a capillary loop. IF-proven anti-BM type GN. Female, 70 years. EM (×17,750)

**Fig. 14.60.** Extracapillary accentuated GN with crescents in 70% of glomeruli. Adenomatoid structure in a crescent (→). Female, 11 years. PAS (×420)

**Fig. 14.61.** Same case as in Figure 14.60. Extensive, somewhat irregularly formed subepithelial deposits (→). EM (×10,900)

**Fig. 14.62.** Same case as in Figure 14.60. Rebiopsy 1.5 years after extracapillary accentuated GN; only axial mesangial enlargement is present besides scattered obsolescent glomeruli (→) with perifocal inflammation. Female, 12.5 years. PAS (×320)



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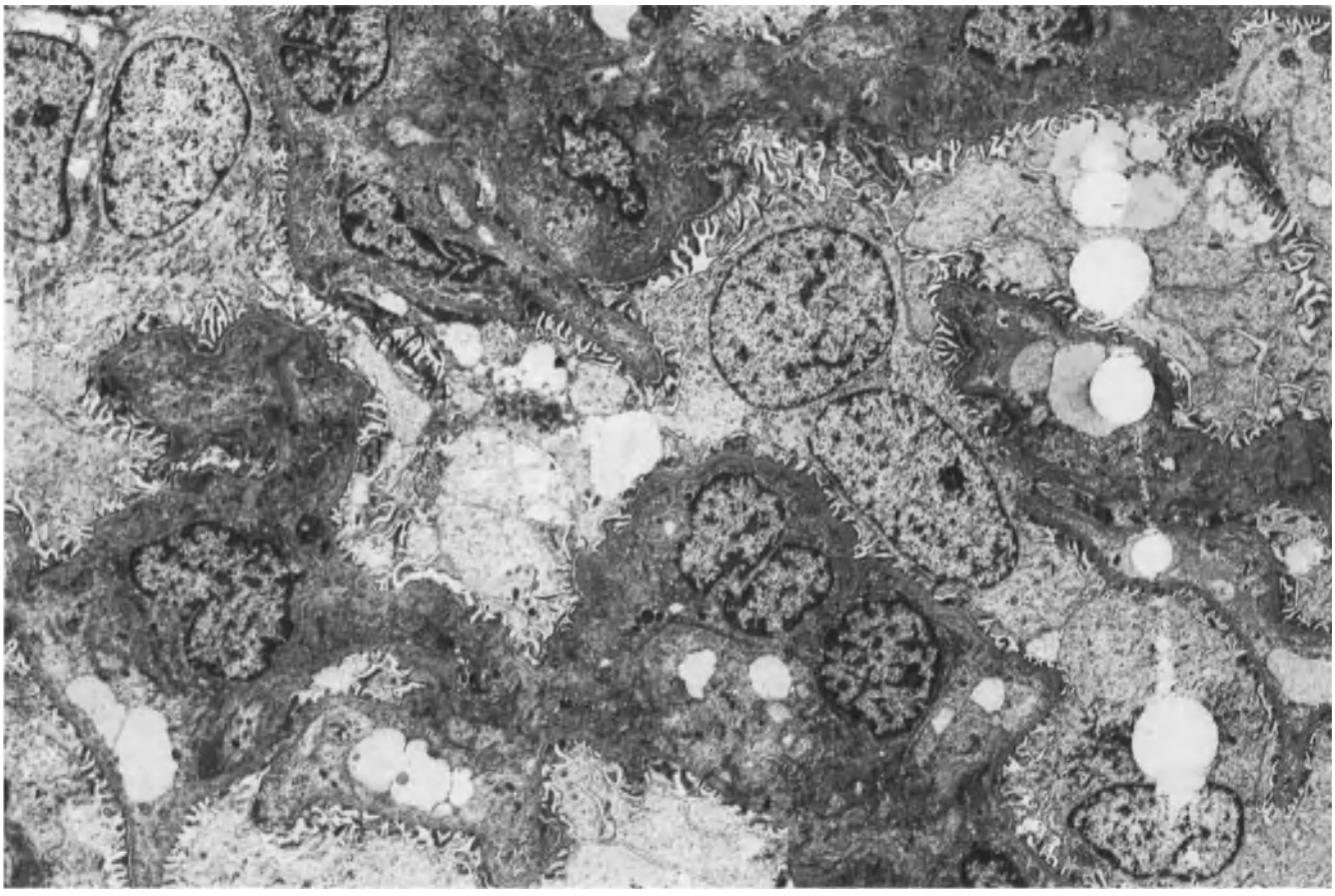


**Fig. 14.63.** Same case as in Figure 14.62. Mesangial enlargement with matrix and cell increase. Note pronounced edematous swelling of podocytes. Female, 12.5 years. EM (×2880)

The discussion of the pathogenesis and etiology of the GN demands a distinction between the immunocomplex and anti-BM type (the latter is discussed on p. 185).
The complex type of extracapillary accentuated GN, as defined in this context, is pathogenetically due to highly or less soluble immunocomplexes (immunocomplexes class I and II: [544]) and etiologically probably associated with streptococci or other etiologic factors [544, 893, 1330, 1484, 1489] considered on p. 215. From 3 out of 17 of our patients developing extracapillary accentuated GN, one was associated with viral hepatitis, one with staphylococcus albus otitis and one with Schönlein-Henoch's purpura. In 6 other patients from this group, a significant elevation of AST-titer was found suggesting a streptococcal etiology (see also [1451]).
Finally, it is again emphasized that a large number of cases of extracapillary accentuated GN must be allocated to segmental focal proliferative GN with or without systemic disease as indicated in reports from the literature (31 out of 33 cases: [1019]; 12 out of 22: [243]; 10 out of 30: [282]; see also: [1815]).

## Membranoproliferative Glomerulonephritis
[635, 1721, 1802]

### Definition

Membranoproliferative GN is characterized by the presence of peripheral capillary loop thickening caused by subendothelial immunodeposits and by mesangial interposition with new formation of subendothelial BM.
In agreement with other investigators [126, 245, 246, 407, 544, 846, 1005, 1484, 1724, 1802] we also feel that so-called lobular GN does not represent a separate disease entity, but only a variety of membranoproliferative GN. Some investigators have formerly rigidly differentiated between membranoproliferative and lobular GN [13, 161, 655, 1713] while others have altered their views on such differentiation [620, 621, 636]. Additionally, we are not convinced that a so-called genuine lobular GN [159a] not belonging to the spectrum of membranoproliferative or intramembranous GN exists at all.
Membranoproliferative GN is also often falsely equated with persisting GN, a view which is certainly understandable on the basis of clinical but not of histopathologic findings.

*Synonyms.* Intracapillary GN [451, 1784], mixed membranous and proliferative GN [231, 985, 1484, 1541], parietoproliferative GN [899] and endomembranous GN [544]. For further synonyms, see Table 13.2.

### Nosology

We recognize the same stages of inflammation and degrees of severity of mesangial involvement as we have done for endotheliomesangial GN (see p. 181). Crescents may be present in 0%–100%.

### Incidence

The frequency of occurrence varies between 3.2% and 17.2% of all GN in needle biopsy material as can be seen from Table 14.11. In reports other than those summarized in Table 14.11 the incidences were: 1.1% [231], 2.2% [408], in children: 6.2% [1730].
Consideration of all published cases [634] shows that males and females are about equally afflicted (156:147). In some series, female patients predominate [165, 231, 635]. Especially afflicted are older children (>5 years: [635]) and young adults [231, 1484, 1730]. In our material, the sex ratio male:female was 1.2:1, and 80% of the patients were <40 years of age. A predominance for the pediatric age group in our material was not present (Fig. 14.64).

Table 14.11. Relative frequency (%) of membranoproliferative glomerulonephritis and intramembranous GN[a] (without glomerular minimal change)

| | Membranoproliferative GN | Intramembranous GN |
|---|---|---|
| Bohle (1976) [163a] | 3.2 (5.7) | |
| Zollinger and Mihatsch | 5.2 (6.8) | 0.6 (0.7) |
| Churg and Duffy (1973) [277] | 8.4 (10.2) | |
| Habib (1973) [621] | 8.9 (17.4) | |
| Morel-Maroger et al. (1973) [1137a] | 7.7 (9.7) | 0.8 (1.1) |
| Cameron (1973) [242b] | 13.3 (20.7) | |
| Germuth and Rodriguez (1973) [544] | 13.5 (19.8) | 0.9 (1.4) |
| Hamburger et al. (1971) [654] | 17.2 (21.8) | 1.8 (2.3) |

[a] For the total number of cases in the series presented above see Table 14.1, p. 188.

### Clinical Findings
(Tables 14.3, 14.4, 14.5; Fig. 14.64)

The disease usually begins insidiously [408, 899] as was already known in the case of intracapillary GN [1784]. Quite frequently [544, 1721, 1723], for example, in 6 out of 36 of our patients (Table 14.5) 30% [634, 635] respectively the clinical symptoms are those of acute GN. In 20% of our cases, acute infection—usually of the upper respiratory tract—preceded the disease (28%: [246]; 42% [634, 635]; see also [231]). There are only few reports which claim assured diagnosis of streptococci as the agent in prior infections [246, 90a]. Manifestation of the disease in the course of systemic diseases, e.g., Schönlein-Henoch's syndrome, is also possible (see p. 317).
None of the initial symptoms are indicative of the disease (Fig. 14.64). Although edema is initially present in half of the patients and proteinuria in 67.6%, it is recalled that both of these symptoms occur with about the same frequency in all forms of GN. Disease onset with macrohematuria is unusual.
The further course of disease is often characterized by frequent attacks (Fig. 14.64): 45% without remission and 30% with temporary remission [634, 635]. At the time of biopsy, patients manifest the following typical symptoms: proteinuria and hematuria are present in almost all patients [165, 231, 246, 634, 635, 1092] and full nephrotic syndrome in half (in 40%: [1091, 1721, 1723]; initially in 64%, later in 84%: [634, 635]). Isolated hematuria and isolated proteinuria are, on the other hand, rare and uncharacteristic.
During the course of the disease, blood pressure fluctuates. Even at disease onset, temporary hypertension is relatively frequent (31%: [634, 635]; 29.7%: Z) and is occasionally accompanied by initial renal insufficiency. Both symptoms may disappear within 2 to 24 months

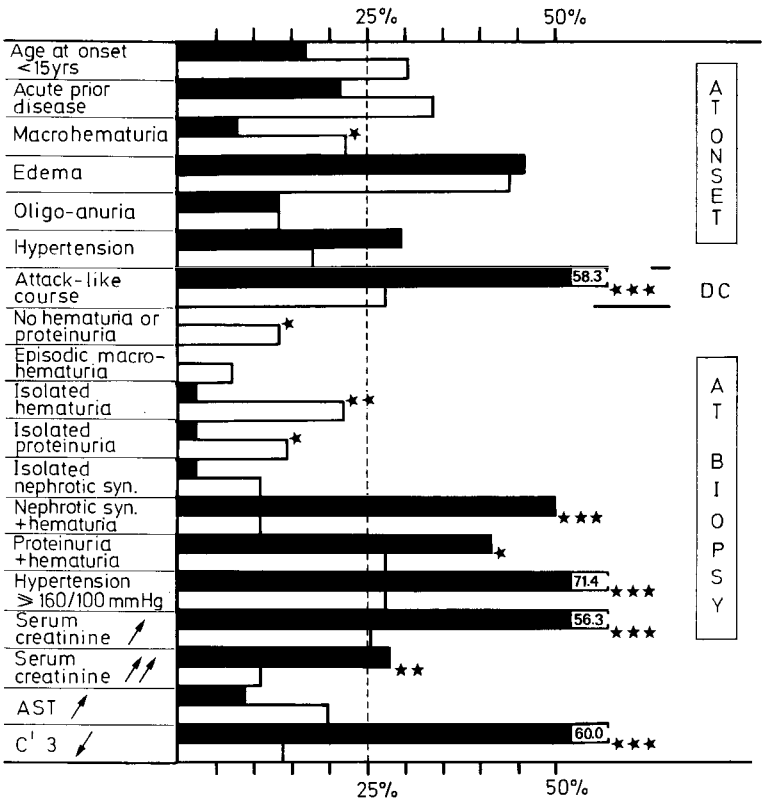



**Fig. 14.64.** Profile of symptoms and clinical findings in membranoproliferative GN
*White columns:* Relative frequency of symptom/finding in all GN
*Black columns:* Relative frequency in membranoproliferative GN
Asterisks indicate characteristic findings for membranoproliferative GN:
*: characteristic
**: very characteristic
***: highly characteristic; DC: disease course

[634, 635, 1802], but during intermittent acute attacks, they may reappear. In the late disease phase, hypertension and renal insufficiency develop in parallel. In our patients, hypertension was present in 70% and about 60% exhibited raised serum urea and creatinine values as manifestations of the concomitant renal insufficiency. In this event, progression to terminal insufficiency [1721, 1723] is reported within 12–20 months.

Pronounced anemia—which is said to occur frequently in lobular GN (10 out of 26 cases: [634, 635])—cannot be simply attributed to renal insufficiency.

Of special diagnostic significance is the decrease in serum C3 which may persist for months and even years [1721, 1802] but which is not obligatory (39% [246]; 26.5%: [90a]; 6 out of 10: Z; see also [544, 1721, 1723]; Fig. 14.64).

However, since a decrease of serum complement also occurs in acute endotheliomesangial GN [909], the determination of several complement components (C1, C2, C3, C4) is especially important since the decrease of C3 alone is typical and an expression of complement activation via the alternative pathway [1721, 1723], whereas the simultaneous depression of the complement factors indicates activation via the classical pathway.

### LM Findings

As already outlined under nosology, the same stages of the disease can be differentiated as in endotheliomesangial GN. Under low magnification, the proliferative stage appears similar to endotheliomesangial GN (Figs. 14.65, 1.1). In the sclerosing stage, however, the segmentally accentuated sclerosing changes in the capillary loops and the pronounced presence of interstitial inflammatory infiltrates are characteristic for membranoproliferative GN (Figs. 14.66, 6.98).

The LM characteristics seen under high power magnification which are common to almost all stages are mesangial circumferential interposition, newly formed subendothelial BM (tram-track picture), more or less extensive subendothelial deposits and accompanying interstitial nephritis. These changes are—in the most frequently found proliferative and proliferative-sclerosing stage—accompanied by a usually pronounced mesangial cell increase (Fig. 14.67). Exceptionally, mesangial cell proliferation is completely absent, so that glomerular findings are dominated by extensive subendothelial deposits and numerous polymorphonuclear leukocytes which characterize the exudative stage of the disease, a finding we saw only once at autopsy (Fig. 6.46).

Thickening of the peripheral capillary loop wall (Fig. 14.68) is due to mesangial interposition, new formation of BM and subendothelial deposits. It does not necessarily occur in all loops, nor are all loops equally severely changed. Doubling of the peripheral glomerular BM can be seen in PAS stain (Fig. 14.68) and even more clearly with PASM stain of semi-thin sections (Figs. 14.69, 6.18). This doubling leads to the typical

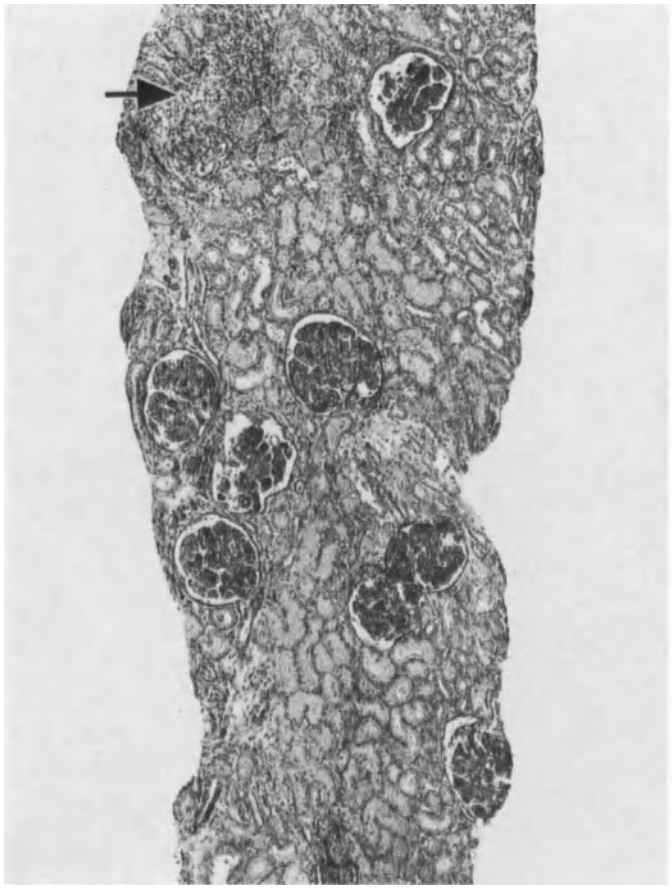


**Fig. 14.65.** Membranoproliferative GN in the exudative-proliferative stage with extensive interstitial inflammation (→). Male, 13 years. PAS (× 56)

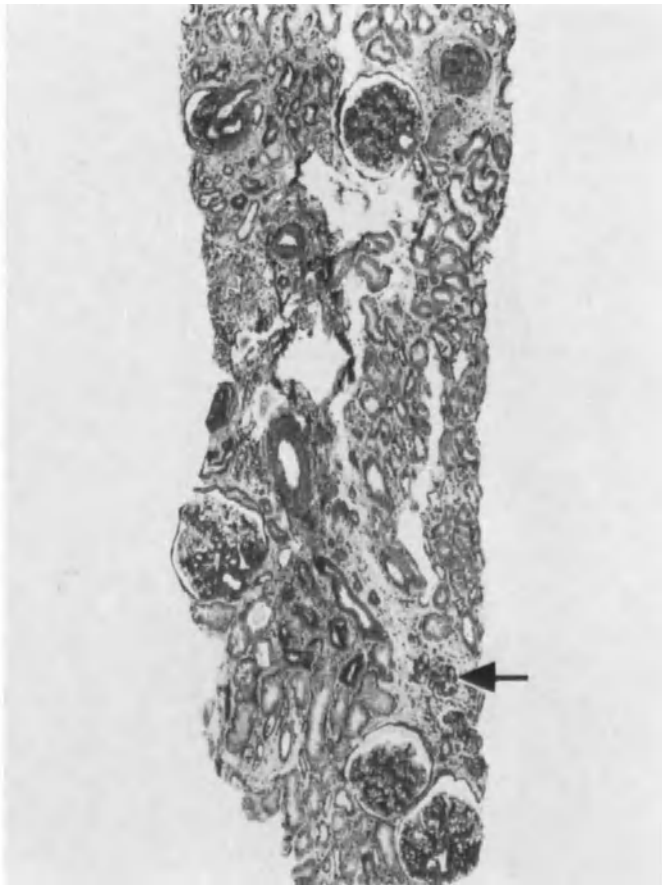


**Fig. 14.66.** Membranoproliferative GN in the sclerosing stage of 11 years' duration. Tubules are occasionally atrophic with thickened BM. Interstitium evidences broad scars with scanty infiltrates (→). Male, 38 years. PAS (× 56)

tram-track picture (especially in more advanced cases) which arises by formation of cross bridges between the newly formed and the old BM (Fig. 14.70), between which the interposed mesangial cells with their oval nuclei can be recognized (Fig. 14.71).

The so-called fibrinoid—often coarse—deposits in the peripheral capillary loops and less frequently in the mesangium are best demonstrated with Masson's trichrome/AFOG stain.

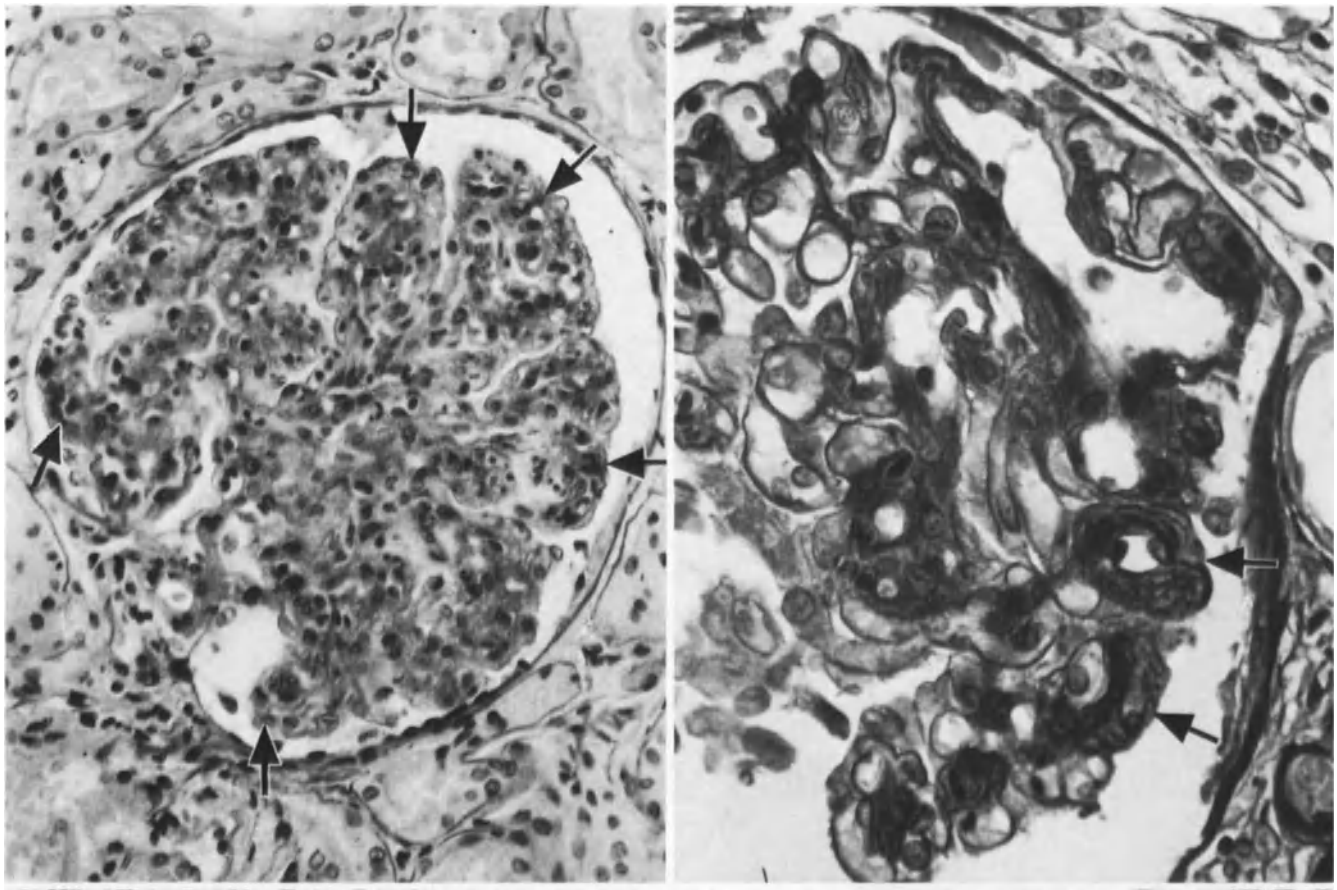
Polymorphonuclear leukocytes are often present in varying numbers in the region of fresh subendothelial deposits. This is also the case in later stages during fresh relapses (Figs. 14.72).

Changes in the mesangium occur in addition to those in the peripheral capillary loops. In the proliferative stage (Fig. 14.67) which may last for months [1723] and was noted in our material after an average duration of illness of 53 weeks (see Table 14.12), a proliferation of varying severity of mesangial cells, but not of matrix, is present. Since the changes in the peripheral capillary loops are often not fully developed in the beginning of the proliferative stages, there may be difficulties in differentiation from endotheliomesangial GN [231, 544, 1332, 1721].

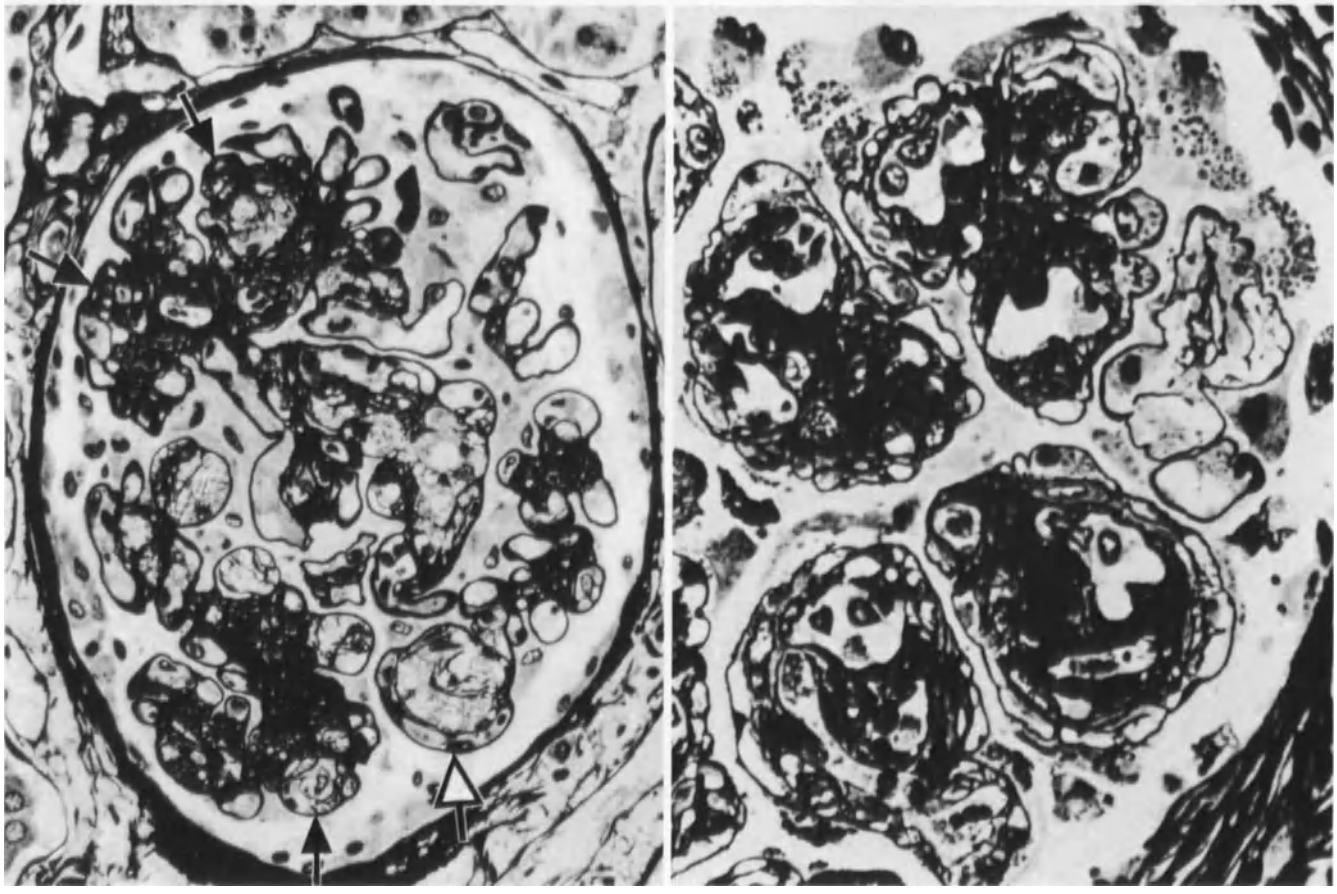
The proliferative-sclerosing stage—as in endotheliomesangial GN—follows the proliferative one (Fig. 14.72), which is distinguished from the former mainly by the increase in mesangial matrix as demonstrable in PAS- and PASM stains (Fig. 14.69). The average duration of illness was about 2 years (Table 14.12).

Transition to the sclerosing stage (Fig. 14.73)—characterized by a decrease of the mesangial cells and their cellular and nuclear size and by an obvious increase in the PASM mesangial matrix—is gradual. The sclerosing stage was present after an average duration of illness of about 3 years (Table 14.12). In this stage, isolated obsolescent capillary loops rich in lipid deposits may be present. Complete capillary loop obsolescence is not uncommon, as in all other stages, and interstitial infiltrates are pronounced (Fig. 14.74).

Extracapillary crescents can be observed in each of the three stages (Table 14.12), especially over severely afflicted capillary loops (Fig. 14.75). In 10 out of 47 of our own cases (13%: [621]) extracapillary crescents, in which segmental crescents were far more frequent than global ones, were demonstrated. Synechiae are also encountered in the presence of extracapillary crescents.



14.67
14.68



14.69
14.70

Table 14.12. Inflammatory stage, disease duration and extracapillary involvement in membranoproliferative glomerulonephritis ($n=47$)

| Phase | Frequency [lobular variant] | Disease duration average (range) in weeks | Frequency of extracapillary involvement | |
|---|---|---|---|---|
| | | | < 50% | > 50% |
| Proliferative | 6[1] | 53 (3–150) | 1 | – |
| Proliferative-sclerosing | 26[8] | 121 (4–450) | 5[3] | 1 |
| Sclerosing | 15[8] | 176 (12–400) | 2[1] | 1[1] |

The entire lesion may assume the characteristics of segmental and, at times, also of focal accentuation in the presence of extracapillary crescents.

The lobular variant is not associated with a specific inflammatory stage (Table 14.12). It is characterized by an especially pronounced diffuse nodular or club-shaped thickening of the mesangium which is due to intense mesangial cell proliferation and/or matrix increase (Figs. 14.76, 14.77). The lobular variant has been reported in 25% (36%: Z) of all cases of membranoproliferative GN [621].

Protein droplet storage and lipid inclusions may be seen in the tubules. Lympho-histio-plasmocytic infiltrates – which may be striking – are found in the interstitium. Furthermore, interstitial edema with transition to sclerosis may be present. Severe destructive inflammation (Fig. 14.78) of vessels is a very exceptional finding.

Membranoproliferative GN is probably far more frequently the cause of contracted kidney than was assumed earlier [1779, 1784]. Of our cases of contracted kidney, 4 out of 20 were due to membranoproliferative GN although at this stage, diagnosis is very difficult due to the predominance of totally obsolescent glomeruli.

## IF Findings

Typical is the occurrence of coarse, granular – occasionally also short or pseudolinear deposits in the peripheral capillary loops, which chiefly contain C3 (Fig. 14.78, Table 14.13) while IgG, IgM, IgA, are simultaneously present in decreasing frequency [105, 128, 231, 636, 743, 1092, 1278]. Membranoproliferative GN associated with ventriculo-atrial shunt is reported to be characterized by an exceptionally pronounced occurrence of IgM [1700]. Fibrin(-ogen) is present in about half the cases (Table 14.13; [1092, 1139, 1607a]; contra: [544, 1278]).

In some instances only C3 is present (40%: [636]; 11%: [1136]; 2 out of 12: Z; 13.3%: [81a]).

The deposits are said to be more pronounced in the early than in the late stages of the disease [1721], a finding we have not been able to substantiate.

Within the glomerulus, C3 and immunoglobulins may be deposited purely peripherally as seen in the majority of cases [81a] or peripherally and mesangially [356, 544, 81a, 1278].

In our material, the intraglomerular distributional pattern of immunoglobulins and C3 vary with the stage of the disease. Thus, in the purely proliferative stage, (two cases), immunoglobulins and C3 are only demonstrable along the peripheral glomerular BM. In the proliferative-sclerosing stage (seven cases), they occur chiefly peripherally and only slightly in the mesangium. In the sclerosing stage (two cases), mesangial deposits predominate.

◁ **Fig. 14.67.** Membranoproliferative GN in the exudative-proliferative stage evidenced by pronounced, thickened glomerular capillary loops (→). Male, 13 years. PAS (×360). Same case as in Figure 14.65 (case published [1802])

**Fig. 14.68.** Membranoproliferative GN. Thickening of glomerular capillary loops (→) accompanied by mesangial enlargement. Male, 43 years. PAS (×650)

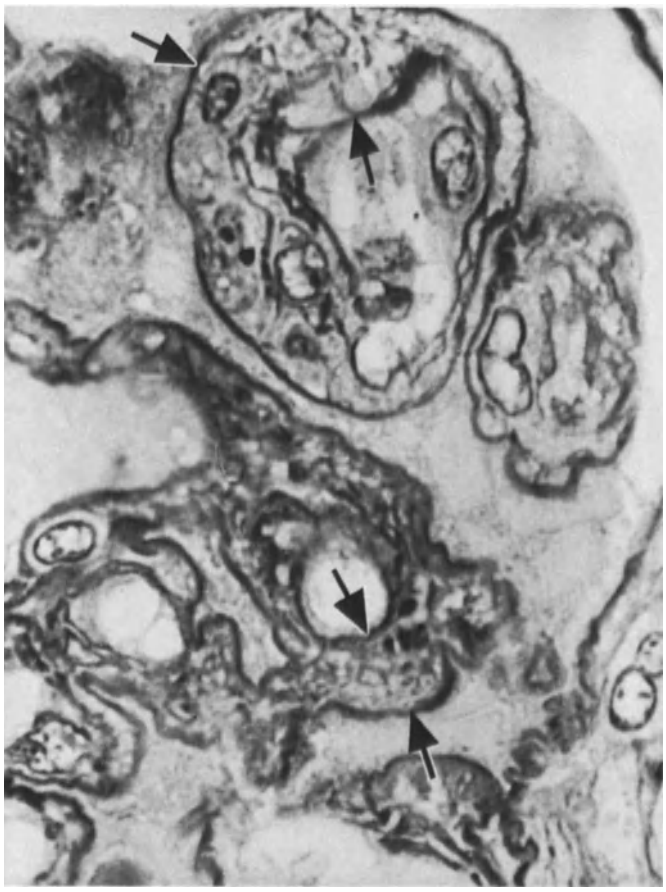
**Fig. 14.69.** Same case as in Figure 14.68. Thickening of peripheral glomerular capillary loop wall (→), doupling of peripheral BM with mesangial interposition (→) as well as enlargement of the mesangium are very evident. Male, 43 years. PASM (×400)

**Fig. 14.70.** Membranoproliferative GN with extensive doubling of peripheral BM (tram-track picture). Female, 73 years. PASM (×800)

Table 14.13. IF findings in membranoproliferative glomerulonephritis ($n=12$/ positive=12)

| | IgG | IgM | IgA | C3 | Fibrin(-ogen) |
|---|---|---|---|---|---|
| Cases tested | 12 | 12 | 7 | 12 | 12 |
| Positive | 10 | 7 | 5 | 12 | 5 |
| Focal | 5 | 3 | 3 | 1 | 3 |
| Diffuse | 5 | 4 | 2 | 11 | 2 |
| Segmental | 3 | 1 | 3 | 1 | 3 |
| Global | 7 | 6 | 2 | 11 | 2 |
| Purely peripheral | 5 | 3 | 3 | 4 | 3 |
| Mesangial and peripheral | 5 | 4 | 2 | 8 | 1 |
| Mesangial | – | – | – | – | 1 |

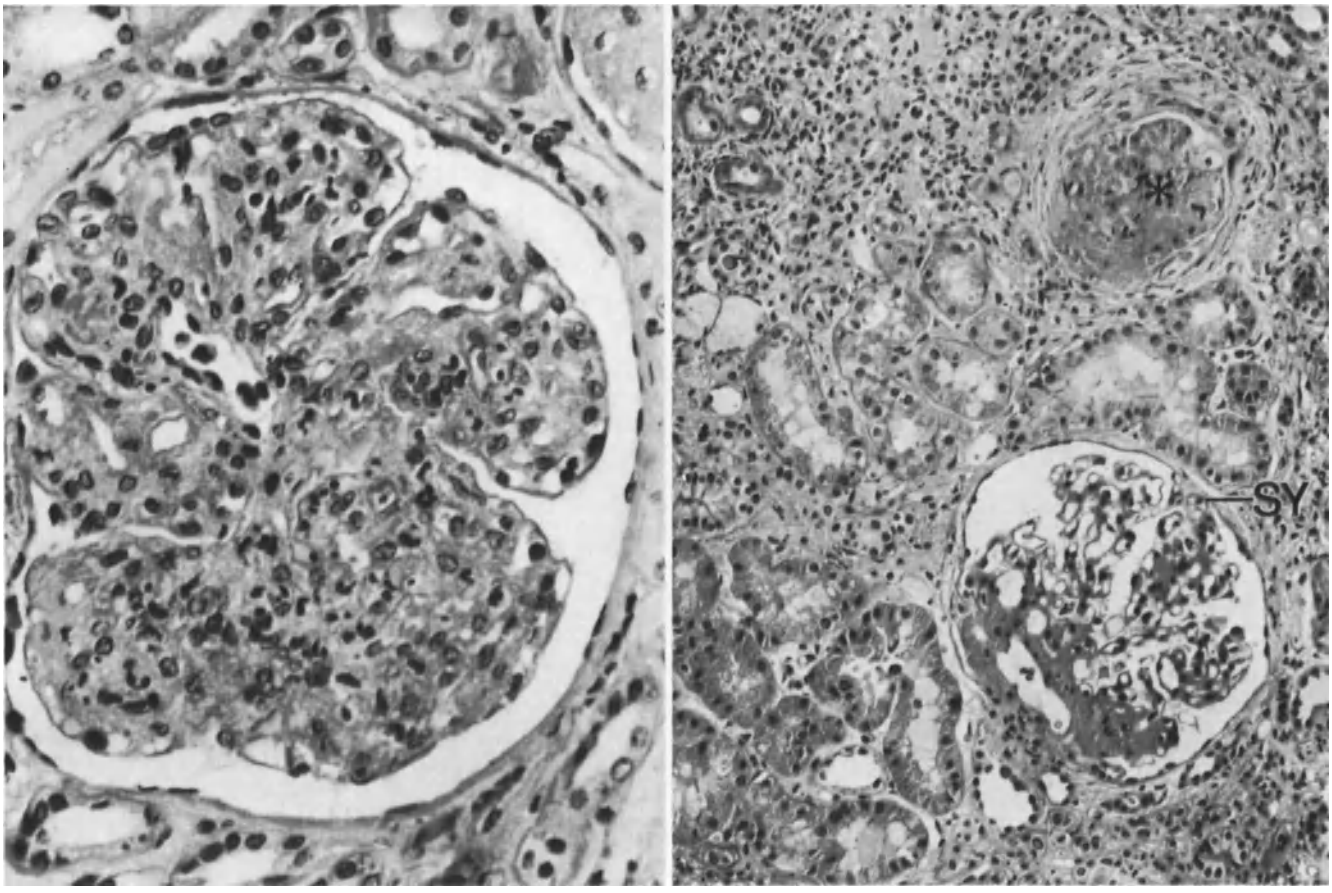
**Fig. 14.71.** Same case as in Figure 14.70. BM doubling (→) with circumferential mesangial interposition. Female, 73 years. Semithin section, PAS (× 1050)



14.71

**Fig. 14.72.** Membranoproliferative GN of 3 years' duration with acute attack. Obliterated glomerular capillary loops and masses of polymorphonuclear leukocytes are present. Extensive subendothelial deposits were demonstrated under EM. Female, 10 years. PAS (× 420)

**Fig. 14.73.** Sclerosing stage of membranoproliferative GN of 9 years' duration. One glomerulus is almost completely obsolescent (*); in the other glomerulus there is segmental obsolescence and a synechia (*SY*). Interstitium exhibits extensive inflammatory infiltrates. Male, 13 years. PAS (× 200)




14.72
14.73

The occurrence of early complement components (C1, C2, C4) is not uniform suggesting a further subdivision of membranoproliferative GN on the basis of IF findings. Sometimes only C3, almost constantly accompanied by properdin, is found [81a, 1092, 1724]. Other times the early complement components (C1, C2, C4) as well as properdin were present [81a, 356]. The common occurrence of properdin and C3 without participation of early complement components indicates complement activation via the alternative pathway (see p. 162). The interpretation of cases in which early complement components are present as well is difficult. It may be assumed that either the complement cascade was activated via the classical pathway primarily, or that these cases represent examples of a hidden biphasic development of complement activation via the alternative as well as secondarily via the classical pathway [356]. Definite conclusions cannot as yet be drawn.

Finally, it must be borne in mind that in the reports cited, membranoproliferative and intramembranous GN are usually not differentiated, which probably confuses the IF pattern reported for membranoproliferative GN.

### EM Findings

The characteristics as seen with EM are subendothelial deposits (Figs. 14.80, 14.81, 6.45), severe peripheral mesangial interposition (Figs. 14.80, 14.81), subendothelial new formation of BM and varyingly severe mesangial proliferation (Fig. 14.82) and/or sclerosis (Fig. 14.83). The mesangial changes may lead to a considerable narrowing of the capillary lumen which finally can become completely occluded.

Following their migration into the periphery of the capillary loop, the mesangial cells form a new, somewhat irregular BM between their cytoplasm and the endothelium (Figs. 14.80, 14.81, 6.33) which accounts for the splitting and doubling of the BM (tram-track picture) seen in LM.

The original BM frequently shows a collapse-like change in the region near the mesangium (Fig. 14.83). In the early stages, the original BM is either slightly thickened or not at all. In later stages, it may become considerably thickened due, in part, to incorporation of deposits. Now and again, findings suggestive of splitting of the original BM are observed which may be very reminiscent of a change seen in Alport's disease (Fig. 14.85).

Hypertrophy of endothelium and arcade formation can also be observed. Endothelial and mesangial foam cells are relatively frequent in advanced stages (Fig. 14.84). Podocytes are edematous or hypertrophied, and often show pronounced formation of microvilli as well as foot process fusion.

The coarse osmiophilic deposits are sickle- or cone-shaped and push the endothelium strongly into the lumen (Fig. 14.86). If endothelial destruction occurs in the region of these deposits, leukocytes may come to lie directly on the BM [985]. In addition to subendothelial deposits, which were present in all our cases, more or less massive deposits were also found in the mesangium (6 out of 19: Z; Fig. 14.83), along the mesangial BM (8 out of 19: Z), the subepithelium (Fig. 14.83; 50%: [90a]; 6 out of 19: Z) and within the BM (Figs. 14.86, 14.87; 7 out of 19: Z; [231, 1802]).

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**Fig. 14.74.** Obsolescent glomerulus in membranoproliferative GN with very extensive periglomerular inflammatory infiltrate. Same case as in Figure 14.68. Male, 43 years. PASM (×240)

**Fig. 14.75.** Severe vascular affliction with cell increase and splitting of the media as well as narrowing of the lumen (→) in a case of membranoproliferative GN with pronounced extracapillary involvement. Female, 40 years. HE (×200)

**Fig. 14.76.** Lobular variant of membranoproliferative GN. Lobular transformation of the mesangium is clearly evident as is the pronounced thickening and doubling of the peripheral glomerular loop wall. An obsolescent glomerulus (*) with a fibrinoid (hyaline) giant deposit (→). Interstitium is considerably thickened and evidences inflammatory infiltrates. Male, 44 years. PAS (×320)

**Fig. 14.77.** Same case as in Figure 14.76. Lobular transformation of the pronouncedly enlarged and sclerosed mesangium and extensive BM doubling (→). Male, 44 years. PASM (×400)

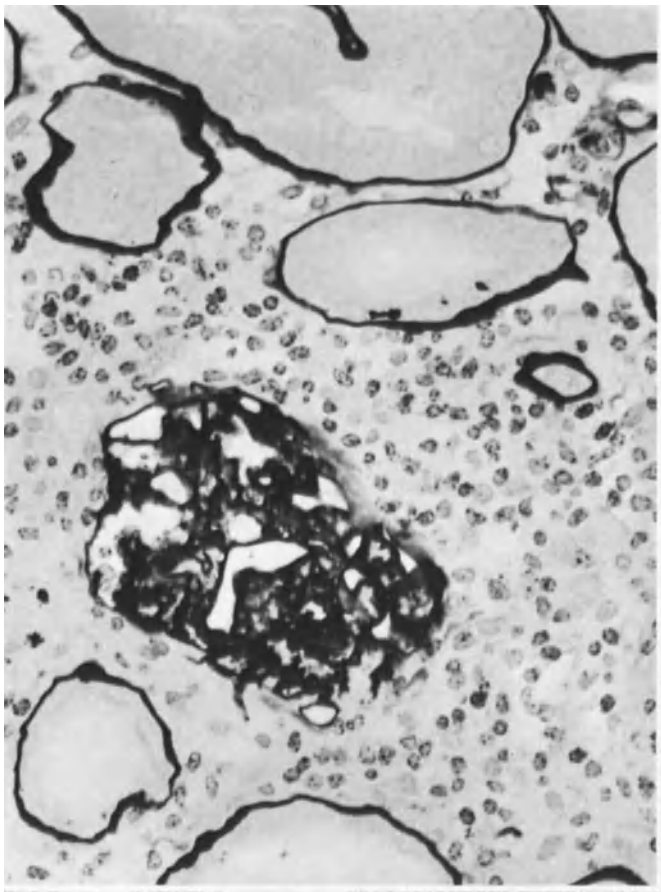
Page 239

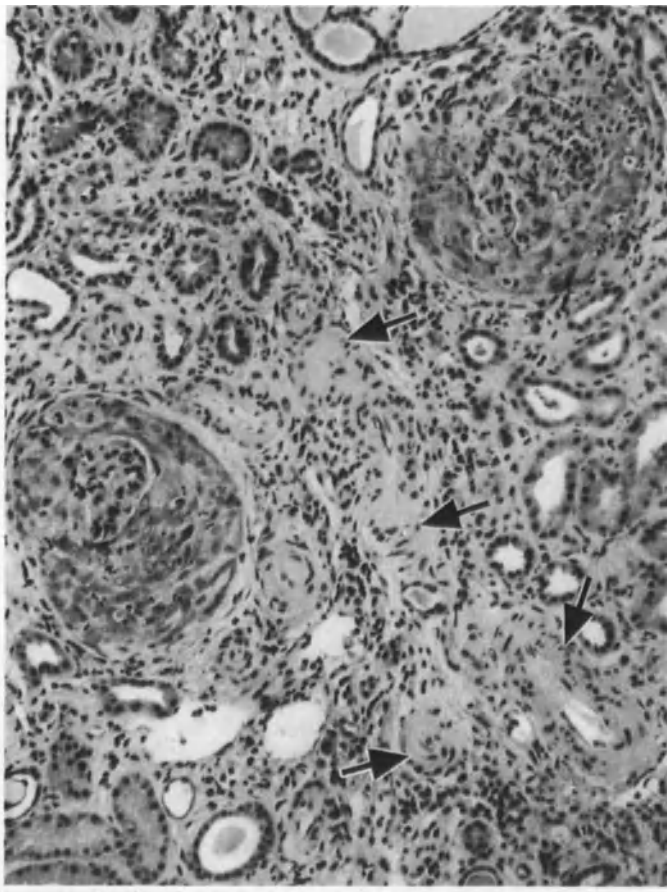
**Fig. 14.78.** Typical massive pseudolinear (coarse) peripheral deposits of C3 in membranoproliferative GN. Note typical lobular pattern. Female, 13 years. IF (×500)

**Fig. 14.79.** Severe endarteritis of an interlobular artery in a sclerosing stage of membranoproliferative GN. Male, 56 years. PAS (×280)

**Fig. 14.80.** Circumferential mesangial interposition with a thin newly formed basement membrane (*BM*). Only a very few isolated subendothelial deposits are present (→) under the original BM showing slight wrinkling. Endothelial cell (*E*), glomerular capillary loop lumen (*CL*), osmiophilic deposit (*D*) in the mesangial matrix. Female, 9 years. EM (×9600)

**Fig. 14.81.** Same case as in Figure 14.80 of membranoproliferative GN. Under the wrinkled and thickened original BM numerous deposits are seen (→), and an interposed and activated mesangial cell is recognizable between the original BM and the newly formed, thinner lamina densa (⇨) which is found lying under the activated endothelium (*E*). There is complete fusion of foot processes and slight increase of osmiophilic substance in podocytes (*P*). Female, 9 years. EM (×8438)





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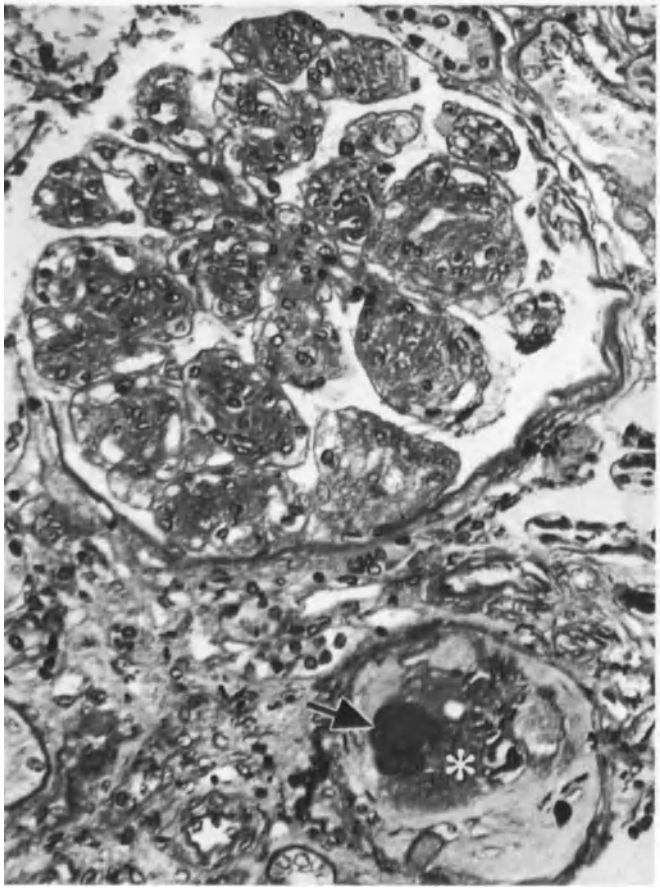

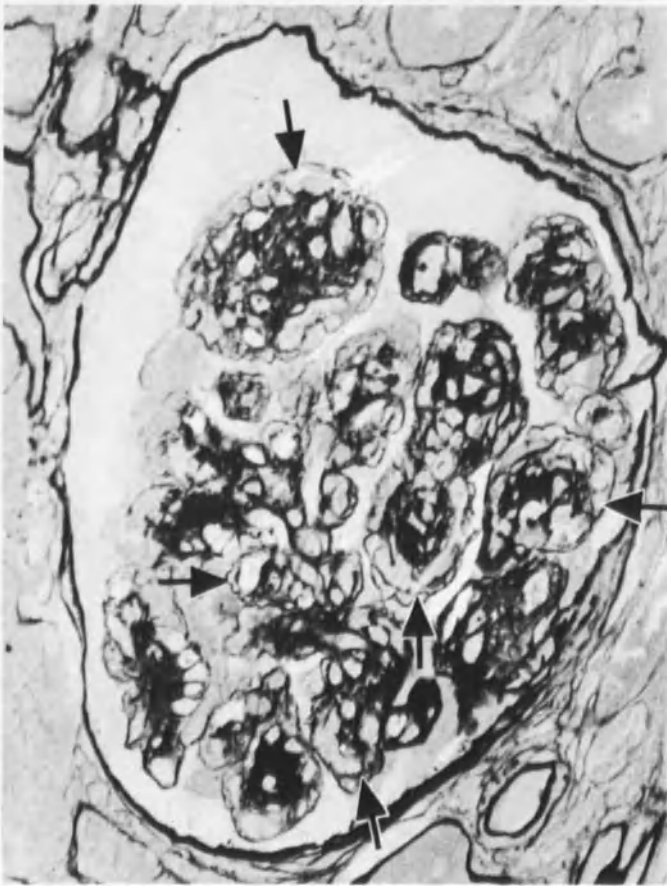

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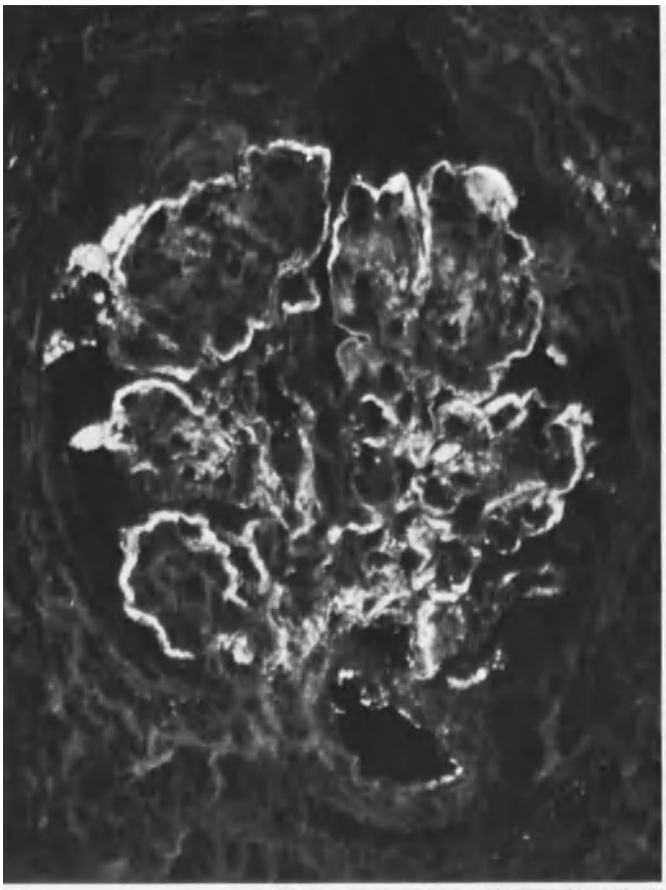

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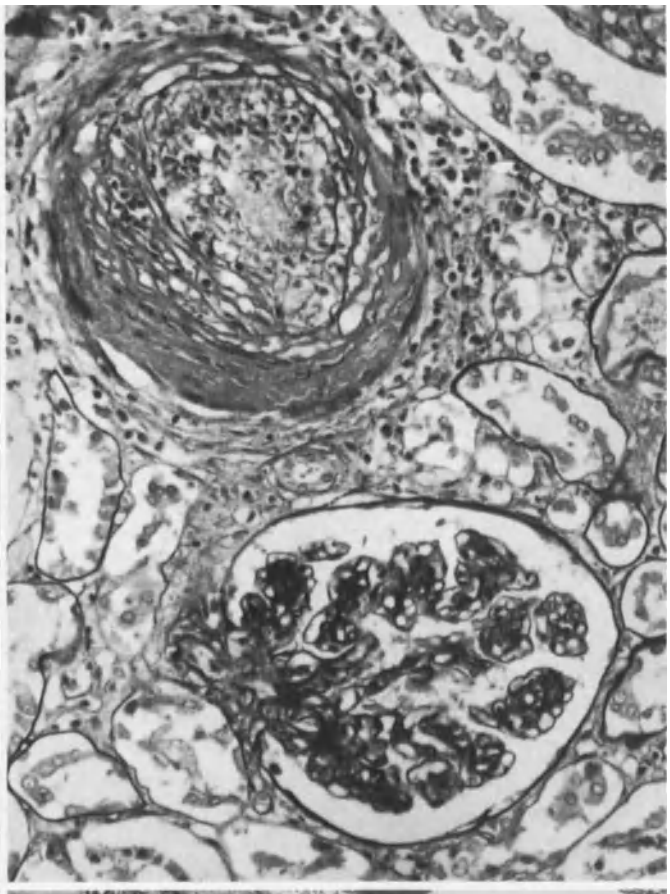

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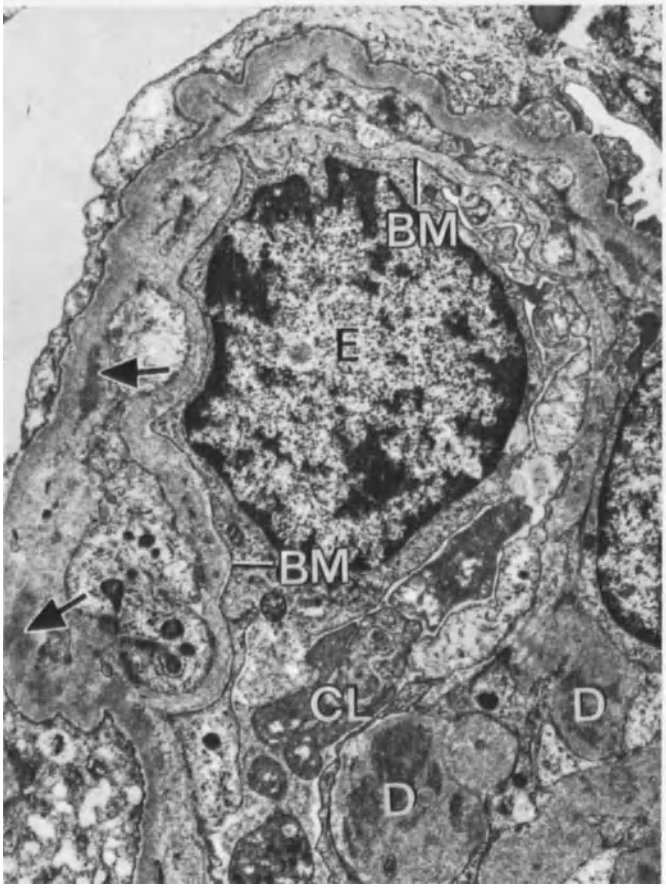


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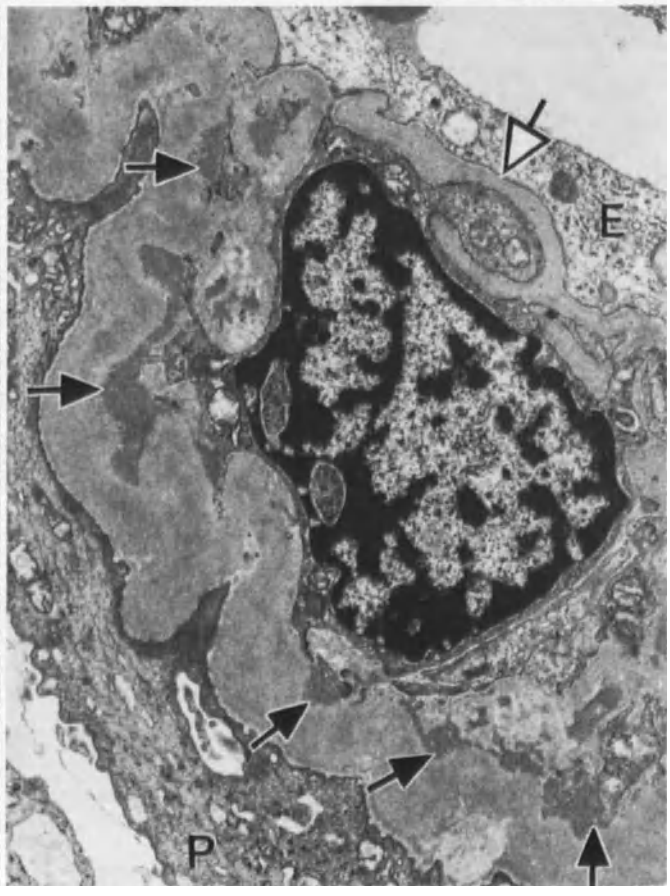
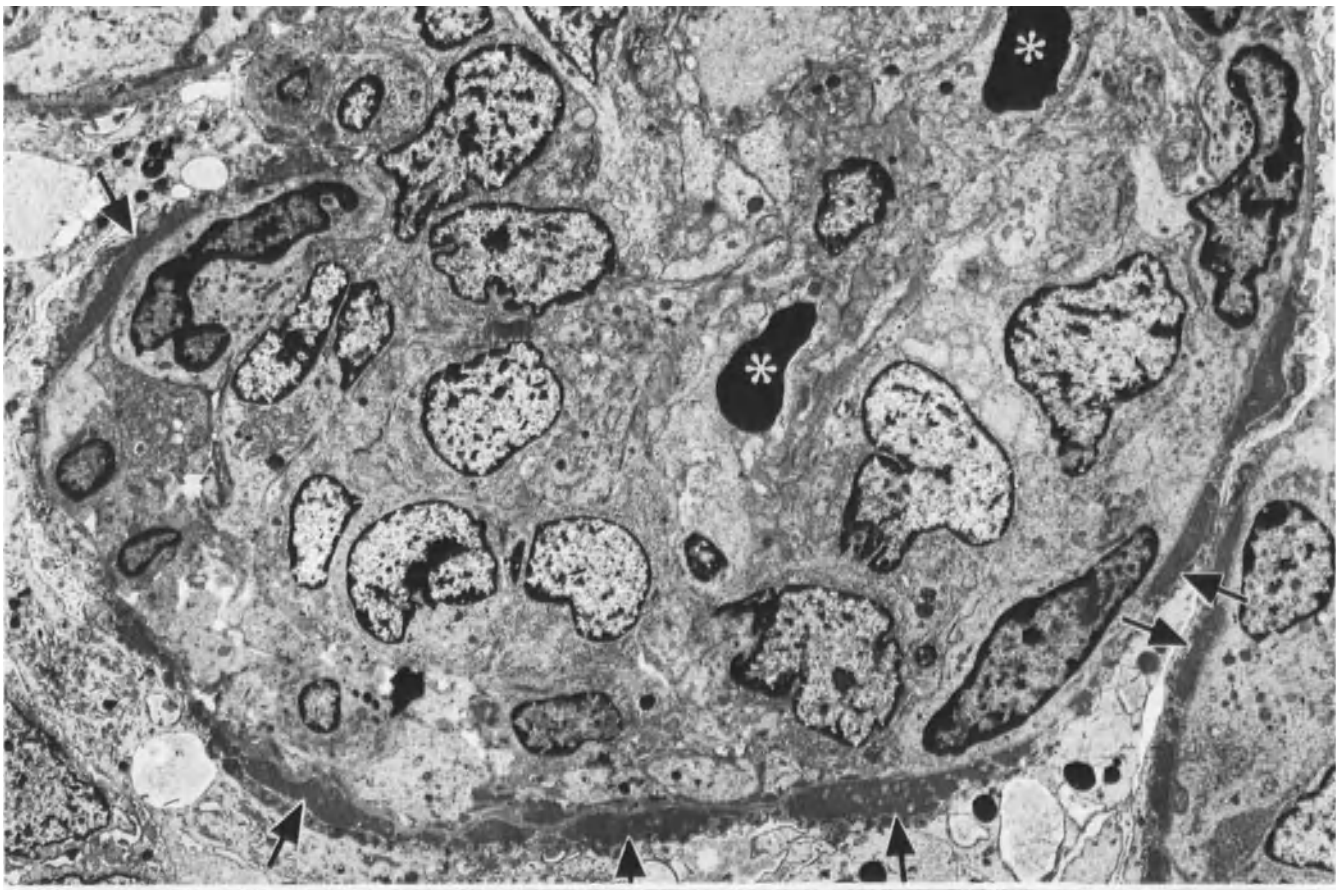



14.81



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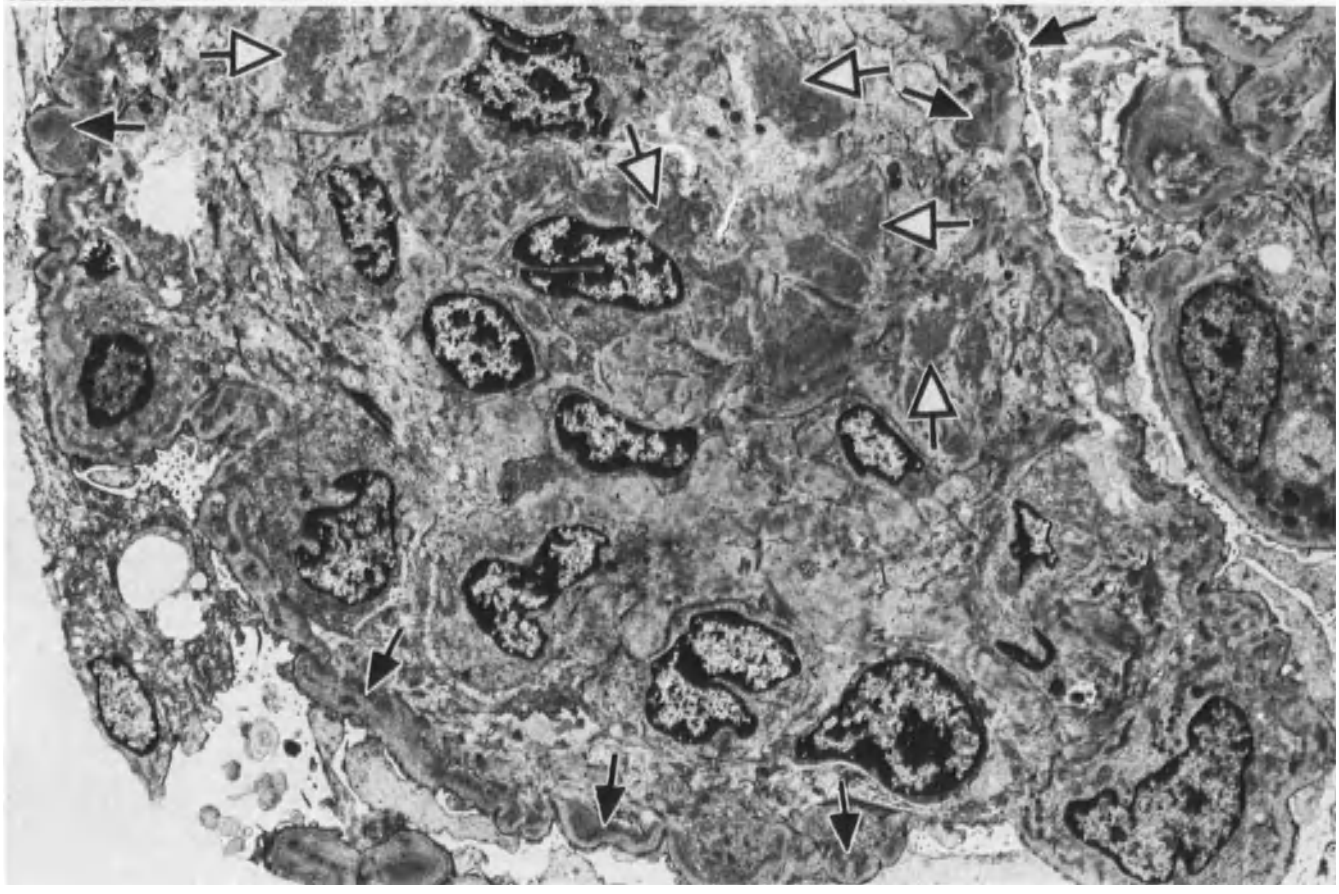

14.83

Subepithelial deposits are generally flatter, more spread out, and less high than humps (Fig. 14.82). Typical humps, however, unquestionably occur (1 out of 19: Z; 3 out of 12: [634, 1484]). We feel that subepithelial deposit formation is the expression of an acute attack. Very broad and isolated subepithelial deposits which, because of spike formation, are reminiscent of epimembranous GN (Fig. 14.88) are also observed [231, 365, 1802]. Such cases form a transition to the findings of the mixed forms (see p. 279). Cases with partly linear, strongly osmiophilic dense intramembranous material are considered by us as a unique disease entity (see p. 252) in contrast to other investigators [634] who consider them as a subform of membranoproliferative GN.

Degradation of the subendothelial deposits is often encountered and is manifested by unsharply demarcated translucent peripheral areas (Figs. 14.90, 6.47, 6.49), by intense vacuolization and occasionally, by formation of thread-like structures (Fig. 14.89). Furthermore, dissolution of the deposits is frequently accompanied by their clumpy desintegration and/or massive fatty transformation (Figs. 14.91, 6.49). In only one of our cases polymorphonuclear leukocytes and, in one other, monocytoid cells were observed participating directly in their destruction (Fig. 14.90).

Crescents show no special features (see p. 100). It noted that fresh proliferative crescents occur in association with very old loop changes, whereby fresh subepithelial deposits are sometimes found on the neighbouring loops.

Due to massive increase of mesangial cells and/or matrix, the mesangium is considerably thickened (Figs. 14.82, 14.83, 14.92). This is especially pronounced in the lobular form and is not necessarily associated with deposits (Figs. 14.93, 6.52). In the early disease stages, mesangial cell elements are often hypertrophic (Fig. 14.82; see also [635]).

The tubular changes are similar to those in endotheliomesangial GN, foam cells, however, are more frequent (Fig. 14.94). In pure membranoproliferative GN, the thickened tubular BM (Figs. 8.25, 8.27) shows no unique characteristics in contrast to intramembranous GN. We have demonstrated a few irregular osmiophilic deposits in blood vessels which are occasionally considerably less electron-translucent than in conventional arteriolosclerosis (Fig. 14.95). The interstitial infiltrates correspond to those seen in LM (Fig. 9.10).

Repeated biopsies taken during the course of the disease [1801, 1802] have shown that the proliferation is by and large reversible. Nevertheless, considerable permanent damage remains and is worsened by each new attack. In one observation, moderately severe extracapilllary involvement (4 out of 16 glomeruli) was observed 3.5 weeks after clinical disease onset without the morphologic characteristics of membranoproliferative GN being present [1801].

After 16.5 months, mesangial thickening, isolated subendothelial deposits, diffuse BM thickening (1 synechia per 12 glomeruli) as well as fresh humps were present. The humps were still observable 22.5 months after disease onset but, 11 months thereafter, they had disappeared, while the number of synechiae increased to 2 per 9 glomeruli.

◁ **Fig. 14.82.** Membranoproliferative GN with severe proliferation of mesangial cells showing enlarged, polymorphic, i.e., activated nuclei. Lumens of glomerular capillary loops have been almost completely displaced. Only two erythrocytes are recognizable (*). Flat subepithelial deposits (→) are the expression of an acute attack. Scanty subendothelial deposits. Male, 13 years. EM (× 3520). Same case as in Figure 14.67, published [1802]

**Fig. 14.83.** In contrast to Figure 14.82, this is a predominantly sclerosing stage with massive mesangial matrix increase. Mesangial cells are only slightly increased and still activated. Osmiophilic deposits are seen subendothelially (→) and mesangially (→). Foot process fusion is complete. Capillary lumens are completely occluded. Female, 29 years. EM (× 3960)

Page 242

**Fig. 14.84.** Extensive foam cell formation in obsolescent glomerular capillary loop in membranoproliferative GN. Masses of lipid-containing vacuoles in probably endothelial cells. Another cell (*) is presumably of mesangial origin. Between podocytes (*P*) and basement membrane (*BM*) newly formed fibrillar material is present. Male, 27 years. EM (× 6730)

**Fig. 14.85.** Peripheral BM injury with subepithelial loosening and formation of a new, thin densa layer (→) in membranoproliferative GN. Male, 62 years. EM (× 21,800)

**Fig. 14.86.** Extensive subendothelial deposits (*D*) in membranoproliferative GN. Isolated small deposits are also present intramembranously (→). Endothelial cells are highly activated showing an obvious increase of cell organelles, especially of the rough endoplasmatic reticulum. Complete foot process fusion is present. Female, 40 years. EM (× 5460)

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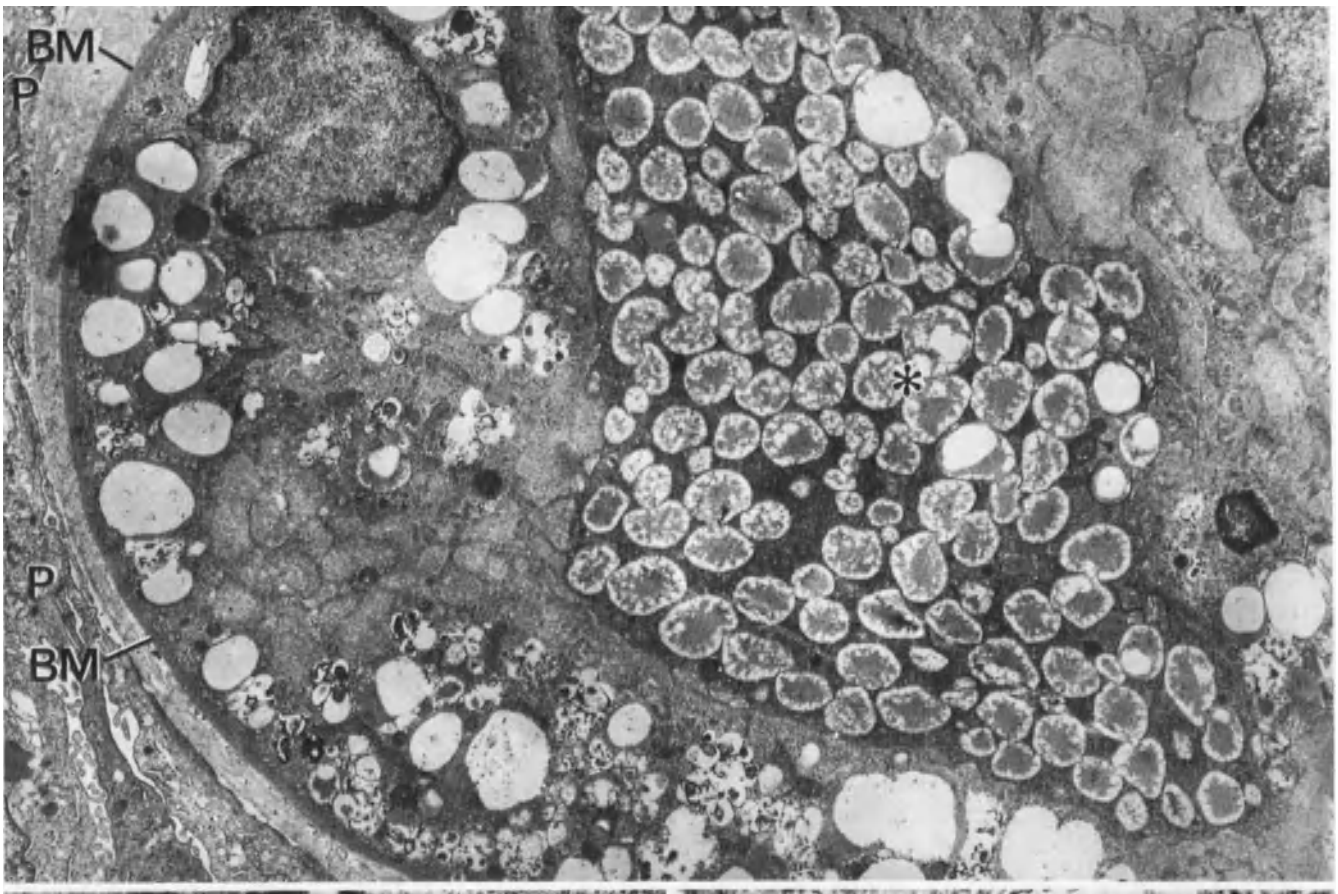
**Fig. 14.87.** Membranoproliferative GN in the proliferative-sclerosing stage. Extensive intramembranous deposits (→). There are swelling and activation of the endothelial (*E*) and mesangial (*M*) cells. Male, 9 years. EM (× 9760)

**Fig. 14.88.** Membranoproliferative GN with an acute attack. Extensive irregular subepithelial deposits (→) somewhat reminiscent of epimembranous GN, and subendothelial deposits (→). Female, 17 years. EM (× 11,200)

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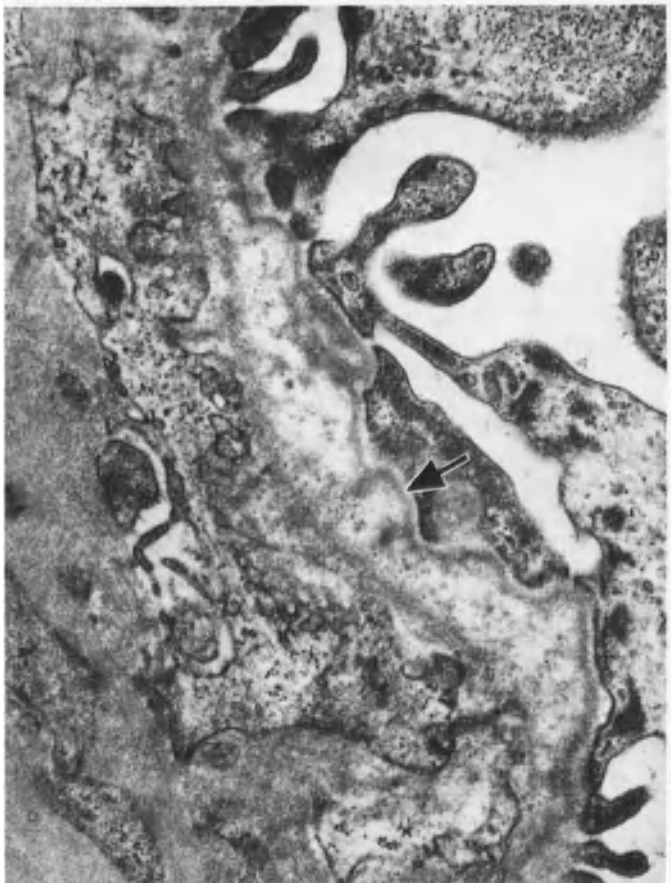

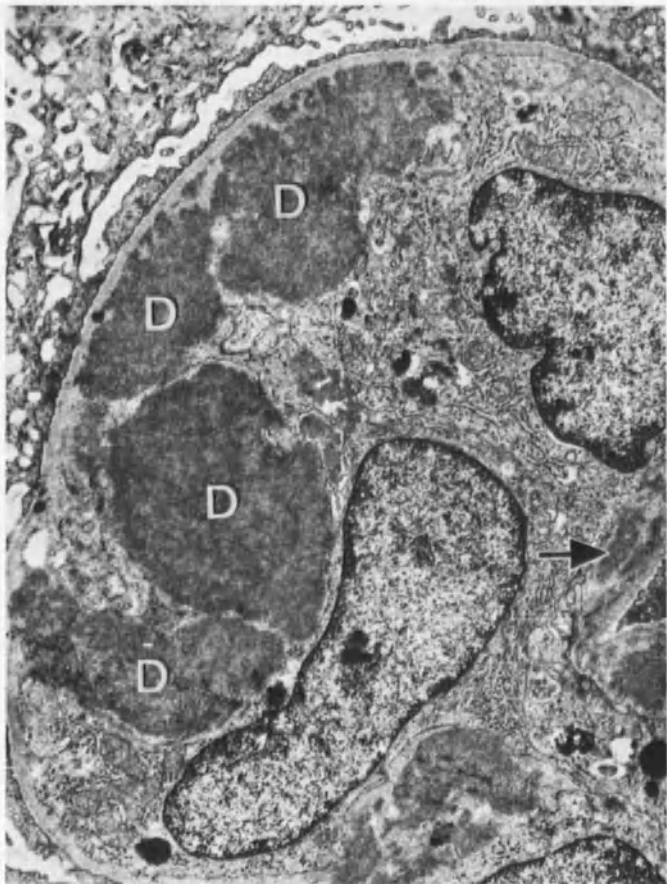


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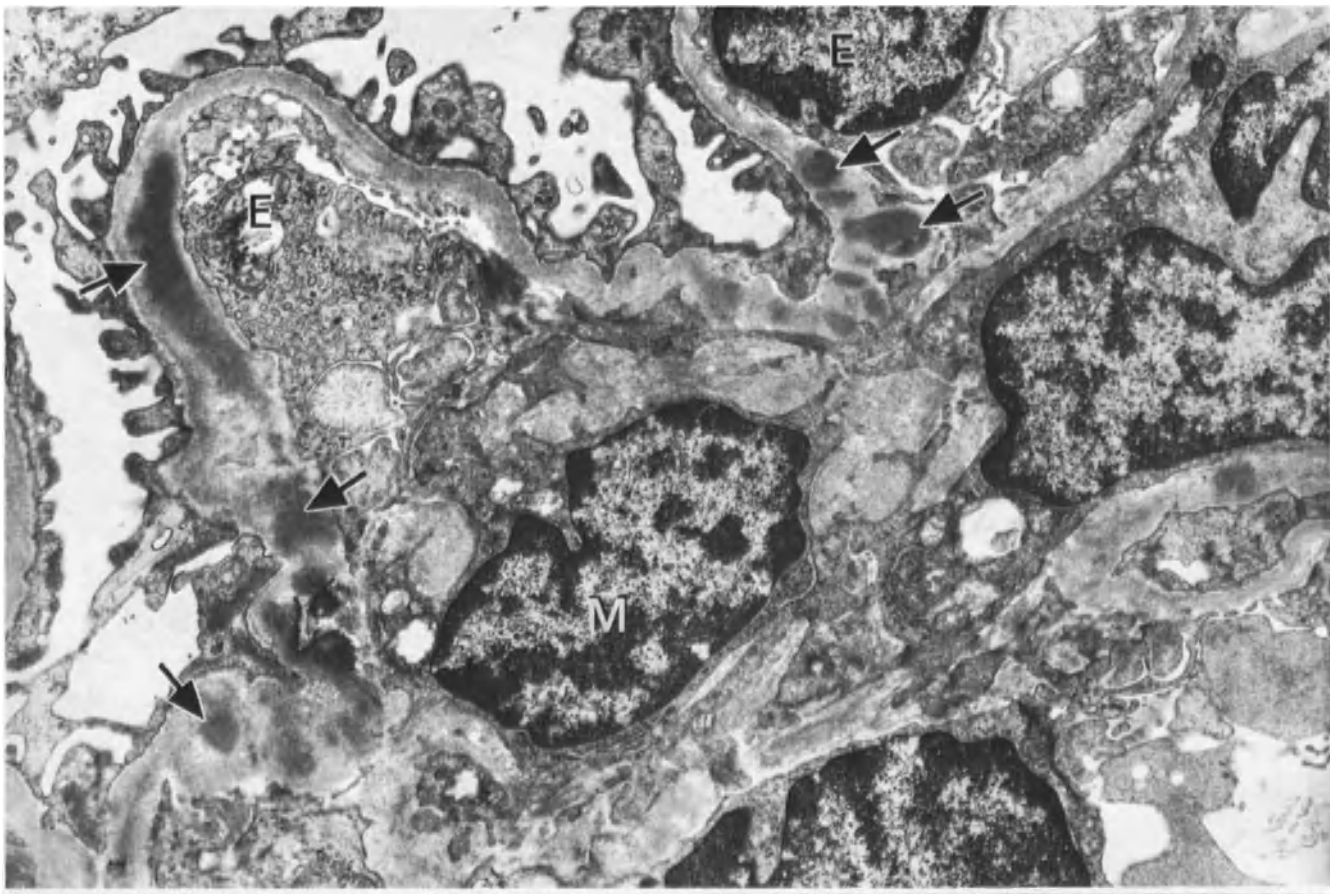


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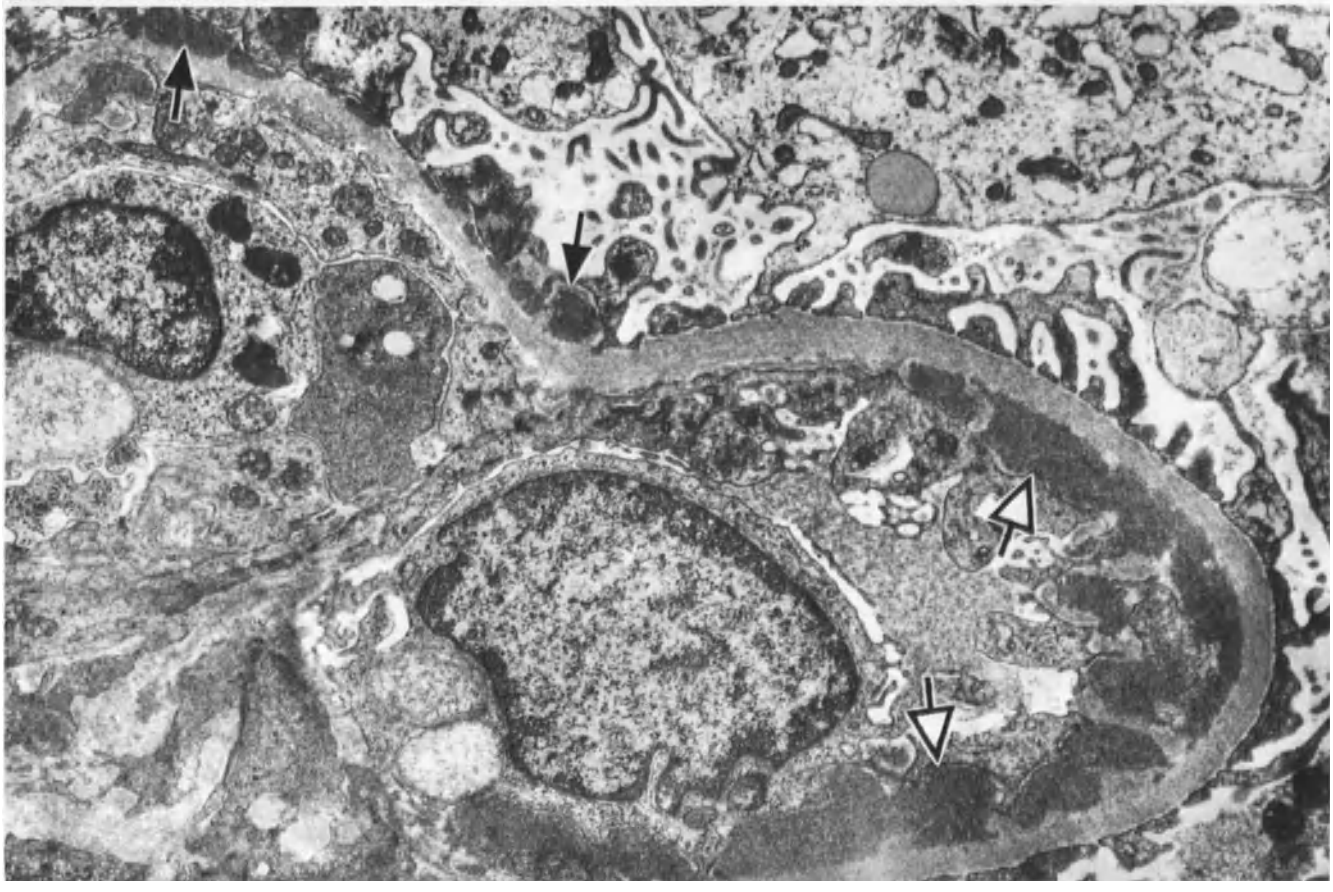

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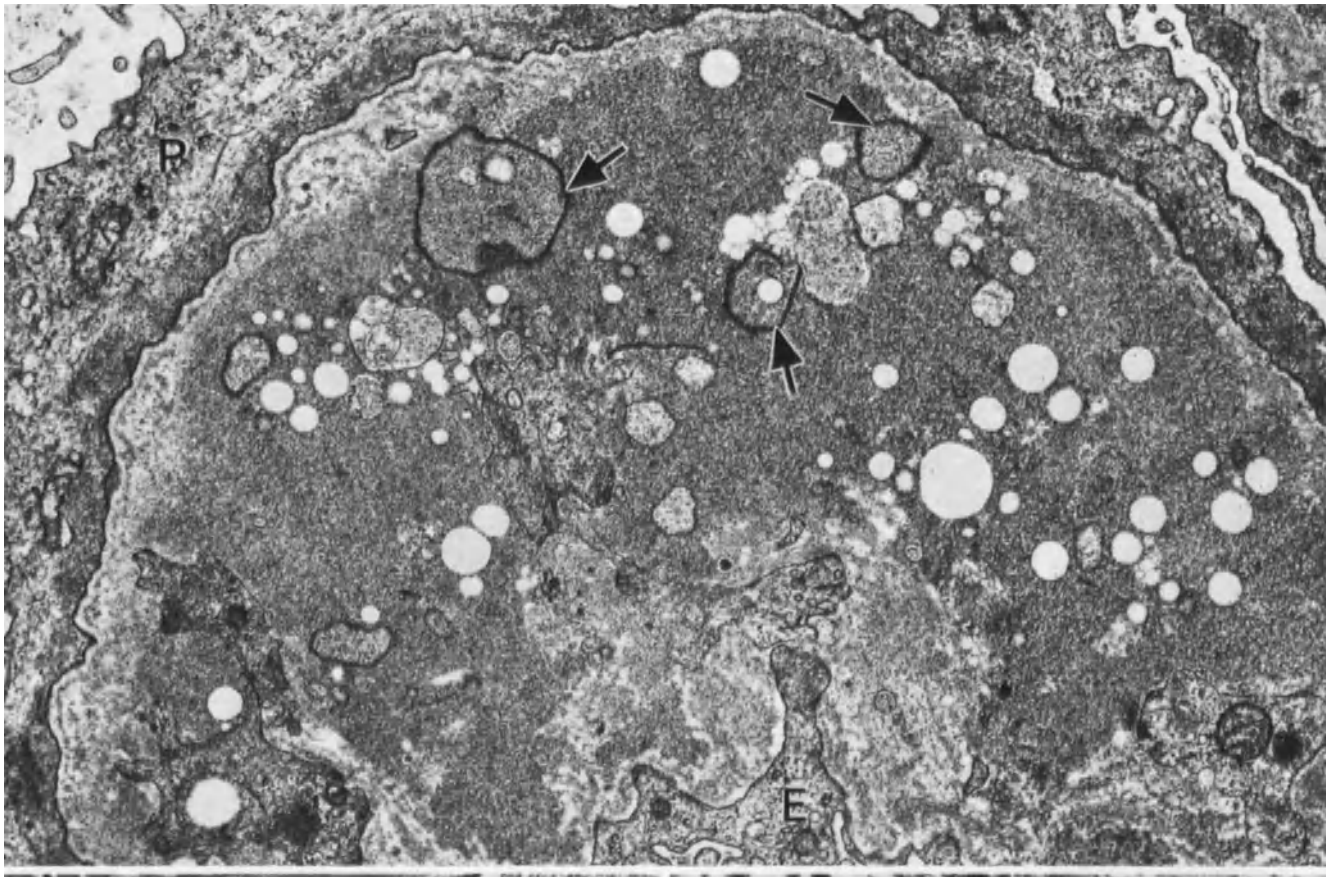


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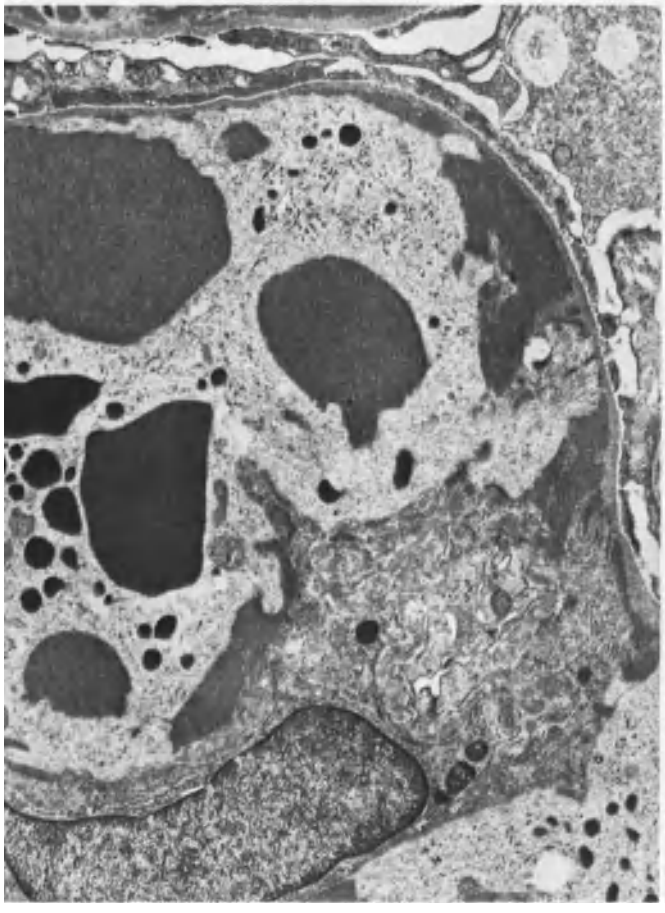

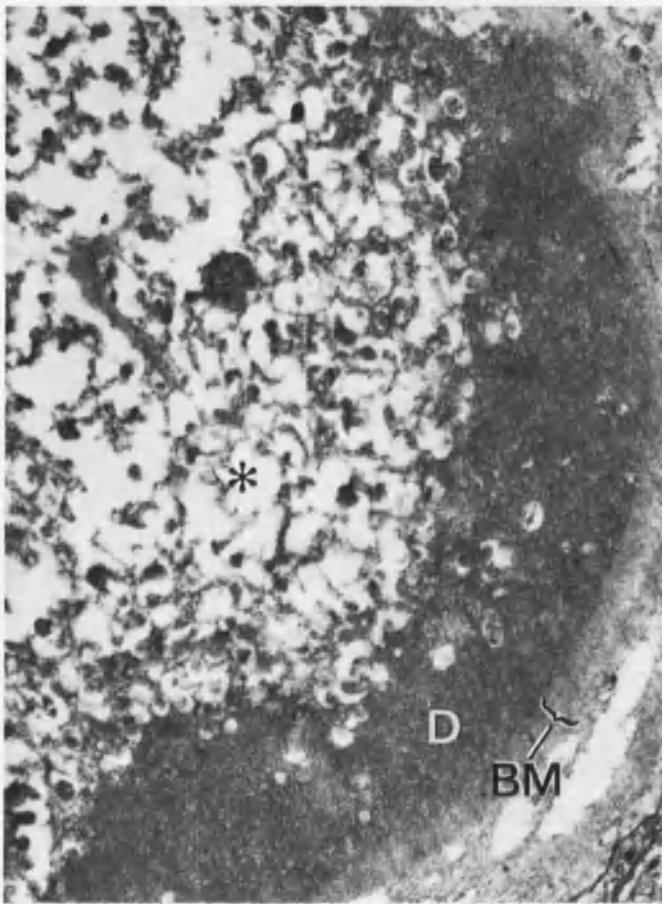


14.90
14.91

## Differential Diagnosis

In advanced stages, the diagnosis of membranoproliferative GN is generally simple due to the presence of the characteristic combination of subendothelial deposits with mesangial interposition and new subendothelial BM formation (tram-track picture) as well as mesangial proliferation and/or sclerosis.

During the early stage of the disease, differential diagnosis with respect to endotheliomesangial GN can be difficult with LM (Fig. 14.96) since in some cases BM doubling may be restricted to a few loops and the deposits may be small. Even in this stage, however, the differentiation is possible with the demonstration of subendothelial deposits in almost all glomeruli with Masson's trichrome/AFOG stain, with IF and EM. In isolated cases, IF study alone may not be sufficient (Fig. 14.97) and the differentiation may prove exceptionally difficult with EM if only very small, isolated partly degraded deposits are present (Figs. 14.98, 14.99).

In relation to mesangial interposition, it should be noted that this change is not pathognomonic for membranoproliferative GN, since it is also encountered in other renal diseases, especially in segmental-focal accentuated GN and in non-GN lesions [835, 1802] such as intravasal coagulation [100] and silicon-nephropathy [1412].

Differentiation of membranoproliferative GN from proliferative FGN is usually not difficult, since the character in the latter is far more pronouncedly segmental and focal, and since subendothelial deposits and mesangial interposition are limited to a few glomeruli and capillary loops.

Delimitation from epimembranous GN is not a problem, since in epimembranous GN mesangial proliferation is almost completely absent and since deposits can unequivocally be demonstrated to lie subepithelially with Masson's trichrome/AFOG stain. Although occasional subendothelial deposits are also found in the late stage of epimembranous GN, they are never as extensive as in membranoproliferative GN, and they seldom lead to formation of mesangial interposition.

A mixed form with the characteristics of membranoproliferative and epimembranous GN together is rare (see p. 279).

From the morphologic standpoint, we feel that idiopathic membranoproliferative GN cannot be differentiated from that in SLE unless hematoxylin bodies are present. Although especially large and extensive subendothelial deposits associated with usually scanty proliferation in the mesangium are observed in membranoproliferative GN in SLE, this combination does not suffice for unquestionable diagnosis.

◁ **Fig. 14.89.** Membranoproliferative GN. Prominent subendothelial deposit with signs of dissolution at the edges as well as numerous lipid vacuoles. Isolated thread-like structures (→). Endothelium (*E*), podocyte (*P*) with completely fused foot processes and increased osmiophilic substance. Female, 32 years. EM (×26,200)

**Fig. 14.90.** Removal of subendothelial deposits by monocytoid cells, which have partially phagocytized them. Female, 56 years. EM (×8600)

**Fig. 14.91.** Terminal stage of dissolution of a subendothelial deposit in membranoproliferative GN contracted kidney. Deposit (*D*), masses of lipid vacuoles and degradation products (*), basement membrane (*BM*). Male, 23 years. EM (×22,300)

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**Fig. 14.92.** Clearly evident enlargement of the mesangium with new formation of new coarse irregular matrix bars surrounding activated mesangial cells in membranoproliferative GN. Only a very few isolated subendothelial osmiophilic deposits are recognizable (→). Lumens of glomerular capillary loops (*CL*) are almost completely occluded by activated endothelial cells (*E*). Male, 37 years. EM (×5480)

**Fig. 14.93.** Lobular variant of membranoproliferative GN. There are severe mesangial enlargement with cell increase and especially prominent coarse, irregular matrix increase. Peripheral glomerular capillary loop lumens are almost completely displaced. Capsule epithelium (*CE*). Male, 44 years. EM (×1550)

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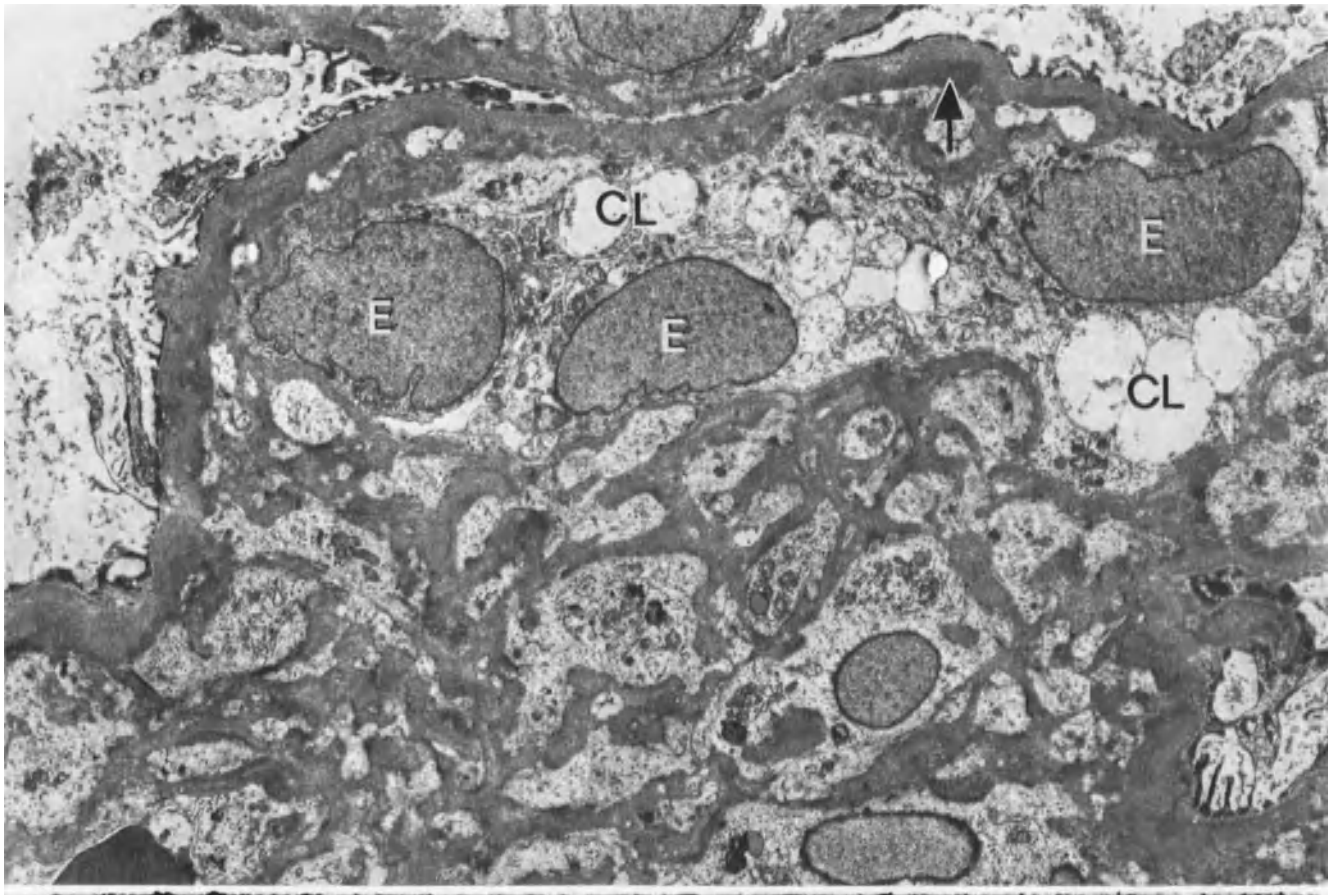
**Fig. 14.94.** Tubular foam cells in membranoproliferative GN. Note connective tissue increase and infiltrates in the interstitium. Male, 60 years. EM (×3320)

**Fig. 14.95.** Arteriole in membranoproliferative GN. BM (→←) is severely thickened and contains numerous clumps of elastin. A few, flat osmiophilic deposits (*D*) are present between the generally atrophic myocytes (*MC*) of the media and the BM. Numerous transformed myocytes are seen subendothelially (*S*). Pronounced inflammatory infiltrates and interstitial deposits ($D_1$) are present in the surroundings. Male, 60 years. EM (×2560)

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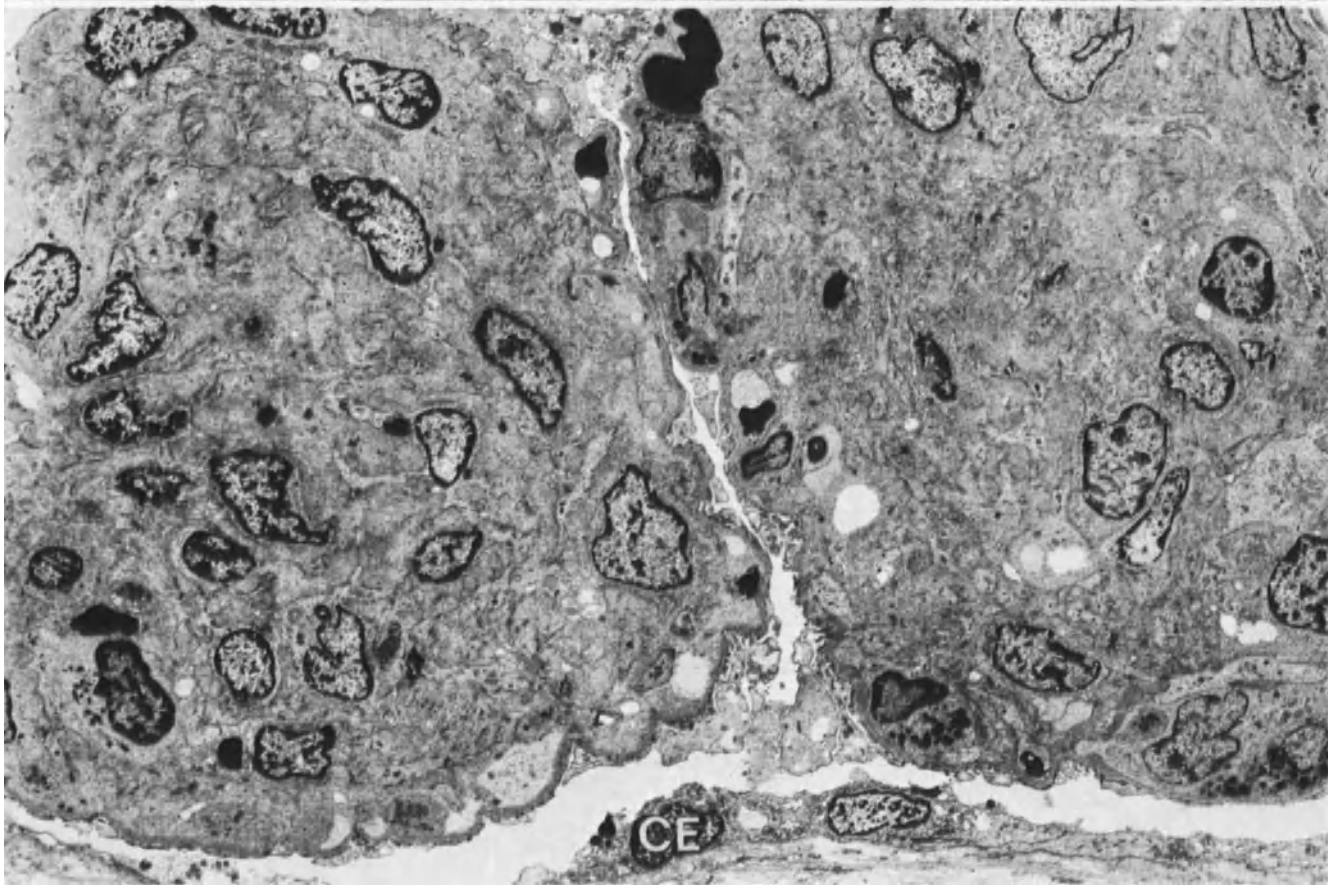


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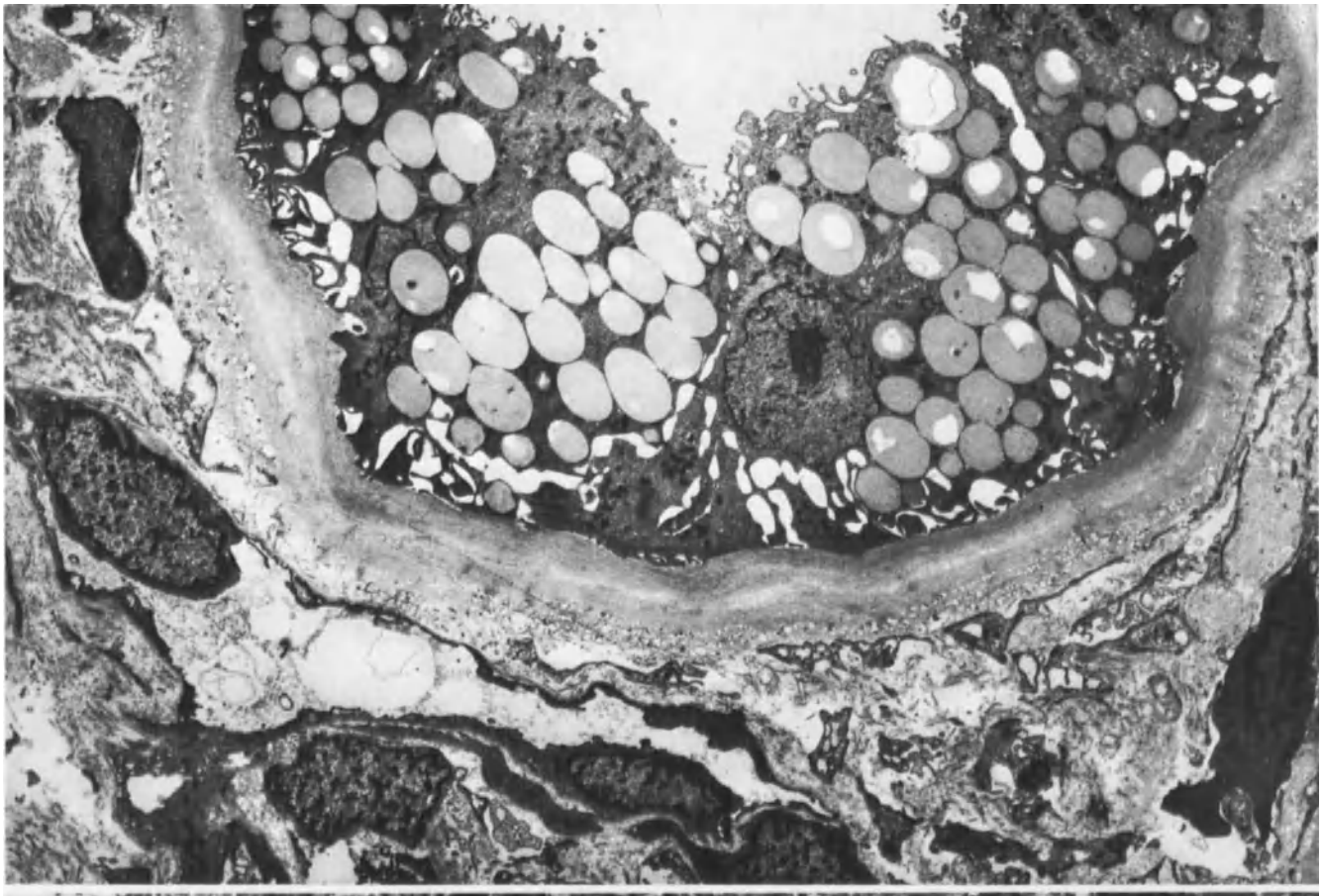

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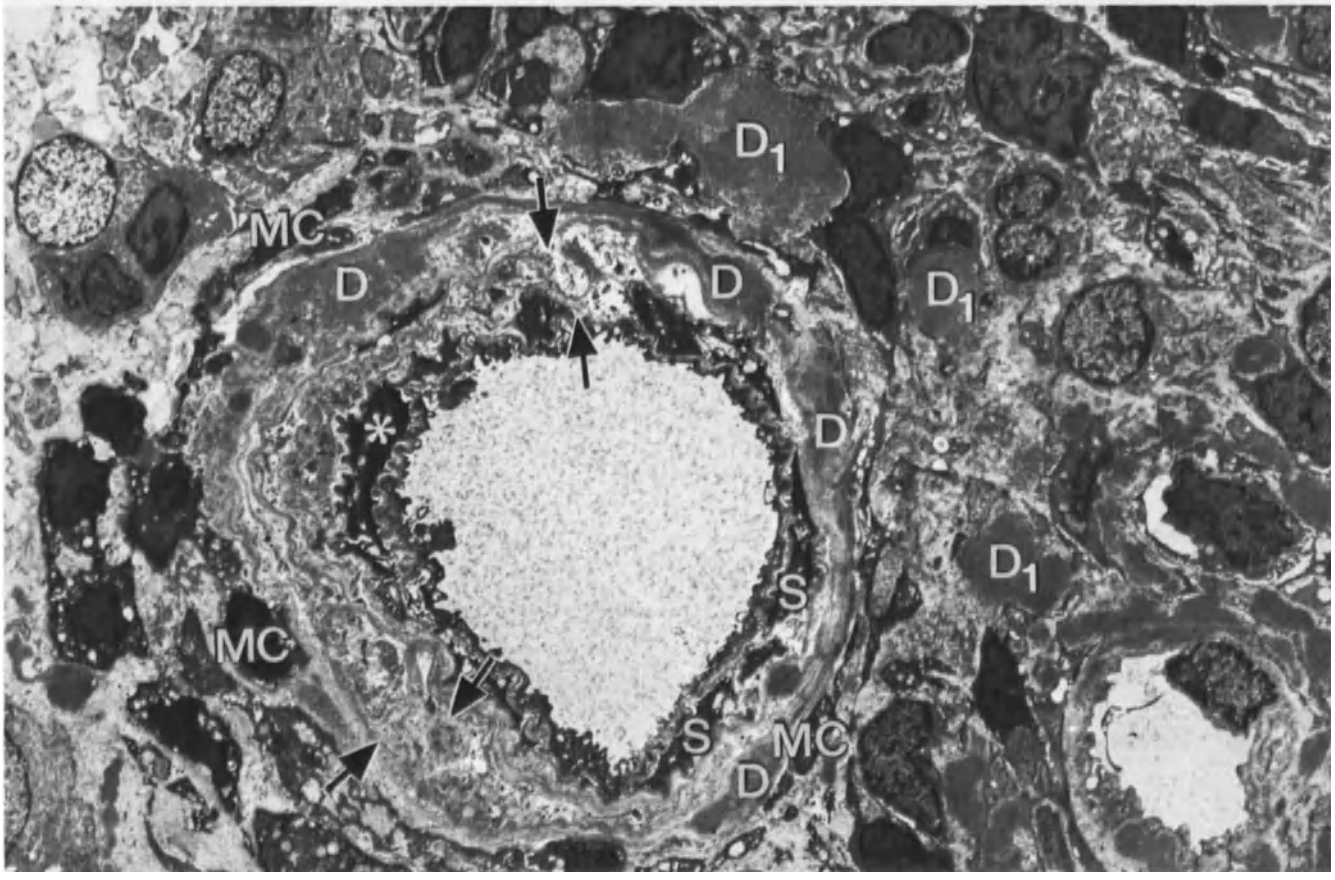


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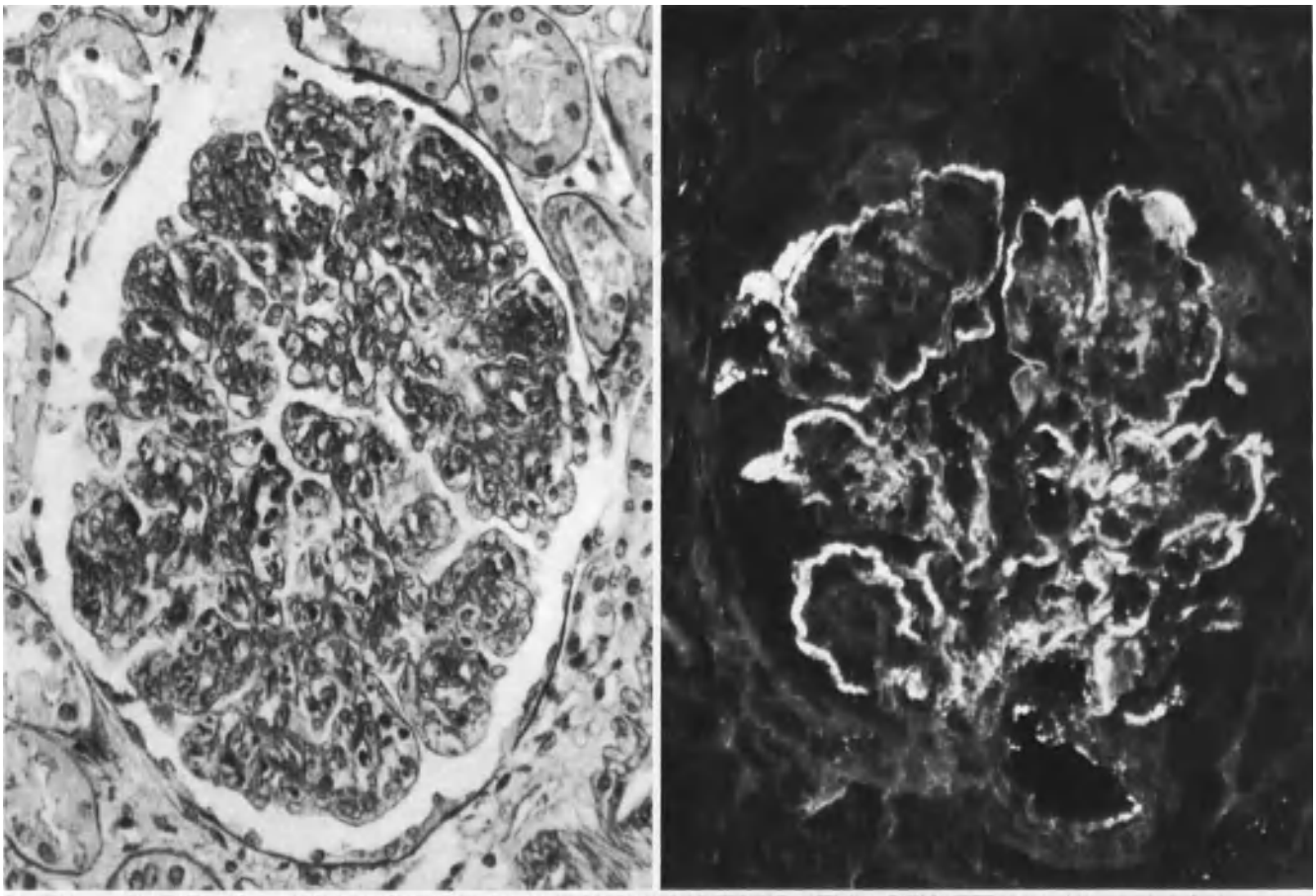

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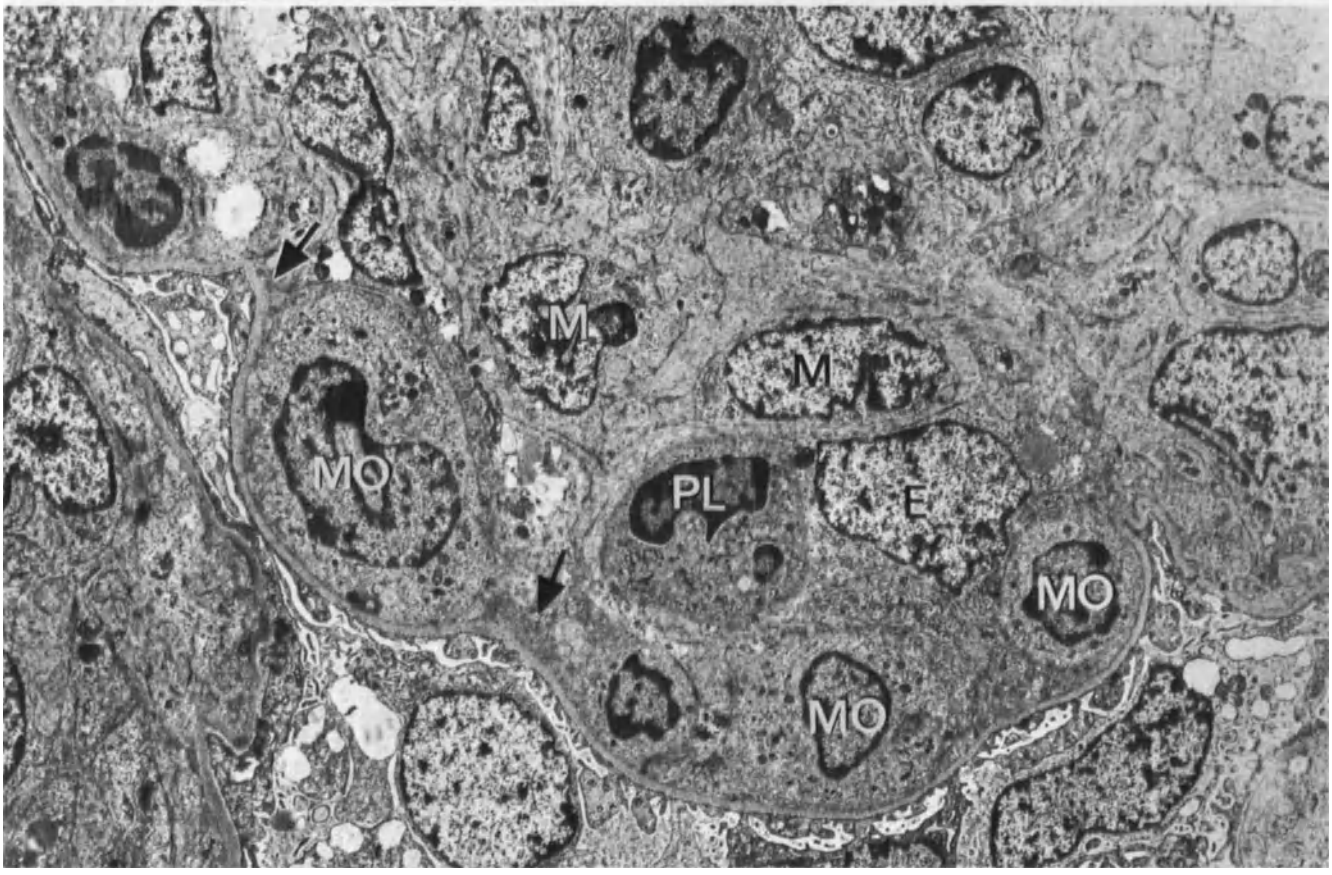


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## Prognosis

The average yearly mortality rate is 6.4%, and the 50% survival rate is reached in the eleventh year of the disease [635]. The 5-year survival rate is 80%, the 10-year 50% [245, 246] or 60–70% [731]. In another series encompassing very advanced cases, the 5-year survival rate was only 20% and no patient with elevated serum creatinine survived more than 3 years [839]. In our own material (Table 14.14) the 10-year survival rate from biopsy was 30%, and from apparent disease onset 40%; these figures more or less correspond to those of others [245, 246, 634, 635]. Of our patients, 40% died from uremia (Table 14.14), 6.6% from nonrenal diseases. Membranoproliferative GN, in addition to extracapillary GN, is reported to be the most frequent cause of renal insufficiency in children [1721].

Prognostically unfavorable clinical findings are nephrotic syndrome, macrohematuria and initial hyperazotemia [245, 246, 635]. Spontaneous remission, which occurs in some cases of membranoproliferative GN [1802] generally promises a favorable disease course.

Extracapillary crescents are of special prognostic significance. Thus, all patients with membranoproliferative GN evidencing more than 30% of extracapillary crescents died within 4 years [635]. We have not been able to confirm this exceptionally unfavorable finding in our material (possibly due to the small case number of 10 patients).

On the basis of our findings, we suspect that the stages of the disease are of great prognostic importance. Thus, the 5-year survival rate of purely proliferative cases is 75%, of proliferative-sclerosing 45%, and in the pure sclerosing cases, none lived longer than 3 years. These values are not statistically significant due to the small number of cases (see Table 14.12, p. 235).

The lobular variety of membranoproliferative GN has no unique prognostic features (see also [635]).

Table 14.14. Prognosis and outcome of membrano-proliferative glomerulonephritis

| Prognosis | Survival rate (%) | |
|---|---|---|
| | 5 years | 10 years |
| From onset of disease | 70 | 40 |
| SE[a] | 9.2 | 9.5 |
| From biopsy | 40 | 30 |
| SE[a] | 11 | 12 |

[a] SE = standard error in %.

*Outcome* (after minimal follow-up of 1 year)

| | | | |
|---|---|---|---|
| Number of patients | 30 | Death in uremia | 40% |
| Total mortality | 46.6% | Complete remission | 3.3% |

Clinically complete remission was reported in 5.7% of a series of children who were followed for 1–18 years [635]; for the lobular variety, the children's remission rate was 11.1% [620]. We have observed complete remission only once in 30 patients (Table 14.14).

However, no complete healing from the morphologic point of view has been reported. Even though "tram-track pictures" may disappear [839, 1033], more or less extensive mesangial proliferation and/or sclerosis nevertheless remains. Relapse in transplants—even after a long post-transplant period—were repeatedly described (7 out of 16: [804, 1063, 1761]; [1461, 1484, 1778]; contra: 0 out of 7 [481]).

## Pathogenesis

Membranoproliferative GN is to be considered as immunocomplex disease [90, 1033, 1092] in which relatively large and poorly soluble immunocomplexes [544] are repeatedly or continuously deposited for a long time. Poorly soluble immunocomplexes are formed in the presence of a moderate excess of AB against a relatively small antigen or with large antigens or antibodies of the IgM class [544]. On the other hand, clinical observations of acute GN possibly due to streptococcal infection suggest a close relationship to endotheliomesangial GN [1721] so that some investigators pose the question as to whether the disease is, in fact, a unique entity [1033, 1730].

The disease is also related to epimembranous GN as is shown in animal experimentation in which, for example 11 out of 15 rabbits given weekly injections of egg albumin and Freund's adjuvant developed membranoproliferative and 4 out of 15 epimembranous GN [889]. These experiments indicate, in our opinion, that membranoproliferative GN is the expression of a relatively rare, specifically individual immunologic reactivity to different antigens.

◁ **Fig. 14.96.** Proliferative stage of membranoproliferative GN, clinically known for 1 month. There is a pronounced hypercellularity, mesangial enlargement and thickening of glomerular loop wall. Female, 13 years. PAS (×400)

**Fig. 14.97.** Same case as in Figure 14.96. Pseudolinear (coarse granular) C3 deposits along the loop BM. Female, 13 years. IF (×400)

**Fig. 14.98.** Same case as in Figure 14.96. Glomerular capillary loop lumens appear to be completely displaced by both monocytes (*MO*) and polymorphonuclear leukocytes (*PL*). As opposed to the IF findings (Fig. 14.97) only a very few isolated small deposits (→) are recognizable subendothelially. Activated endothelial cell (*E*), mesangial cell (*M*). Podocytes are very swollen. Female, 13 years. (×3850)

The importance of properdin in activating the complement system has been recognized for quite some time [231, 1723]. The significance of the C3 nephritic factor as well as that of others which have not been clearly defined in the pathogenesis of membranoproliferative GN cannot, at this time, be reliably estimated (see p. 162 and [1092, 1550, 1650, 1721]; (for inherited C2 deficiency see: [1813]).

**Etiology**

The etiology of the disease is unknown and the significance of the various factors implicated as causative are controversial. This disagreement also holds with respect to the role of streptococci which is advocated by some investigators [544] and completely rejected by others [408, 1092].

In some of the cases, an elevation of the antistreptolysin titer has been observed (28%: [245]; 10%: Z; 11%: [631]; see also p. 231). It is also known that an acute attack of membranoproliferative GN can be engendered by an acute intercurrent respiratory tract infection [5].

The disease, however, occurs to a far greater extent in association with nonstreptococcal infections (32%: [631]), a finding which may be fortuitous.

It is interesting to note that 51 out of 64 cases of GN in malaria evidenced the typical membranoproliferative form ([1730]; see also [147, 679]). In malaria, however, an almost specific GN form, i.e., lacking mesangial proliferation, has been reported [1729] and also been confirmed by us. But we did not observe the numerous lacunae with osmiophilic material in the lamina densa which were described as characteristic [1729] (Figs. 14.100, 14.101).

Membranoproliferative GN is also encountered in heroin or other drug addictions in association with nephrotic syndrome and possibly hepatitis [1614a, 1631]. In these cases, it is not known whether the drugs themselves, or contaminants with bacteria, virus, or the solvent alone function as the antigen [423]. 65–75% demonstrated a considerable increase in serum IgM [335]. Other GN forms, e.g., glomerular minimal change, sclerosing FGN, have been observed among drug addicts [423, 597a].

Membranoproliferative GN has been noted in acute rheumatic fever [544], polyarthritis [1130b], ventriculoatrial shunt [893, 1700], Lyll's disease [886], Waldenström's disease (macroglobulinemia) associated with angitis and myositis due to the presence of cryoglobulins [962] as well as in two of our patients suffering from essential cryoglobulinemia.

Furthermore, de novo membranoproliferative GN has been noted in patients with liver transplants and ALG treatment, which is thought to be the cause of the lesion [334]. Finally, in three cases of sickle cell anemia, it was possible to demonstrate an analogous form with proximal tubular epithelial antigen [1244, 1572, 1233b], which was possibly released into the circulation by ischemia. Membranoproliferative GN occurs rarely in malignancies (see Table 14.8; [521a]).

Furthermore, viruses as causative agents should be considered. In one observation [1531] 500–1000 Å-sized Epstein-Barr virus and hepatitis B-antigen (200–300 Å) were demonstrated by IF as well as by EM in a rather special form of the disease with newly formed subepithelial BM, a change which we have often observed in association with virus-like particles (see p. 99).

In 273 cases of chronic aggressive hepatitis from the literature, kidney involvement was present in 65 cases [197], GN similar to that in SLE in 10, membranoproliferative GN in 9 (see also [192]) and epimembranous GN in 10 cases (see also [9, 299, 423, 609, 862, 1531]). In 9 cases of hepatitis, 5 demonstrated epimembranous GN, 2 membranoproliferative, and 2 endotheliomesangial GN [609].

Anti-BM-AB were present in 12 out of 12 patients with chronic, active (aggressive) hepatitis [952]. In children with nephrotic syndrome caused by GN, 52% had hepatitis B-surface antigen within glomerular immunocomplexes [211]. GN associated with hepatitis B is reportedly characterized by an exceptionally protracted course [222, 615, 1531]. We have a total of 5 autopsy cases of hepatitis-associated GN of which 4 were membranoproliferative and 1 epimembranous GN.

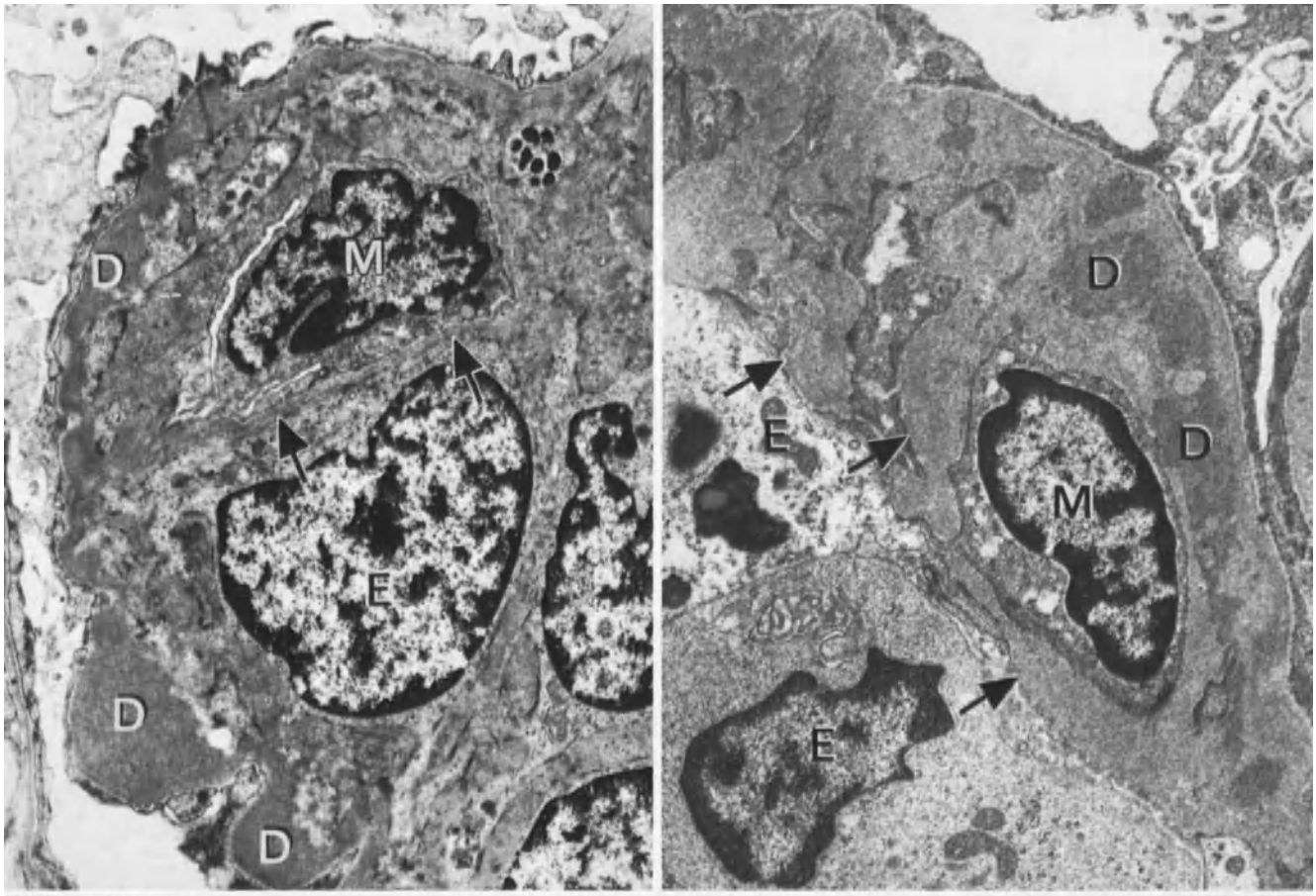
The membranoproliferative-like GN occurring with liver cirrhosis not associated with hepatitis is supposed to be due to an autoallergic response either to the elevated serum IgA or to formation of immunoglobulins against antigens from the gastrointestinal tract [241].

Membranoproliferative GN in association with systemic diseases such as SLE—which was present in 5 of our patients—is treated in greater detail on p. 326.

**Fig. 14.99.** Membranoproliferative GN with coarse subendothelial deposits (*D*) which exhibit translucent edges. Between the activated endothelial cell and the interposed mesangial cell (*M*) a new thin densa lamella (→) has formed. Female, 14 years. EM (×8160) ▷

**Fig. 14.100.** Membranoproliferative GN associated with malaria. Between the swollen and activated endothelial cells (*E*) which contain some telolysosomes and the interposed mesangial cell (*M*) a new densa layer (→) has developed. Mesangial cell borders on subendothelial osmiophilic deposits (*D*). Male, 43 years. EM (×10,800)

**Fig. 14.101.** Same case as in Figure 14.100. Generalized hypercellularity of glomerular capillary loops and increase of mesangial matrix are present. Glomerular capillary loop lumen has been largely displaced by proliferated endothelial or mesangial cells (→). Podocytes are compressed and evidence cystoid-widened organelles. Older exudate in capsular space (*), split capsular BM (*CBM*). Male, 43 years. EM (×1500)

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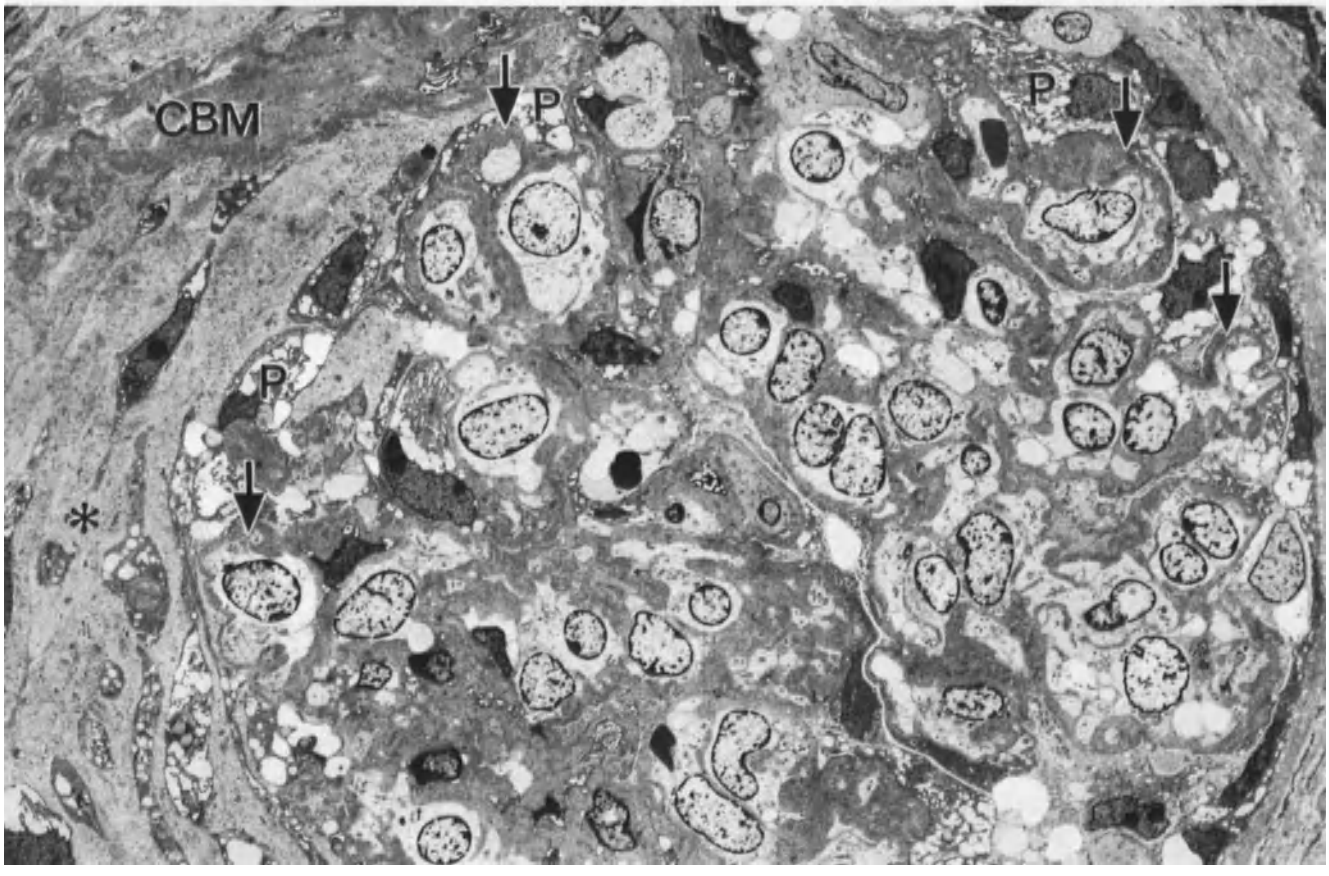


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In conclusion, membranoproliferative GN has no specific etiologic cause, but represents a special immunologic reaction to a wide variety of antigens, as it is the case in other forms of GN.

## Intramembranous Glomerulonephritis

### Definition

Intramembranous GN [524, 631] is characterized by a severe thickening of the glomerular BM caused by the deposition of linear band-like, highly osmiophilic (= dense material) and fibrinoid material in the lamina densa as well as in the BM of tubules, Bowman's capsules and arterioles.

### Nosology

Although intramembranous GN with LM, EM, and IF shares many similarities with membranoproliferative GN, we consider intramembranous GN as a unique entity (contra: [35, 631]) because of the morphology of the intramembranous material and because of the lack of data indicating common etiology and pathogenesis for intramembranous and membranoproliferative GN.

***Synonyms.*** Laminal GN [544], dense deposit disease [987], membranoproliferative GN with intramembranous deposits [631] and proliferating GN with dense intramembranous deposits [126]. The lesion has also been referred to as one of electron-dense alteration of kidney ([524]; see also Table 13.2).

### Incidence

The disease has been reported to occur in 0.6% [165], 1.5% [90a], 1.7% [35], 2.5% [524] (see also Table 14.11) of GN biopsies and in 14.7% [231], 15% [1652] and 34% [631] of membranoproliferative GN.
The sex ratio male:female is 1.18:1 (i.e., 96:81) as summarized from published series [35, 165, 231, 524, 631, 987, 1652].
The disease usually becomes manifest before the age of 15 (see Fig. 14.102). The average age at disease onset is 12 years and less than 6% of cases become manifest beyond the age of 30 [35, 165, 231, 524, 631, 987, 1652].

### Clinical Findings
(Tables 14.3, 14.4, Fig. 14.102)

Intramembranous GN often begins insidiously and is signaled by edema and proteinuria in more than 75% of the patients accompanied by microhematuria in more than 50% (Fig. 14.102). At disease onset, a full nephrotic syndrome is often already present. More rarely, the disease may be announced by macrohematuria or with the symptomatology of acute GN [1652]. Initial hypertension is seldom observed (Fig. 14.102). In almost half of the patients, the disease is preceded by prior illness—usually an infection of the upper respiratory tract [631, 1652] and less frequently scarlet fever [524]. In one-fourth of

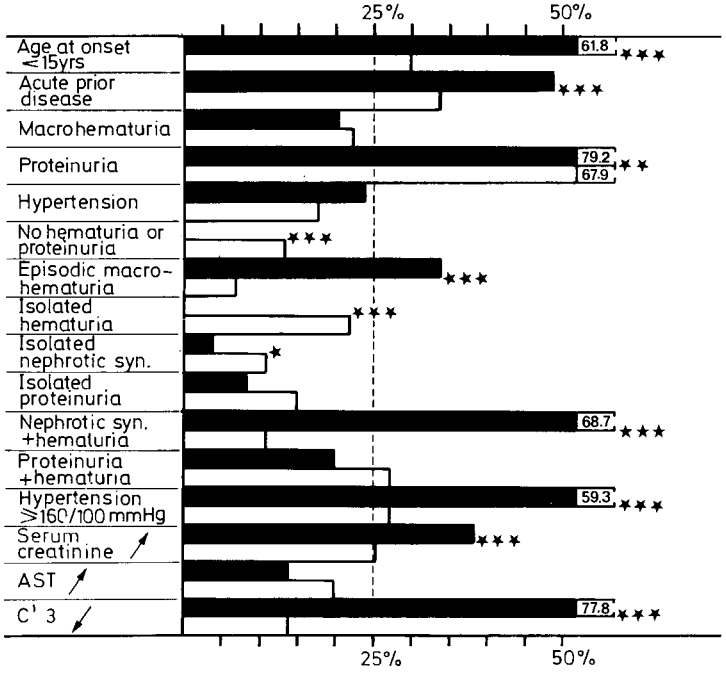


**Fig. 14.102.** Profile of symptoms and clinical findings in intramembranous GN
*White columns:* Relative frequency of symptom/finding in all GN
*Black columns:* Relative frequency in intramembranous GN (data from the literature, see Table 14.3). The upper five findings (age of onset to hypertension) refer to disease onset. The remaining were noted at some point during the disease and are compared to our findings in all GN observed at time of biopsy
Asterisks indicate characteristic findings for intramembranous GN:
*: characteristic
**: very characteristic
***: highly characteristic

the cases, urinary abnormalities are discovered fortuitously [524, 631].

After onset, the disease may either become stationary (7 out of 34: [35]) demonstrate recurrent attacks (11 out of 31: [35]), or, more frequently, become progressive until terminal renal insufficiency ensues (15 out of 34: [35]; see also [631]). During the course of the disease, more than 30% of the patients evidence episodes of macrohematuria (Fig. 14.102).

At the time of bioptic diagnosis, clinical examination reveals nephrotic syndrome accompanied by hematuria in about 70% of the patients. Isolated nephrotic syndrome or isolated hematuria or the absence of both are rare and atypical. The pathologic urine findings are associated with hypertension in about 60% of the patients [1652]. More than one-third of the patients evidence an increase in serum urea and creatine.

Renal insufficiency may be already present at disease onset, disappears during the further course of the disease and then reappears and rapidly leads to terminal renal insufficiency [35, 631, 1652].

Decrease in the serum level of C3 is an especially significant finding which, in contrast to its transitory reduction in endotheliomesangial GN [911, 909] and its frequently fluctuating behavior in membranoproliferative GN, may remain depressed for years. However, in contradistinction to an earlier assumption [631], not every patient exhibits a decrease in serum C3 (11 out of 19: [1652]). Decrease of other complement components (C1, C4) is less frequent [631, 1652]. C3 nephritic factor is often demonstrable (13 out of 19: [1652]).

### LM Findings

All the glomeruli are more or less similarly changed. They usually show severe thickening of the peripheral glomerular BM which appears to encircle the entire glomerular convolute; they also evidence mesangial cell proliferation and/or sclerosis of varying intensity (Fig. 14.103). The BM thickening is caused by band-like or short linear deposited material of variable thickness. After overstaining with PASM, the material is strongly argentophilic, otherwise it is completely negative. Furthermore it is luxol fast blue positive, but negative for Sudan black B, sometimes red in Masson's trichrome/AFOG stain. HE and PAS stains bestow a hyaline-like refractile property to the BM (Fig. 14.104). In addition to the thickening of the original BM, focal-segmental distributed mesangial interposition (22 out of 44: [631]; 4 out of 6: Z) as well as new BM formation subendothelially have been found in some of the cases. The other findings are by and large similar to those encountered in membranoproliferative GN, i.e., cell and mesangial matrix increase which vary in extent from case to case, but which are quite frequently so pronounced as to present a lobular picture (7 out of 44: [631]; 2 out of 6: Z). Crescents are occasionally encountered (13 out of 44: [631]; 2 out of 6: Z).

The tubular BM is also thickened – even if only focally – by the peculiar fibrinoid material (6 out of 6: Z; Fig. 14.105); this material is more rarely found in BM of Bowman's capsule (2 out of 6: Z) and more rarely still of small and large blood vessels (1 out of 6: Z; Fig. 14.111).

In our cases, which were all advanced, the interstitium evidenced pronounced lympho-histio-plasmocytic infiltration. On the other hand, constant interstitial changes are said to be absent in the early stages of the disease [245].

### IF Findings

A summary of the IF findings is presented in Table 14.15. All immunoglobulins as well as fibrin(-ogen) are very inconstantly present, and, if present, usually in granular focal-segmental distribution. Only C3 is regularly demonstrated in a partly linear, partly coarse granular fashion along the peripheral glomerular BM and in the mesangium, as well as in the BM of tubules and Bowman's capsule [631, 1136, 81a]. The results for early complement components (C1, C2, C4) and for properdin, however, are not consistent, but the number of cases investigated is still too small to draw definite conclusions.

The presence of C3 only might indicate C3 activation via the alternative pathway. However, the fixation of anti-C3 on the dense material is considered by others to be an artifact [128].

Deposits are reported to feature spontaneous fluorescence [654]. We could not confirm this either for spontaneous fluorescence or fluorescence after thioflavin T staining.

### EM Findings

The severe thickening of capillary loop BM (in our cases up to 16,000 Å) is caused by very extensive accumulation of compact, often linear or small-nodular dense material (Figs. 14.107, 14.108) which exhibits, under high magnification, a finely granular character (Fig. 14.106). Thus, we cannot confirm the homogeneous character reported by others [524].

In its massive occurrence, this dense material is absolutely characteristic for intramembranous GN. By its localisation in the lamina densa and strong osmiophilia (Fig. 14.109) it can be clearly distinguished from subendothelial deposits undergoing dissolution which are also occasionally observed in addition to the intramembranous material (1 out of 2: Z; 8 out of 14: [631]). Also observed are mesangial deposits (Fig. 14.107; 14 out of 14: [631]; 7 out of 19: [1652]; 1 out of 2: Z; rarely: [231], see also [524]), subendothelial deposits (2 out of

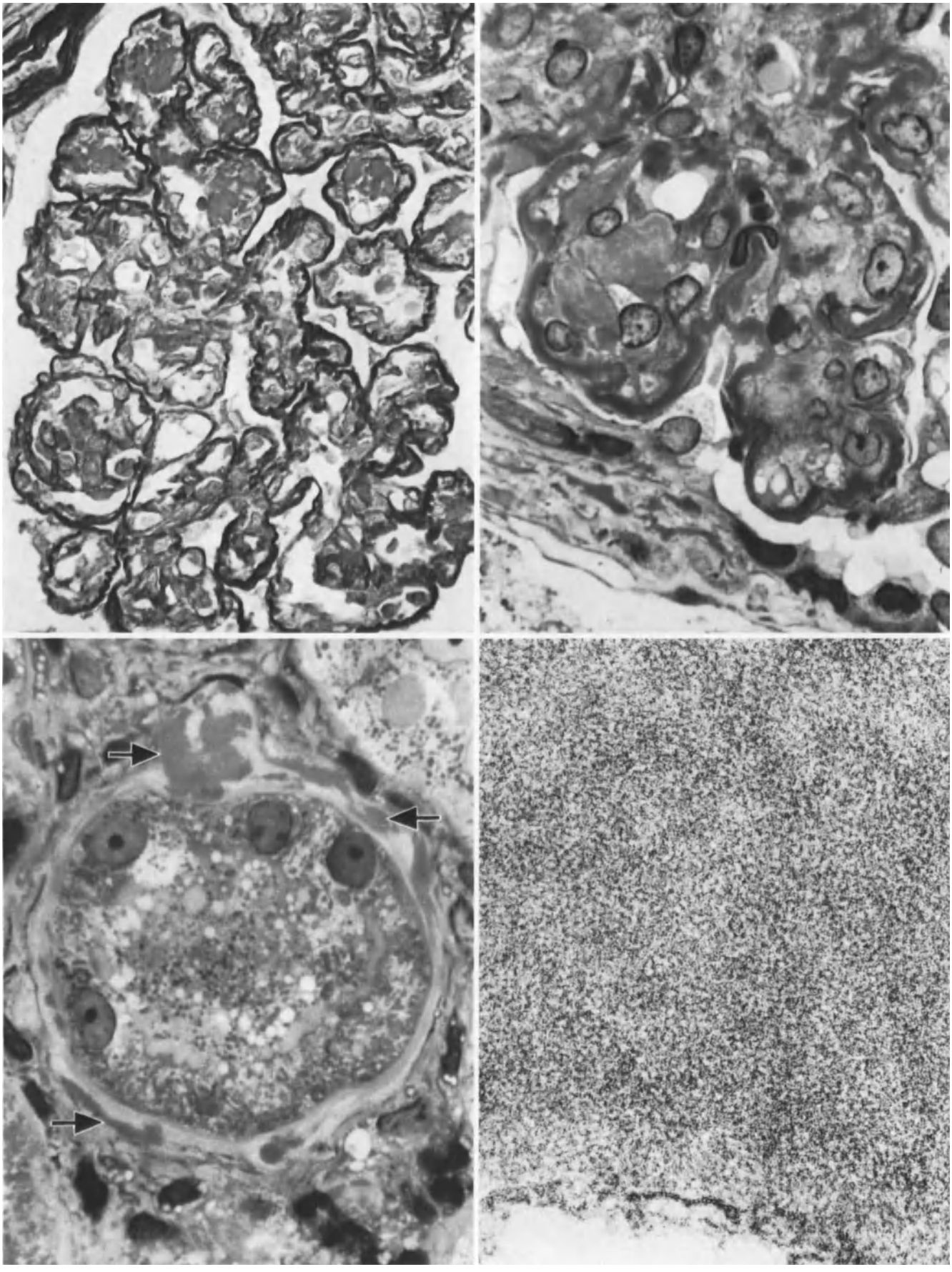

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Table 14.15. Glomerular IF findings in intramembranous glomerulonephritis

| Investigator | Cases positive/total | IgG | IgM | IgA | Fibrin (-ogen) | C3 | C1, C2, C4 | Properdin |
|---|---|---|---|---|---|---|---|---|
| Bariety et al. (1970) [90a] | 5/5 | 0/5 | 3/5 | 0/5 | 2/5 | 5/5 | | |
| Zollinger and Mihatsch (1971) | 1/2 | 0/2 | 0/2 | 0/1 | 0/2 | 1/2 | | |
| Burkholder et al. (1973) [231] | 7/7 | 6/7 | 4/5 | 5/6 | | 5/5 | 2/2 | 1/1 |
| Germuth and Rodriguez (1973) [544] | 2/2 | 1/2 | | | | 2/2 | | |
| Mac Donald (1973) [987] | 2/2 | 2/2 | 2/2 | 1/2 | 2/2 | 1/2 | | |
| Morel-Maroger et al. (1973) [1137a] | 4/4 | 0/4 | 3/4 | 0/4 | 0/4 | 4/4 | | |
| Peters et al. (1973) [1258] | 2/2 | 0/2 | 2/2 | 2/2 | | 2/2 | 1/2 | |
| Bohle et al. (1974) [165] | 4/4 | 2/4 | 2/4 | 1/4 | – | 4/4 | | |
| Jenis et al. (1974) [769] | 3/3 | 1/3 | 3/3 | 0/2 | 0/2 | 3/3 | 0/2 | 2/2 |
| Habib et al. (1975) [631] | 12/12 | 0/12 | 0/12 | 0/12 | 0/12 | 12/12 | 0/12 | 0/12 |
| Barbino et al. (1976) [81a] | 10/10 | 3/10 | 3/10 | 0/10 | 0/10 | 10/10 | | |
| Vargas et al. (1976) [1652] | 12/12 | 0/12 | 3/12 | 0/12 | 8/12 | 10/12 | 0/9 | |
| Davis and Cavallo (1976) [356] | 3/3 | 3/3 | 3/3 | 0/3 | 0/3 | 3/3 | 3/3 | – |
| Total ($n$) | 67/68 ~100% | 18/68 ~26% | 28/52 ~54% | 9/63 ~14% | 12/52 ~23% | 62/66 ~94% | 6/30 20% | 3/15 20% |

14: [631]; 1 out of 2: Z; very rarely: [231]) and in the early disease stages subepithelial deposits as well as humps (2 out of 19: [1652]; 6 out of 14: [631, 769]). Dense material is also present in the BM of Bowman's capsules (Fig. 14.108) and tubules (Figs. 14.108, 14.110; 2 out of 2: Z). Subendothelially, the arterioles contain extensive homogenous dense material which is partly short-linear and partly nodular (Fig. 14.111). It is distinguishable from the heavy granular deposits observed in arteriolosclerosis.

◁ **Fig. 14.103.** Intramembranous GN. Glomerular capillary loop BM is much thickened, prominent, and appears to encircle the entire loop convolute. Material within the BM is argyrophilic. Mesangium is frankly enlarged; dense material therein is nonargyrophilic. Female, 41 years. PASM (×700)

**Fig. 14.104.** Same case as in Figure 14.103. Slight glomerular hypercellularity as well as severely thickend, compact hyaline BM are evident. Semi-thin section, toluidine blue (×950)

**Fig. 14.105.** Same case as in Figure 14.103. Extensive deposition of dense material (→) in BM of a proximal tubule. There is pronounced accompanying interstitial inflammation. Semi-thin section, toluidine blue (×850)

**Fig. 14.106.** Same case as in Figure 14.103 illustrating the fine-granular structure of the dense material in intramembranous GN. EM (×128,000)

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**Fig. 14.107.** Same case as in Figure 14.103. Linear deposits of a dense, highly osmiophilic material in peripheral BM with isolated interruptions (→). Numerous unclearly delimited, less osmiophilic deposits of dense material (*D*), a few of which demonstrate degradation granules (⇾), are present in the extraordinarily coarse-clumpy thickened mesangium. Only one glomerular capillary loop lumen—which contains an erythrocyte (*)—appears to be still patent. Podocytic foot processes are completely fused. No silver impregnation! Female, 31 years. EM (×3730)

**Fig. 14.108.** Same case as in Figure 14.107. Intramembranous dense material appears in the glomerular capillary loops and in the capsular BM (⇾) and is more abundant in the neighboring tubular BM (→). Podocytes (*P*) exhibit vacuolization and the capsular epithelium (*CE*) is very swollen. EM (×1740)

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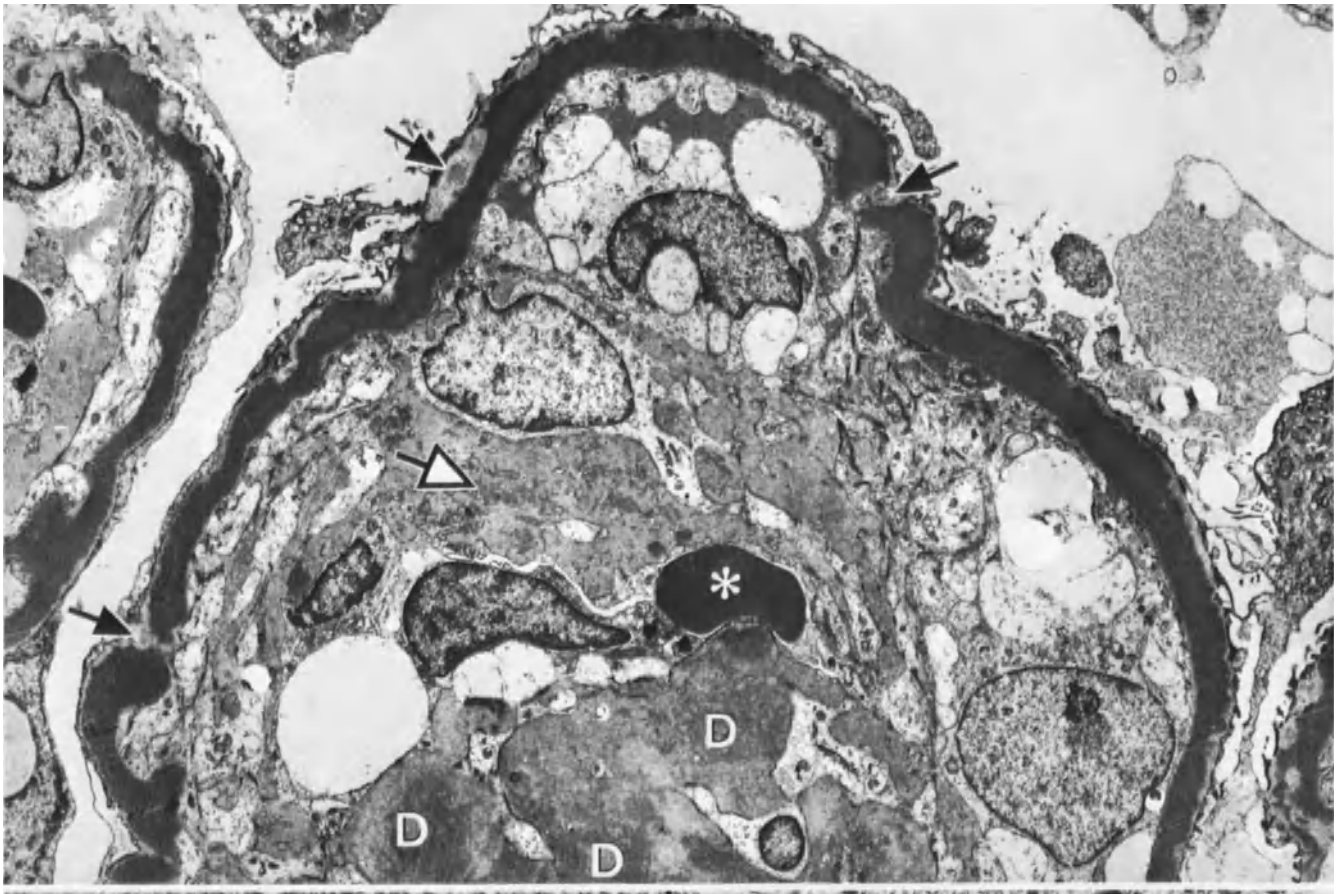
**Fig. 14.109.** Intramembranous GN. Dense material in glomerular BM exhibits signs of dissolution as shown by translucent areas surrounding centrally granular osmiophilic deposit residues as well as by the thread-like structures (→). Podocytic foot processes are completely effaced. Female, 41 years. EM (×13,500)

**Fig. 14.110.** Same case as in Figure 14.109. Severe vacuolar degeneration of dense material deposited in tubular BM. Tubular cells have been destroyed and replaced by monocytoid elements. EM (×3500)

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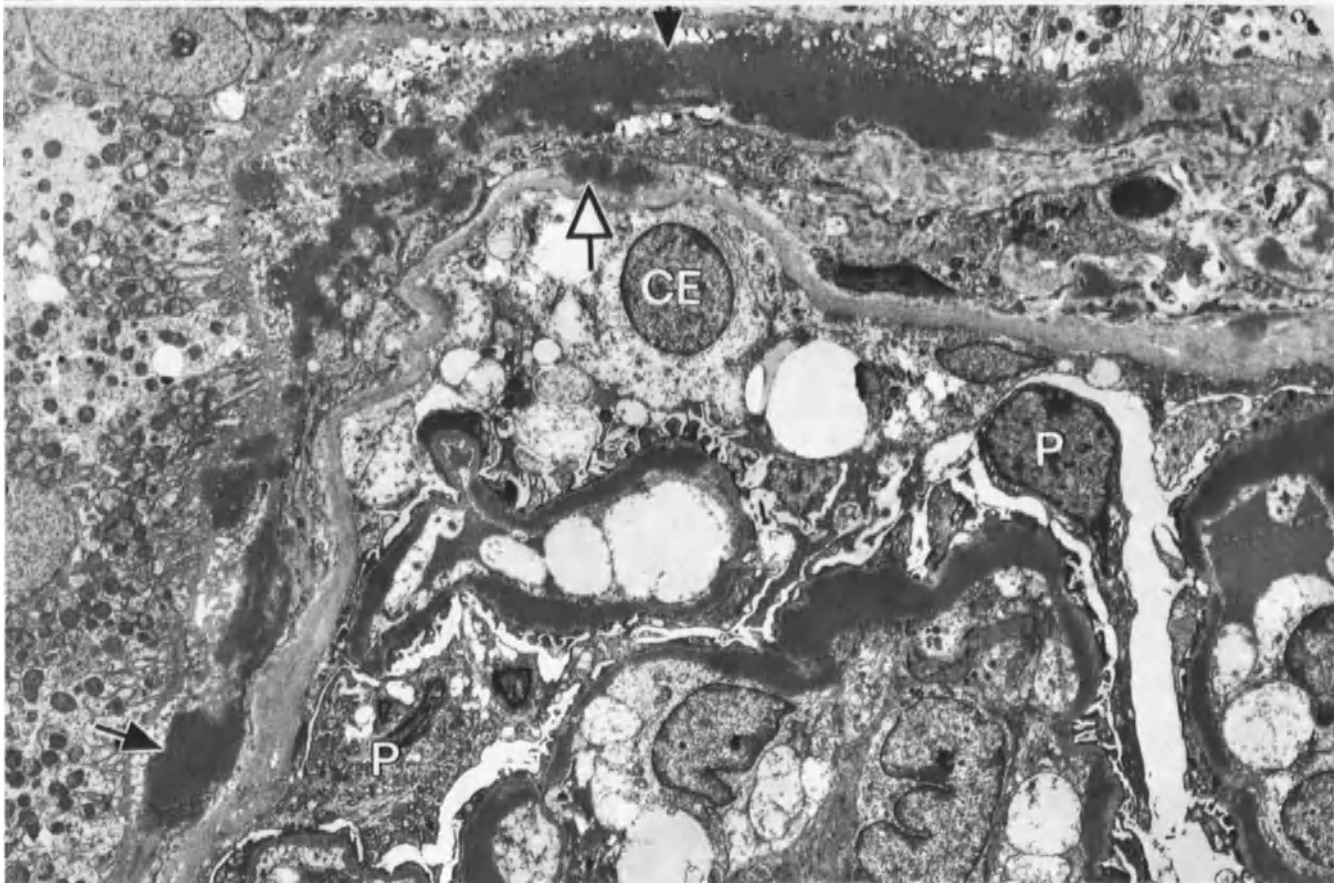


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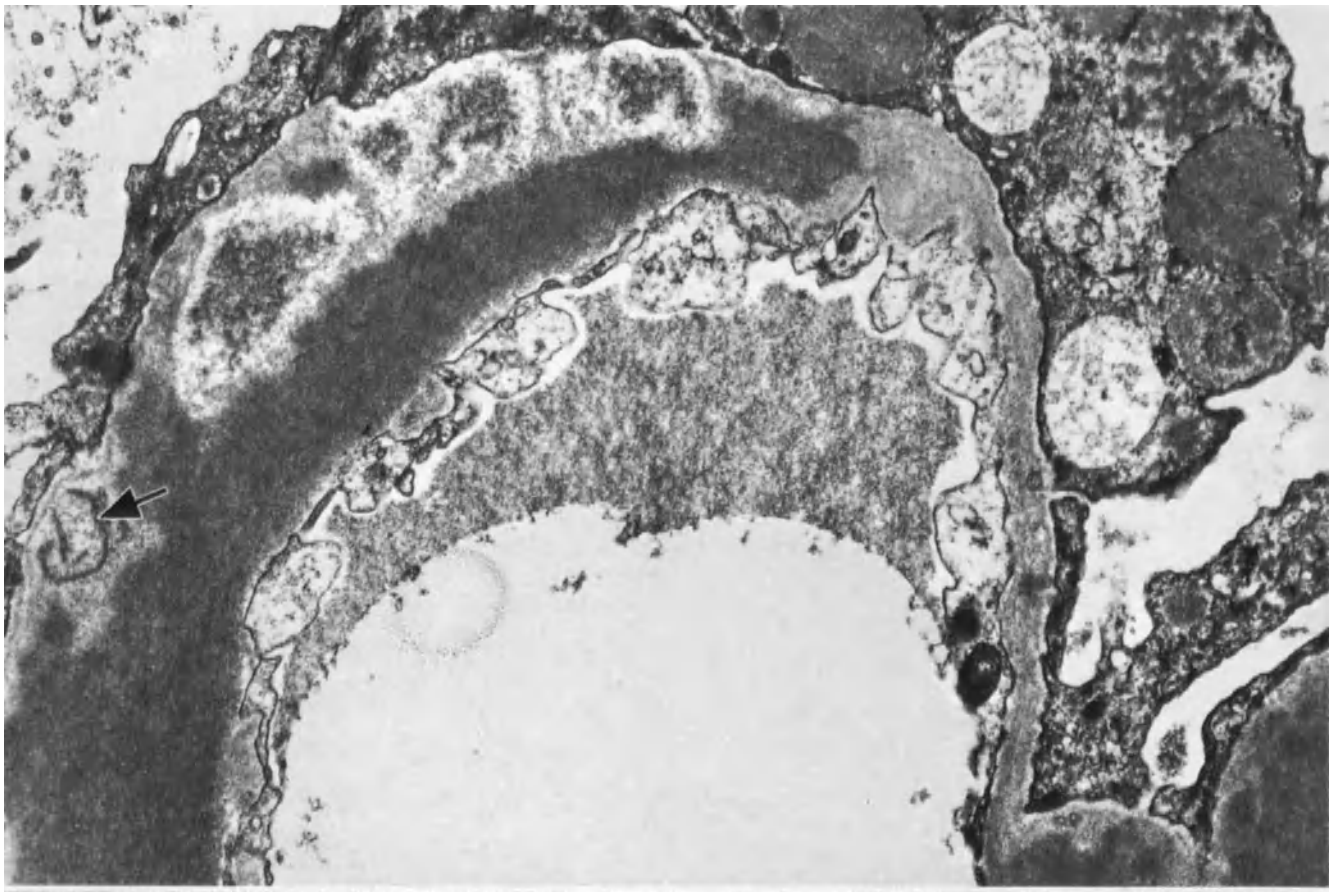

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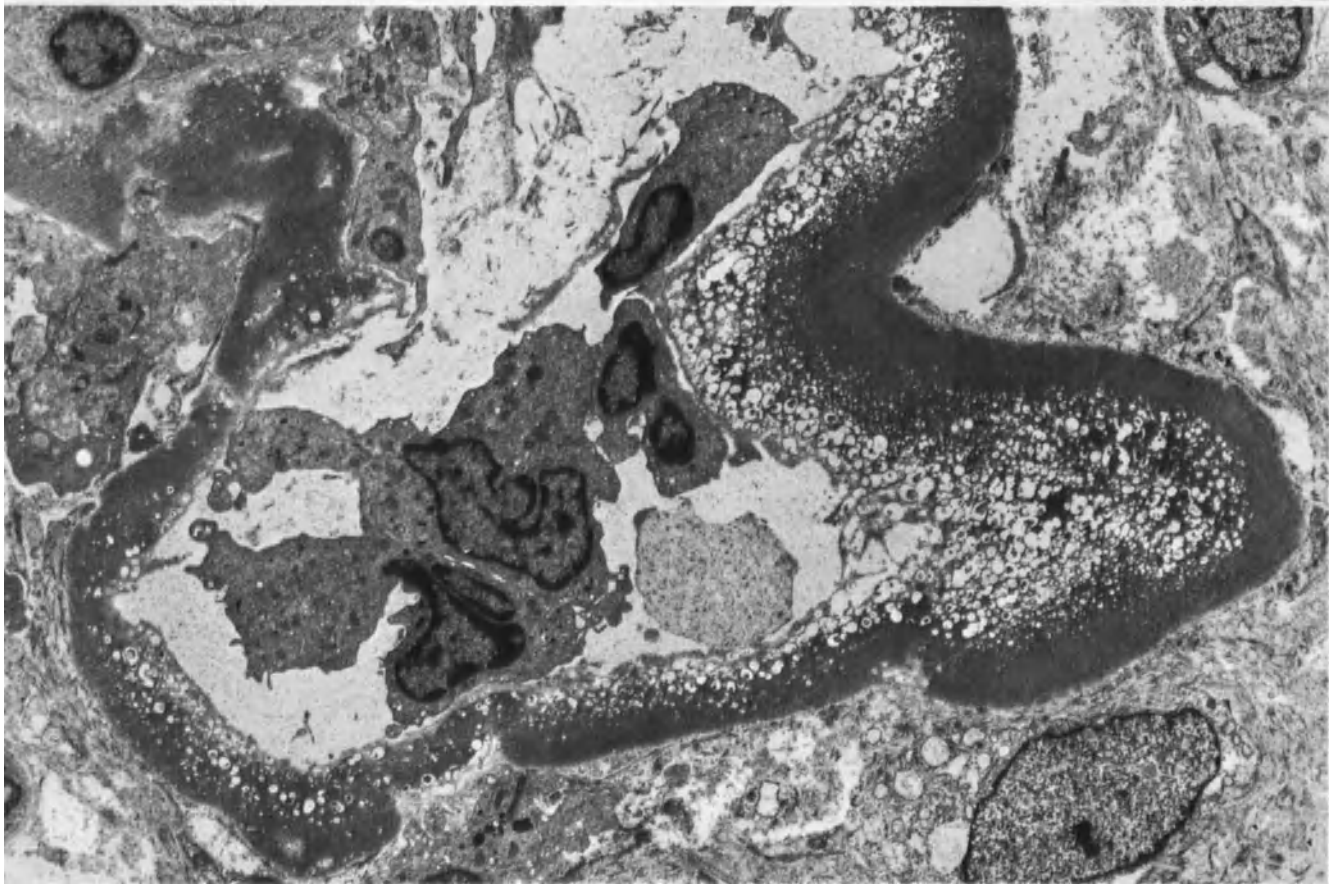

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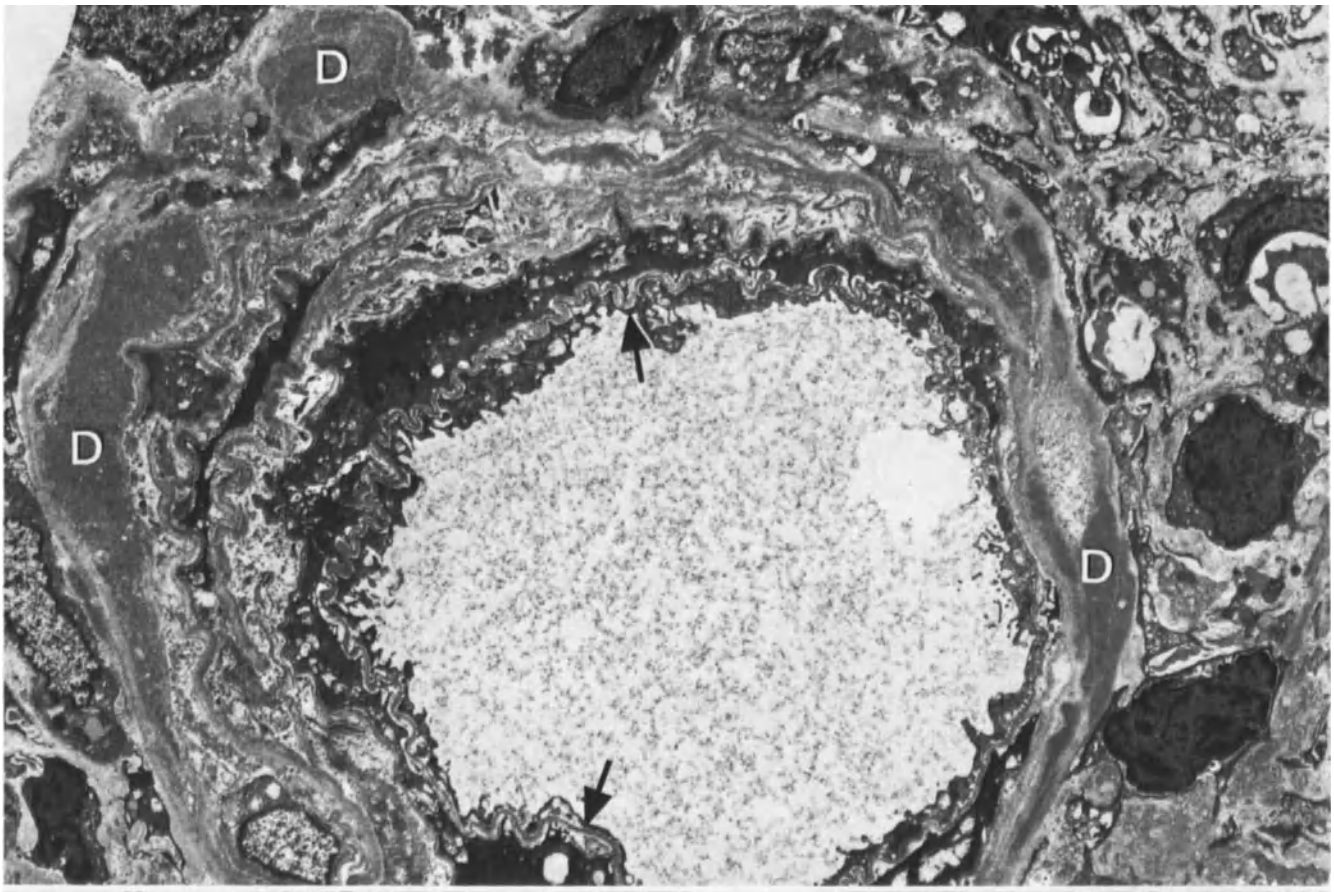
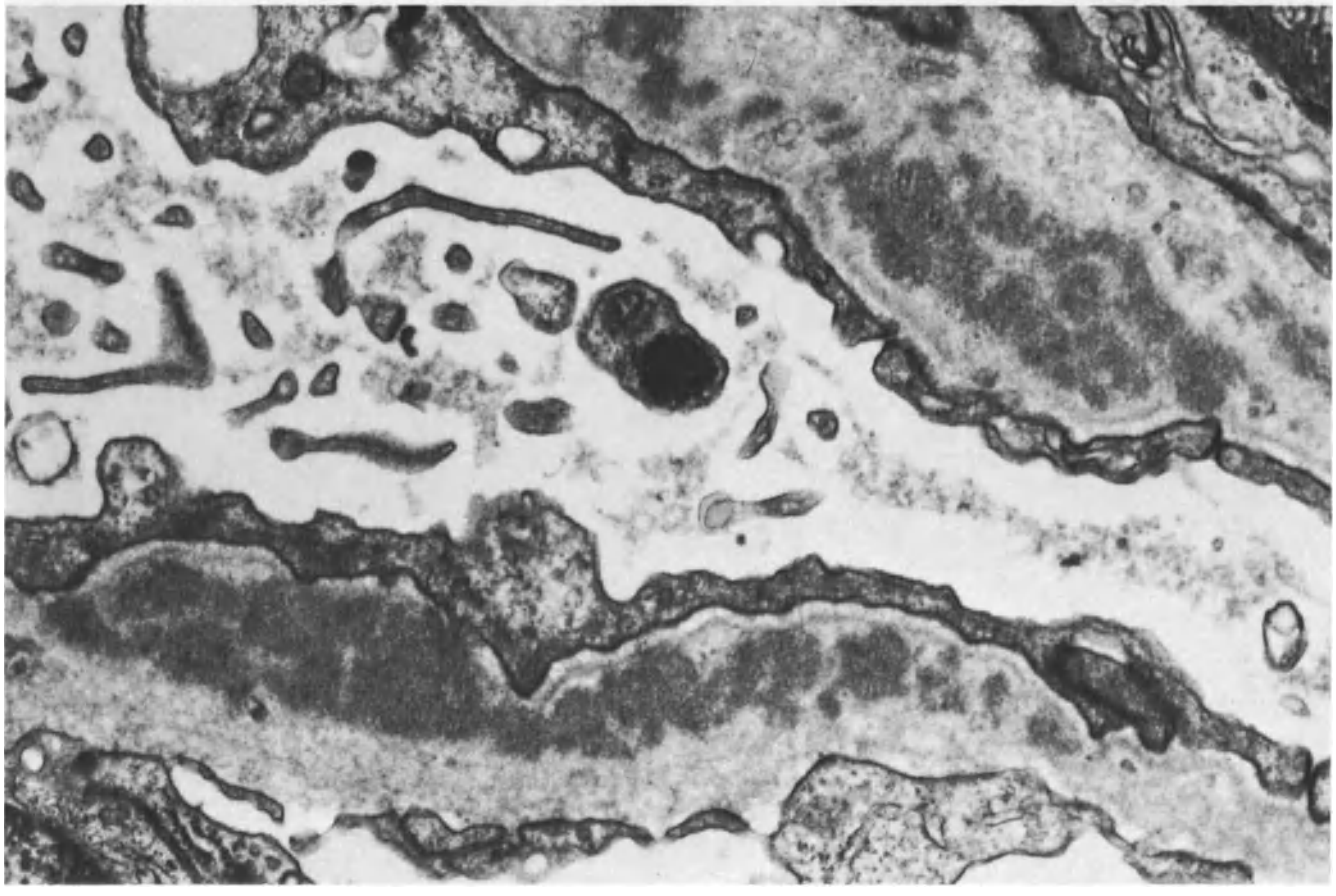



14.111



14.112

## Differential Diagnosis

Membranoproliferative GN presents the only differential diagnostic problem. But this is usually easily resolved by use of Masson's trichrome/AFOG stain, by the unusual staining characteristics in PASM stain, and by the hyaline shining and refractile property in HE and PAS-stain in intramembranous GN. The final proof is presented by EM demonstration of the band-like, linear dense material in the glomerular loop BM as well as the constant affliction of tubular BM and, at times, of Bowman's capsules and arterioles.

The smaller, finely granular deposits occasionally encountered in endotheliomesangial GN are clearly different from the dense material seen in intramembranous GN.

Nor should there be any problem in differentiating the short-linear deposits found in the early stages of epimembranous GN if the localization of the deposits and the qualitatively different IF finding in the intramembranous form are appropriately considered.

Alport's disease, in which we have observed massive intramembranous deposits very similar to those in intramembranous GN in one case (Fig. 14.112), may be difficult to differentiate. In Alport's disease, however, the deposits are not quite as massive and lamellation, reticulation and fragmentation of the lamina densa—which are so typical for this entity—are not present in intramembranous GN.

◁ **Fig. 14.111.** Same case as in Figure 14.109. Arteriolar change in intramembranous GN. Extensive fine-granular dense osmiophilic material (*D*) is present in the severely degenerated media. Subendothelial BM (→) is unchanged. Female, 41 years. EM (×3640)

**Fig. 14.112.** Coarse intramembranous deposits, probably due to insudation into the peripheral glomerular capillary BM in unambiguously demonstrated Alport's syndrome in an 18-year-old female whose sister evidenced typical BM changes of the syndrome in EM. Note that deposits are bulkier, not as diffuse and less dense and osmiophilic than those occurring in intramembranous GN (Figs. 14.107, 14.108, 14.109). EM (×32,100)

## Prognosis

The prognosis for intramembranous GN is reportedly not very different from that of membranoproliferative GN [621, 631]. The annual mortality rate is given as 6% [621], the 5-year survival rate varies between 72% and 83% [35, 524, 631] the 10-year survival rate between 38% and 58% [35, 524, 631]; 8 out of 19 patients presented with terminal renal insufficiency after an average of 33 months of disease ([1652]; see also [769, 987]). In our own material, 3 out of 5 patients with crescents died within 2 years, the others without crescents are still alive after 3 and 5 years respectively.

Recurrence of dense intramembranous material in renal transplants has been reported in 12 out of 14 patients, usually within the first year after transplantation [524, 1652]. In one patient, these deposits were already present 1 month after transplantation [524]. A significant intraglomerular proliferation was observed in 4 out of 12 patients and 3 out of 12 developed significant clinical symptoms [524, 1652]. As a rule, relapses of this GN occur within 1–3 years after transplantation [126, 99a, 231, 245, 523, 524, 631, 1625].

## Pathogenesis

The pathogenesis of intramembranous GN is completely obscure, a fact which lends credibility to the argument that the lesion is a unique disease entity and not a variant of membranoproliferative GN (contra: [165, 621, 631]).

The assumption that intramembranous GN is a glomerulonephritis of the anti BM-AB type, as suggested by the occasional linear IF findings [987], has been discarded since anti-BM-AB have not been demonstrated in the serum [987].

Apart from this, the occurrence of positive IF findings in the majority of cases suggests an immunologic basis for the disease (Table 14.19). The fact that practically only C3 occurs might indicate C3 activation via the alternative pathway. This assumption of the immunologic role in the disease is further strengthened by the occurrence of a constantly low C3 serum value in the presence of a normal C4 level [631, 1652].

Against the assumption that the dense deposits encountered in the lesion consist of C3 is the fact that in simple membranoproliferative GN—which is occasionally only C3 positive—the morphology of findings is not that of dense deposits. Additionally, histochemical and chemical examinations have shown that the dense material does not consist of immunoglobulins or complement but of an abnormal glycoprotein [524, 527a].

Should the dense material prove to be a glycoprotein, its recurrence in renal transplants would indicate that it arises from a substance circulating in the patient's

blood which either induces formation of an abnormal glycoprotein, in the podocytes or becomes deposited in the BM itself.

The presence of dense deposits in the BM as early as 4 weeks following transplantation [524] is, we feel, evidence against podocytic induction. Otherwise extremely intense podocytic synthesizing activity which, however, cannot be identified morphologically, should be present. Therefore, we think that a substance circulating in the patient's serum is deposited in the BM even though the anticipated deposition of the substance in other organs has not been demonstrated. As of now, for example, no dense deposits in skin vessels have been identified [1652].

Furthermore, analysis of sequential transplant biopsies has shown that the dense material is first demonstrable near the vascular pole and the mesangial areas which is rather more indicative of deposition than of local synthesis [99a].

**Etiology**

In partial or total lipodystrophy, 20–60% of the patients from various series have shown nephropathies which rarely correspond to intramembranous GN [774a, 1482b]. However, 12 cases of intramembranous GN associated with lipodystrophy have been published [631, 656, 1312a, 1652, Z]. We consider this association to be of great significance since it may provide a key for the understanding of intramembranous GN. Whether the acute preceding infections [524, 631, 1652], e.g., scarlet fever, mycoplasma [401a] etc., are causally related to intramembranous GN is obscure (see also: [1811]).

## Epimembranous Glomerulonephritis

### Definition

Epimembranous GN [416, 1359] is characterized by thickening of the peripheral glomerular BM due to subepithelial deposits and by the new formation of BM substance without constant mesangial proliferation.

***Synonyms.*** Idiopathic membranous GN [686], membranous glomerulopathy [278], nonproliferative GN with extramembranous deposits [620], extramembranous GN (stages I–III) and membranous GN (stage V) [621], extramembranous GN [90, 126], transmembranous glomerulopathy [544] (see also Table 13.2).

### Nosology

Since there is no constant mesangial proliferation, the lesion is noncommittally described by many investigators as glomerulopathy [88, 89, 416, 544, 1484]. We allocate it, however, to the GN group of diseases, since epimembranous GN is an immunocomplex disease as are other forms of GN. Due to the subepithelial localization of the immunocomplexes in the lesion, no constant morphometrically demonstrable cell increase is present [1624b]; contra: [1705]. The designation "epimembranous" appears to us to be more appropriate than "membranous" which has been used for decades to designate various lesions.
Six different stages in the evolution of epimembranous GN can be recognized (see also [91, 416, 1359]):

Stage 1. Subepithelial deposit formation
Stage 2. Spike formation
Stage 3. Incorporation
Stage 4. Repair
Stage 5. Progressive glomerular obsolescence
Stage 6. Acute relapse.

### Incidence

Statistics are difficult to compare, since cases of SLE are sometimes included or excluded. The overall frequency in all needle biopsies has been reported as 3.3% [408], 5.9% [654], 8% [163], and 14.5% including lupus cases [544]. For frequency among all forms of GN see Table 14.16. In cases of GN with nephrotic syndrome, the rate has been given as 39% [242] and in those with nephrotic syndrome in general between 9% (children: [636]) and 46% [1484]; see also [161, 616, 661, 671, 1484]. In adults, males are clearly more frequently afflicted than females: 5:4 [572]; 3:1 [445]; 1.5:1 [163]; 1.1:1 [278]; 1.5:1 [122]; 2.4:1 [Z]. Children are far less afflicted than adults (23.4% of pediatric GN; Table 14.16) and male predominance is even more striking, 3.6:1 [636]; 4:1 [163].
The age range is very broad (1–92 years) with an average between 40 and 50 [3, 161, 278, 1359]. The mean age of our patients is $41 \pm 19$ years.

Table 14.16. Relative frequency of epimembranous glomerulonephritis[a], ( ) = without glomerular minimal change

| | | |
|---|---|---|
| Habib (1973) [621] | (9.9%) | 5.0% |
| Cameron (1973) [242b] | (12.2%) | 7.8% |
| Zollinger and Mihatsch | (10.4%) | 8.0% |
| Hamburger et al. (1971) [654] | (10.3%) | 8.1% |
| Bohle et al. (1976) [169a] | (14.8%) | 8.4% |
| Morel-Maroger et al. (1973) [1137a] | (15.3%) | 12.2% |
| Churg and Duffy (1973) [277] | (17.0%) | 14.0% |
| Germuth and Rodriguez (1973) [544] | (22.0%) | 14.9% |

[a] For number of cases in different series see Table 14.1.

### Clinical Findings
(Tables 14.3, 14.4, 14.5, Fig. 14.113)

The beginning of the disease is often so insidious that about half of the patients in large case series are discovered by chance [122, 633]. In the other cases, progressive edema (Fig. 14.113) exhibiting a frequency of almost 70% in our material, was the most important finding pointing to the disease. Very rarely, the disease may also commence like typical acute GN with macrohematuria and oligo-anuria ([1332]; Table 14.5). Manifestation in the course of SLE is also frequent (see p. 326).
The absence of acute prior illness is very characteristic for the disease (see Fig. 14.113; 9 out of 50 cases: upper respiratory tract infection, scarlet fever, pneumonia [633], see also [408]). Before definite bioptical diagnosis, the disease was stationary in 40% of our patients, recurrent in about 20%, and progressive in about 25%.
At the time of biopsy, in about 60% of the cases (Fig. 14.113), the clinical picture is dominated by a nephrotic syndrome (85%: [445, 1648]), whereas in the initial stages of the disease, it may be absent (42%: Z; 6%: [661]; 33%: [408]) and especially so in children [633]. Proteinuria, which demonstrates wide fluctuation from day to day, is unselective [1359]. Reports on the frequency of microhematuria evidence disparate findings. Thus, it has been reported present at disease onset in three-fourths of patients (39 out of 46: [633]) and in 50% [122], while in our material it was absent in three-fourths of patients at the beginning of the disease and at the time of biopsy (Fig. 14.113).
Data relating to hypertension also exhibit considerable variation (22% of patients: [408], 42%: [278], two-thirds

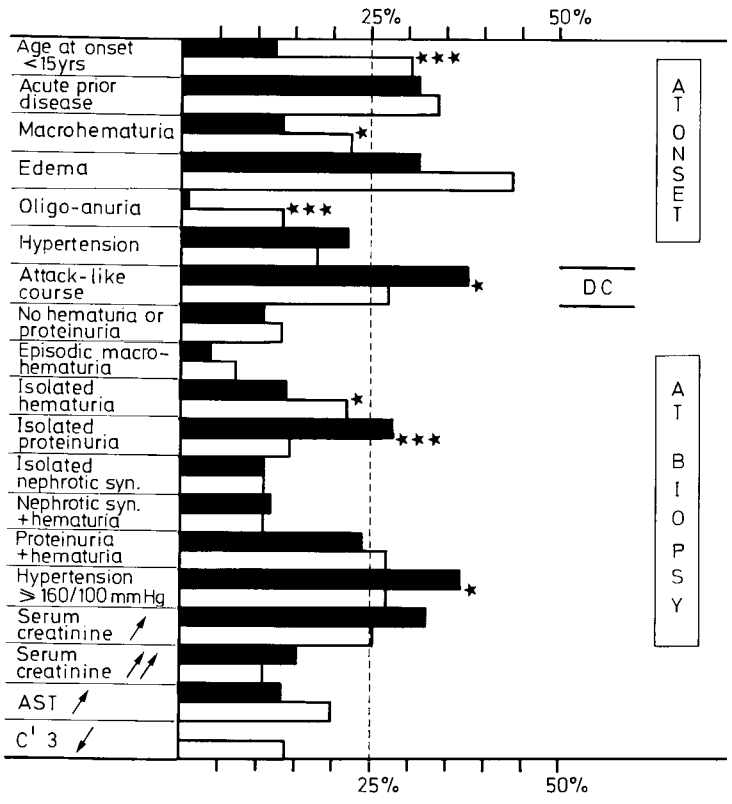


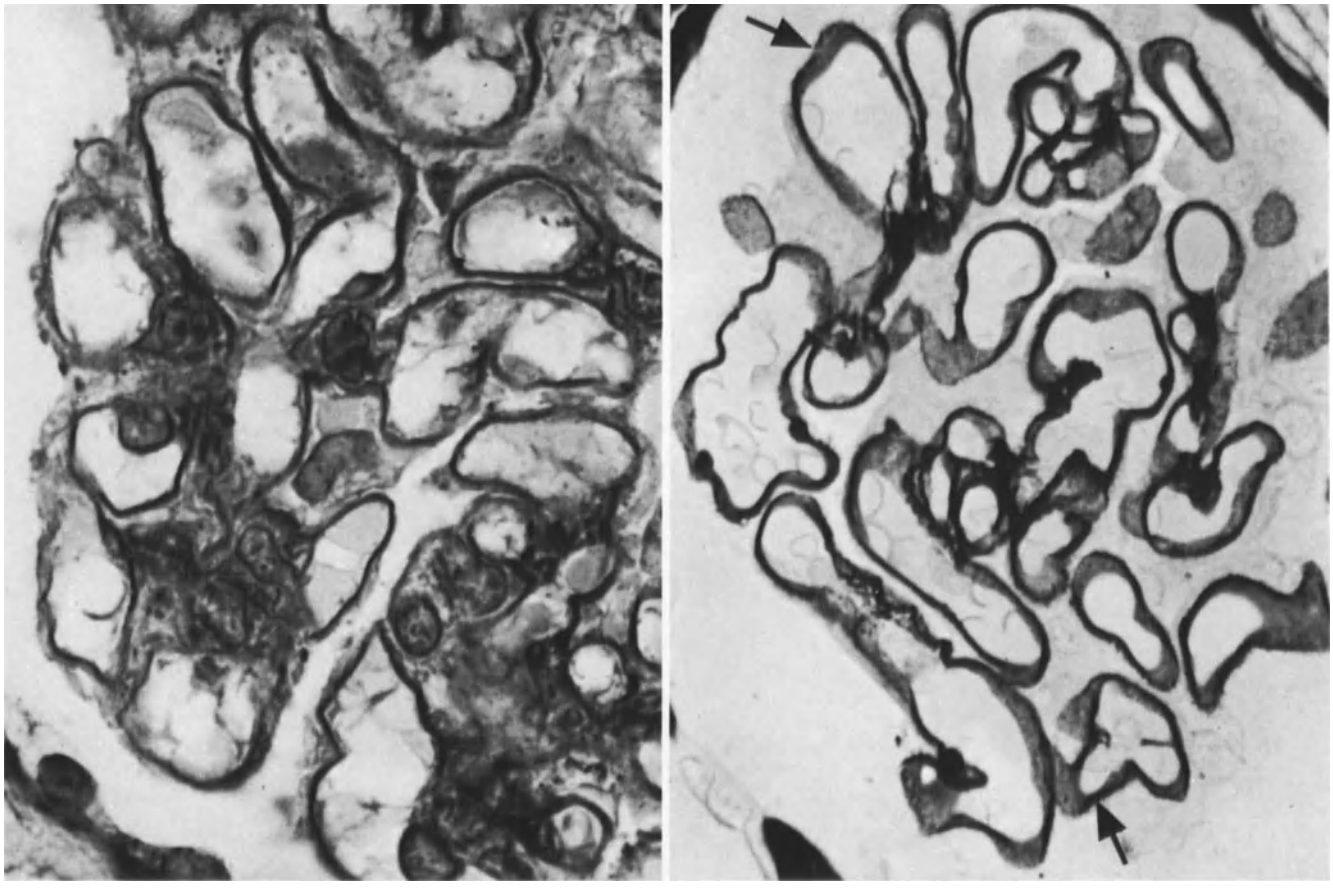

**Fig. 14.113.** Profile of symptoms and clinical findings in epimembranous GN
*White columns:* Relative frequency of symptom/finding in all GN
*Black columns:* relative frequency in epimembranous GN
Asterisks indicate characteristic findings for epimembranous GN:
*: characteristic
**: very characteristic
***: highly characteristic; DC: disease course

of patients: [1204], 37%: [122]; 38%: Z; see also [3, 1484]). In our material, hypertension was as frequently encountered in the early morphologic stages (1 and 2) as in later (3 and 5). With few exceptions (2 out of 17 cases: [572]; Fig. 14.113; see also [633]) hypocomplementemia was absent.
Deterioration of renal function is insidious. Its sudden occurrence should always arouse suspicion of secondary renal vein thrombosis [1281].

## LM Findings

***Stage I. Subepithelial Deposit Formation.*** An extremely early stage characterized by numerous polymorphonuclear leukocytes (three cases: [1332], and one: Z) is very rarely observed and may simulate endotheliomesangial GN. Later, changes typical of epimembranous GN will develop [1333].
In typical cases (HE and PAS stains) the glomeruli are—with the exception of focal minimal mesangial change (Fig. 14.114)—by and large unaltered (Fig. 14.115). In some of these cases, Masson's trichrome/AFOG stain reveals flat, subepithelial deposits (Fig. 14.116), but in PASM stain, there is no evidence of spike formation (Fig. 14.115). Only the few protein droplets in tubular epithelial cells will usually indicate the presence of a glomerular lesion. Focal and segmental glomerular involvement [407, 633] are rarely observed, and when so, they represent a very early stage (one of our own cases).
Accordingly, the LM diagnosis at this point of the disease may prove to be impossible [91, 1359, 1484] and the insufficient diagnosis of glomerular minimal change—which is always present—will be usually made. This finding alone can explain the supposition that epimembranous GN develops from the minimal change [712].
The interstitium is practically unaffected; we encountered findings indicative of interstitial nondestructive accompanying nephritis in only one case (rheumatoid arthritis treated with gold and penicillamine). Others have reported interstitial edema with scanty infiltrates [686]. Vessels and tubular BM are unchanged.
We wish to note at this point that we have never observed a statistically significant increase in vascular, tubular, or interstitial changes with respect to the various stages (I–IV) of the lesion.
The early stage may last for 2 years [278]. In our material the average duration of disease was 22 weeks (range: 10–50 weeks).
This stage is frequently observed in cases caused by drugs, e.g., penicillamine and gold, since their administration usually directs attention towards the side effects associated with their use (9 out of 10: [1628]).

***Stage II. Spike Formation.*** This stage has been reported to last as long as 4 years after its onset [278]. We saw



14.114
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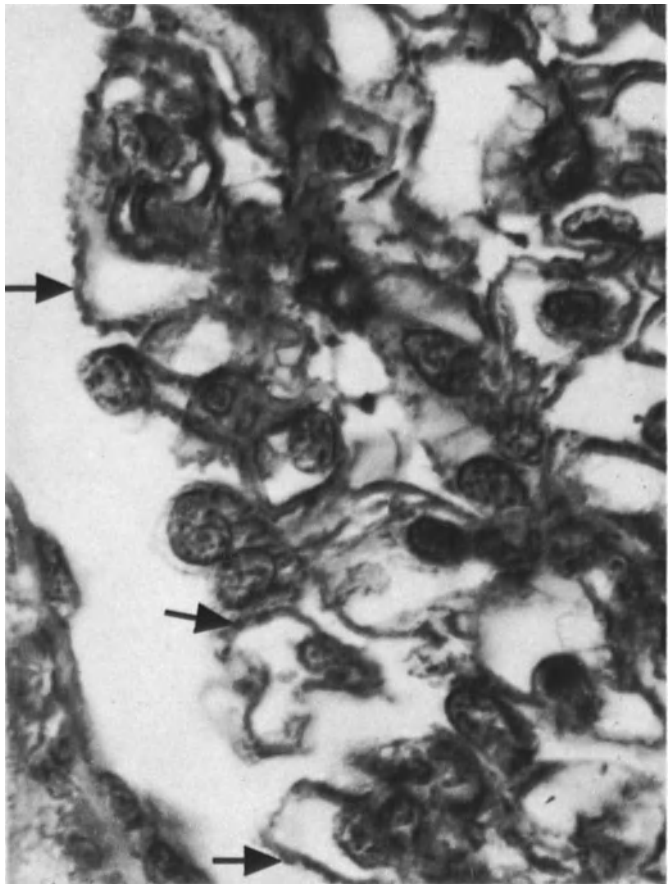


14.116

**Fig. 14.114.** Apparently, a completely unchanged capillary loop BM of a glomerulus in a case of epimembranous GN (stage I) demonstrated unequivocally with EM. There is no cell proliferation. Female, 42 years. Semi-thin section, PAS (×850)

**Fig. 14.115.** Same case as in Figure 14.114. Peripheral BM shows minimal irregularities on the outer surface at very few sites (→). Note lack of mesangial involvement. Cf. Figure 14.119. PASM (×540)

**Fig. 14.116.** Very fine subendothelial deposits are evident (→) in this case of epimembranous GN (stage I) associated with gold therapy. Female, 21 years. PAS (×720)

it after an average duration of disease of 26 weeks with a range of 3–150 weeks (see also [416]).
All the glomeruli are slightly enlarged and the BM is defenitely homogeneously thickened (Fig. 14.117). In thin PAS-stained sections, a somewhat irregular outer contour is occassionally observed in the thickened peripheral BM. With Masson's trichrome/AFOG stain, extremely fine, flat, reddish granules are seen subepithelially. These granules are not stained with PASM; they are separated from each other by very fine PASM positive BM spikes (Fig. 14.118).
In some cases the BM itself is not yet obviously thickened, or appears merely suggestive of such thickening in PASM stain. The podocytes are slightly enlarged.
The impression gained is of a mild focal increase of cells and matrix in the mesangium [410, 1797] which we could not objectify in this stage morphometrically [1624b]; (contra: [1705]). We have not been able to demonstrate mesangial matrix deposits in this stage as has been reported by other investigators (10 out of 24: [633]).
The capsular epithelium is unchanged or only slightly swollen, and evidences scanty protein droplets. Protein droplets are always present in the tubules, and vacuoles are frequent. Vessels and interstitium are practically unaffected; interstitial infiltrates are very rare.

***Stage III. Incorporation (Endomembranous) Stage.*** This stage may last 3–4 years or even longer [278, 572].
We found an average duration of illness of 76 weeks with a range of 10–250 weeks.
As seen in the PAS stain, the BM is much thickened (Fig. 14.119) and seems to be split into two thin layers. They are joined together by very fine cross connections which develop from the original spikes (Figs. 14.119, 14.120). Some spikes have been reported present even after 5 years [92]. The spaces between ladder rungs are often stained red with Masson's trichrome/AFOG stain. At this stage, a few isolated synechiae (Fig. 14.121) and capillary loop obliterations have rarely been observed.
The increase in the mesangial matrix is now usually evident and has been shown by morphometry to be statistically significant in comparison to stages I and II [416, 1359, 1624b, 1797]. Although mesangial cell increase is present in an occasional glomerulus, morphometrical analysis has shown that this increase is not statistically significant ([1624]; contra: [1750]; [1797]).
The tubules contain massive lipid vacuoles and protein droplets in their cytoplasm and numerous casts in their lumens. The interstitium shows patchy fibrosis but rarely diffuse sclerosis [686]. It also evidences sparse infiltrates of predominantly lymphocytic character and, occasionally, numerous foam cells (symptomatic lipoid nephrosis).

***Stage IV. Repair Stage.*** Knowledge of LM findings are incomplete and are based on only a few individual observations. Unquestionable diagnosis is surely difficult with respect to stage III [92, 278, 503, 532, 1372, 1593].

***Stage V. Progressive Glomerular Obsolescence.*** We observed this stage in our material averagely after 93 weeks of illness with a range between 15 and 350 weeks. It is characterized by increase in the number (>10%) of globally or segmentally obsolescent glomeruli [416, 1068]. In our autopsy material, glomerular obsolescence is significantly more frequent statistically in the juxtamedullary than in the subcapsular zone. Interstitial changes featuring focal and diffuse fibrosis (4 out of 13: Z), (Figs. 14.122, 14.123), more or less extensive tubular atrophy and mild interstitial accompanying nephritis with only scanty interstitial infiltrates correspond to the number of destroyed glomeruli.
Mesangial matrix increase in the nonobsolescent glomeruli is clearly evident [1624b].
Segmental crescents, which we observed in 10% of all our cases, are mainly found in stage V; they are less frequent in stage III. In general, rarely more than 10% of glomeruli are involved (2 out of 7: Z; see also [1068]). However, crescents may—in occasional cases—involve nearly all glomeruli, so that in LM, extracapillary accentuated GN may be simulated [1131b, 1136].

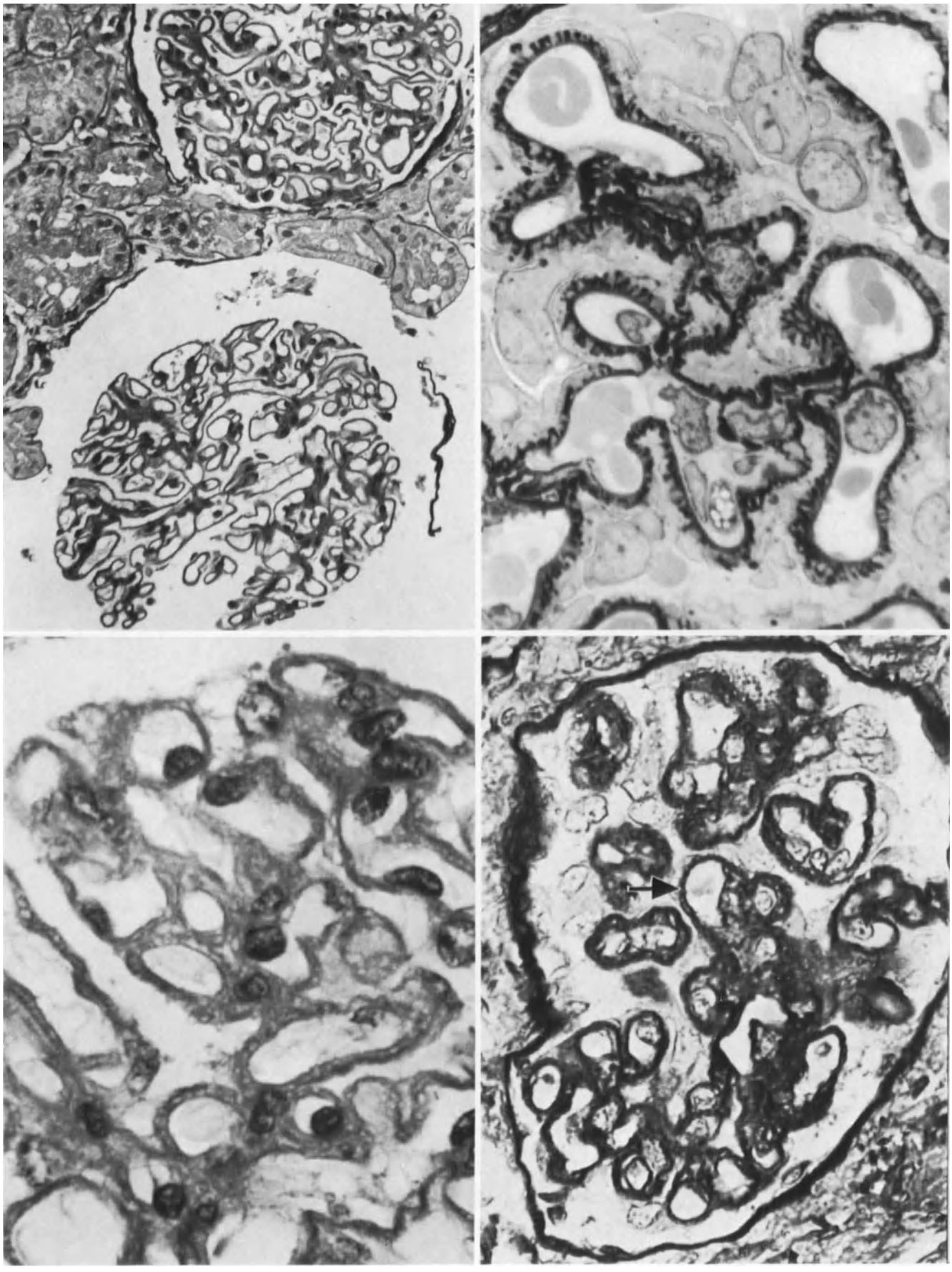
***Stage VI. Acute Relapse.*** Demonstration of an acute relapse is difficult with LM and can only be diagnosed with certainty in stages III–V. With LM and using Masson's trichrome/AFOG stained material, fresh, small, and partially short linear deposits or newly formed focal-segmental spikes can be seen on the already extensively thickened peripheral capillary loops.

**Fig. 14.117.** Epimembranous GN in stage II. Slight thickening of peripheral glomerular BM without cell proliferation. Male, 33 years. PAS (×300) ▷

**Fig. 14.118.** Same case as in Figure 14.117. Black-appearing spikes which lie on outer surface of glomerular BM are now very easily recognizable. Between the spikes, deposits can be assumed. Semi-thin section, PASM (×1000)

**Fig. 14.119.** Same case as in Figure 14.114, but 4 years later. Stage III of epimembranous GN is now present. Numerous clear lacunae are recognizable in the highly thickened peripheral BM, i.e., ladder-like configuration. Male, 37 years. PAS (×870)

**Fig. 14.120.** Same case as in Figure 14.119 but in PASM stain which permits clear presentation of the ladder configuration of the peripheral BM (→) (×620)



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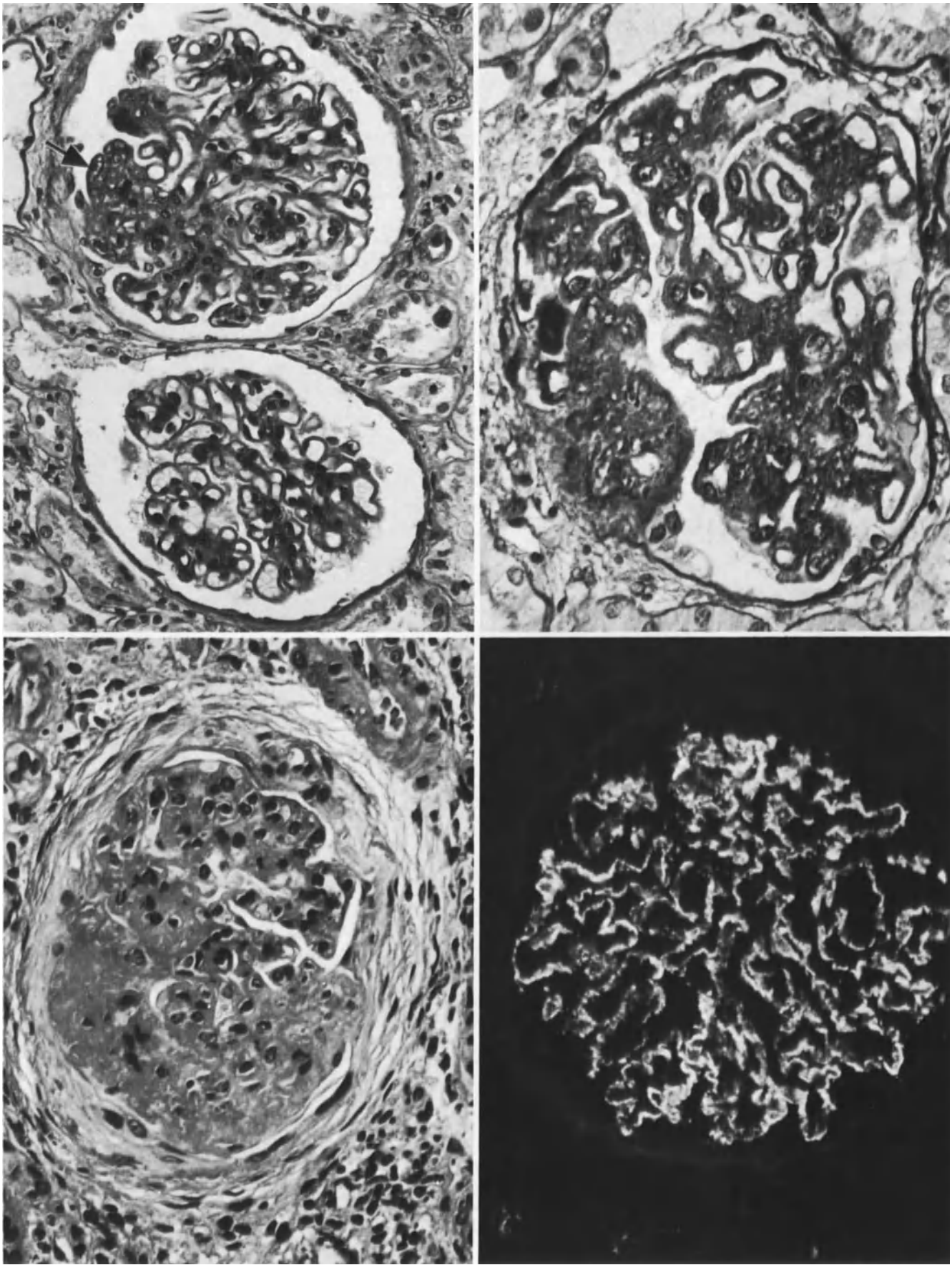


14.121
14.122
14.123
14.124

### IF Findings

Fine to coarsely granular deposits of IgG and C3 are found densely packed along the peripheral BM (Fig. 14.124). Our own findings are given in Table 14.17. The deposits correspond to the osmiophilic deposits seen in EM [91, 92, 1167, 1359] (for immuno-EM see: [354a]). Complement deposition is less coarse than it is in endotheliomesangial and membranoproliferative GN [127]. Due to their close arrangement to each other, the deposits occasionally appear to be linear (pseudolinear deposits: [410, 1168]). Genuine linear IF deposits in epimembranous GN are observed and in exceptional cases are supposed to arise by formation of AB against membrane components as a consequence of BM injury caused by subepithelial immunocomplexes [855].

In the early as well as late stages, the deposits are, in general, diffusely and globally distributed. Focal-segmental distribution is rarely observed (1 out of 20: Z; [633]) in the early stage. IF is usually negative in the healing or repair stage [89, 1168, 1359].

Table 14.17. IF findings in epimembranous glomerulonephritis ($n=20$)

| | IgG | IgM | IgA | C3 | Fibrin(-ogen) |
|---|---|---|---|---|---|
| Cases tested | 20 | 20 | 16 | 20 | 18 |
| Positive | 20 | 17 | 5 | 19 | 4 |
| Diffuse | 19 | 14 | 5 | 17 | 4 |
| Focal | 1 | 3 | 0 | 2 | 0 |
| Global | 18 | 13 | 3 | 16 | 3 |
| Segmental | 2 | 4 | 2 | 3 | 1 |
| Peripheral | 17 | 15 | 5 | 11 | 4 |
| Mesangial 3 peripheral | 1 | – | 3 | – | |
| Mesangial | – | 1 | – | 5 | – |

◁ **Fig. 14.121.** Epimembranous GN, stage III. Glomerular capillary loop BM is much thickened. A loop convolute is obliterated (→). Over this convolute a synechia with the capsule is present. Male, 48 years. PAS (×320)

**Fig. 14.122.** Epimembranous GN stage V. Glomerular capillary loops are obsolescent and evidence synechiae, present in many glomeruli throughout the kidney. Male, 18 years. PAS (×520)

**Fig. 14.123.** Epimembranous GN in stage V. There is subtotal glomerular obsolescence with severe proliferation of capsular connective tissue and pronounced interstitial infiltrates. Male, 36 years. HE (×480)

**Fig. 14.124.** Heavy coarse-granular IgG deposits in the glomerular BM in epimembranous GN. Male, 34 years. IF (×410)

In the very early stage (I), C3 may even be lacking whereas later (stages II, III, V), it is usually present in a diffuse and global pattern. IgG (except in rare instances in the very early stage I) is nearly always diffusely and globally distributed as is IgM in the early stages. However, in stages III and V IgM more often demonstrates segmental patterns.

In stages I and II, the deposits were encountered only along the peripheral glomerular BM but, in the later stages, IgM and C3 were more often found in the mesangium alone or in the mesangium and periphery (see also [1284]). IgM and especially IgA and fibrin(-ogen) are less frequently demonstrable than IgG (IgM: 32%: [743, 1136]; IgA: 6%: [128]; 50%: [89]; Table 14.17). An obvious predominance of IgM or IgA for any of the different stages does not seem to exist [91, 89, 128, 1359]. Differences between idiopathic and symptomatic cases are not encountered.

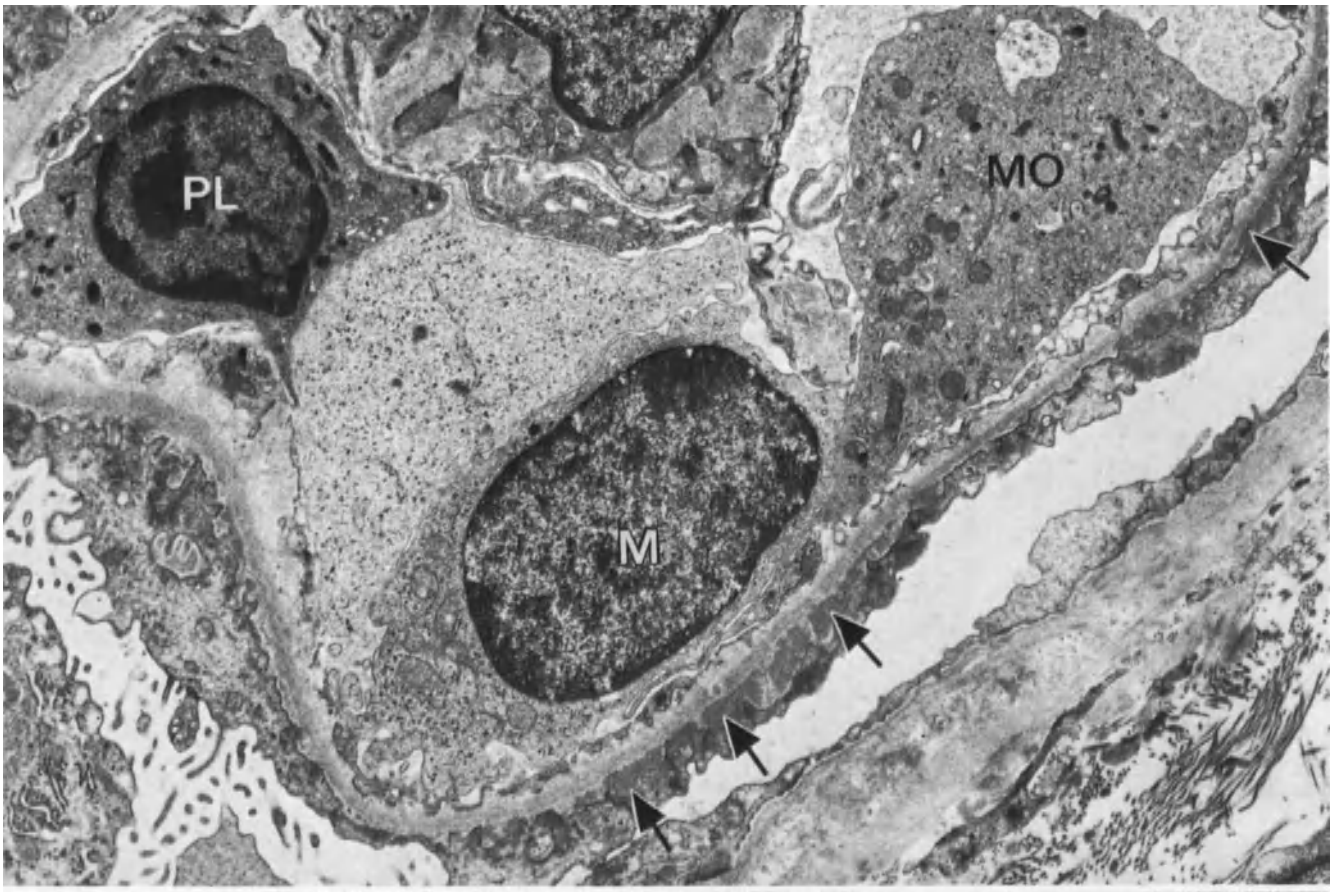
### EM Findings

***Stage I. Subepithelial Deposit Formation.*** EM permits unequivocal diagnosis in contrast to LM. Small, usually flat subepithelial osmiophilic deposits which are often arranged in groups (Fig. 14.125) can be demonstrated. They are obviously more electron-dense than the lamina densa and they lie under the limiting membranes between the foot processes of the podocytes (Fig. 14.126; [1628]). The size of the deposits in our material is $3000 \pm 1960$ Å. The number of deposits can vary considerably from loop to loop. The subepithelial side of the nonthickened BM is still rather smooth in this stage, but the lamina rara externa is missing in the region of the deposits.

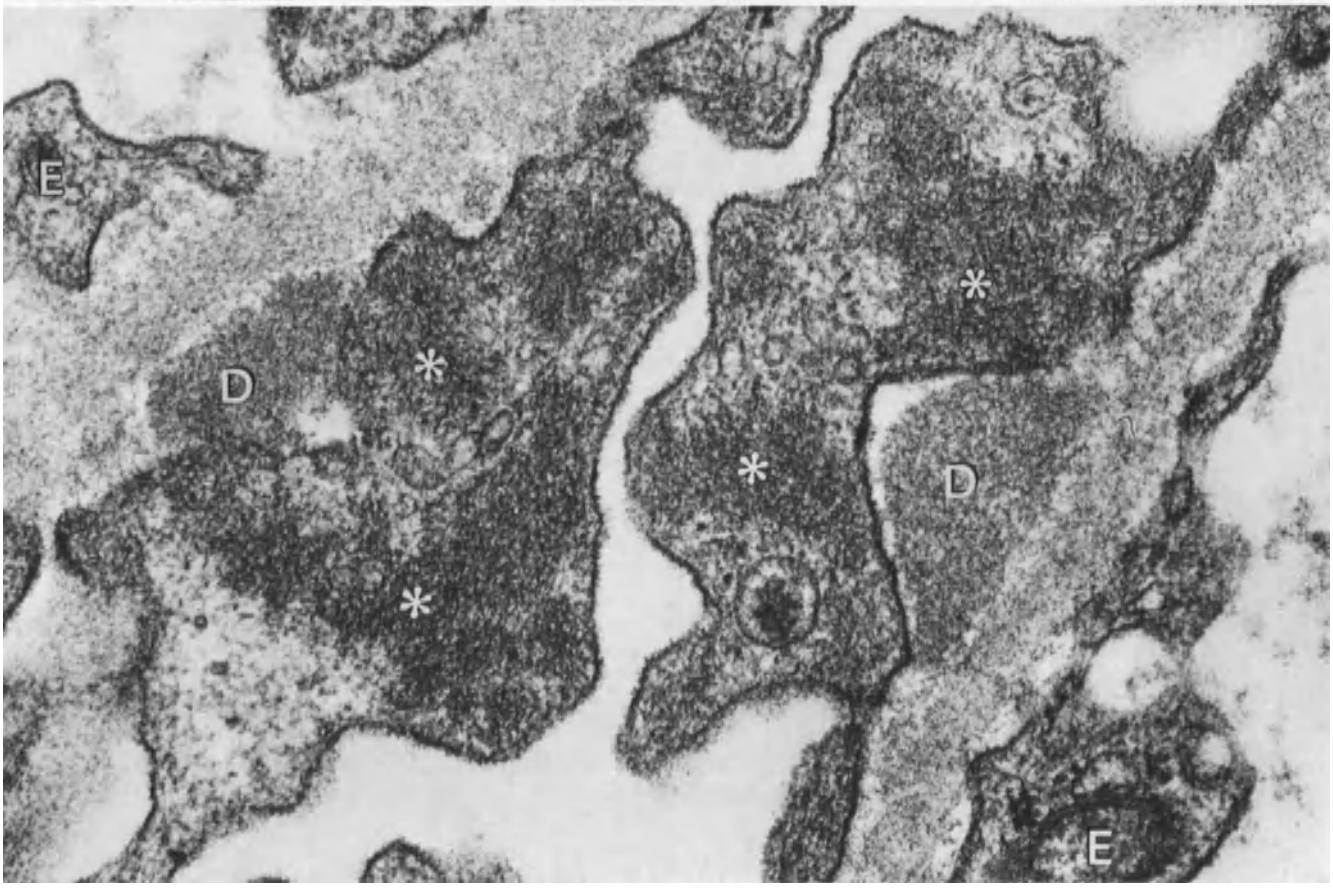
Deposits cannot be demonstrated in the mesangium. The matrix is finely structured and the cells are reported as being hypertrophied or shrunken [1284], findings which we have not been able to confirm.

In 3 out of 10 clinical cases of typical gold nephropathy (but unfortunately without IF findings) no ultrastructural changes have been described [1628].

***Stage II. Spike Formation.*** In contrast to stage I, the osmiophilic deposits are increased in both number and size (Fig. 14.127) and now measure $8470 \pm 4100$ Å. The deposits are completely homogeneous and their delimitation from the lamina densa is sometimes vague (Fig. 14.127). In sections they are seen to be bordered forceps-like on both sides by radially arranged extensions of the lamina densa. These spikes (Figs. 14.127, 14.128, 6.30) are also called spicules [1484] and striae [89, 91, 92]. They are 350–4000 Å wide at the base (400–2500 Å: [1372]) and 0.3 to 1.0 µm long. In isolated instances, a tendency to complete encompassment of the deposits, i.e., new formation of subepithelial lamina densa and rara externa, is observed (Figs. 14.128,




14.125




14.126

14.129). The total thickness of the BM (including the deposits) now amounts to 13,700 ± 7000 Å. In addition to the subepithelial deposits, finely structured deposits are now occasionally found in the original lamina densa (3 out of 11: Z).

The endothelium is swollen and partially hypertrophied (Fig. 14.127) and the fenestrations are occasionally absent. Virus-like formations, which have been described now and again (Fig. 14.129), are not obligatory for epimembranous GN [1045]. In contrast to stage I, the podocytic foot processes are now completely fused in the region of the deposits (Fig. 14.128) and their osmiophilic substance is considerably increased.

The mesangial matrix (8 out of 11: Z) (Fig. 14.130) and mesangial nuclei (7 out of 11: Z) are slightly to obviously increased. We were not able to demonstrate mesangial matrix deposits in this stage. A few deposits along the mesangial BM were observed in only 1 out of 11 cases (Z) which corresponds to the IF findings in this stage. Capsular epithelium and BM are unaffected.

Tubular, vascular and interstitial findings correspond to LM observations. Osmiophilic deposits are absent in tubules and vessels.

***Stage III. Incorporation (Endomembranous) Stage.***

The BM is much thickened (8000–30,000 Å: [1359]; 14,900 ± 5600 Å: Z). The densa layer covering all deposits in an arch-like manner, has now developed massively (Figs. 14.131, 14.132) forming a new, second subepithelial lamina densa. Thus, the outer BM surface has become severely coarsely arched.

◁ **Fig. 14.125.** Epimembranous GN in stage I following gold therapy. Numerous, somewhat irregularly formed epithelial osmiophilic deposits are discernible (→). Podocytic foot processes are completely fused. A polymorphonuclear leukocyte (*PL*) and two monocytoid cells (*MO/M*) can be seen in the capillary lumen. Same case as in Figure 14.116. Female, 21 years. EM (×6800)

**Fig. 14.126.** Same case as in Figure 14.125. Marked increase of osmiophilic substance (*) is seen in podocytes overlying subepithelial deposits (*D*). Endothelium (*E*). EM (×60,900)

The deposits lie between the two LM recognizable densa layers (endomembranous position: [92]). They are demarcated from each other by wide, radial rungs of densa material (Fig. 14.132; [88, 91]). The size of the deposits (11,400 ± 3670 Å) is not significantly different from that occurring in stage II. The deposits themselves are progressively altered; they become coarsely granular, somewhat loose, and usually lie embedded in a translucent material. Total absence of osmiophilic deposits is rare, and in such cases, only empty lacunae remain (Fig. 14.133 "moth-eaten" appearance: [88, 89, 91, 1484]). It is questionable whether removal of the material takes place by auto-oxidation [1593, 1594, 1628a]. We do not believe that the empty lacunae in the BM seen in stage III are the result of destroyed podocytic cytoplasmic processes. Positive IF findings in this stage also point to immunodeposits in the process of dissolution.

The above-mentioned lacunae as well as the coarsely granular deposits undergoing breakdown often contain large groups of oval, 800 Å-sized virus-like blebs (see p. 92) as well as elongated structures partially of a whorled thread-like character with a diameter of 200 Å. According to serial sections, the structures appear to be membranous in nature and are said to have arisen by degradation of cellular and membranous material in the BM [87]. They have a periodicity of about 100 Å (Fig. 14.134). We found these structures in 11 out of 13 cases in stage III but only once in stage II.

Page 270

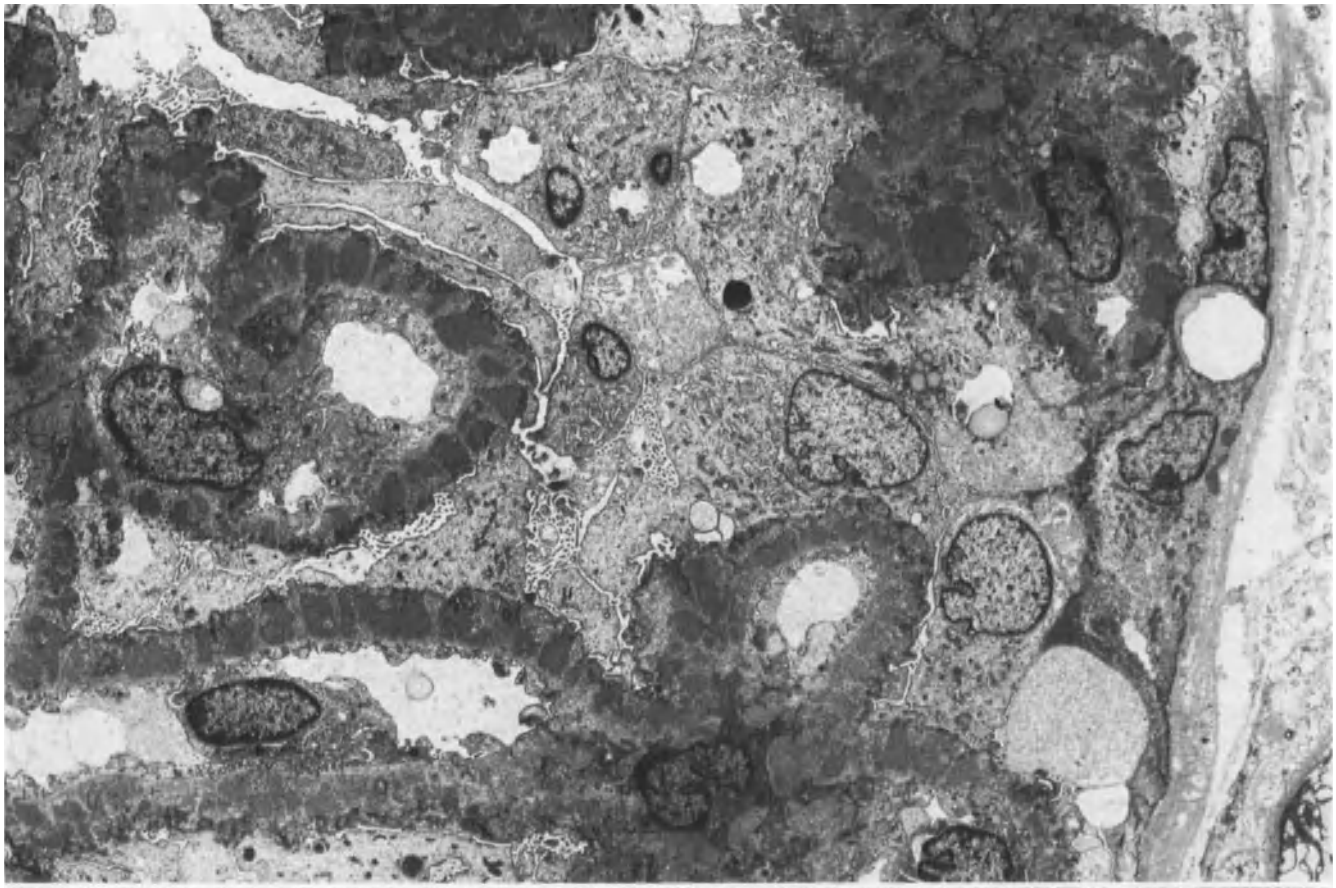
**Fig. 14.127.** Epimembranous GN in stage II. Massive spike formation is present between subepithelial deposits which lie very close to each other. Endothelium and mesangium are almost unchanged. Podocytes are severely swollen, activated, vacuolized and exhibit scanty protein and lipid droplets. Female, 70 years. EM (×2630)

**Fig. 14.128.** Same case as in Figure 14.127. There are clearly evident spikes (*S*) between the osmiophilic deposits. Osmiophilic substance in podocytes (*P*) is increased. Endothelial cell (*E*). Female, 70 years. EM (×37,100)

Page 271

**Fig. 14.129.** Same case as in Figure 14.127. A few spikes touch each other subepithelially by means of their roof-like spreading (→). Increased osmiophilic substance is present in podocytes (*P*). Textile-like structures in endothelial cell (*) besides vacuolar distention of organelles. Subendothelially, pronounced irregularity of BM, thickening of lamina rara interna and formation of a new uniformly thin densa layer (⇾) are present. Female, 70 years. EM (×37,100)

**Fig. 14.130.** Epimembranous GN in stage II. Very pronounced mesangial matrix (*M*) increase but no obvious cell increase. Male, 48 years. EM (×2560)



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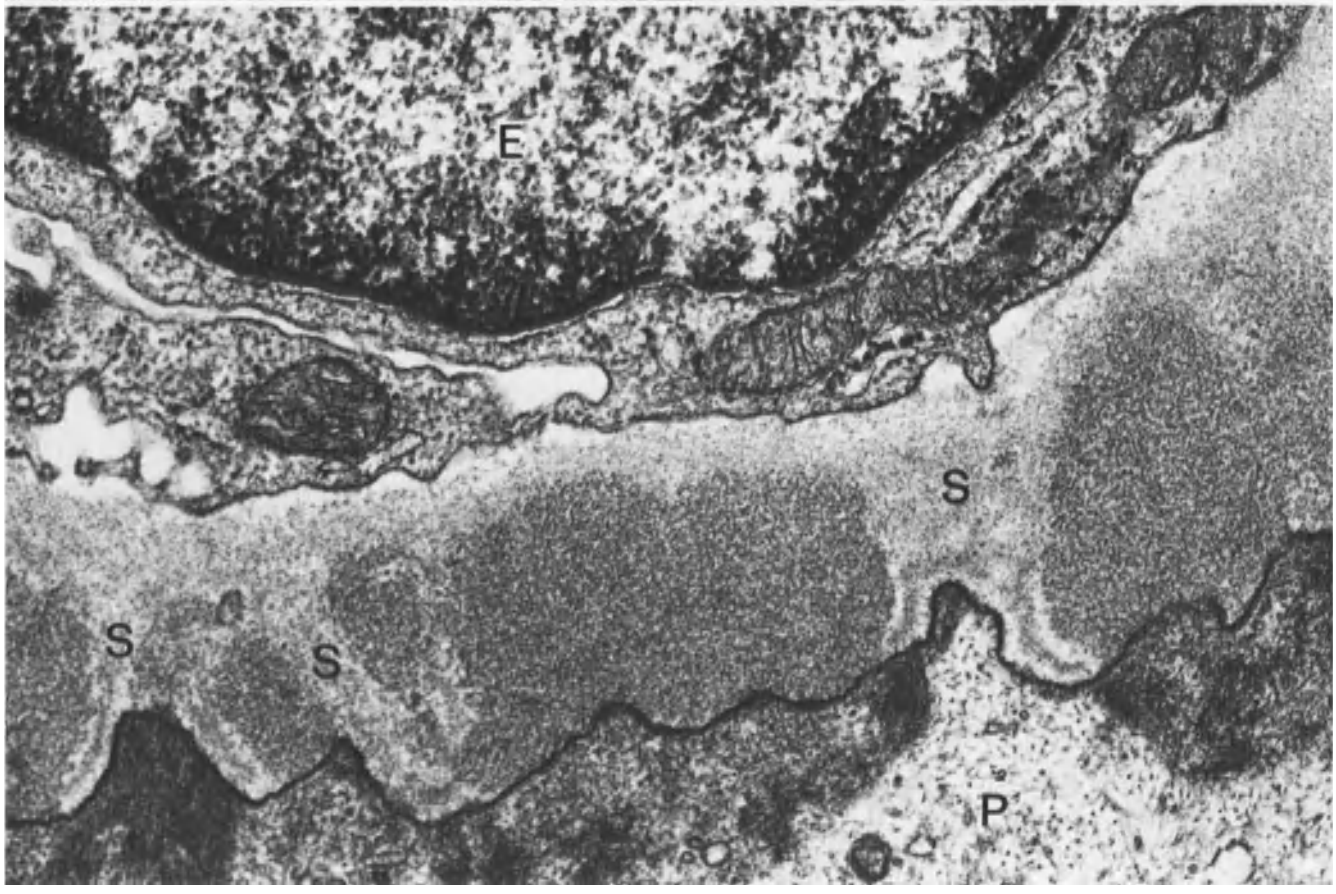


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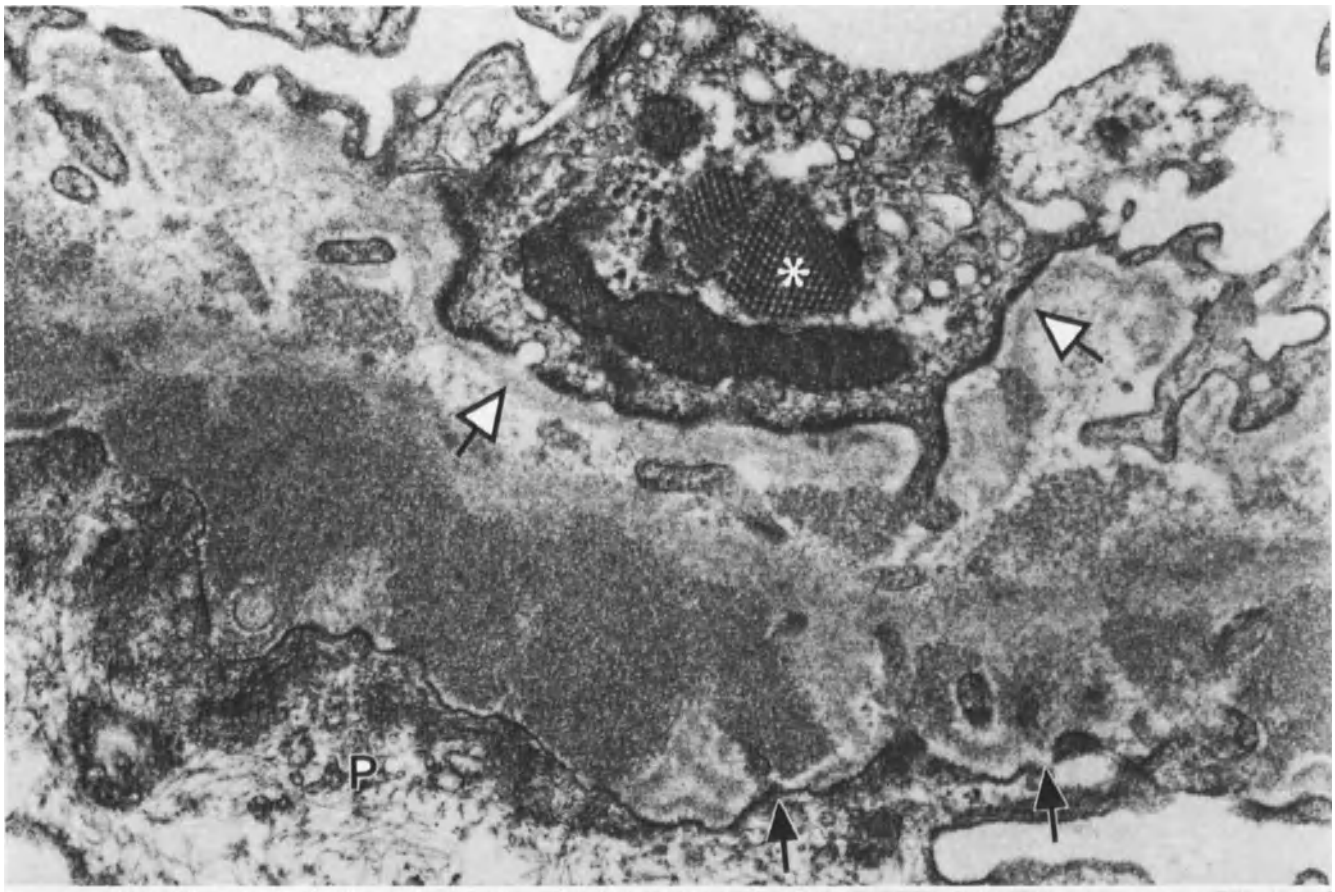


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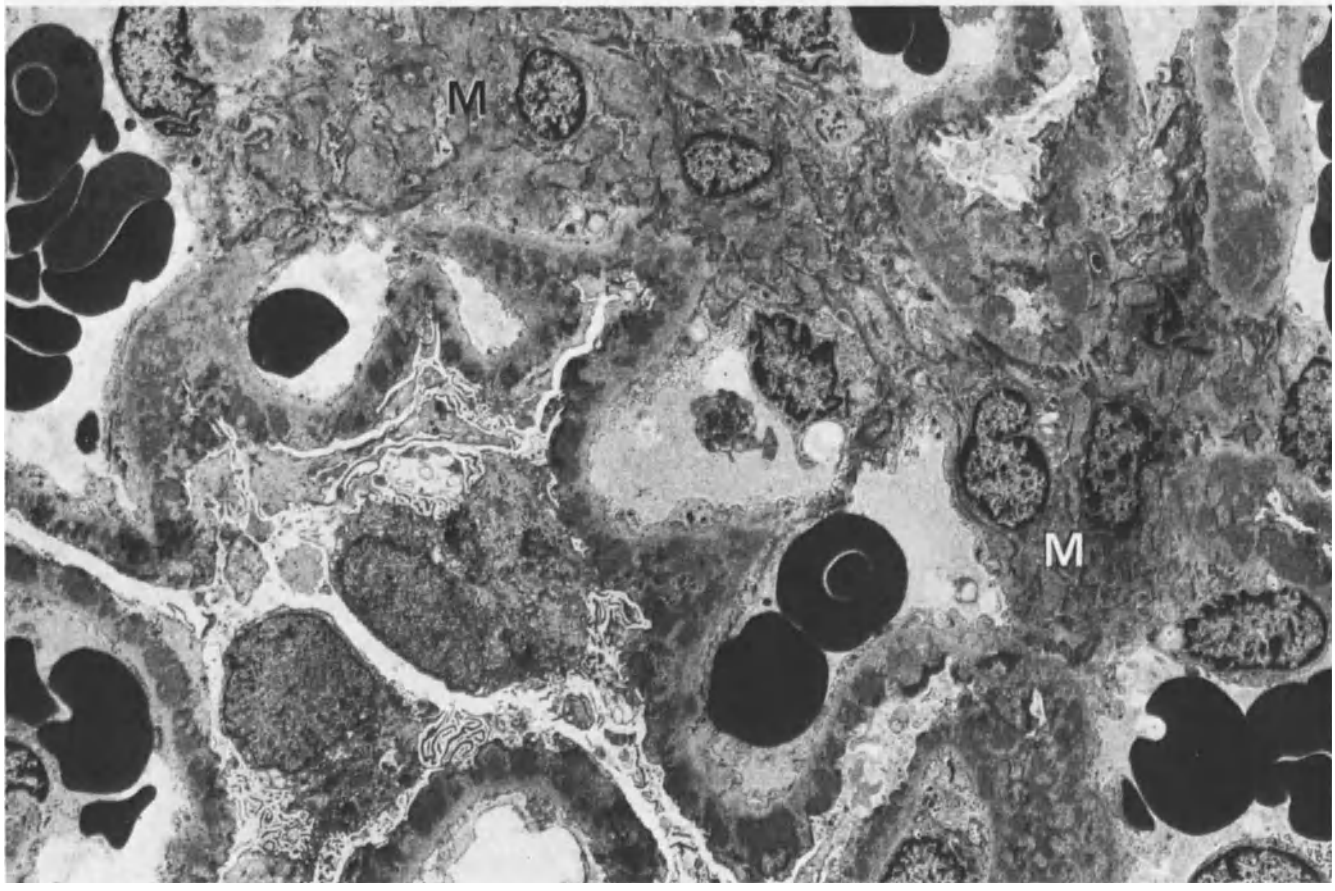


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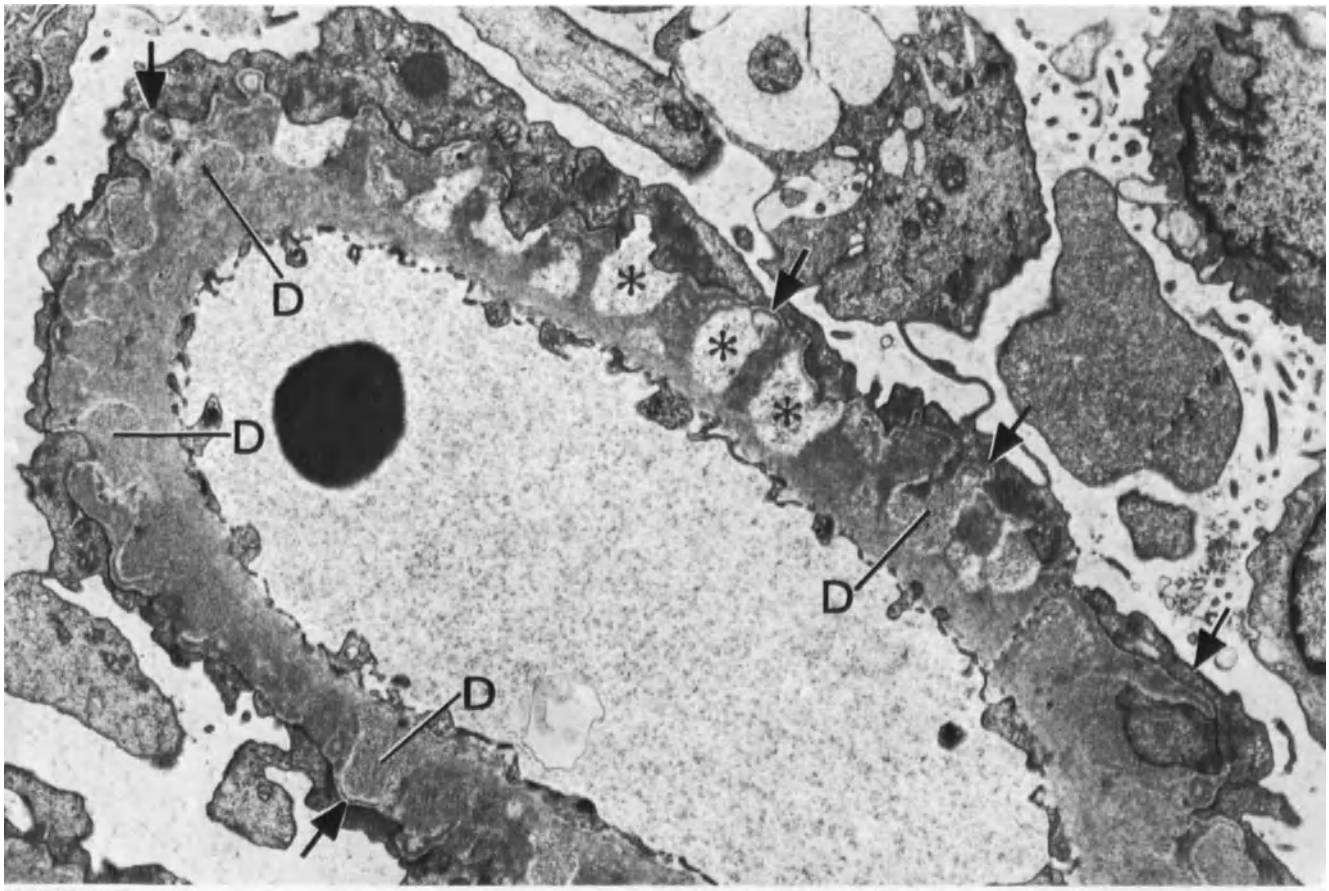


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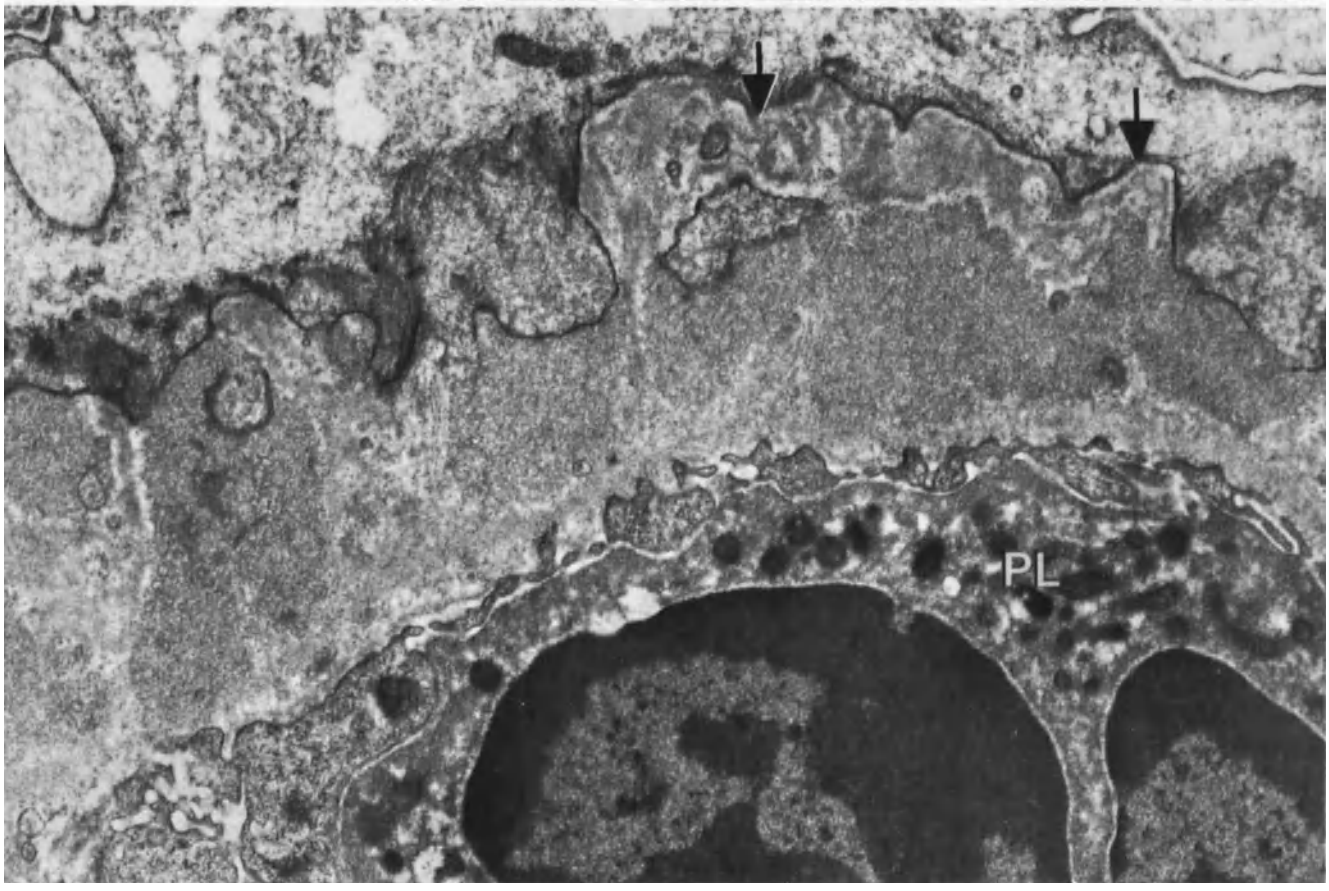



14.132

In stage III, primarily intramembranous deposits are more often observed (4 out of 13: Z). The mesangial proliferation (6 out of 13: Z) is not severe [92]; the mesangial matrix is increased with varying severity (9 out of 13: Z). Deposits in the mesangium and along the mesangial BM were each present in 3 out of 13 cases (Z).

The remaining elements—with the exception of the blood vessels—revealed no new aspects. In the arteries and arterioles, occasionally within the BM or outside of it, finely granular osmiophilic deposits of about 200 Å attributed to immunologic processes have been described [1176]. They are reported to be different from those occurring in hypertensive vasculopathy which are coarser (see also [122]). We have confirmed this finding in 1 out of 13 cases in which, however, severe hypertension was present and in which, accordingly, we attributed it to hypertension and not to immunologic processes.

Interstitium and tubules are only mildly changed as already described under LM.

***Stage IV. Repair Stage.*** In this stage, osmiophilic deposits are absent; their electron translucent residues have migrated subendothelially in severely reduced numbers (Fig. 6.31). The outer structure of the BM has again become more or less smooth; the lamina densa is loose and irregular (Fig. 14.135).

The total thickness of the BM is very much increased with respect to the norm (Fig. 14.135; [88, 91, 503, 1372]) and its outer surface is still somewhat wavy.

***Stage V. Progressive Glomerular Obsolescence.*** The EM findings are similar to those observed with LM. The glomerular BM shows changes as described in stages II to IV.

◁ **Fig. 14.131.** Same case as in Figure 14.117. Epimembranous GN in stage III. Under LM, stage II was assumed. Some of the osmiophilic granular deposits (*D*) are still clearly recognizable. They are covered by a thin densa and rara externa layer (→) which join the spike together. Additionally, numerous translucent lacunae (*), which are also covered by newly formed BM, and which still contain deposit residues, are also present. Whereas podocytes evidence complete fusion of foot processes, endothelium is practically unchanged. Male, 33 years. EM (×8400)

**Fig. 14.132.** Epimembranous GN in stage III, with roof-shaped new formation of lamina rara and a relatively thin densa layer (→). A polymorphonuclear leukocyte (*PL*) is seen in a glomerular capillary loop. Female, 60 years. EM (×21,360)

***Stage VI. Acute Relapse.*** Fresh subepithelial deposits are not infrequently found in the late stages (Fig. 14.136) which demonstrate the same degree of osmiophilia as the deposits encountered in stage I (7 out of 13: Z; see also [633]).

## Differential Diagnosis

In the early stage, differentiation from glomerular minimal change is difficult—or even impossible—with LM, but easy with EM and IF.

In stages II and III, only differentiation from membranoproliferative GN may sometimes be difficult with LM. The spikes demonstrable with PASM stain and the absence of substantial mesangial proliferation are clearly indicative for epimembranous GN, while massive subendothelial deposits, severe BM splitting with mesangial interposition and obvious mesangial proliferation with pronounced interstitial infiltrates point to membranoproliferative GN.

The combination of subendothelial and numerous subepithelial deposits with spikes in the presence of only scanty mesangial proliferation should direct initial suspicion to the membranoproliferative variety in SLE [1797]; see also p. 326 and secondly to the mixed form of epimembranous and membranoproliferative GN.

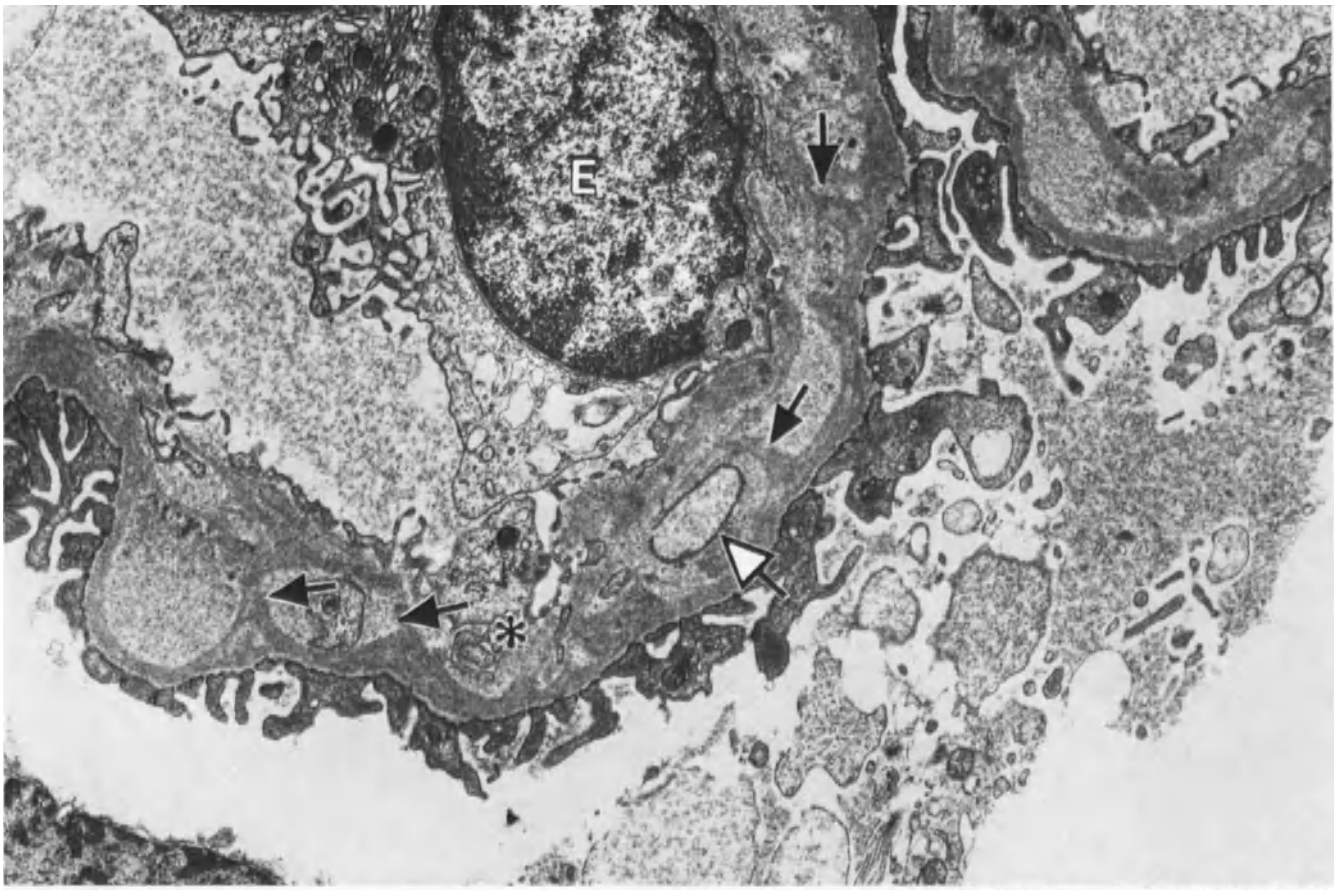
The stage of progressive glomerular obsolescence with transition to contracted kidney may present great difficulties; if spikes are not demonstrable, the diagnosis of GN contracted kidney—without more exact classification—is sometimes unavoidable, even with EM [1359]. Even diabetic glomerulosclerosis (Kimmelstiel-Wilson), can be difficult to distinguish from the stage of progressive glomerular obsolescence [416, 1167], if hyaline nodules, red in van Gieson's stain, are lacking. To be sure, in diabetic glomerulosclerosis, mesangial thickening is usually more extensive and arteriolosclerosis is always present.

Difficulties with respect to transplant glomerulopathy will hardly ever arise. Severe transplant glomerulopathy is already recognized in LM by the complete absence of spikes and the large cell-free interspace between the two completely separated BM layers.

In the symptomatic form of epimembranous GN (with known basic disease and etiology: 19 out of 69: [1167]) only the epimembranous variety of SLE-GN (8 out of 69: [1167]; see also [3, 91, 126, 416, 1539] and p. 326) can, although rarely, be diagnosed in the presence of hematoxylin bodies.

Furthermore, the symptomatic forms cannot be differentiated from the idiopathic [3, 416, 1539, 1628E]. The unequivocal identification of gold-induced cases requires microradiography.

The numerous cases of combined renal vein thrombosis (see p. 503) and epimembranous GN (5 out of 125: [278];

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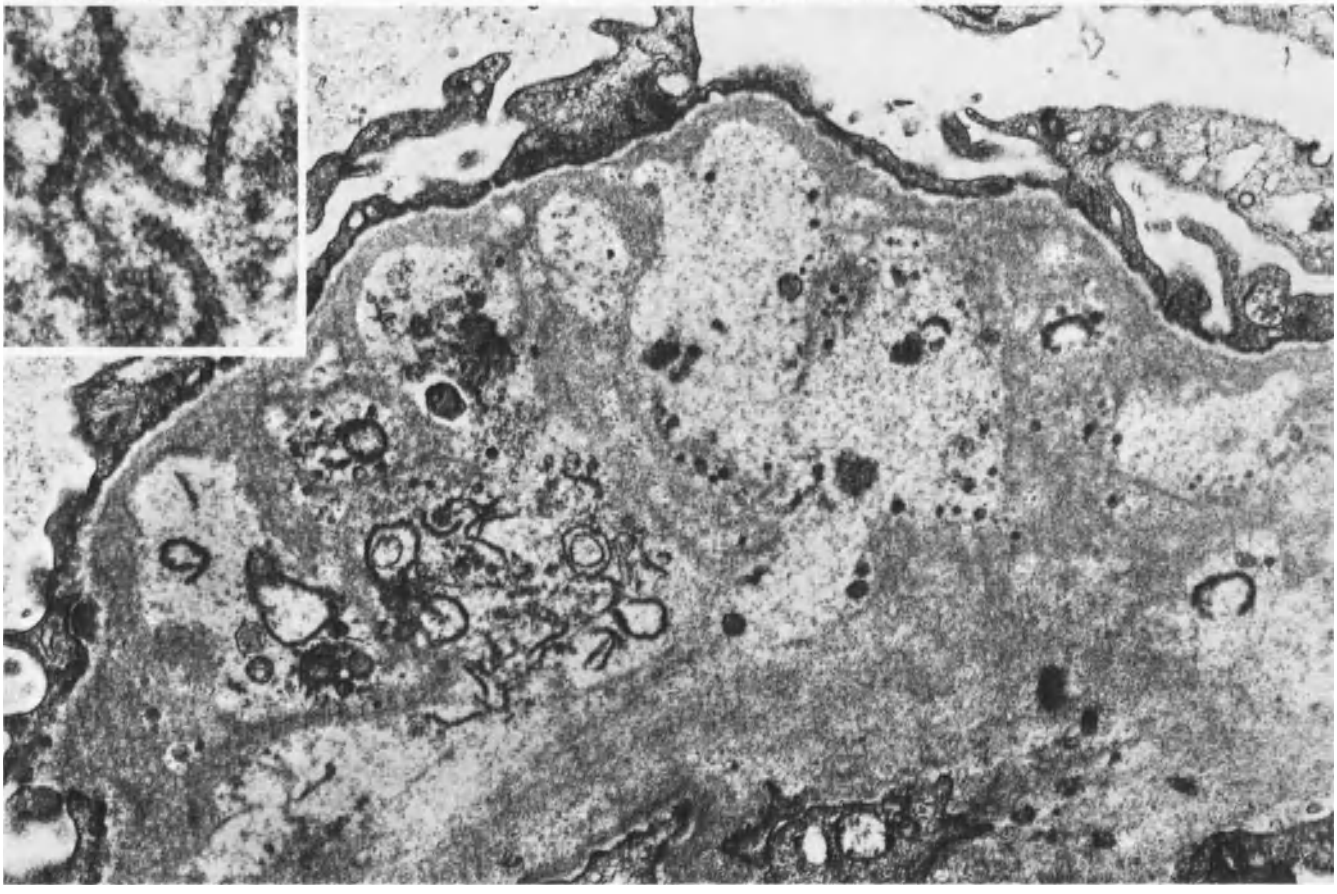


14.134

1 out of 72: Z) present an additional diagnostic problem. According to our experience, the presence of numerous leukocytes in the capillary loops as well as massive dilatation of the loops themselves help (at most in the early stage) in the diagnosis of associated renal vein thrombosis. Diffuse interstitial edema in the early stage and corresponding sclerosis in the late stage are slightly more reliable clues to the presence of thrombosis [1367].

## Prognosis

The overall prognosis is not as bad as was previously assumed [1272, 1281]. This is especially true for symptomatic forms associated with syphilis, drugs, etc., which heal after appropriate treatment of the underlying disease or withdrawal of the noxious substance [94, 317]. The prognosis for children—especially those under 10 years of age—appears to be better than that for adults (20% and 44% cure, and 40% and 33% death in uremia: [633, 1204]). The 5-year survival rate is reported to be between 45–100% [1281] and in our own material at 75% (Table 14.18; 80%: [572]; 69%: [503]; 45%: [661]; 60%: [417]; see also [3]). Within the first 10 years, survival was reported as 56% [503] and 60% (Table 14.18). The long-term outlook (15-year survival rate) is not good (37%), however, when one considers all stages together (see Table 14.18). The picture is different when early and late stages of the disease are considered separately. In this case, the 15-year survival rate from biopsy onwards is 85% in stages I and II in contrast to only 14% for the later stages (III, V).

The overall complete remission rate is reported to be 17% [407] as it is in our own material (Table 14.18).

Table 14.18. Prognosis and outcome of epimembranous glomerulonephritis

| Prognosis | Survival rate (%) | | |
|---|---|---|---|
| | 5 years | 10 years | 15 years |
| From disease onset | 75 | 60 | 37 |
| SE[a] | 5.7 | 7.3 | 9.6 |
| From biopsy | 76 | 57 | 28 |
| SE[a] | 6.9 | 7.2 | 15.2 |
| From biopsy | 85 | 85 | 85 |
| Stages I and II, SE[a] | 8.8 | 8.8 | 8.8 |
| From biopsy | 70 | 43 | 14 |
| Stages III and V, SE[a] | 8.5 | 9.5 | 12.8 |

*Outcome* (after minimal follow-up of 1 year)

| | Total | Stage I, II | Stage III, V |
|---|---|---|---|
| Patient number | 45 | 20 | 25 |
| Died (total) | 42.2% | 20% | 60% |
| Died in uremia | 26.6% | 0% | 48% |
| Complete remission | 17.4% | 30% | 8% |

[a] SE standard error in %.

In the remaining patients, the lesion remains stationary for years (20%: Z) or undergoes spontaneous remission (10%: Z; see also [3, 126, 407, 1272, 1359]). Progression of the disease is observed in over 40% [407] (33%: Z) of the patients and lasts for as long as 27 years: [503]. Isolated attacks with deterioration are not rare (25% in children: [636]; 33%: [1204]; 5%: Z).

If early and late stages are considered separately, in stages I and II 30% of patients were considered as cured and 15% as being improved clinically in our material, whereas in stages III and V 48% died from uremia and only 16 were considered as cured or improved. Similar results were reported by other investigators who demonstrated in rebiopsies recovery in stage I in 8 out of 14 patients and no morphologic impairment, whereas in later stages, only 3 out of 62 improved ([122]; see also [445]).

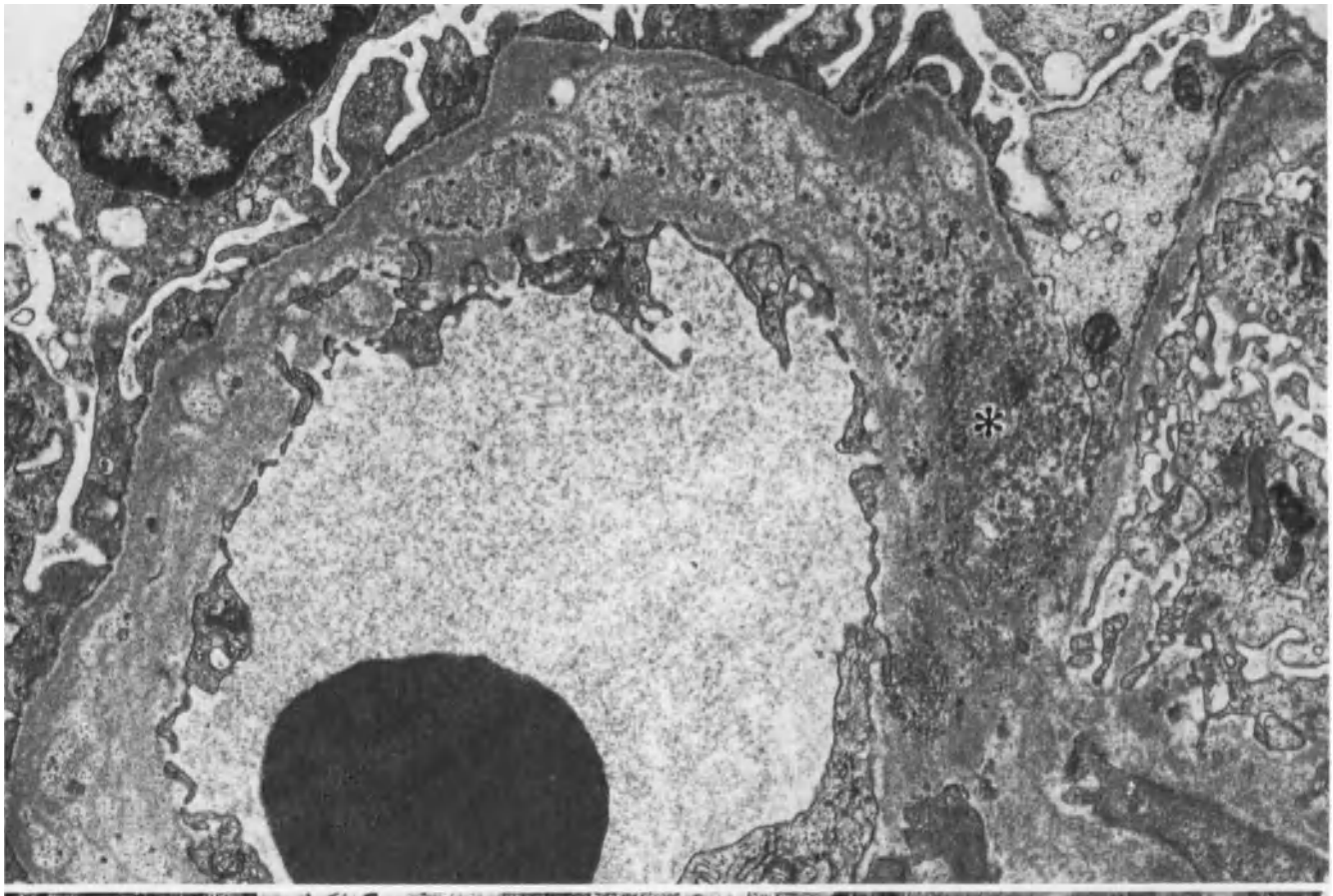
Death usually occurs in renal insufficiency or is due to infection (corticoid therapy!) or, in 15% of cases, to renal vein thrombosis [278] which is heralded by sudden, rapid deterioration of renal function.

Disappearance of positive IF findings and osmiophilic deposits is usually associated with reduction or even complete remission of proteinuria and is a favorable prognostic development while early appearance of hypertension is a poor prognostic sign [122, 1167, 1168].

Two reports of relapses in transplants 2 and 11 months respectively after transplantation [332] stand in contrast to 5 transplants without relapse [1290].

◁ **Fig. 14.133.** Epimembranous GN in stage III. Formation of "ladder rungs" (→) through dissolution of osmiophilic deposits. Isolated endothelial cytoplasmic elements are present in BM (*). Thread-like structure within a dissolved deposit is discernible (⇨). Highly activated endothelial cell (*E*) with slight arcade formation is seen in the capillary lumen. Podocytic foot processes are somewhat coarse but not fused. Female, 49 years. EM (×10,400)

**Fig. 14.134.** Epimembranous GN in stage IV. In the somewhat tangentially sectioned BM, masses of clumpy, granular, and thread-like degradation particles are present in translucent areas previously containing deposits. Complete fusion of podocytic foot processes. Male, 51 years. (×19,200)
*Inset:* Higher magnification of thread-like structures which clearly evidence a bilamellar configuration as well cross striations. (×83,500)

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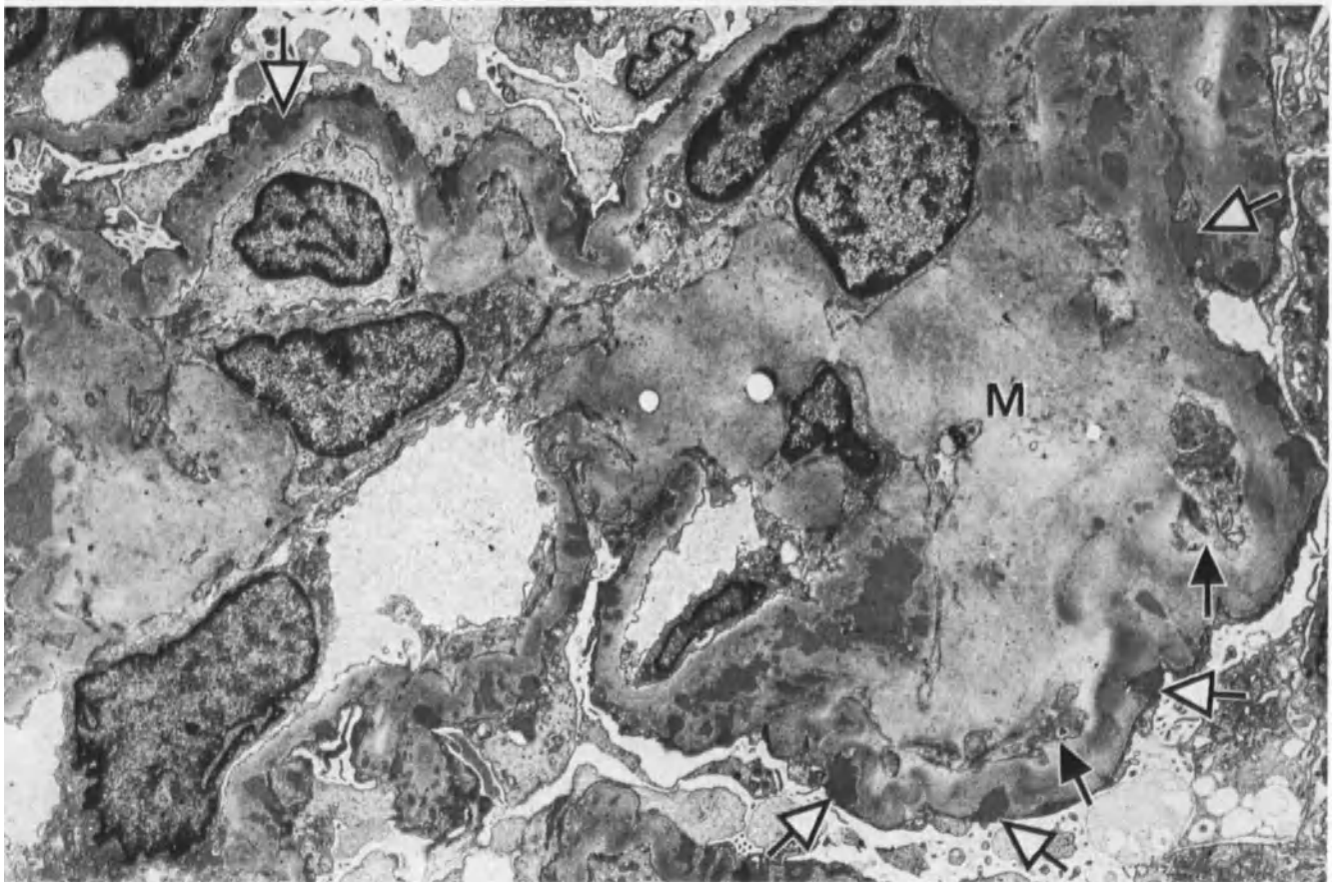


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## Pathogenesis

There is general agreement that the lesion is an immunocomplex glomerulopathy [1359] due to transient, protracted or recurring circulation of immunocomplexes [544, 1372].

In many cases, an autoimmune disease (SLE in 42% of all epimembranous GN: [544]; 6.7%: Z) is present or probably present [254, 1072] in which autoproteins (possibly cell elements) are denatured by drugs, etc., and become antigens (see below).

Experimentally, the lesion has been elicited by long-term administration of heterologous serum in association with faulty antibody formation (immunocomplexes class I: [544]) or in association with adequate antibody formation and blockade of the RHS in rabbits [381]. Following repeated injection of homologous kidney homogenate (renal mitochondrial protein) or egg albumin in Freund's adjuvant, the same result was obtained in rats and rabbits [693, 1712] although some of the animals developed membranoproliferative GN.

A few investigators maintain the view that epimembranous GN is a degenerative noninflammatory lesion [3, 1359, 1484]. Since it is an immunocomplex disease which, due to the localization of the deposits, does not lead to constant glomerular cell proliferation [1624b], we consider the assumption of the glomerulonephritic nature of the lesion to be justified.

## Etiology

Etiology of the *idiopathic form* is, by definition, unknown [1167, 1359]. There is no relationship to streptococcal diseases. Unfortunately, the incidence of the idiopathic form in children is still very high (50 out of 69: [1167]; 50 out of 50: [633]) but it is nearly as high (78.5%) in our material (see Table 14.19) comprising mainly adults.

Table 14.19. Etiology of epimembranous glomerulonephritis ($n$= 60)

| | |
|---|---|
| Viral hepatitis | 8.3% |
| SLE | 6.7% |
| Gold therapy | 4.8% |
| Penicillamin therapy | 1.6% |
| Malignant tumor | 1.6% |
| Idiopathic | 78.5% |

The number of symptomatic cases increased during the last decade. The bulk of symptomatic cases consist of epimembranous GN in SLE (6.7%: Z; 42%: [544]). Although SLE is not clarified etiologically, its pathogenesis at least is understood.

Etiologically, unambiguous cases belonging to the *symptomatic form* are observed in association with drugs: especially gold therapy for polyarthritis [183, 811, 934, 1025, 1507, 1583, 1628, 1648, 1693; Table 14.19; experimental: [1176]). In our own three cases, gold was demonstrable histochemically in one of the cases and—using atomic absorption-analysis—in all three in considerably different amounts (relative amounts: 1:2:22). Others have demonstrated gold by EM in tubular epithelium and unequivocally confirmed its presence by electronprobe microanalysis [1693a].

Further cases are encountered associated with anticonvulsive therapy (children: [1613]) and with D-penicillamine therapy [760]. Mercury-containing agents [90, 247]—such as used by coloured people for skin bleaching [827] and as shown experimentally and empirically [1788] can also lead to epimembranous GN. We have observed one autopsy case each after arsenic and benzol trichlorethylene poisoning. Whether the drugs or toxic substances act as haptens [183, 1176] or by a toxically induced structural damage of tissue proteins [90] is not known. Gold is a confirmatory example for the second hypothesis since it is stored in cells and thus destroys mitochondria. Drug vehicles may play a role in causing the disease [417]. The disease has also been found associated with pregnancy in 8 cases [275a].

Further symptomatic cases have been noted during the course of long-lasting infections such as congenital syphilis [810], acquired syphilis [148, 190], malaria [16, 403a] and sarcoidosis [1045, 1415]. In acquired syphilis, treponemal antigens can be demonstrated in the deposits [526, 1217b]. Common to all these cases is the disappearance of deposits and normalization of BM following drug withdrawal or cure of the basic disease (contra: [1765]). A special form with hypocomplementemia but without malaria has been reported in the tropics [1140]. There are reports relating epimembranous GN to malignant tumors [521a] (bronchus carcinoma: [52, 317, 544, 972]; cervix carcinoma: [544]; breast carcinoma: [972];

◁ **Fig. 14.135.** Same case as in Figure 14.134. Epimembranous GN in stage IV. Masses of granular (virus-like) particles (*) which are thought to be degradation granules are seen in the areas of former deposits. BM is still irregular and obviously thickened. Male, 51 years. EM (×14,150)

**Fig. 14.136.** Epimembranous GN in stage V with acute relapse (stage VI): massive, uniformly homogeneous enlargement of mesangium (*M*) with practically complete occlusion of peripheral glomerular capillary loop lumens (→). Numerous fresh subepithelial deposits (↠) indicating acute attack. Female, 58 years. EM (×2520)

squamous cell carcinoma of the tongue and colonic carcinoma: [318]; malignant lymphoma: [345, 609, 822, 972]; see Table 14.8). It is thought that tumor-associated antigens lead to immunocomplex formation [822, 972] as is the case in colon and bronchial carcinoma in which the carcino-embryonic antigen has been demonstrated [317, 318, 322] within the immunocomplexes (see also: [345, 694a, 957a], for survey: [1812]).

Finally, viruses can be responsible for epimembranous GN and especially hepatitis B virus (1 out of 31: [544]; 5 out of 9 in chronic hepatitis B: [608]; children with persisting hepatitis: [151]; see also [9, 197, 299, 424, 617, 872a] and p. 250). In our own biopsy material, we encountered this association once following acute viral hepatitis B and once during the course of chronic, aggressive hepatitis B of 7 years' duration. In three further cases there was anamnestic evidence of viral hepatitis (but hepatitis B surface AG determination was not done, Table 14.19). Hepatitis B surface antigen can be demonstrated in immunocomplexes within the kidney [211]. The clinicoserologic examination for viruses—especially hepatitis B virus in proven cases of epimembranous GN—is certainly indicated for the future.

Further support for a viral etiology is provided by the occasional EM demonstration of virus-like structures [822]. These particles are also found in NZB mice and in Aleutian mink [265, 682]. The renal disease observed in these two animal types are most probably caused by virus, and it is very similar to epimembranous GN. Some investigators, however, have interpreted the disease in mink as membranoproliferative GN [392]. For epimembranous GN and renal vein thrombosis, see p. 505.

## Mixed Form of Epimembranous and Membranoproliferative Glomerulonephritis

### Definition

This form is characterized by the combination of extensive subepithelial and subendothelial deposits and by a pronounced mesangial proliferation and mesangial interposition.

***Synonyms:*** Acute poststreptococcal GN with failure to resolve [559], acute GN with mesangial proliferation and extramembranous deposits [531]; transitional forms [1593, 1709].

### Incidence

The change is unquestionably rare and has been reported in 4 out of 1368 biopsies in clinical GN [624], in 0.2% of biopsies, and 0.4% of biopsies in GN (Z) and in 9 out of 31 of membranoproliferative GN [231]. In studies relying exclusively on LM, the frequency may be underestimated, since confusion with membranoproliferative or epimembranous GN is possible.
Most patients are over 20 years of age. The disease predominantly affects women (see also [231]).

### Clinical Findings

Acute onset in the form of poststreptococcal GN was reported twice [559] and the other patients in this series demonstrated an insidiously progressive nephrotic syndrome with hematuria. Isolated instances of hypertension occur and, according to one report [559], persisting hypocomplementemia. It is not possible to clinically separate this disease from other forms of GN [531].
In three of our own cases (women aged 15–38 years) the disease developed insidiously and edema, microhematuria and proteinuria were present upon clinical examination. Later, our patients evidenced nephrotic syn-

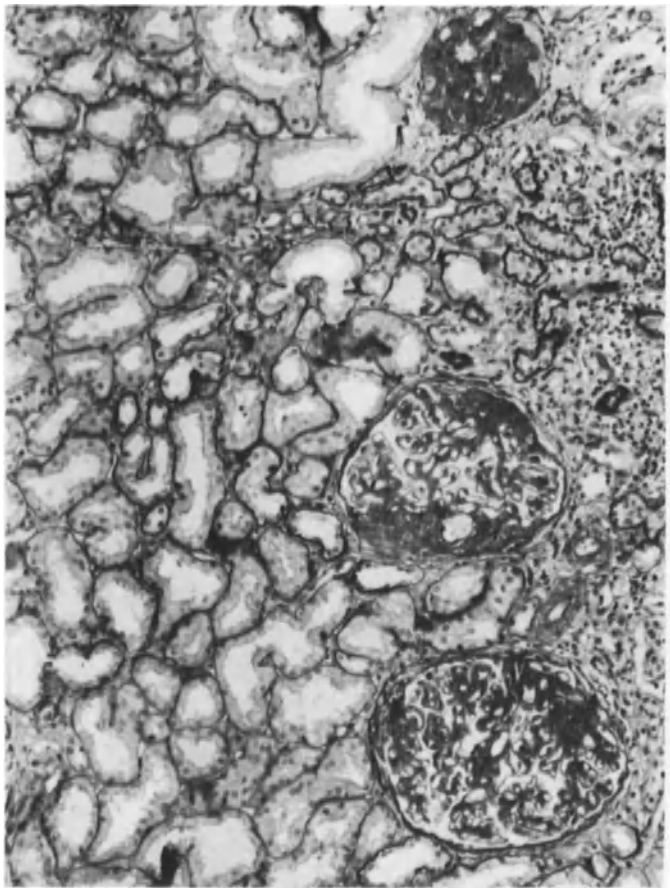


**Fig. 14.137.** Mixed form of membranoproliferative and epimembranous GN. Under LM, a diffuse segmentally accentuated membranoproliferative GN would be diagnosed. Male, 18 years. PAS (×110)

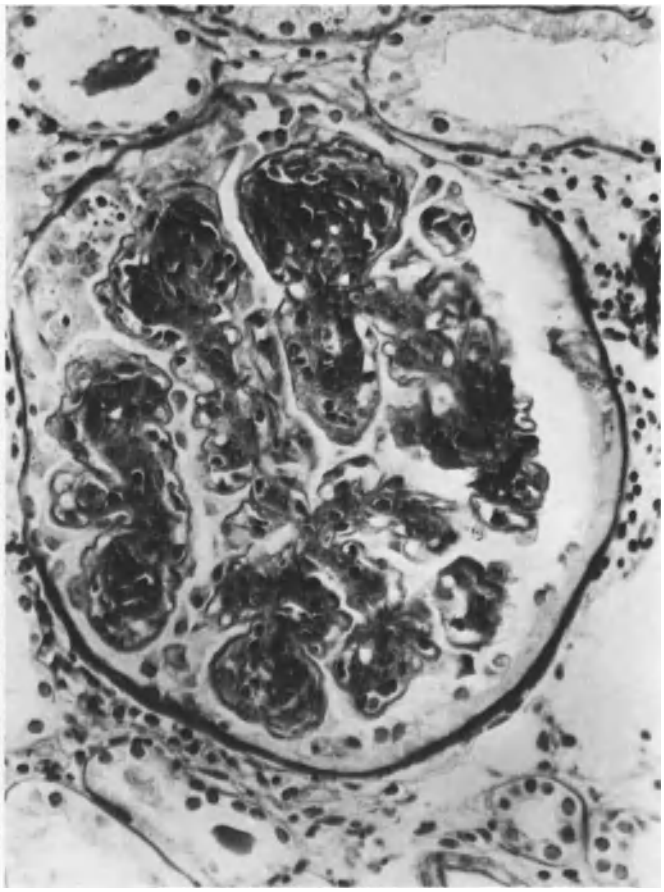
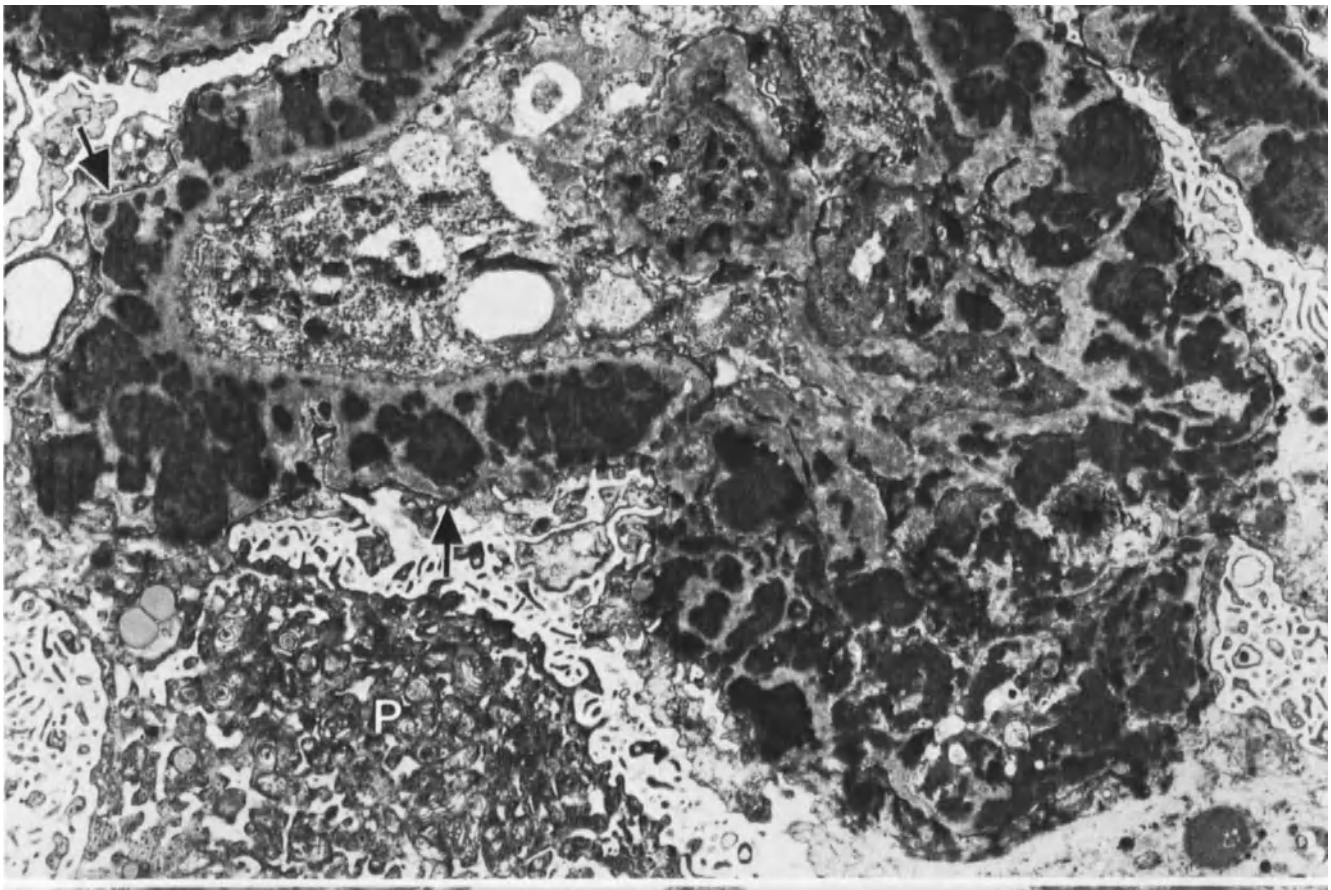


**Fig. 14.138.** Same case as in Figure 14.137. Membranoproliferative component with lobular transformation of glomerulus and pronounced periglomerular inflammation are evident. PAS (×200)

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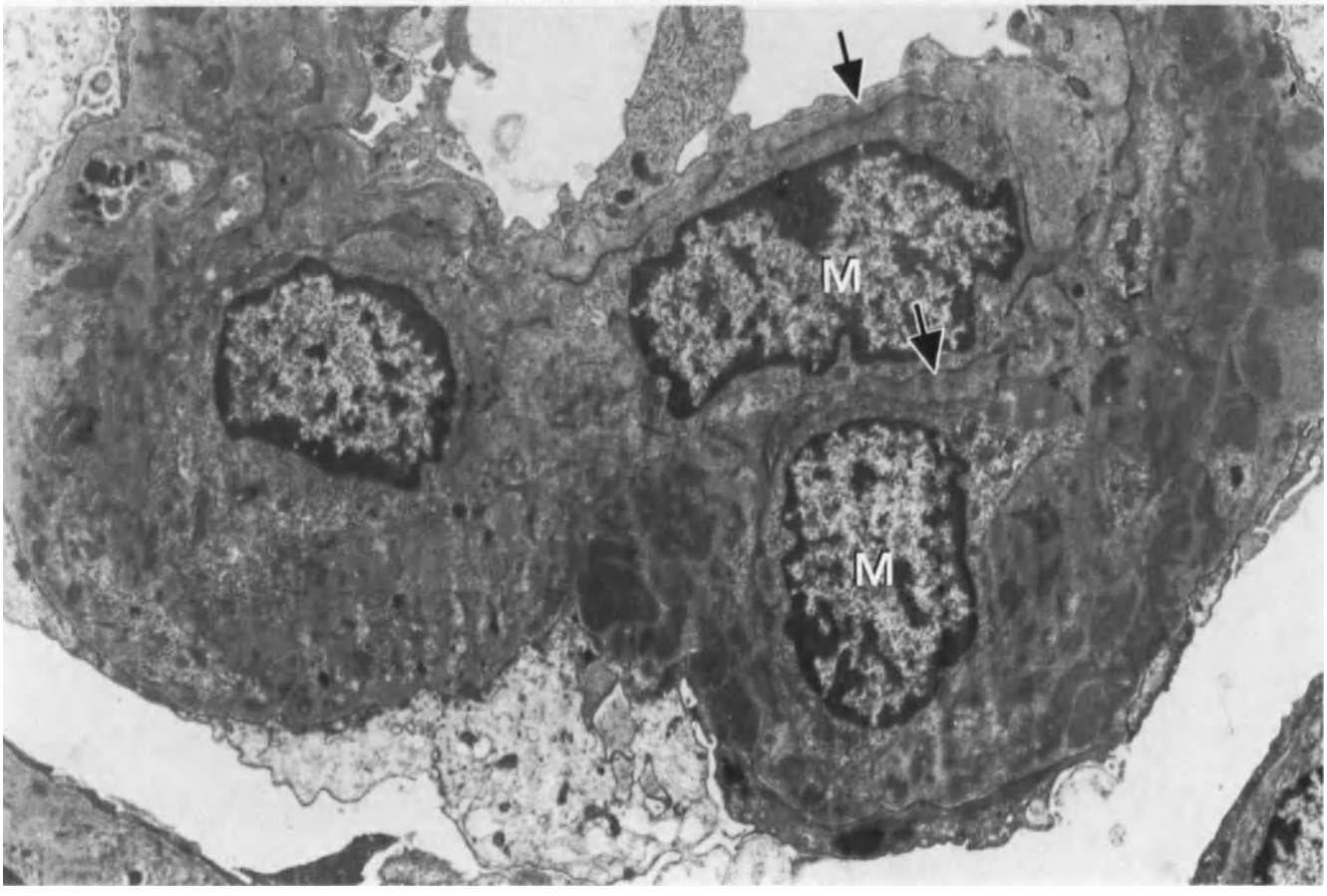



14.140

drome, hypalbuminemia, and hyperlipemia, and one had microhematuria, 1 out of 2 hypocomplementemia, and 1 out of 3 hypertension. One of the patients subsequently developed SLE. Another died after 1 year of observation from the consequences of diabetes mellitus that required varying doses of insulin which were very difficult to gauge. No insulin AB were found in this case.

### LM Findings

One encounters either the findings of membranoproliferative or of lobular GN with or without isolated spikes or findings of epimembranous GN with severe mesangial cell and matrix increase (Figs. 14.137, 14.138; see also [531]) as well as subendothelial fibrinoid deposits. Partial crescents may be present as well [531]. The presence of a mixed form is only clearly apparent with EM.

### IF Findings

In the only two known reports [231, 531], IgG and complement were found diffusely distributed in granular form, as were IgM and properdin [231].

### EM Findings

The very numerous subepithelial deposits (Fig. 14.139) and nodular intramembranous [559] osmiophilic deposits (Fig. 14.140) are immediately apparent; they are unclearly delimited from the lamina densa throughout (see also [531]).
Obvious mesangial interposition is seen in the capillary loop periphery (Fig. 14.140). Furthermore, intense mesangial proliferation with nuclear increase occurs. In our cases (3 out of 3), there were subendothelial osmiophilic deposit formation and a few instances of mesangial interposition.

### Differential Diagnosis

With respect to epimembranous GN, mesangial proliferation and enlargement are unusual findings. These findings are present in epimembranous GN, if at all, in late stages. Subendothelial deposits and mesangial interposition are always absent.
On the other hand, the presence of large numbers of subepithelial deposits is unusual for membranoproliferative GN as is their unclear delimitation from the lamina densa.

### Prognosis

Our material has not provided observations of sufficiently long duration to permit a reliable judgement. In findings of another investigator, which must be viewed with caution due to the large number of cases presented, 23 out of 31 were cured and only one fatality was reported [531].

### Pathogenesis and Etiology

It is thought that the size and solubility of the immunocomplexes determine the form of GN which ultimately develops. At present, it cannot be stated whether the so-called mixed form represents a unique disease entity, or whether it is merely a rare transitional form in a continuous spectrum of possible immune reactions.
It should also be borne in mind, as our observations have shown, that other underlying diseases such as diabetes mellitus, which also involve the kidney, can modify the finding in GN in such a way that no typical GN form can be recognized.

◁ **Fig. 14.139.** Same case as in Figure 14.137. Very extensive, completely irregular epimembranous deposits are sometimes covered by newly formed BM (→). Severe cystoid degeneration of podocyte (*P*) and microvilli formation are present. EM (×5600)

**Fig. 14.140.** Same case as in Figure 14.137. In addition to very extensive subepithelial deposits, mesangial interposition (*M*) with new formation of a subendothelial (→) BM is clearly recognizable. Male, 18 years. EM (×6530)

# 15. Foccally Accentuated Glomerulonephritis

## Embolic, Purulent Focal Glomerulitis, and Thrombotic-Induced Glomerulonephritis

The diagnostics of this group of diseases is difficult at autopsy, and even more so in needle biopsy in which the problem is further complicated by scanty material consisting predominantly of cortical tissue. It is noted that it is especially the focally accentuated GN forms (FGN) in which the changes are frequently—and predominantly in the early stage—restricted to the corticomedullary region and hence easily elude biopsy.
Despite the inherent difficulties, every effort should be made to thoroughly assess biopsy material since it is often possible to establish the diagnosis of the underlying disease purely on the basis of morphologic findings (e.g., FGN in subacute bacterial endocarditis, Goodpasture's syndrome, Wegener's syndrome, embolic purulent focal glomerulitis, SLE, etc.).

### Definition

FGN afflict, as seen under LM, only a part of the glomeruli (focal as contrasted to diffuse) and in an individual glomerulus, only a part of the loops (segmental as contrasted to global in diffuse GN, see also [685]). Furthermore, many cases of FGN evidence a disease course characterized by repeated attacks [620, 1711, 1797].
On the basis of this definition, we wish to emphasize the following four points:

1. The only GN which merits the designation of genuine focal GN is embolic purulent glomerulitis. All other forms are better designated as focally *accentuated* GN, since in addition to segmental focal changes under LM, diffuse lesions are often encountered in EM [1399] or in IF [620, 816, 1136]. The borderline between diffuse GN and FGN is, accordingly, ill defined. It is very probable that mild cases of diffuse GN lead to late focal and segmental changes [410, 654] as has been demonstrated experimentally in Masugi nephritis [1785] under LM.
2. Morphologic signs of repeated clinically acute attacks may be absent due to healing or due to sampling error.
3. With progression of the disease—as a consequence of many attacks—a diffuse and panglomerular affliction may be present as in FGN in subacute bacterial endocarditis, Goodpasture's syndrome, SLE, etc. [689, 791].
4. The number of severely afflicted glomeruli is of prognostic significance (multi-/pauciglomerular affliction: [1064]).

## Embolic, Purulent Focal Glomerulitis

### Definition

Hematogenous bacterial or mycotic metastases to the glomerulus (the first kidney filter).

### Incidence

This form is rarely seen in needle biopsy, with the exception of acute pyelonephritis with hematogenous dissemination (see p. 426). We encountered it in 341 out of 25,000 autopsies, i.e., 1.4%, and in 0.09% of renal biopsies.

### Clinical Findings

In severe dissemination, sepsis or pyemia dominate the clinical picture, whereas in milder instances, pyuria, bacteruria, mild proteinuria, and hematuria are the constant symptoms.

### LM Findings

The glomeruli function as the primary intrarenal filter and are therefore afflicted in massive hematogenous bacterial dissemination of high virulence and/or in decreased resistance, (Fig. 15.1). In less severe cases only the intertubular vessels (second filter) are involved. In a few glomeruli, isolated loops are filled with bacterial or fungal emboli and fibrin (Fig. 15.2). Mesangium, cap-

sular space, neighboring loops, and periglomerular interstitium contain masses of polymorphonuclear leukocytes.
The initially segmental lesion is rapidly transformed into a global one by extension of the inflammation. In protracted disease, small abscesses develop which extend into the surroundings.

### IF Findings

The IF findings are insignificant; thus, in one of our cases, the glomeruli were completely negative. In another case, focal-segmental distributed C3 was present uniquely in the periphery; fibrin(-ogen) was not present.

### EM Findings

Capillary loops, capsular spaces, and the surrounding are heavily infiltrated with polymorphonuclear leukocytes. Loop necroses and BM interruptions are very common. Otherwise, loop BM and other glomerular elements are unaltered with the exception of severe degenerative changes in tissue near necrotic foci. In one of our cases, we encountered *Candida albicans* in the capsular space (Fig. 15.2, 15.3).

### Differential Diagnosis

Differentiation from acute pyelonephritis with direct intrarenal spreading is necessary even though between these disease entities only quantitative differences are present. In pyelonephritis, coalescence of purulent foci is more extensive than in embolic, purulent glomerulitis where abscessing foci tend to be restricted to the glomeruli and to their immediate vicinity. Care must be used in not confusing changes arising in vivo with post-mortem intravascular bacterial overgrowth (Fig. 15.4).

### Prognosis

In the presence of sepsis and pyemia, the prognosis depends on the underlying disease; otherwise with scanty glomerular dissemination, scarification is probably the rule i.e. prognosis is favorable.
One might suspect in bacteremia that a few such glomerular foci occur more frequently than is usually imagined. Since the implicated glomeruli are secondarily globally afflicted, the scar will be global and not segmental. It is known that chronic lesions (pyelonephritis) develop only from the foci associated with the second renal filter, the vasa recta spuria, whereas always—present isolated glomerular foci (primary filter) heal by glomerular obsolescence [1791]. Isolated obsolescent glomeruli with periglomerular fibrosis and intact blood vessels in biopsy and autopsy material could be, among other possibilities, the consequence of discrete hematogenous dissemination.

### Pathogenesis and Etiology

Embolic, purulent FGN is a consequence of the hematogenous dissemination of virulent microorganisms of which strepto- and staphylococci are the most common (*E. coli* less so). Today, fungi have become relatively more frequent (14 out of 341:Z; Fig. 15.3).
In our autopsy material, 69 out of 341 cases were due to endocarditis ulcerosa or ulceropolyposa; 41 out of 341 cases developed postoperatively and 16 out of 341 cases were ascribable to infections associated with agranulocytosis. In 151 cases, the disseminating foci were not identified. Finally, immunopathologic processes are said to be involved [520].

## Segmental-Focal Glomerulonephritis in Subacute Bacterial Endocarditis

### Definition

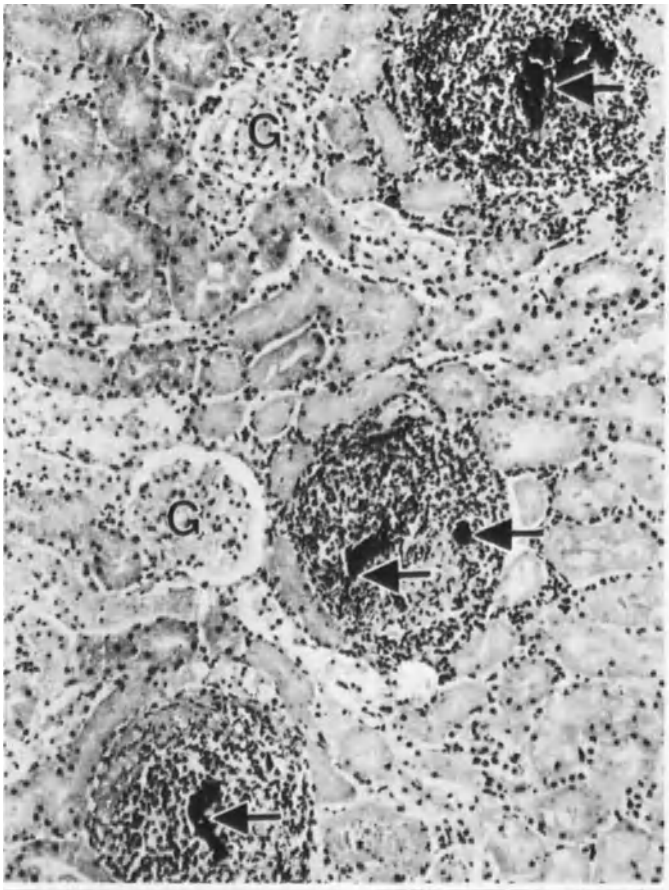
This condition is a nonpurulent form of GN occurring in subacute bacterial endocarditis (endocarditis lenta) in association with capillary loop thrombosis (thrombocapillaritis Löhlein).

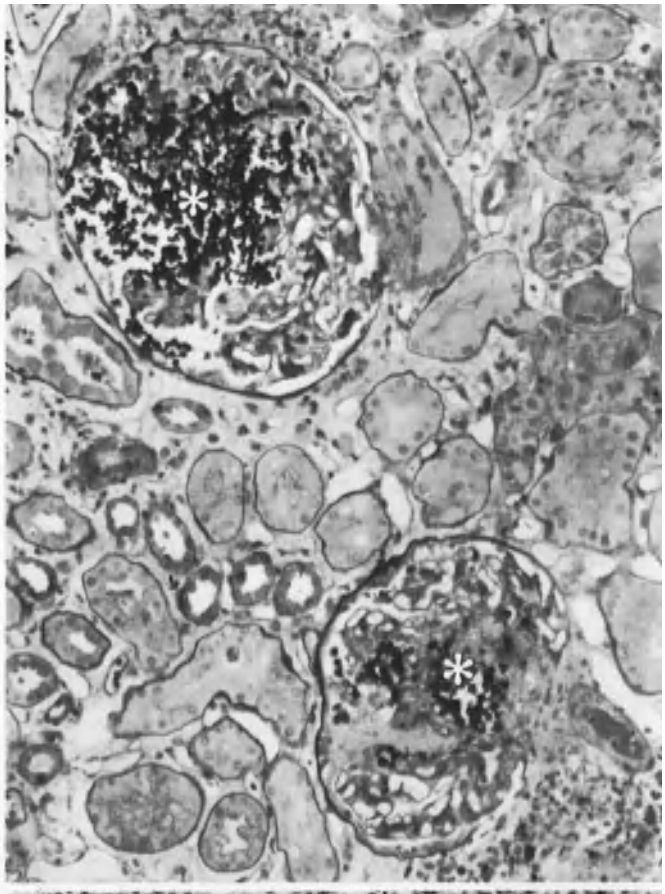
### Incidence

In our autopsy material comprising 27,570 cases, we found 160 cases of bacterial endocarditis of which only 11 were FGN, in contrast to 69 cases of embolic purulent glomerulitis. There has been no obvious change in the incidence of FGN in subacute bacterial endocarditis during the last 20 years. In untreated cases of bacterial endocarditis the incidence of FGN is suspected to be about 30%. We are not aware of data relating to biopsy material.

### Clinical Findings

Microhematuria appears, at the earliest, 6 weeks after onset of endocarditis. Macrohematuria is indicative of infarction. Proteinuria occurs in three-fourths of the patients and uremia in one fifth for which cardiac insufficiency may be involved as a prerenal factor. Hypertension is rarely encountered.



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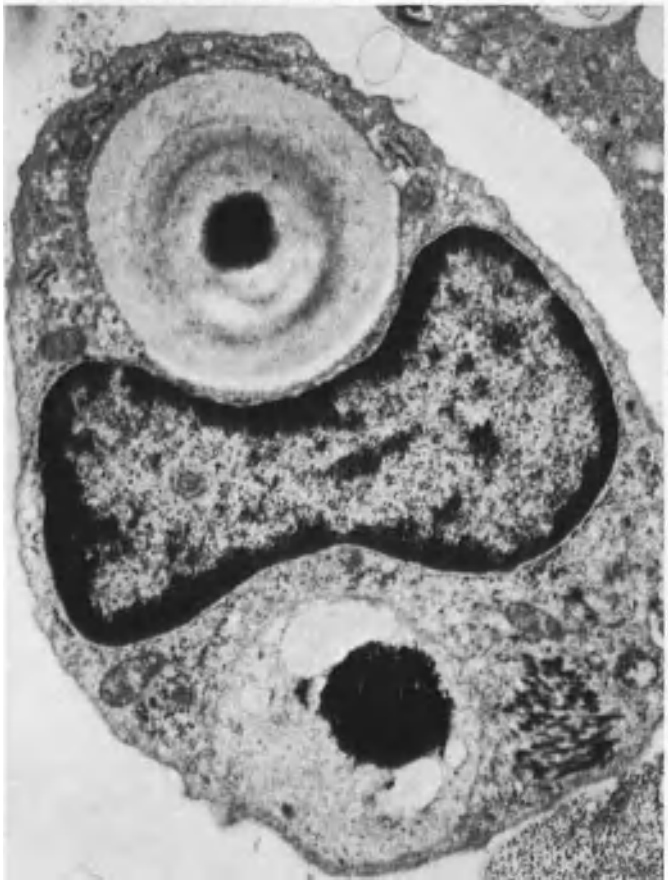
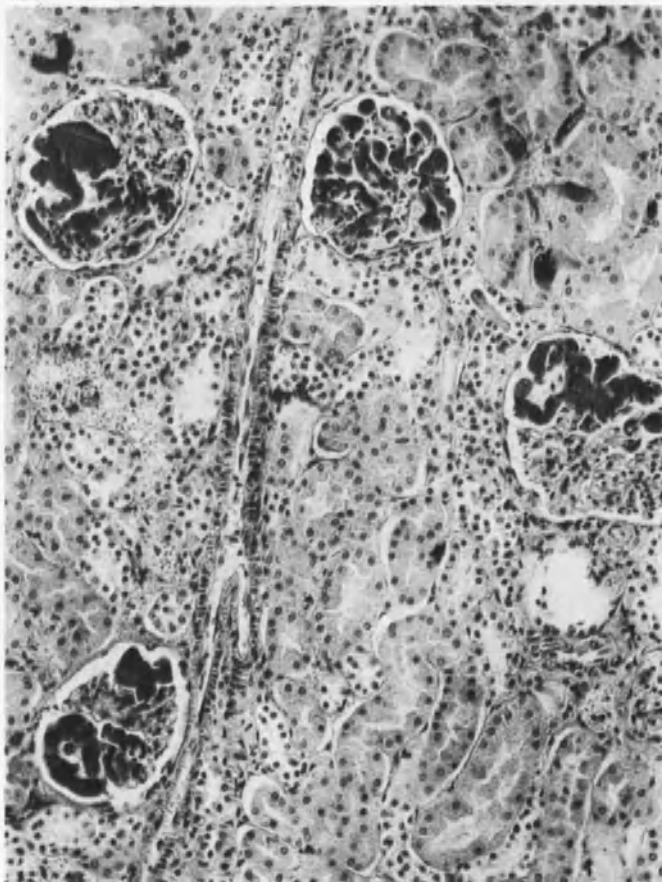




15.3
15.4

In the absence of therapy, diffuse GN may result from a relapsing disease course which can only be correctly interpreted in the presence of fresh FGN [612, 658].

### LM Findings

A variable number of glomeruli contain eosinophilic thrombotic fibrillar masses (Fig. 15.5) which are usually restricted to one loop, and often covered by segmental crescents.
The capillary loop wall is generally necrotic and the BM partially destroyed. Severe cellular proliferation of the mesangium with accompanying infiltration of monocytoid cells and a few polymorphonuclear leukocytes is present and may be also seen in neighboring loops.
Tangential sections may bypass the thrombus and only include mesangial cell proliferation but we have never encountered complete absence of thrombi (7 out of 9: [612]) in our autopsy material. Diffuse, endotheliomesangial GN (Fig. 15.6) has been reported in a few cases ([47, 179]; 1 out of 8: Z); experimentally by presensitization with streptococcus viridans: [47]). Segmental scars and synechiae with Bowman's capsules are typical of older lesions. We were struck by the pronounced wideness of the fibrosed segmental crescents (Fig. 15.7).
Interstitial vessels show no specific changes, but extensive accompanying lympho-plasmocytic interstitial infiltrates and a usually patchy protein droplet storage in the proximal tubules is encountered.

◁ **Fig. 15.1.** Embolic purulent focal glomerulitis: three afflicted glomeruli are shown which have been completely destroyed by leukocytes surrounding massive colonies of bacteria (→). Note two unchanged glomeruli (*G*). Cresyl violet (×90)

**Fig. 15.2.** Embolic purulent focal glomerulitis in candida albicans (*) pyemia in a 5-year old renal transplant. Female, 47 years. PAS (×200)

**Fig. 15.3.** Same case as in Figure 15.2. Phagocytized candida spores in a monocytoid cell located in the lumen of an intertubular blood vessel. Female, 47 years. EM (×10,970)

**Fig. 15.4.** Massive bacterial colonies in glomerular capillary loops probably grown post mortem in panmyelopathy. Male, 7 years. HE (×85)

### IF Findings

Ten cases of GN associated with subacute bacterial endocarditis reported up to now [179, 612, 823] showed, with IF, granular deposits of gamma globulin or IgG respectively and C3 in eight patients whereas two cases of diffuse GN were entirely negative [179].

### EM Findings

In one case, we observed segmental loop obliteration with isolated osmiophilic deposits (Fig. 15.8). The capsular BM bordering the crescents was enormously thickened and riddled with degenerative granules and vacuoles or, it was split and revealed cellular permeation as well as formation of collagen (Fig. 15.9).
It is stated in the only report known to us in the literature that subepithelial deposits as well as occasional humps have been observed in association with staphylococcal endocarditis. In cases associated with streptococci, deposits are supposed to lie more subendothelially and intramembranously [612].

### Differential Diagnosis

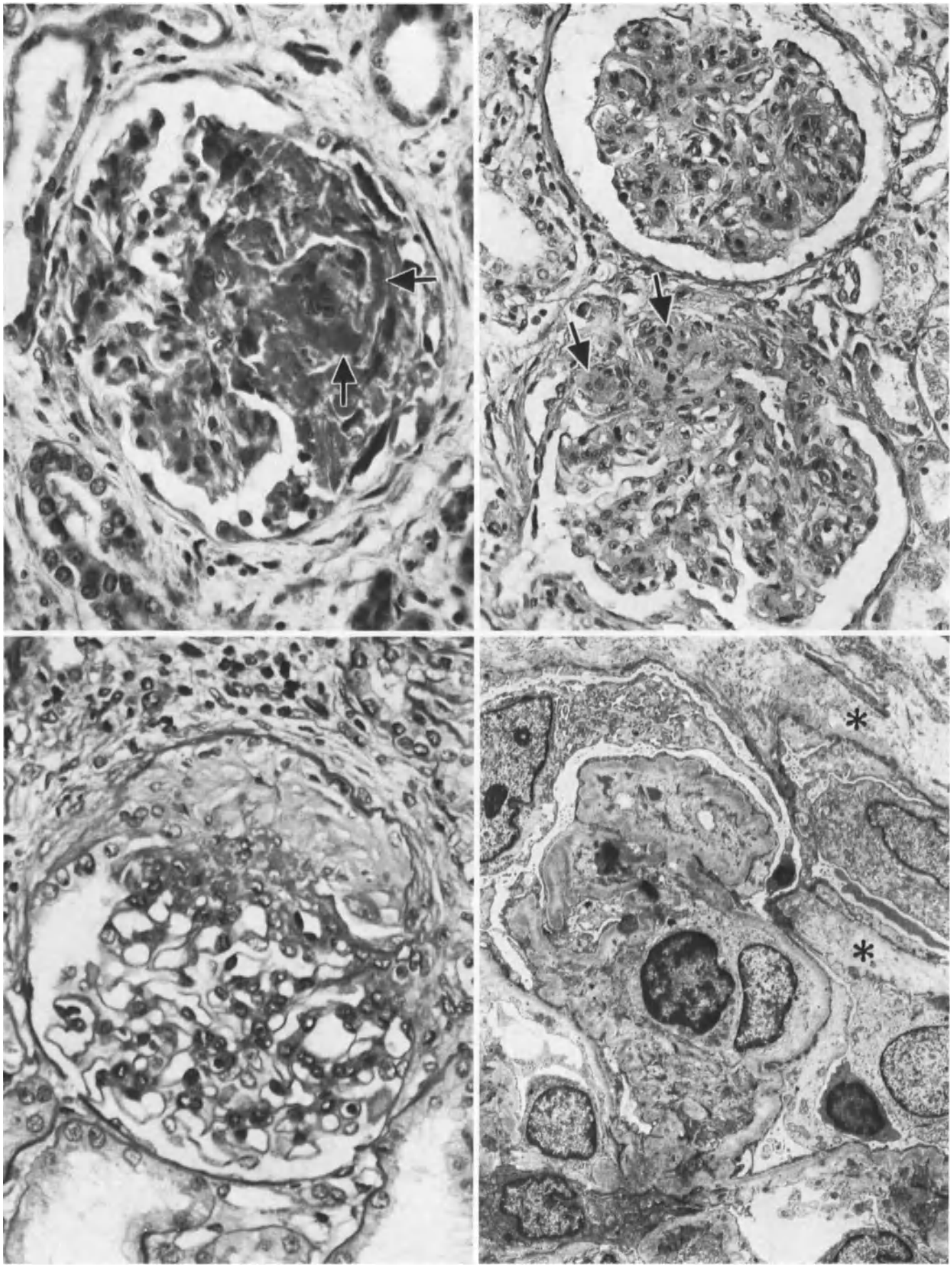
Differentiation from generalized intravasal coagulation is easy due to the smaller number of loop thrombi and the more pronounced inflammatory glomerular reaction in FGN associated with subacute bacterial endocarditis.
FGN occurring in Wegener's and Goodpasture's syndrome is characterized by a significantly more pronounced glomerular destruction.
The rare diffuse form of GN encountered in subacute bacterial endocarditis cannot be distinguished from common endotheliomesangial GN with LM.

### Prognosis

In the pre-antibiotic era, uremia was occasionally observed in the presence of progressive affliction of all glomeruli ("secondary" diffuse GN). Usually, however, the patients succumb from cardiac failure or from embolic complications. If antibiotic therapy is used early enough, the lesion tends to heal with focal-segmental scars.

### Pathogenesis

The lesion may be viewed as analogous to fibrin-rich subacute bacterial endocarditis, i.e. local thrombus formation caused by microorganisms (thrombocapillaritis),



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15.8

but the EM and IF findings suggest involvement of immunologic reactions as well. Whether or not FGN in subacute bacterial endocarditis is a special form of immunocomplex disease [612] must surely await further clarification. This is so, even if thrombus-free glomeruli show hypercellularity [685] and the findings in kidney eluates of specific antibodies against the bacteria which caused endocarditis [951], do point in this direction.
In addition to endocarditis, infected pulmonary vein thrombus or sepsis from lung cavitation may, in rare cases, be the underlying disease [1791].

### Etiology

Among causative organisms, *Streptococcus viridans* is the most important followed by staphylococci.
The rarity with which proliferative FGN is encountered in autopsy material may be due not only to better therapeutic management but also to the change in the spectrum of causative microorganisms in endocarditis: in 77 cases (identification of more than one bacterium in 23 cases) of our autopsy material we have encountered the following microorganisms: *Staphylococcus aureus haemolyticus* 50%; *S. viridans* 11%; *Pseudomonas aeruginosa* 8%; *E. coli* 6%; *Candida albicans* 6%; *Pneumococci* 4%; *Proteus* 4%, *others* 11%.

## Segmental-Focal Glomerulonephritis Associated With Generalized Intravasal Coagulation

The finding of sclerosing FGN after a period of time following assured clinical or bioptic identification of intravasal coagulation (3 out of 16 autopsy cases: Z) suggests that a significant number of such cases may arise in association with this process (see also [1047, 1654]).
Insidious and/or relapsing intravasal coagulation (e.g., thrombotic thrombocytopenic purpura, microangiopathy, hemolytic uremic syndrome) along with its thereby-caused fibrin insudation [1690] initiate an inflammatory reaction of the proliferative type not only in arterial vessels but also in the glomeruli (Figs. 15.10, 15.11, 15.12). These changes are described in more detail on p. 499.

◁ **Fig. 15.5.** FGN in subacute bacterial endocarditis. Some glomerular capillary loops are necrotic and filled by compact-appearing fibrin thrombi (→). Slight proliferation of capsular epithelium. HE (×300)

**Fig. 15.6.** FGN in subacute bacterial endocarditis with diffuse glomerular involvement. The findings are those of diffuse endotheliomesangial GN in the proliferating-sclerosing stage. The only striking feature are the two obsolescent glomerular capillary loops with adhesion to the capsule (→). HE (×290)

**Fig. 15.7.** Sclerosing stage of GN in subacute bacterial endocarditis without diffuse glomerular affliction. Note extensive synechiae over obsolescent glomerular capillary loops. Slight periglomerular inflammation. Female, 52 years. PAS (×300)

**Fig. 15.8.** Same case as in Figure 15.7. Obsolescent glomerular capillary loops are covered by a segmental crescent rich in fibrillar material (*). Female, 52 years. EM (×3580)

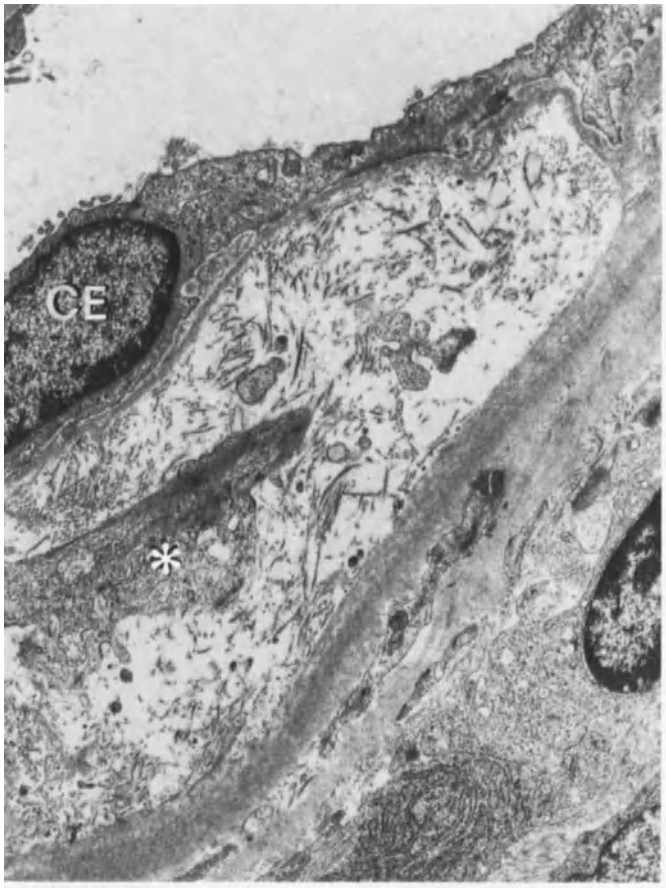
Page 288

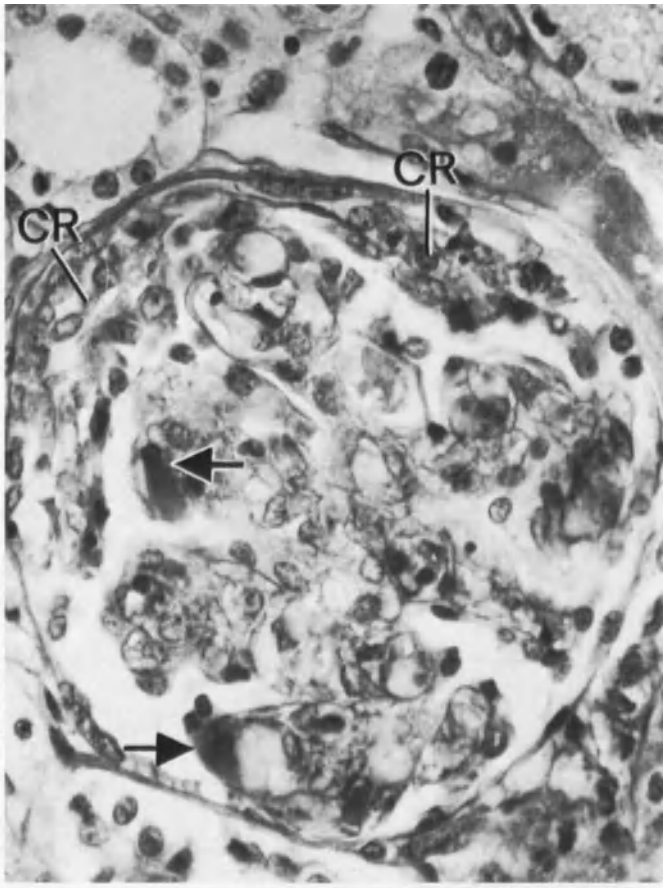
**Fig. 15.9.** Same case as in Figure 15.7. Capsular BM in sclerosing stage (→) and proliferative-sclerosing stage ( ) of FGN. PAS gen fibers are present in the thickened and split BM, as well as a cell process (*). Capsule epithelium (*CE*). Female, 52 years. EM (×8000)

**Fig. 15.10.** Acute intravasal coagulation in septicemia with E. coli. Fibrin thrombi are seen in two glomerular loops (→). Note proliferation of capsular epithelium (*CR*). Female 37 years. PAS (×430)

**Fig. 15.11.** Hemolytic-uremic syndrome in a 64-year-old male patient with antierythrocyte antibodies and bronchial carcinoma. Two glomeruli showing recurrent attacks: exudative-proliferative stage (→) and proliferative-sclerosing stage (▷) of FGN. PAS (×200)

**Fig. 15.12.** Sclerosing stage of FGN 2.5 months after severe intravasal coagulation. Synechia (*SY*) is present over the obsolescent glomerular capillary loops. Male, 37 years. PAS (×500)

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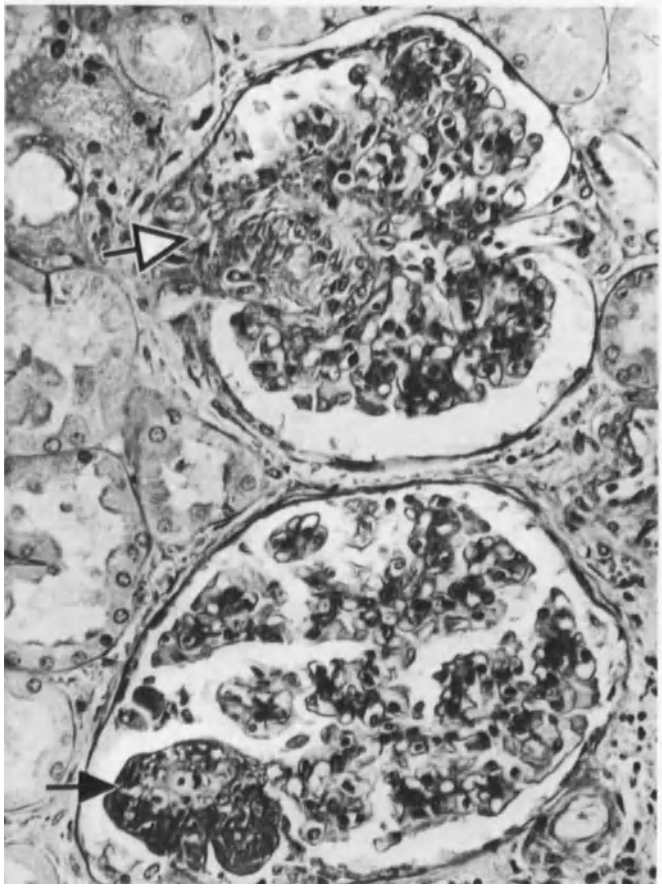

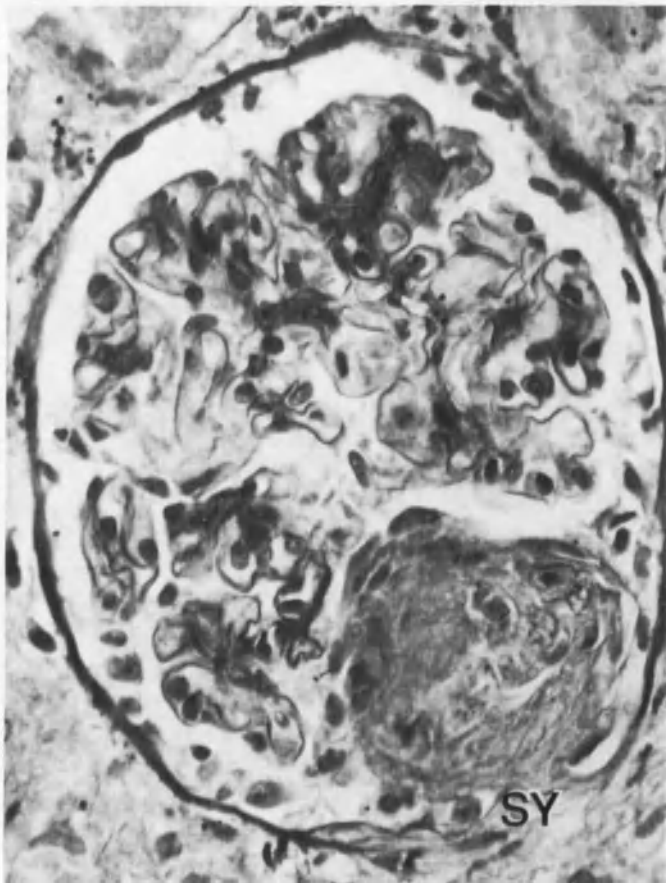


15.11
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# Segmental-Focal Proliferative and Sclerosing Glomerulonephritis Focal-Global Sclerosing Glomerulonephritis and Overload Glomerulitis

## Segmental-Focal Proliferative Glomerulonephritis (Proliferative FGN)

### Definition

In this group of lesions, all forms of segmental-focal FGN are considered which are not associated with purulent embolism or intravasal coagulation. It is noted that segmental-focal proliferative GN is essentially a diffuse GN which simulates in LM a segmental-focal lesion. The segmental glomerular lesions are characterized by subendothelial deposits and BM doubling with mesangial interposition and occasionally loop necrosis. The segmental glomerular lesions are often covered by segmental crescents. Focal means that the nonsegmentally changed glomeruli show no or minimal glomerular lesions [621].

In addition, we include in this group cases showing the above-mentioned segmental glomerular changes and, in the other glomeruli, more pronounced mesangial proliferation (GN with focal-segmental mesangiocapillary changes: [840a]; focal membranoproliferative GN: [621]). We felt entitled to enlarge this group of GN, since there are no differences with respect to the more restricted definition as far as intraglomerular deposit distribution and its major consequences are concerned. Further, after regression of diffuse proliferation, the morphologic picture will be that of segmental-focal GN in the stricter sense [163, 281, 595].

### Nosology

Three different stages: exudative, proliferative, proliferative-sclerosing, different degrees of mesangial involvement, as well as forms without crescents and with less than 50% crescents can be differentiated. A sclerosing phase of this form cannot be differentiated with certainty from segmental-focal sclerosing FGN.

### Incidence

The incidence of this GN varies considerably from investigator to investigator (see Table 15.1) between 3.3% and 32.1% of all GN. If "genuine focal GN" is considered alone, the series of one investigator group [163a] gave the incidence as 1.9% in all GN (also: 13%: [689]; 15.7%: [409]).

Table 15.1. Relative frequency of segmental-focal proliferative glomerulonephritis including systemic diseases, ( )=without glomerular minimal changes[a]

| | | |
|---|---|---|
| Cameron (1973) [242b] | 2.1% | (3.3%) |
| Churg and Duffy (1973) [277] | 7.2% | (8.7%) |
| Habib (1973) [621] | 8.3% | (16.3%) |
| Hamburger et al. (1971) [654] | 8.4% | (10.6%) |
| Bohle et al. (1976) [163a][a] | 9.6% | (16.9%) |
| Zollinger and Mihatsch | 17.3% | (22.6%) |
| Morel-Maroger et al. (1973) [1137a] | 25.6% | (32.1%) |
| Germuth and Rodriguez (1973) [544] | 31.3% | (46.0%) |

[a] For total number of cases in different series, see Table 14.1.

Male patients are far more frequently afflicted than females (2.2:1:Z; see also [621, 163A]; 1:1: [405]) and all age groups are equally involved [405].

### Clinical Findings

(Tables 14.3, 14.5, Fig. 15.13)

The disease frequently begins as typical acute GN (Table 14.5). In more than 40% of the patients it follows an infection—usually situated in the upper respiratory tract—or manifests itself frequently in the course of systemic diseases, e.g., SLE, Schönlein-Henoch's purpura, etc. (24–42%: [621, 1309]). Initial macrohematuria is characteristic, even though other symptoms of acute GN are absent. On the other hand, oligo-anuria is rarely observed at disease onset. Proteinuria is present in about 75% of the patients, edema in 40%, and hypertension in 25% at the initial clinical examination.

The disease usually exhibits a stationary course (see also [620]; contra: [1722]). The leading symptoms at the time of diagnosis are proteinuria and hematuria which are present in more than 50% of the patients.

Also typical is the occurrence of a nephrotic syndrome associated with hematuria which is observed in about 20% of the patients. The high incidence of proteinuria and hematuria has been confirmed by others (82%: [621]) while nephrotic syndrome with hematuria was observed in only 10% of cases. An isolated nephrotic syndrome [621], isolated proteinuria or hematuria or the absence of any urine findings whatsoever are, however, uncharacteristic.

Hypertension is encountered in about 30% (children: 13%: [621]) of the patients and hyperazotemia in about 50%. Complement is rarely decreased (12%). The antistreptolysin titer is raised in about 25% of the cases. Respiratory infections are reported in the literature in 24–42% of the cases [621, 1309].

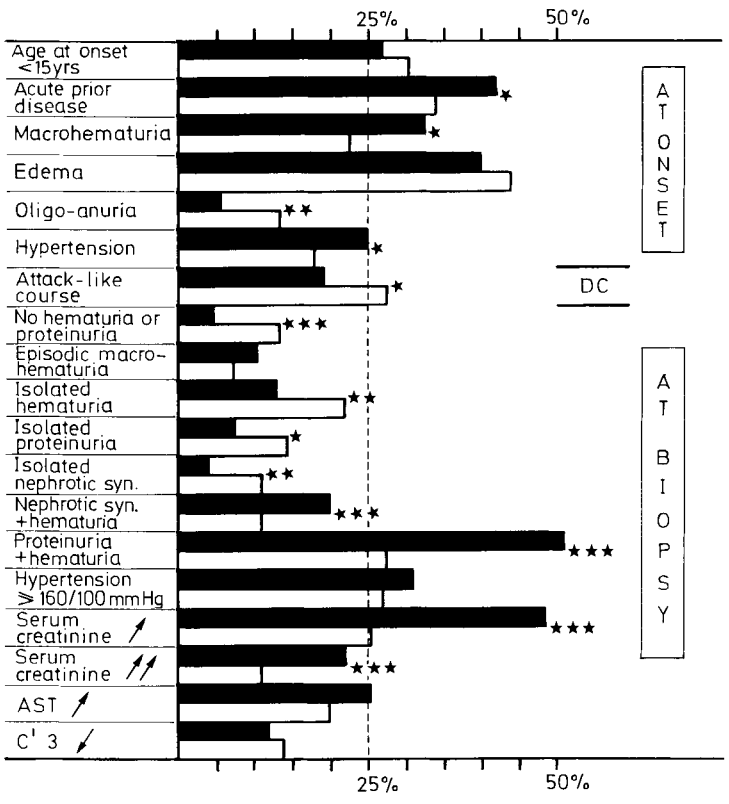



**Fig. 15.13.** Profile of symptoms and clinical findings in proliferative FGN
*White columns:* Relative frequency of symptom/finding in all GN
*Black columns:* Relative frequency in proliferative FGN
Asterisks indicate characteristic findings for proliferative FGN:
*: characteristic
**: very characteristic
***: highly characteristic; DC: disease course

### LM Findings

The overall phasic development of the glomerular changes is essentially the same as described in endotheliomesangial GN, but the segmental and—partly less so—focal character is clearly evident (Figs. 15.14, 15.15).
Segmental-focal distributed loop necroses accompanied by focally increased polymorphonuclear leukocytes or frank increase of mesangial cells—and later also of the matrix—are found according to the stage of the change under investigation (Figs. 17.1, 17.15, 17.16). It is noted that in the proliferative and proliferative-sclerosing stages, BM doubling with mesangial interposition in the region of the subendothelial deposits is practically always demonstrable in the particularly severely changed loop segments. The other glomeruli show minimal mesangial changes.
In other cases, rather intense axial-mesangial proliferation in the nonsegmentally changed glomeruli is seen. We assign these cases also to proliferative FGN since they can develop into this form in the strict sense following regression of the diffuse proliferative changes (see also [163, 281, 595]). The purely proliferative stage was encountered usually after 12 weeks duration of illness (range: 1–250 weeks), the proliferative-sclerosing stage after 50 weeks (range:2–850 weeks).
Segmental (partial) crescents covering the most severely damaged loops are a very frequent finding which was present in our material in more than 50% of cases (Fig. 9.99). Fibrosed crescents and proliferating crescents occurring side by side reflect an attack-like course (Fig. 15.16).

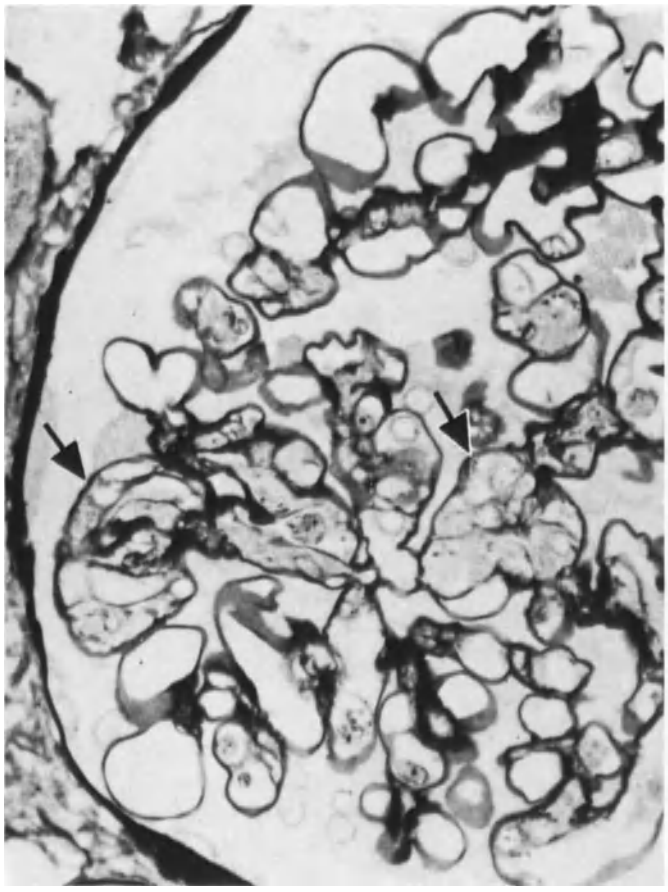
### IF Findings

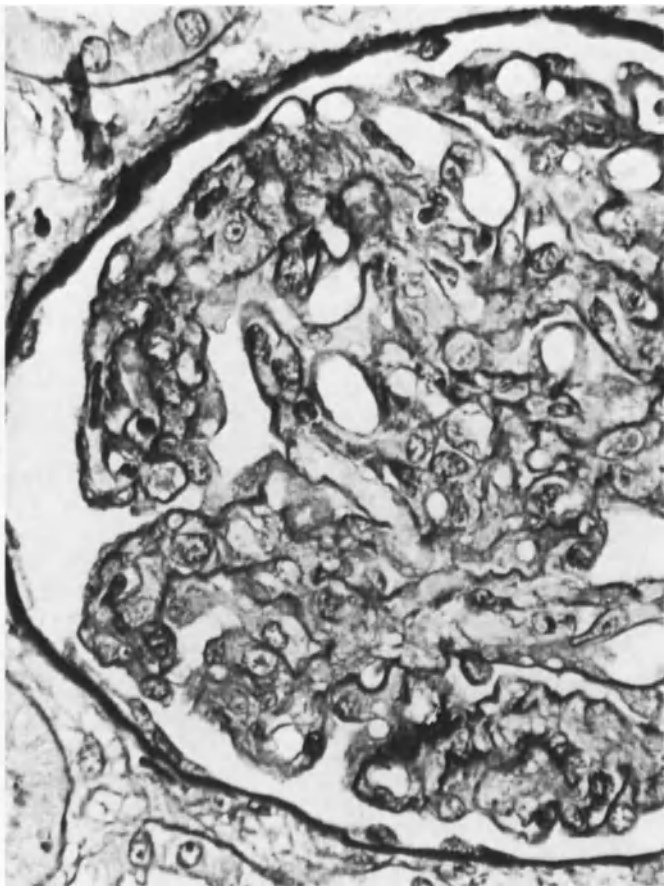
IgG, IgM, and C3 are found in about the same frequency, while fibrin(-ogen) or IgA occur less often (see Table 15.2). IgG shows a predominantly diffuse and global distribution, while IgM, C3, and fibrin(-ogen) can also evidence a focal-segmental distribution pattern. If systemic diseases and IgA nephritis are not considered, IgM and C3 are more frequently found than IgG; IgA and fibrin(-ogen) are found still less frequently.
For the most part, the granular deposits are distributed only peripherally or mesangially and peripherally. A similar involvement of the glomeruli with C3, occasionally in association with IgM, IgG and fibrin(-ogen) was reported in another series of cases [1136, 1139]. In 1 out of 3 of the cases from these series, IF findings were completely negative [1139]; we have not encountered IF-negative cases.

### EM Findings

The findings are not essentially different from those encountered in the diffuse forms (Fig. 15.17). The glomeruli

15.14
15.15





15.16

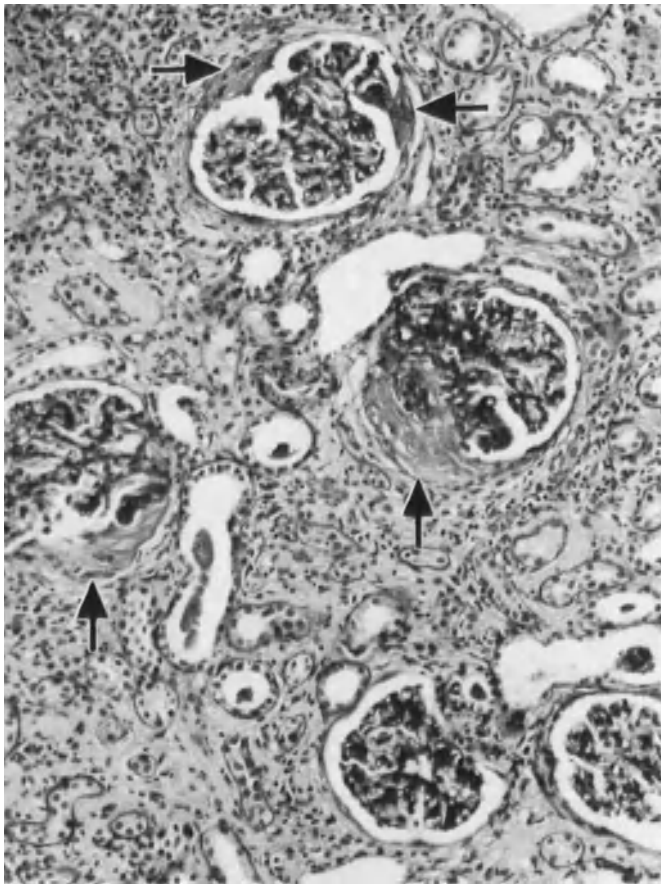


**Fig. 15.14.** Proliferative FGN. Two glomerular capillary loops are clearly seen to be occluded by proliferation (→). Male, 34 years. PASM (×680)

**Fig. 15.15.** Same case as in Figure 15.14. Endothelial proliferation, entirely occluding glomerular capillary loops, is clearly evident. Male, 34 years. PAS (×680)

**Fig. 15.16.** Recurring proliferative FGN with typical focal and segmental affliction and severe extracapillary involvement (→). Interstitium is pronouncedly broadened and evidence inflammatory infiltration. Female, 62 years. PAS (×140)

Table 15.2. IF findings in segmental-focal proliferative glomerulonephritis ($n=33$; positive = 33)

| | IgG | IgM | IgA | C3 | Fibrin-(-ogen) |
|---|---|---|---|---|---|
| Cases tested | 33 (22) | 33 (22) | 24 (16) | 33 (22) | 33 (22) |
| Positive | 25 (14) | 30 (20) | 13 (5) | 32 (21) | 12 (6) |
| Diffuse | 16 (7) | 12 (4) | 7 (1) | 18 (11) | 7 (3) |
| Focal | 9 (7) | 18 (16) | 6 (4) | 14 (10) | 5 (3) |
| Global | 20 (11) | 17 (9) | 8 (1) | 22 (14) | 6 (3) |
| Segmental | 5 (3) | 13 (11) | 5 (4) | 10 (7) | 6 (3) |
| Peripheral | 13 (8) | 14 (11) | 6 (4) | 14 (11) | 6 (3) |
| Peripheral and mesangial | 11 (5) | 14 (7) | 6 (1) | 12 (5) | 4 (2) |
| Mesangial | 1 (1) | 2 (2) | 1 – | 6 (5) | 2 (1) |

() Without inclusion of IgA nephritis [4], Schönlein-Henoch's purpura [4] and SLE [3 cases].
Frequency of combination for the cases () without inclusion of IgA: Ig(G,M) + C3 = 8 times; Ig(G,M) + C3, fibrin(-ogen) = 5 times; IgM + C3 = 5 times; others 4 times.

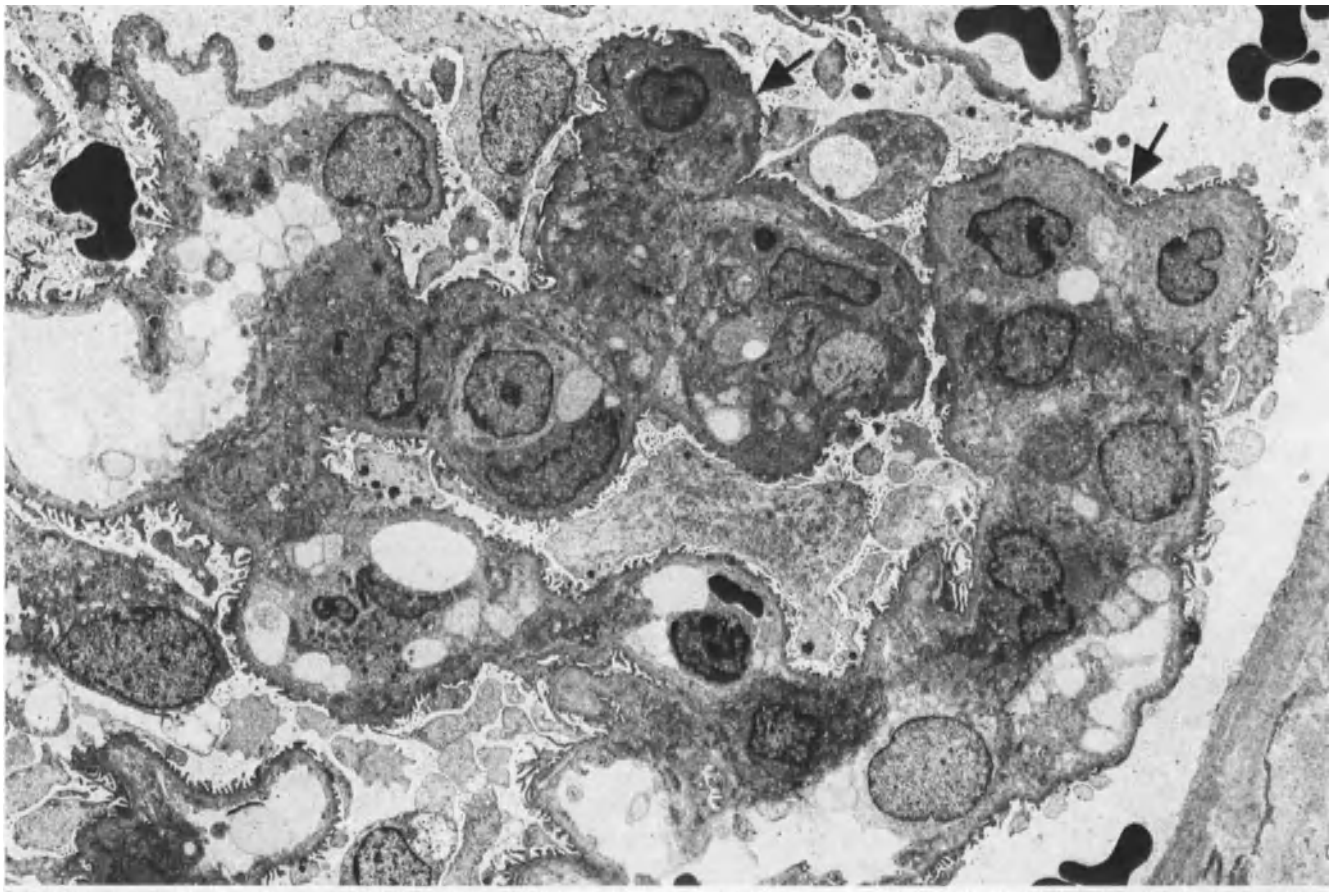
show hypertrophy and swelling of the endothelium (Fig. 15.18) and usually swelling of the podocytes and a fusion of foot processes which is of varying severity. Mesangial cell proliferation and matrix increase – depending on the stage – are present in practically all cases in variable degree and are found in nonsegmentally changed glomeruli as well as deposits in various locations (see below).
Glomeruli with segmental changes are characterized by an especially pronounced mesangial cell proliferation which is in the proliferative-sclerosing stage accompanied by a marked mesangial matrix increase. Furthermore, complete obliteration of the glomerular loops by proliferated mesangial cell elements is frequently present. In about three-fourths of our cases, we encountered mesangial interposition and new formation of BM subendothelially (Fig. 15.19) which were restricted to the segmentally changed glomeruli. Mesangial interposition occurs mainly in the region of the larger subendothelial deposits (38 out of 54:Z; Fig. 15.20). Additionally, deposits are also frequently found along mesangial BM (26 out of 54:Z), in mesangial matrix (22 out of 54:Z) and intramembranously (20 out of 54:Z). Subepithelial deposits (10 out of 54:Z) and humps (10 out of 54:Z) are considerably less frequent. Unspecific BM damage is usually encountered (Fig. 15.21) – also in nonsegmentally affected glomeruli. For further EM details see Figures 6.9, 6,22, 6.34, 6.57, 6.64, 6.80, 6.88.
The segmental crescents, which especially frequently develop over the severely afflicted loop segments, are identically to those described for the diffuse forms of GN (see p. 218).

## Differential Diagnosis

In the presence of proliferative FGN, attention should be initially directed to systemic disease (e.g., Schönlein-Henoch's syndrome, SLE) or to IgA nephritis, the diagnosis of which depends on IF examination.
The diagnosis of proliferative FGN and its differentiation from diffuse forms of GN is generally easy. In proliferative FGN – and especially with low-power magnification – it is typically seen that only scattered, individual glomeruli are afflicted with segmental changes only, and that segmental crescents frequently lie over the afflicted loop segments.
However, in all cases in which proliferative changes are more pronounced in the other glomeruli and in which the picture of diffuse GN is simulated, demonstration of focal-segmental loop obliteration and subendothelial deposits (Masson's trichrome/AFOG stain) with mesangial interposition and BM doubling will permit diagnosis of proliferative FGN.
Occasionally, diffuse endotheliomesangial GN may simulate proliferative FGN when only a few glomeruli demonstrate extracapillary crescents. In such cases, however, global crescents predominate in endotheliomesangial GN as contrasted to proliferative FGN in which segmental crescents are dominant. Although subendothelial deposits are observed exceptionally in endotheliomesangial GN, mesangial interposition is not associated with them.
Decision is more difficult in cases in which diffuse extracapillary crescents are present. In these instances, diagnosis of primary FGN is often only possible by the EM demonstration of focal-segmental distribution of subendothelial deposits and mesangial interposition. But since this differentiation – especially in advanced cases – is hardly ever possible using LM alone, we allocate this form with more than 50% of glomerular involvement to extracapillary accentuated GN.

**Fig. 15.17.** Proliferative FGN. In the glomerulus, only two capillary loops (→) exhibit endothelial proliferation and an isolated polymorphonuclear leukocyte. No deposits are present. Male, 24 years. EM (×2100) ▷

**Fig. 15.18.** Proliferative FGN: highly activated endothelial cells (*E*) in a glomerulus that is not segmentally afflicted, occasionally evidencing ballooning (*). Mesangial cells are likewise activated and swollen (*M*). Podocytes are edematous but without noteworthy foot process fusion. BM is unchanged. Male, 43 years. EM (×6090)



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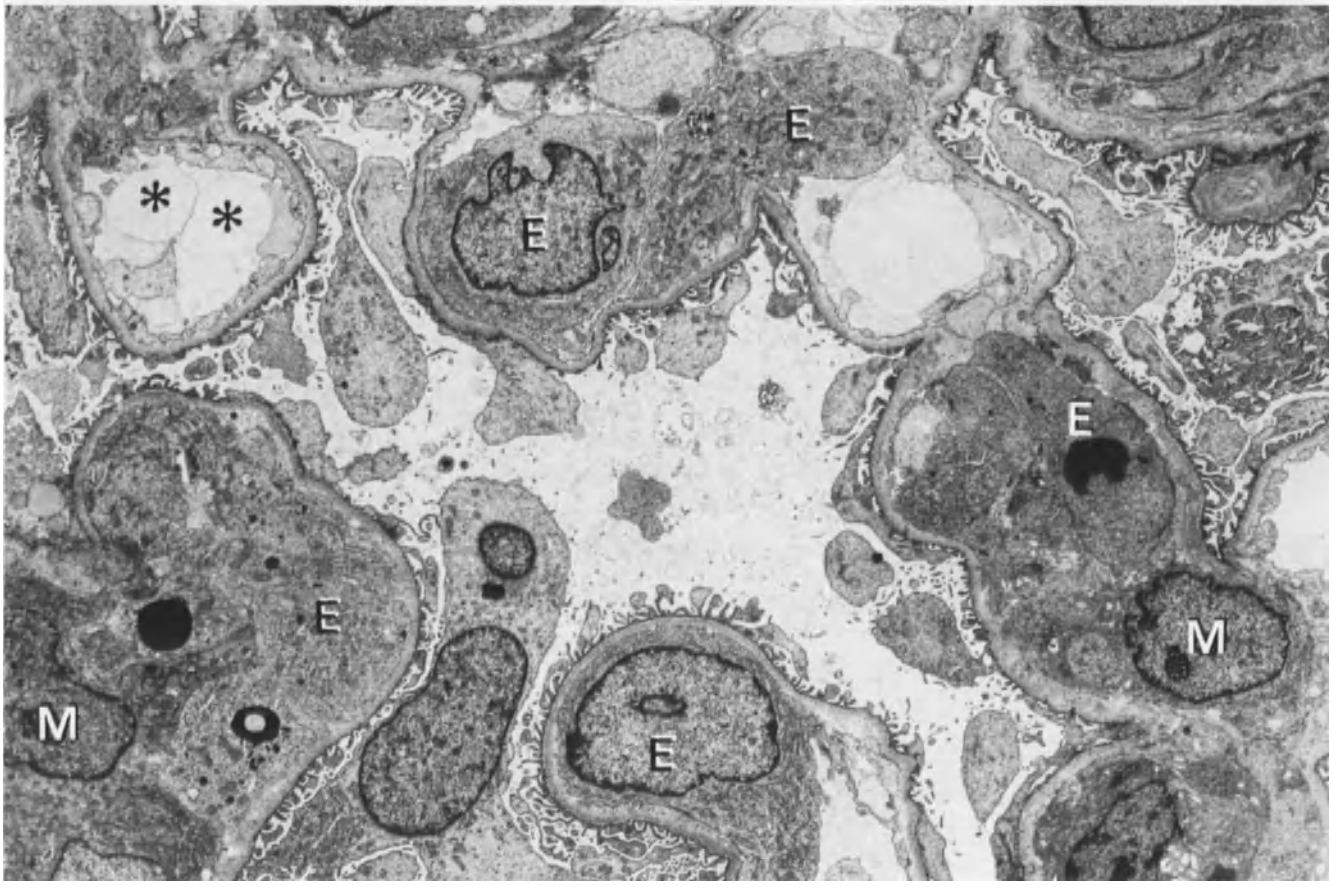


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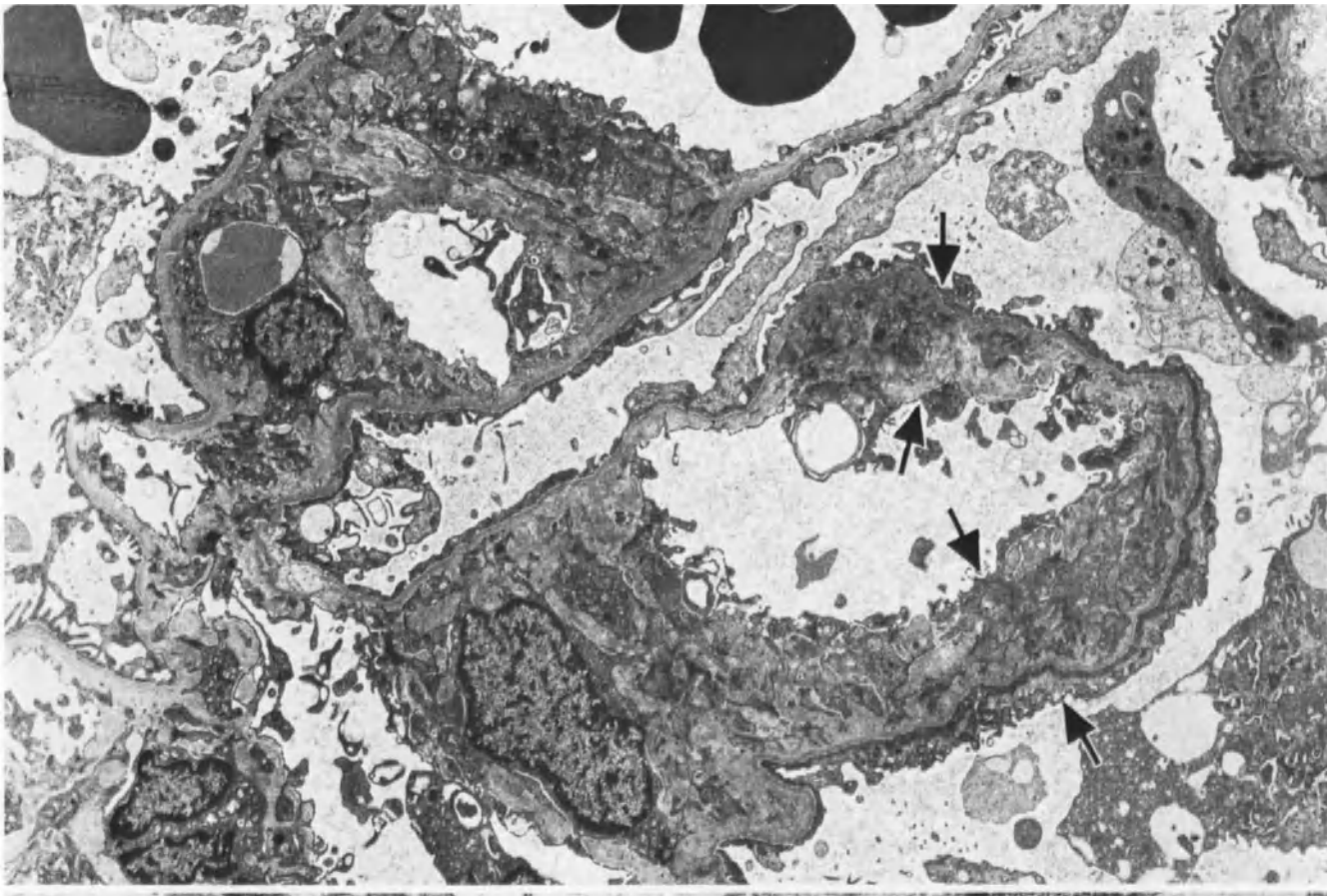
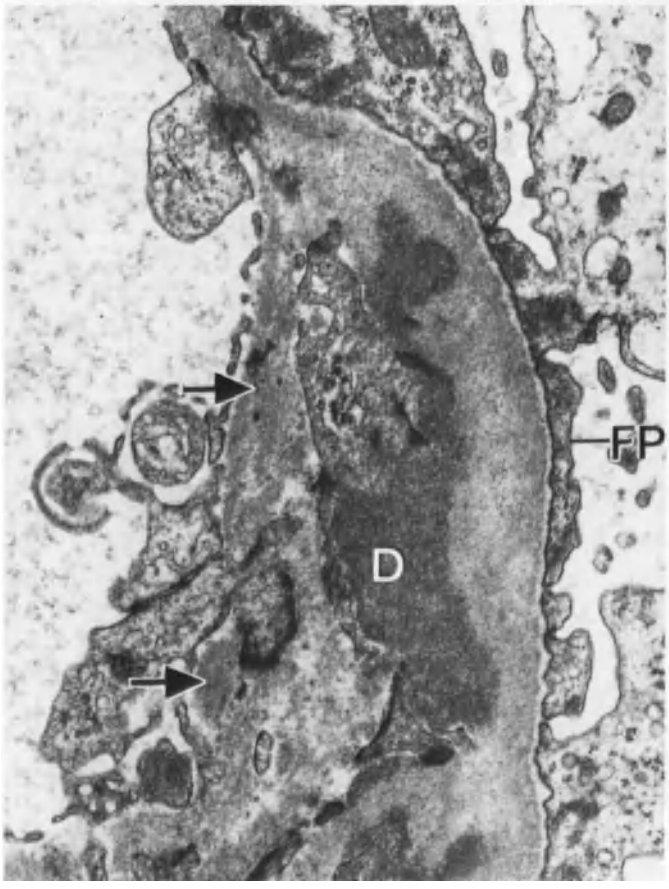
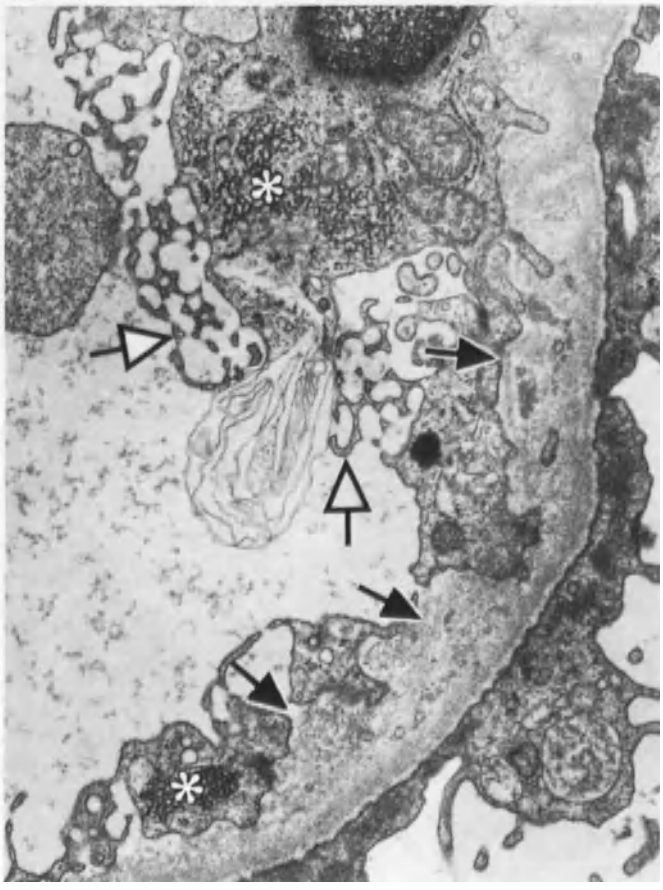


15.19



15.20
15.21

Differentiation with respect to diffuse membranoproliferative GN is usually not difficult (although the different morphologic parameters—subendothelial deposits, BM doubling with mesangial interposition—are identical) since in membranoproliferative GN, subendothelial deposits (under LM) and BM doubling with mesangial interposition are diffusely and globally distributed. Furthermore, mesangial interposition is more often circumferential in diffuse membranoproliferative GN than it is in proliferative FGN in which usually only a part of the loop is afflicted.

Differentiation of proliferative FGN from sclerosing FGN poses no problems since in the latter, proliferation that is always generally evident in proliferative FGN, is practically absent. On the other hand, the purely sclerosing stage of proliferative FGN cannot readily be differentiated, in our opinion, from sclerosing FGN although crescents are not an integral part of the latter disease.

No difficulty should be experienced in distinguishing FGN from epi- and intramembranous GN.

## Prognosis

Prognosis varies considerably. The overall survival rate (Table 15.3) in our cases without crescents for 10 years is 58%, whereas for those with crescents (< 50%) 36%. Claims for cure oscillate between 5.8% [409] and 28.9% (children: [620]). Cure was observed in our cases without crescents in 18.7% compared to only 8.7% in those with crescents (< 50%). In the majority of cases (78.3%), the clinical symptoms and the morphologic picture (68.3%) persist [620]; (see also [407, 1068, 1309]). Death due to uremia was found in 20% of cases without and, in 41.6% with crescents (Table 15.3). Morphologic parameters closely related to the prognosis are crescents (see Table 15.3) and interstitial and tubular changes [405].

Table 15.3. Prognosis and outcome in segmental-focal proliferative glomerulonephritis

| Prognosis | Survival rate (%) | | |
|---|---|---|---|
| | 5 years | 10 years | 15 years |
| Without crescents | | | |
| From disease onset | 84 | 58 | – |
| SE[a] | 5.3 | 9.6 | – |
| From biopsy | 75 | 56 | – |
| SE[a] | 6.9 | 10.5 | – |
| With crescents (< 50%) | | | |
| From disease onset | 67 | 36 | 33 |
| SE[a] | 6.3 | 9.3 | 9.6 |
| From biopsy | 54 | 31 | – |
| SE[a] | 6.6 | 7.3 | |

[a] SE = standard error in %.

*Outcome* (minimal follow up 1 year)

| Patients | Without crescents | With crescents < 50% |
|---|---|---|
| | $n=48$ | $n=60$ |
| Death | 29.2% | 56.6% |
| Death in uremia | 20.8% | 41.6% |
| Complete remission | 18.7% | 8.3% |

## Pathogenesis

In general, the lesion is considered as diffuse GN in which changes in LM are predominantly segmental and focal. The diffuseness of the IF findings in the majority of cases supports this point of view (see also [1186]; see Table 15.2). Pathogenetically, the following factors are involved: deposition of poorly soluble immunocomplexes (class 2 immunocomplexes = mesangiopathic type: [544]); duration and extent of immunocomplex deposition; local factors, e.g., mesangial transport and phagocytic capability.

The last two factors mentioned probably play an especially important role since even poorly soluble immunocomplexes can be completely taken up in the mesangium without coming to lie in the periphery if their deposition is of short duration and of low concentration. On the other hand, when such complexes are deposited in large amounts or over a long time, the mesangial transport and phagocytic capability can be exceeded (at least in some glomeruli) and the complexes come to lie in the subendothelial space where they give rise to mesangial proliferation into the capillary lumen and to BM doub-

◁ **Fig. 15.19.** Proliferative-sclerosing FGN. There is obvious mesangial interposition in glomerular capillary loop periphery with formation of a new second BM subendothelially. These changes have given rise to massive thickening of glomerular capillary loop wall (→←). Activated mesangial cells. Edematous and hypertrophied podocytes. Male, 18 years. EM (×4140)

**Fig. 15.20.** Same case as in Figure 15.19. Extensive subendothelial deposits (*D*) with mesangial interposition and formation of a new second BM (→). Fusion of podocytic foot processes (*FP*). Male, 18 years. EM (×13,100)

**Fig. 15.21.** Proliverative FGN. Considerable loosening of the lamina rara interna (→). The endothelium is highly activated and demonstrates arcade formation (⇨). Tubular structures are seen in the endothelial cytoplasm (*). Complete foot process fusion is present. Male, 63 years. EM (×16,600)

ling with mesangial interposition [544]. This could explain the segmental and focal character under LM.
Accordingly, in contrast to membranoproliferative GN in which poorly soluble immunocomplexes also play a role, it appears that mesangial clearance function is of greater significance. This is supported by the fact that, as opposed to membranoproliferative GN in which—in the early proliferative stage—immunocomplexes are exclusively found in the loop periphery, in proliferative FGN, immunocomplexes are already found within the mesangium even in the proliferative stage.
On the other hand, the more frequent occurrence of loop necrosis in proliferative FGN indicates qualitative differences among the immunocomplexes. Experimental findings indicate that insoluble immunocomplexes may also play a pathogenetic role in proliferative FGN ([520; contra: [544]). Finally, all questions relating to complement activation, participation of properdin, the role of the C3 nephritic factor and similar factors remain unanswered in proliferative FGN, so that a clear-cut distinction from diffuse membranoproliferative GN cannot yet be drawn (compare histogram Fig. 6.34).

### Etiology

It seems that streptococcal infections rarely give rise to this form of FGN. A few cases have been described in association with acute rheumatic polyarthritis [598] and malaria (11 out of 77: [828]). Furthermore, the lesion has been reported in heroin addicts suffering from staphylococcal endocarditis [1425] and in association with subacute bacterial endocarditis [179]. The etiologic factors possibly operative in our cases are summarized in Table 15.4; they substantiate the commonly held view that the majority of cases with known etiology are due to systemic diseases or IgA nephritis (see Chap. 17). Of 120 patients, 22 suffered from systemic disease, e.g., SLE or Schönlein-Henoch's purpura (see also [544]). IgA nephritis comprises 16.6% of the IF-investigated cases. FGN is also frequently encountered in hypersensitivity angitis [794a]; see p. 536. Scattered cases developed after streptococcal, staphylococcal, and a variety of viral infections. In about half the cases, the possible etiology could not be determined.

Table 15.4. Etiology of segmental-focal proliferative glomerulonephritis ($n=120$)

| | |
|---|---|
| Bacteria: 5% | – Scarlet fever |
| | – Streptococcal and staphylococcal empyema |
| | – Streptococcal erysipelas |
| | – Staphylococcal abscess |
| | – S. albus shunt nephritis |
| | – Coli-endocarditis |
| Virus: 4.2% | – Mumps |
| | – Mononucleosis infectiosa |
| | – Cytomegalovirus |
| | – Rubella |
| | – Hongkong-virus influenza |
| Systemic disease: 18.3% | – Schönlein-Henoch's syndrome (11×) |
| | – Lupus erythematodes disseminatus (11×) |
| 16.6% | – IgA nephritis (based on IF investigates cases) |
| Etiology unknown ≈55%. | |

## Segmental-Focal Sclerosing Glomerulonephritis (Sclerosing FGN)

### Definition

This form of FGN is essentially a diffuse GN [1401] simulating, in LM, a segmental-focal lesion with the predominant feature of segmental-focal sclerosis. We consider segmental-focal hyalinosis [620] with massive fibrinoid deposition in the loop periphery, which was previously distinguished from segmental-focal sclerosing GN, to be merely a variation of this sclerosing form (see also [741, 1401]) as is focal-global sclerosing GN (see also [630, 1055]).

***Synonyms*** see Table 13.2.

### Incidence

In overall biopsy material this form has been reported with an incidence of 4.5% [277], 2.2% [163, 1312, 1313], 3.3% [741] and of 6.2% (Z). In pediatric biopsies the incidence is given as 5.4% [621]. The incidence among GN in general varies between 5.1% and 18.6% (Table 15.5; 9.4% [43]).

Table 15.5. Relative incidence of segmental-focal sclerosing glomerulonephritis, ( )=without glomerular minimal change[a]

| | | |
|---|---|---|
| Bohle et al. (1976) [163a] | 2.9% | (5.1%) |
| Cameron (1973) [242b] | 6.4% | (10.1%) |
| Morel-Maroger et al. (1973) [1137a] | 7.3% | (9.2%) |
| Habib (1973) [621] | 8.2% | (16.1%) |
| Churg and Duffy (1973) [277] | 8.6% | (10.4%) |
| Zollinger and Mihatsch (1975) | 14.4% | (18.6%) |

[a] No data available from [544] and [654]. For total number of cases in different series, see Table 14.1.

Males are—according to some investigators—more afflicted than females; 2:1 [629], 1.3–1.5:1 [163, 558, 1102], 1.5:1 (Z). Other investigators report males and females to be equally affected [244] and still others a predominance of females [1732]. In children, the lesion appears in 63% of patients before the fifth year of life [621]; in our material, the pediatric age group was statistically less often affected than the adult. The highest incidence was found in young adults between 20 and 40 years (21 years: [770]); 54% of the patients were younger than 30 years (see Table 14.3).

**Clinical Findings**
(Tables 14.3, 14.4, 14.5, Fig. 15.22)

The first clinical symptom is proteinuria which is usually accompanied by microhematuria [244]. In children, full-scale NS—associated with hematuria in about 50% of the cases—is generally present at disease onset [630]. In our material, 70% of the patients evidence proteinuria and about 30% hematuria of which half is manifested as macrohematuria (10–20% macrohematuria: [244, 630, 1732]. Initial hypertension was noted in 22% of our cases (34%: [244]). The disease manifested itself in 29% of patients [630] following an infection usually in the upper respiratory tract (31%: Z). Rarely, the disease may begin with typical signs of acute GN (see Table 14.6; 3 out of 22: [1732]).

The further course of the disease is variable. In addition to stationary and progressive courses, cases proceding with attacks were characteristic (40%: Z; 38%: [630]). Attacks are rarely characterized by episodes of macrohematuria (4%: Z; 1 out of 34: [244]; 1 out of 22: [1732]). Far more typical are repeated attacks of nephrotic syndrome ([1732]; 20 out of 88: [630]).

At the time of (bioptical) diagnosis, about two-thirds of the patients evidence nephrotic syndrome which is usually accompanied by microhematuria [407, 630, 770, 1401, 1430, 1732]. The other patients have proteinuria and microhematuria. The nephrotic syndrome is said to be more frequent in children than in adults [1189b]. Isolated proteinuria or nephrotic syndrome are rare ([1732]; 10 out of 98: [630]). Contrary to these findings, we encountered proteinuria in only 65% of our patients in whom nephrotic syndrome was present in one-third. The proteinuria was accompanied by hematuria in one-half of the cases (Fig. 15.22). Isolated hematuria occured in 14% but was rarely in the form of macrohematuria (Fig. 15.22). Hypertension increases in frequency during the course of the disease (36.6%: Z; 12 out of 22: [1732]; 7 out of 17: [558]; 5 out of 24: [1430]). Hyperazotemia, which is already present at disease onset in some patients (12 out of 88: [630]), becomes more frequent during the course of the disease (32.7%:Z, see also [630]). Acute irreversible renal failure has seldom been reported [1307a]. In general, normocomplementemia is encountered (Fig. 15.22; see also [244, 630, 1732]).

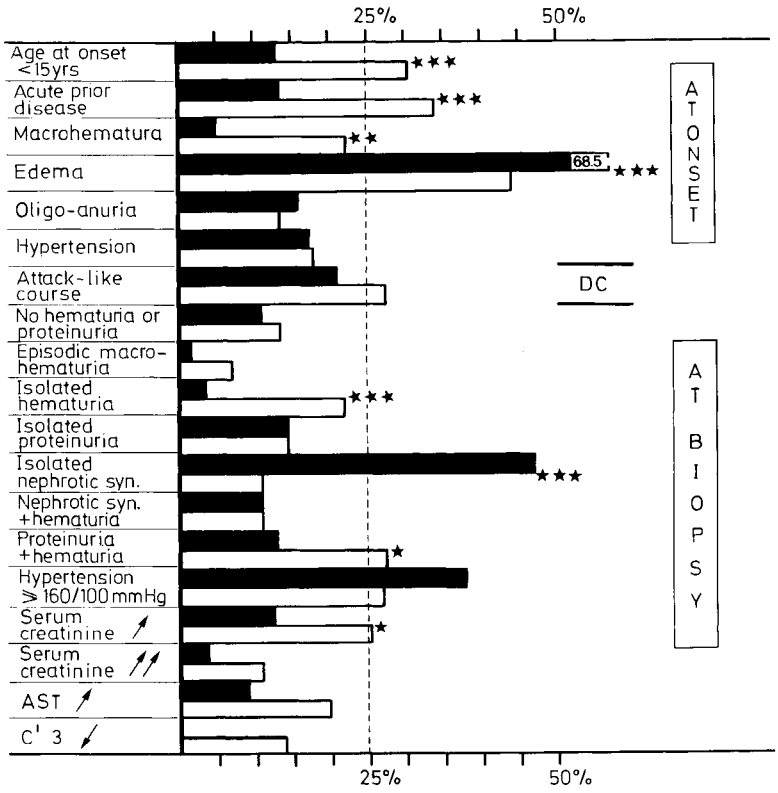
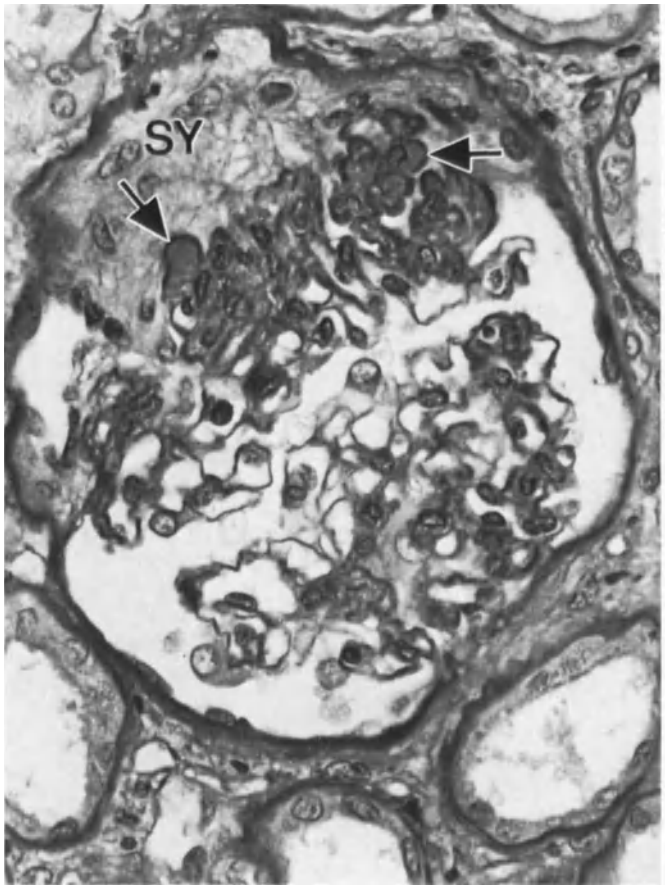
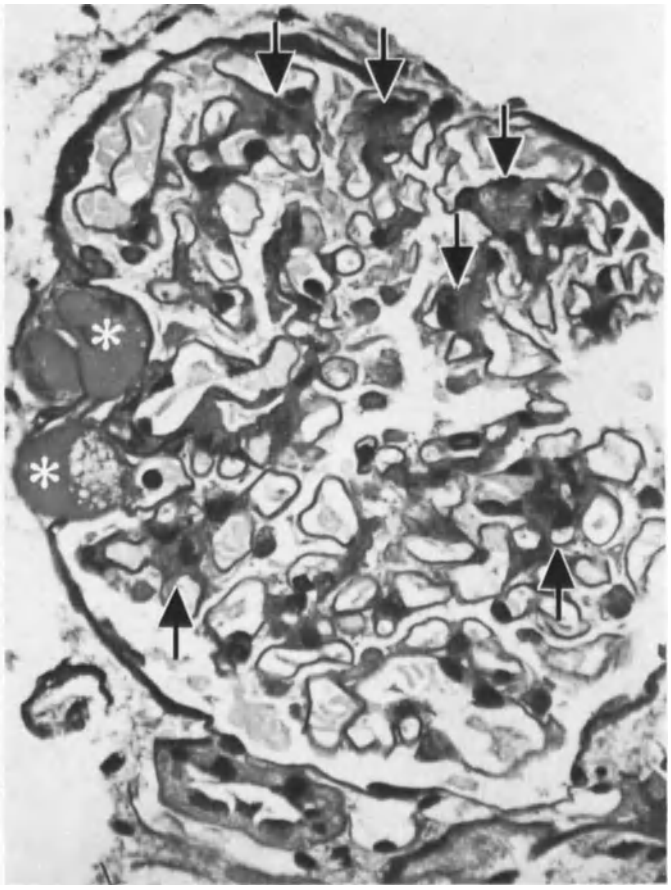



**Fig. 15.22.** Profile of symptoms and clinical findings in sclerosing FGN
*White columns:* Relative frequency of symptom/finding in all GN
*Black columns:* Relative frequency in sclerosing FGN
Asterisks indicate characteristic findings for sclerosing FGN:
*: characteristic
**: very characteristic
***: highly characteristic; DC: disease course



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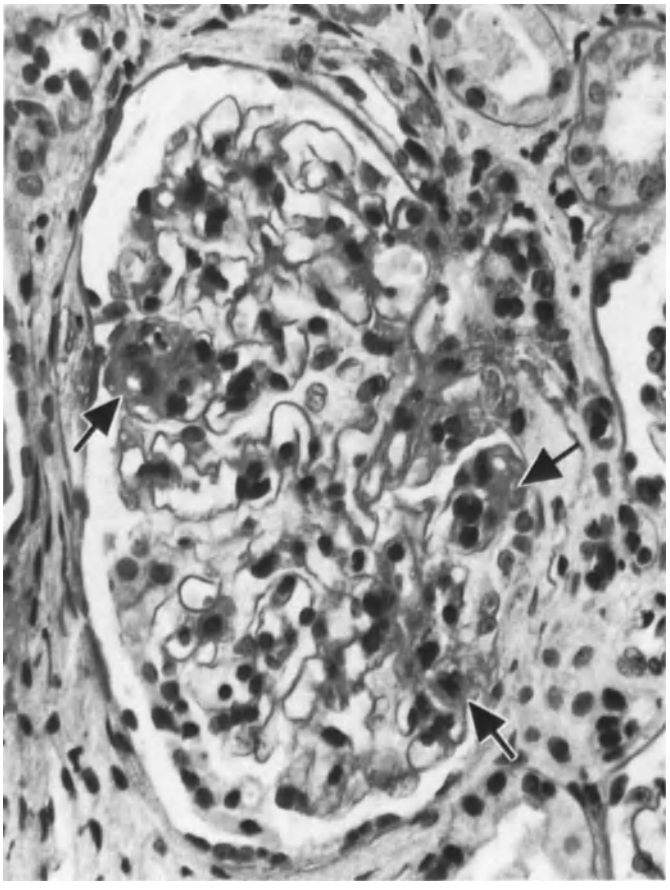

15.25

**Fig. 15.23.** Sclerosing FGN with extensive synechia (*SY*). So-called hyaline giant deposits in peripheral glomerular capillary loops (→). In the affected segment, there is mesangial sclerosis. Other segments are nearly unchanged. Male, 48 years. PAS (×710)

**Fig. 15.24.** Sclerosing FGN. In addition to glomerular minimal change (→), two glomerular capillary loops which are adhering to the capsule are occluded by hyaline giant deposits (*), one shows signs of vacuolar degeneration (cf. Fig. 15.30) Male, 23 years. PAS (×480)

**Fig. 15.25.** Minimal segmental mesangial proliferation (→) in sclerosing FGN. Remaining glomerular capillary loops are completely unchanged. Male, 56 years. PAS (×310)

Familial occurrence of the disease has been repeatedly observed [630, 1430, 1469a].

## LM Findings

The segmental-glomerular changes are mainly pronounced in the juxtamedullary zone (see also [770, 1055, 1068]) and have been reported in 11 out of 64 pediatric cases as occurring exclusively in this zone [630]. Since this lesion does not involve all glomeruli, we suggest serial sections to avoid erronous classification of these cases as glomerular minimal change and to provide more reliable quantitative data.

The most striking feature is either segmental sclerosis, which extends from the glomerular hilus (Figs. 15.23, 16.4), or hyalinosis (giant fibrinoid deposits, Fig. 15.24, see also [1659]) with segmental loop obsolescence and endothelial or mesangial foam cells (see also [407]).

Fat vacuoles are often recognizable in giant deposits. Synechiae are frequently encountered over the changed loops (Fig. 15.21). In cases with numerous giant deposits, we often find BM doubling with mesangial interposition [1140]. Even in the early disease stage, glomeruli with giant deposits do not show obvious mesangial cell increase greater then minimal insular mesangial hypercellularity (Fig. 15.24).

The rest of the glomeruli which, at first glance, may appear unaffected, often demonstrate a minimal, insular, mesangial hypercellularity and matrix increase upon closer examination (Fig. 15.25; see also [621, 741]). Completely obsolescent glomeruli are sometimes considerably disintegrated and show blurred contours (Fig. 15.26).

In the interstitium, we found isolated nests of foam cells and a constant – if patchy – but often disproportionally severe fibrosis with scanty lymphocytic infiltrates. In the presence of larger fibrinoid deposits, they were of a lympho-plasmocytic character. Patchy tubular atrophy with BM thickening is nearly always present (see also 1068).

## IF Findings

Besides negative findings, deposits of IgM and/or C3 in focal-segmental distribution (Fig. 15.27), which are sometimes finely and sometimes coarsely granular and also comma-shaped, are frequently seen peripherally or peripherally and mesangially [179, 321, 630, 741, 1139, 1607] (see Table 15.6). Positive findings for IgG are rather rare (Table 15.6; 2 out of 10: [1139]; see also [1607, 1659]).

Frequent linear deposition of IgM, complement or IgG has also been reported [1607]. In heroin addicts, a partly linear staining pattern [1018] or massive granular deposition of IgM and C3 were observed [1554].

Table 15.6. IF findings in segmental-focal sclerosing glomerulonephritis ($n=12$, positive = 11)

| | IgG | IgM | IgA | C'3 | Fibrin(-ogen) |
|---|---|---|---|---|---|
| Cases tested | 12 | 12 | 8 | 12 | 12 |
| Positive | 4 | 9 | 0 | 9 | 1 |
| Diffuse | 2 | 3 | | 4 | 1 |
| Focal | 2 | 6 | | 5 | 0 |
| Global | 2 | 2 | | 1 | 0 |
| Segmental | 2 | 7 | | 8 | 1 |
| Peripheral | 2 | 2 | | 4 | – |
| Mesangial and peripheral | 1 | 5 | | 4 | 1 |
| Mesangial | 1 | 2 | | 1 | – |

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**Fig. 15.26.** Sclerosing FGN. Completely obsolescent and partially destroyed glomerulus. Extensive inflammatory infiltration of the surroundings is characteristic for this lesion. Male, 48 years. PAS (×360)

**Fig. 15.27.** Pronounced segmental deposits of C3 in sclerosing FGN. Only a few deposits are also present in other segments (→). Male, 32 years. IF (×400)

**Fig. 15.28.** Sclerosing FGN. There is severe thickening of the BM in the region of the afflicted glomerular capillary loops. Isolated subendothelial deposits (→) are present as well as considerable activation of mesangial cells (*M*) and edematous swelling of podocytes with foot process (*FP*) fusion. Male, 56 years. EM (×3320)

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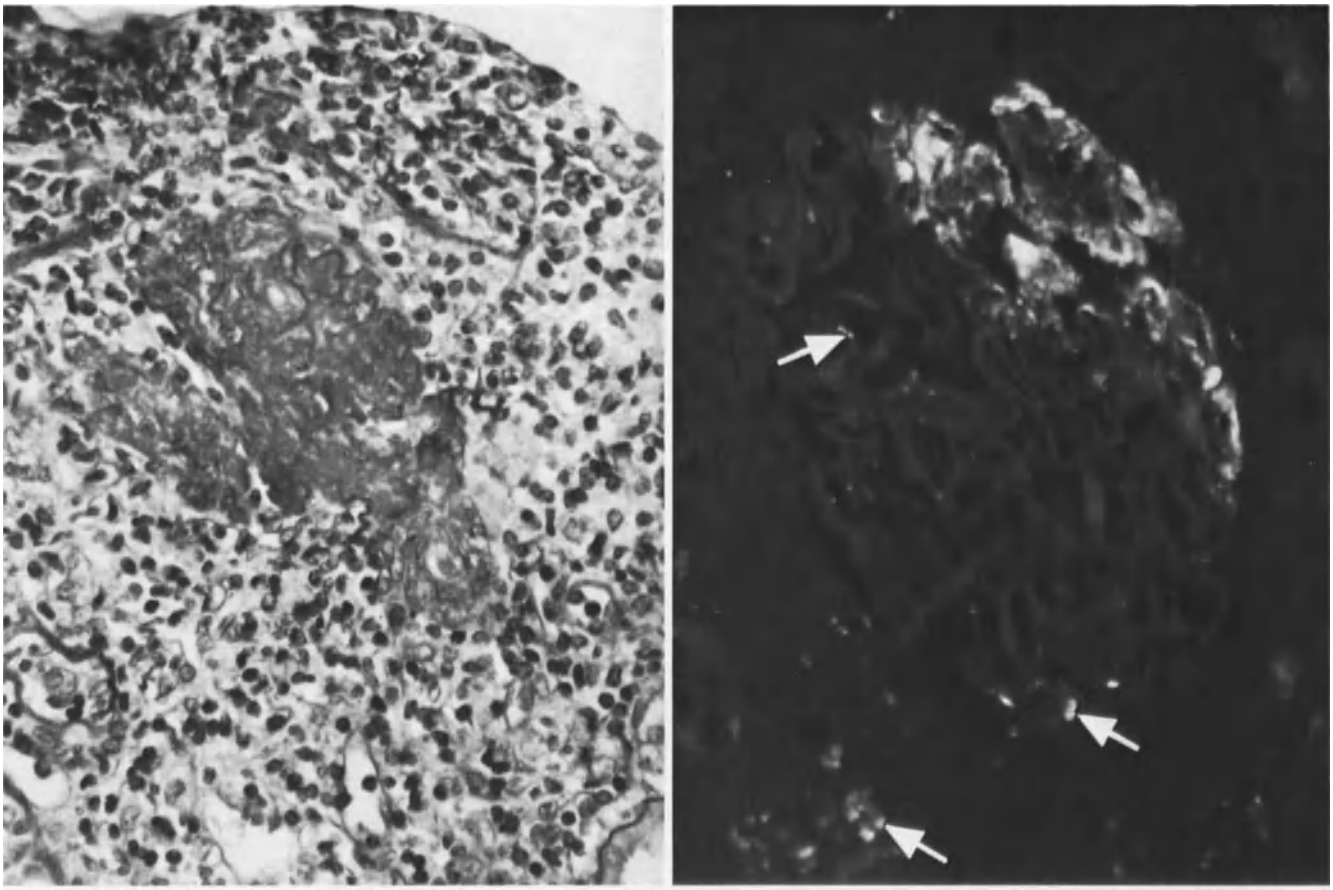
**Fig. 15.29.** Segmental glomerular capillary loop collapse with severe wrinkling of the BM in sclerosing FGN. Female, 66 years. EM (×8680)

**Fig. 15.30.** Sclerosing FGN. These findings are the equivalent to those seen in Figure 15.24. Massive peripheral hyaline giant deposits (*D*) with synechia and extensive vacuolar degeneration containing lipids (*). Capsular basement membrane (*CBM*), capsular epithelium (*CE*), fibrillar-permeated capsular exudate (*FI*). Original glomerular capillary loop BM (→). Male, 23 years. EM (×3500)

**Fig. 15.31.** Sclerosing FGN. Isolated subendothelial deposit (*D*) with a translucent halo due to resolution. Numerous total interruptions of glomerular capillary loop BM are present (→). Massive thickening of lamina rara interna (⇾) and areas of splitting of the lamina densa (*) are seen. Male, 11 years. EM (×9460)



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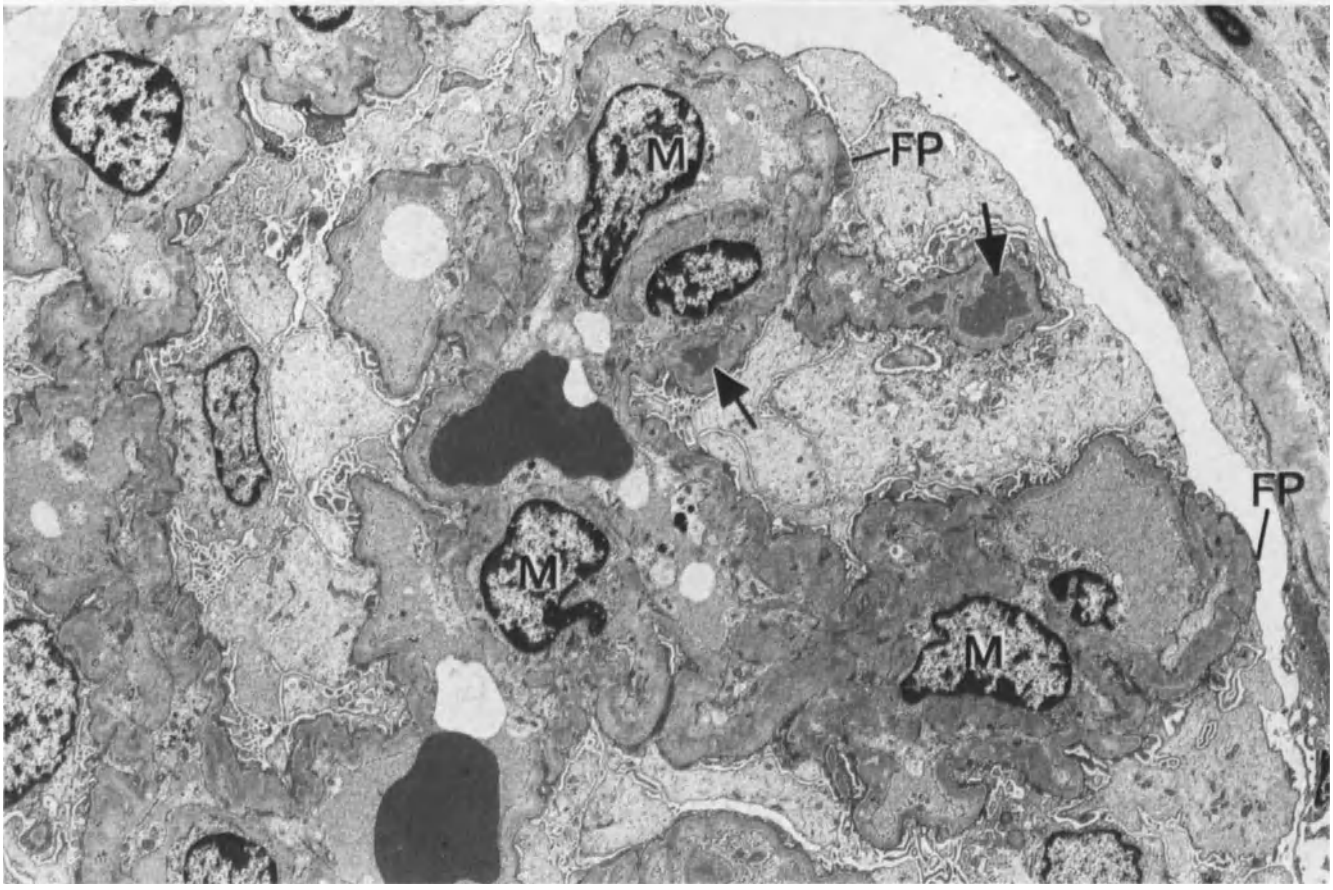


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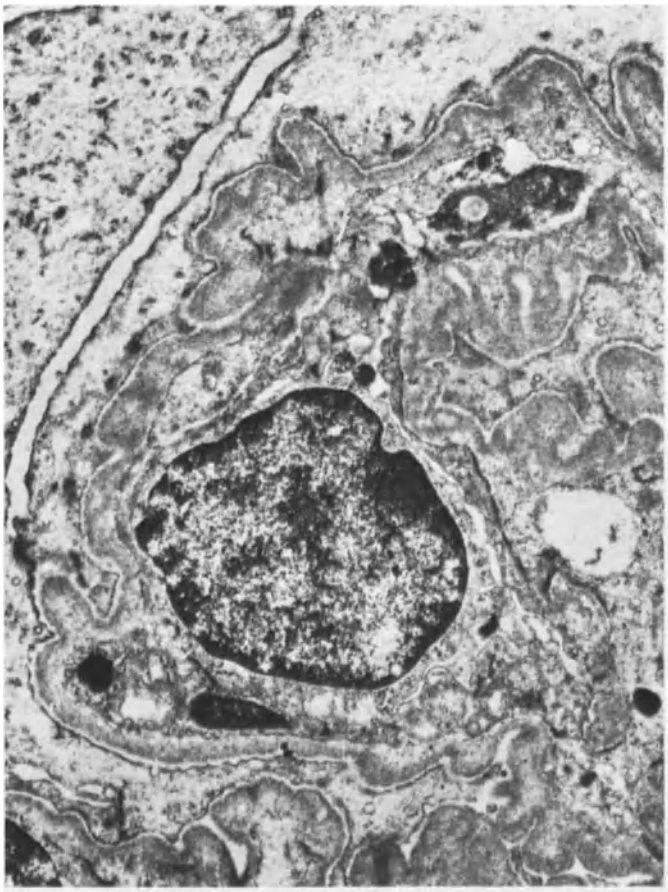

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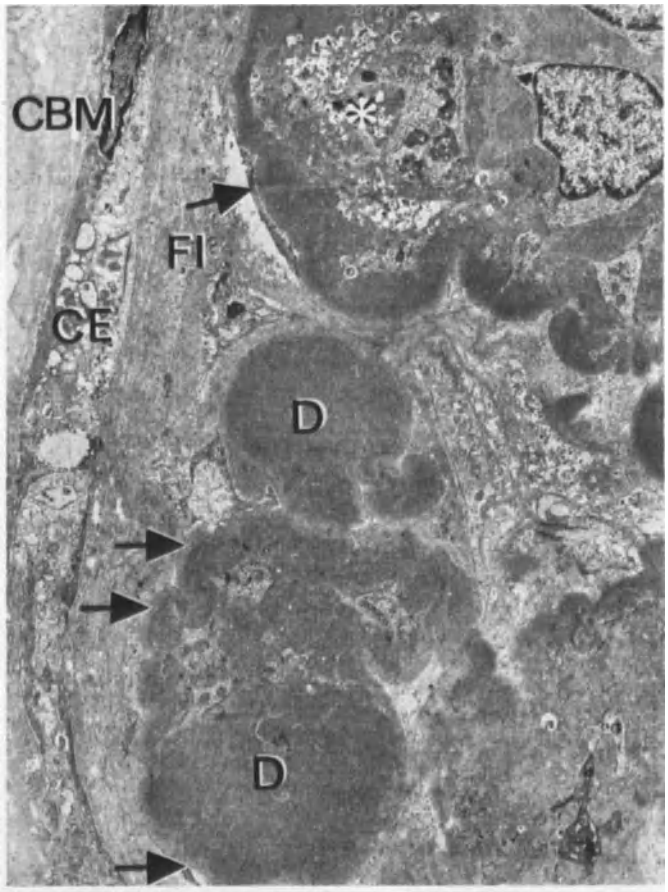


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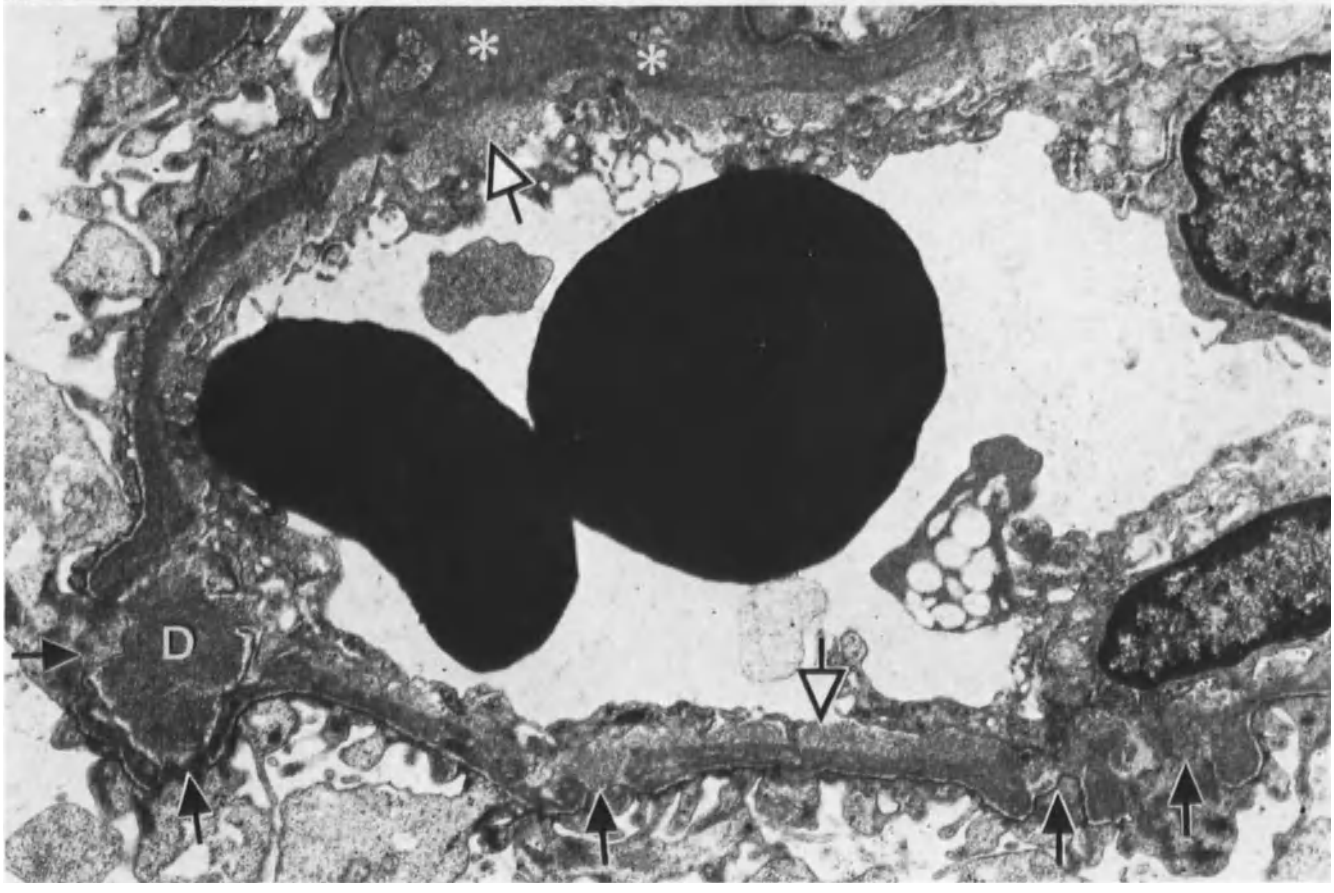


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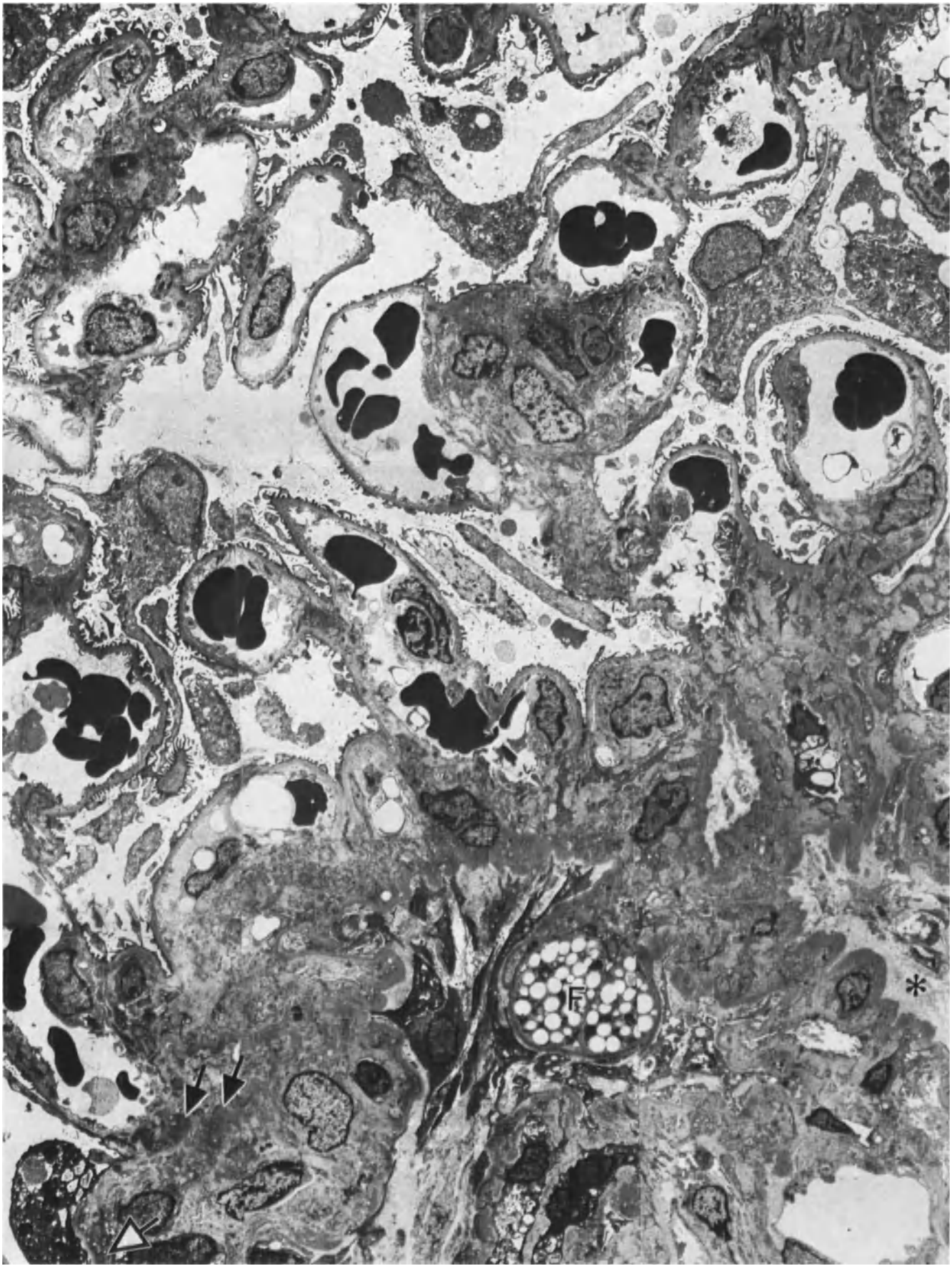



15.32

### EM Findings

The podocytes evidence severe fusion of foot processes, vacuoles and hyaline droplets in the region of the changed loops (Figs. 15.28–15.30; see also [597]). Other investigators maintain that all loops exhibit these changes [1659], a finding which we could only confirm in half of our cases. Endothelial foam cells were present in 2 out of 20 of our cases and 3 out of 20 showed marked protein storage in addition to endothelial hypertrophy and arcade formation in about half the cases. In completely obsolescent glomerular segments (see also [741]) only isolated deposits can be encountered.

Obsolescence of individual loops only is very common, (Figs. 15.28, 6.50) and they sometimes exhibit typical secondary collapse changes (Fig. 15.29). Giant deposits lie subendothelially [770, 1189a] in the periphery of the loop (Fig. 15.30; 8 out of 20: Z). Intramembranous deposits (Fig. 15.31; [741]) were found in our material in 10 out of 20 cases, deposits along the mesangial BM in 5 out of 20, and in the mesangial matrix in 5 out of 20 [1189a]. Subepithelial deposits are always absent.

Lipid vacuoles are frequent in the center of giant subendothelial deposits (Fig. 15.30; see also [1401]). BM thickening and mesangial matrix increase (Fig. 15.32) are very pronounced in the afflicted loop segments [281, 846, 1177]. We found a slight mesangial cell increase—in neighboring loops—in 16 out of 20 cases, a finding not confirmed by others [1732]. BM doubling with mesangial interposition was seen in 10 out of 20 cases, whereas BM defects (Figs. 15.33, 15.34, 6.55) were rare. We noted focal thickening of the lamina rara interna in 13 out of 20 of our cases (Figs. 15.31, 15.33; see also [596]). Degradation granules are predominant in obsolescent loops, (Figs. 15.35, 15.36). Nonsegmentally affected glomeruli show minimal insular mesangial hypercellularity and matrix increase (Fig. 15.37; see also [1400, 1401]). Tubular and interstitial changes correspond to those described under LM.

◁ **Fig. 15.32.** Sclerosing FGN with isolated endothelial (?) foam cells (*F*). Between the podocytes and BM of obsolescent glomerular capillary loops, newly formed fibrillar material is present (*). In addition to mesangial deposits (→) isolated subendothelial deposits (⇨) are present. There is pronounced mesangial matrix increase and slight mesangial cell increase. Partly hypertrophied podocytes demonstrate dilated endoplasmatic reticulum, large vacuoles, and lipid droplets (near⇨). Male, 18 years. EM (×2010)

### Differential Diagnosis

Consideration must be given to so-called overload glomerulitis (see p. 308) in pyelonephritis (Figs. 15.38–15.41), to segmental obsolescence in hypertension and sequelae of intravasal coagulation and to Alport's syndrome. In the latter, segmental glomerular sclerosis (Fig. 23.27) is a frequent finding in advanced stages, but only rarely in association with giant fibrinoid deposits. Finally, isolated glomeruli with segmental obsolescence are found in children without any renal dysfunction [872b].

Thus, the morphologic picture of sclerosing FGN is not specific although the association of segmental glomerular sclerosis (obsolescence) and interstitial inflammation is characteristic. Accordingly, the diagnosis must be based on clinical data. To rule out other diseases, e.g. Alport's syndrome, EM investigation is urgently needed. EM investigation also allows exclusion of purely hypoxic damage which is suggested by collapse changes in the afflicted loop segments in sclerosing FGN. This exclusion is possible due to the absence of hypoxic changes in the nonsegmentally changed loops and the unaffected glomeruli. In our opinion, there are no reliable morphologic parameters for the delineation of the sclerosing stage of proliferative FGN from sclerosing FGN although the presence of numerous sclerosed crescents is indicative of the former. There are no problems in the differentiation of sclerosing FGN from other GN.

### Prognosis

In general, prognosis is poor. Depending on the follow-up time, 25–50% (100%: 1055) procede to renal insufficiency [43, 621, 629, 1102, 1659, 1732]. The progression is said to be more rapid in adults than in children [1189b]. The 10-year survival rate of our patients was 57% (see Table 15.7). Among our 89 patients followed for longer than 1 year, about 40% died, 30% of uremia, and only 8.9% are in complete remission.

Transition into focal-global sclerosis and ultimately to findings of end stage kidney appear to be typical on the basis of evidence from five sequential biopsies [741].

Prognosis seems to be all the poorer the more severely the interstitial changes are developed [782] and the more the glomeruli exhibit segmental sclerosis and hyalinosis [872b]. Relapses in renal transplants are reported [720, 1020]; 2 out of 3: [1659]; contra: 0 out of 2: [321]).

### Pathogenesis and Etiology

Some investigators view the lesion as a unique disease entity [621, 635, 558, 1055], e.g., as a noninflammatory

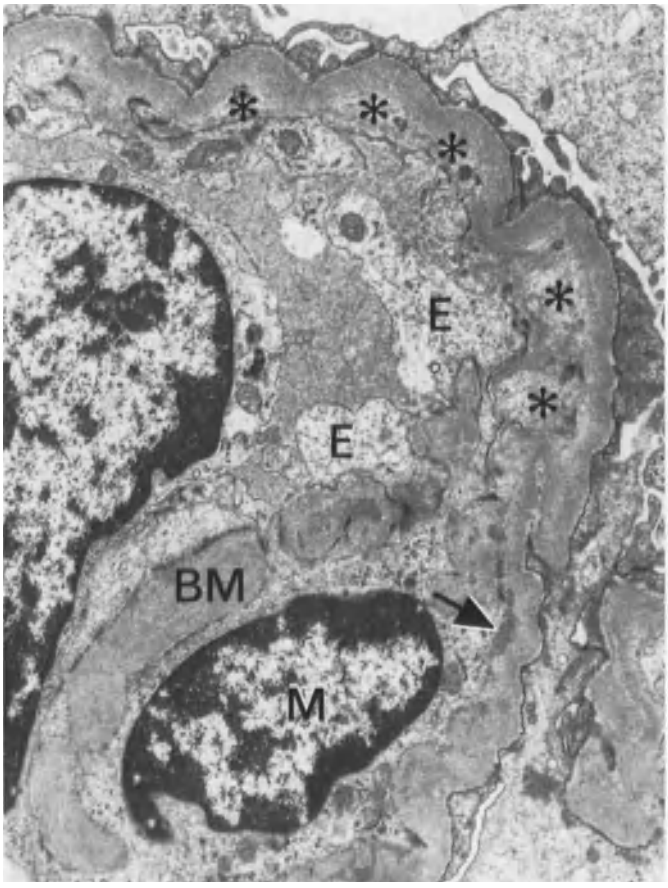



**Fig. 15.33.** Glomerular capillary loop periphery in sclerosing FGN. Mesangial interposition (*M*) with massive new formation of a second subendothelial basement membrane (*BM*) are present. Remnants of a very small subendothelial osmiophilic deposit can be recognized (→). Numerous translucent areas (*) partly with degradation granules are present in the wrinkled BM. There is also endothelial (*E*) edema and almost complete fusion of podocytic foot processes. Male, 54 years. EM (×9460)

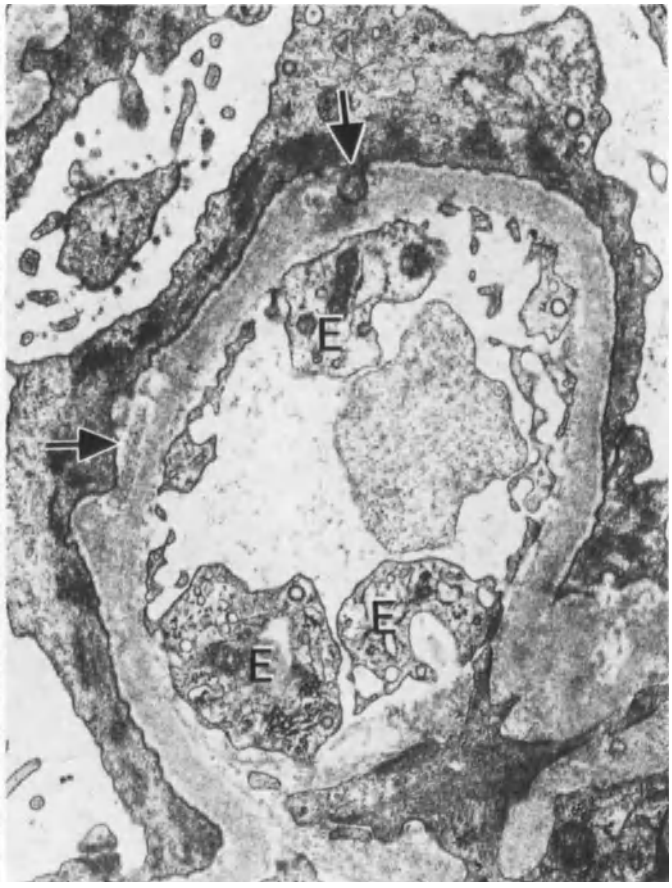



**Fig. 15.34.** Severe damage (→) of the peripheral glomerular BM in sclerosing FGN. Note hypertrophy of endothelium (*E*) and complete fusion of podocytic foot processes as well as increased osmiophilic substance. Female, 36 years. EM (×18,000)

Table 15.7. Prognosis and outcome in segmental-focal sclerosing glomerulonephritis

| Prognosis | Survival rate (%) | | |
|---|---|---|---|
| | 5 years | 10 years | 15 years |
| From disease onset | 77 | 57 | 52 |
| SE[a] | 4.3 | 5.7 | 6.0 |
| From biopsy | 64 | 42 | 37 |
| SE[a] | 5.5 | 6.9 | 7.3 |

[a] SE = standard error in %.

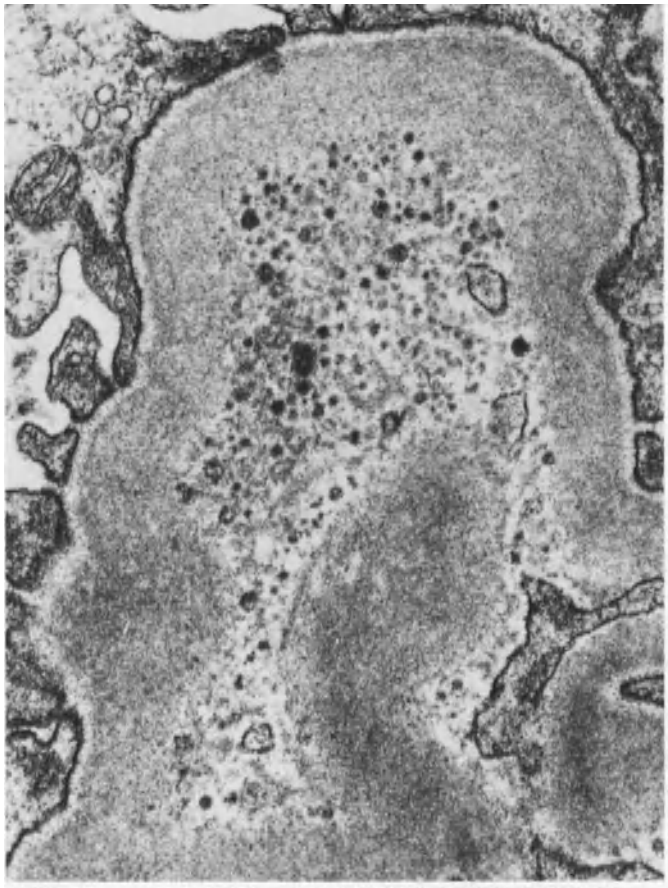
*Outcome* (minimal follow up 1 year)

| Patients | $n=89$ |
|---|---|
| Death | 39.3% |
| Death in uremia | 29.2% |
| Complete remission | 8.9% |

**Fig. 15.35.** Obsolescent peripheral glomerular capillary loop in sclerosing FGN. Lamina densa is obviously thickened and unclearly delimited on its inner aspect where masses of oval virus-like structures are present. Partial foot process fusion is present. Male, 54 years. EM (×30,000) ▷

**Fig. 15.36.** An obsolescent peripheral glomerular capillary loop with a wrinkled and thickened basement membrane (*BM*). A loose newly formed fibrillar material is present between the BM and podocyte (*). Foam cells with numerous myelin structures and lipid vacuoles are seen in a foam cell in the original glomerular capillary loop lumen. Male, 32 years. EM (×7250)

**Fig. 15.37.** Sclerosing FGN: sectors appearing practically unchanged in LM show under EM an increase of the mesangial matrix and even more slightly of mesangial cells (*M*), i.e., glomerular minimal change. A single subendothelial osmiophilic deposit near the mesangium (→) is present. Capsular epithelial cells are scarcely changed. Podocytes are highly edematous without foot process fusion. Male, 53 years. EM (×2830)



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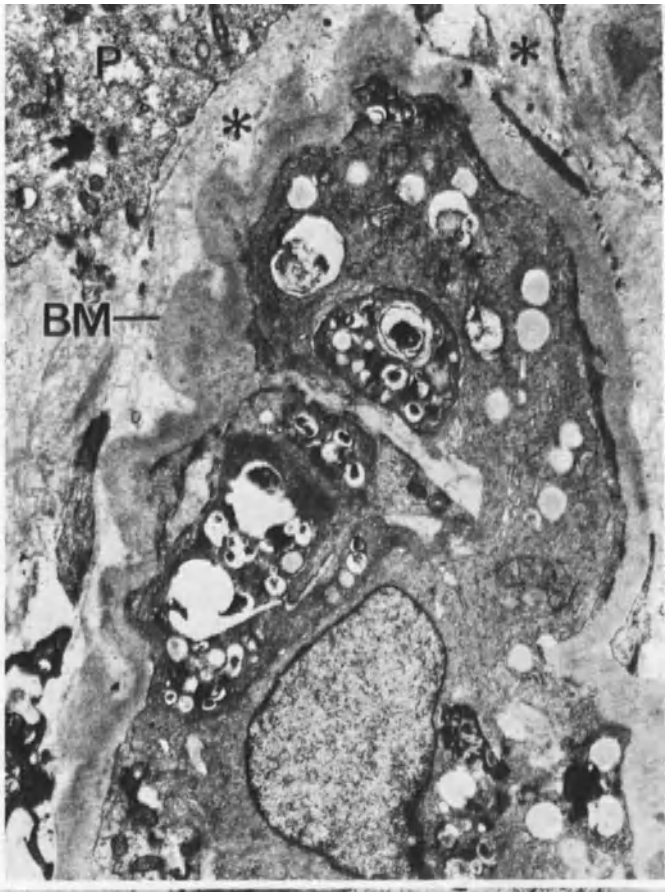


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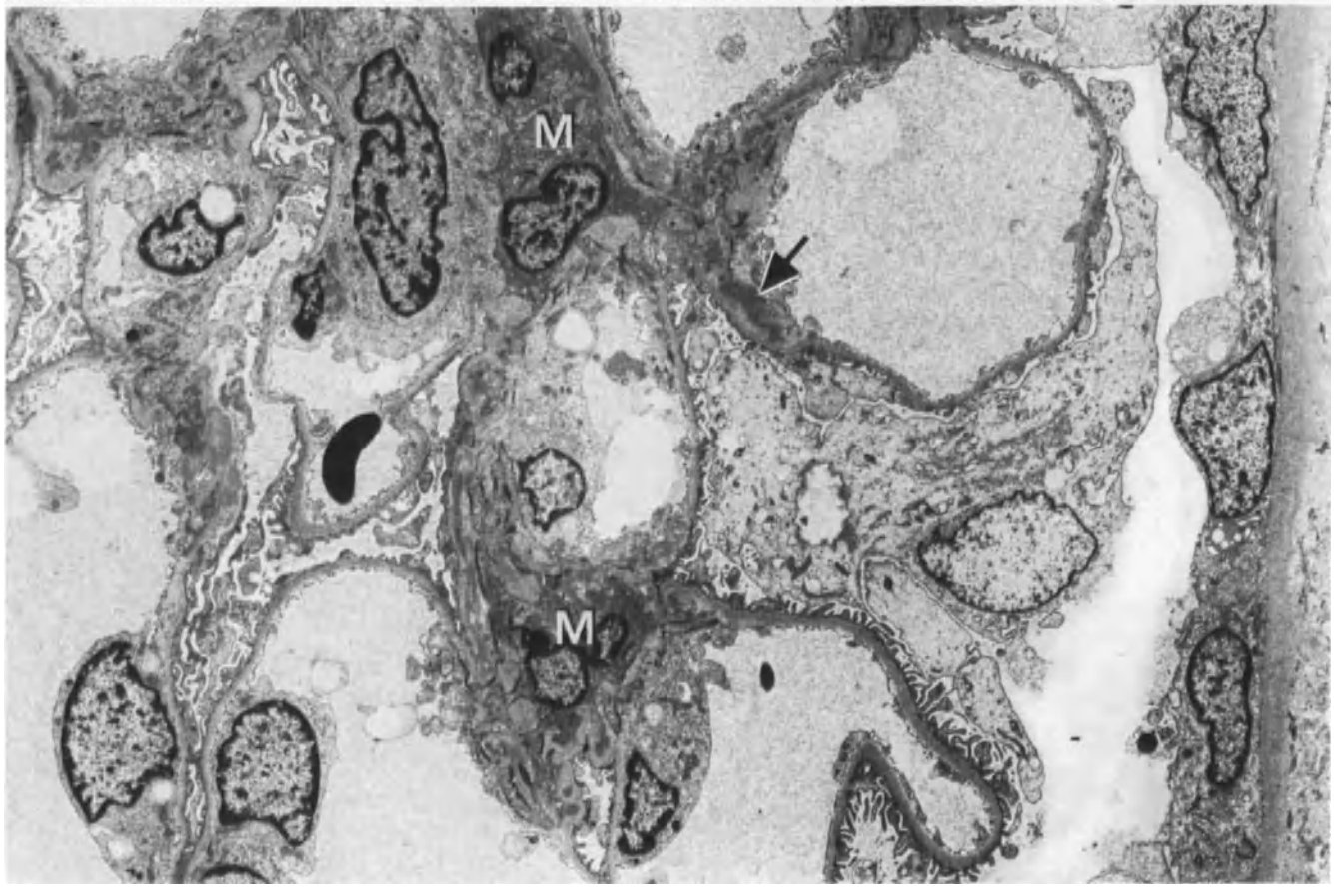


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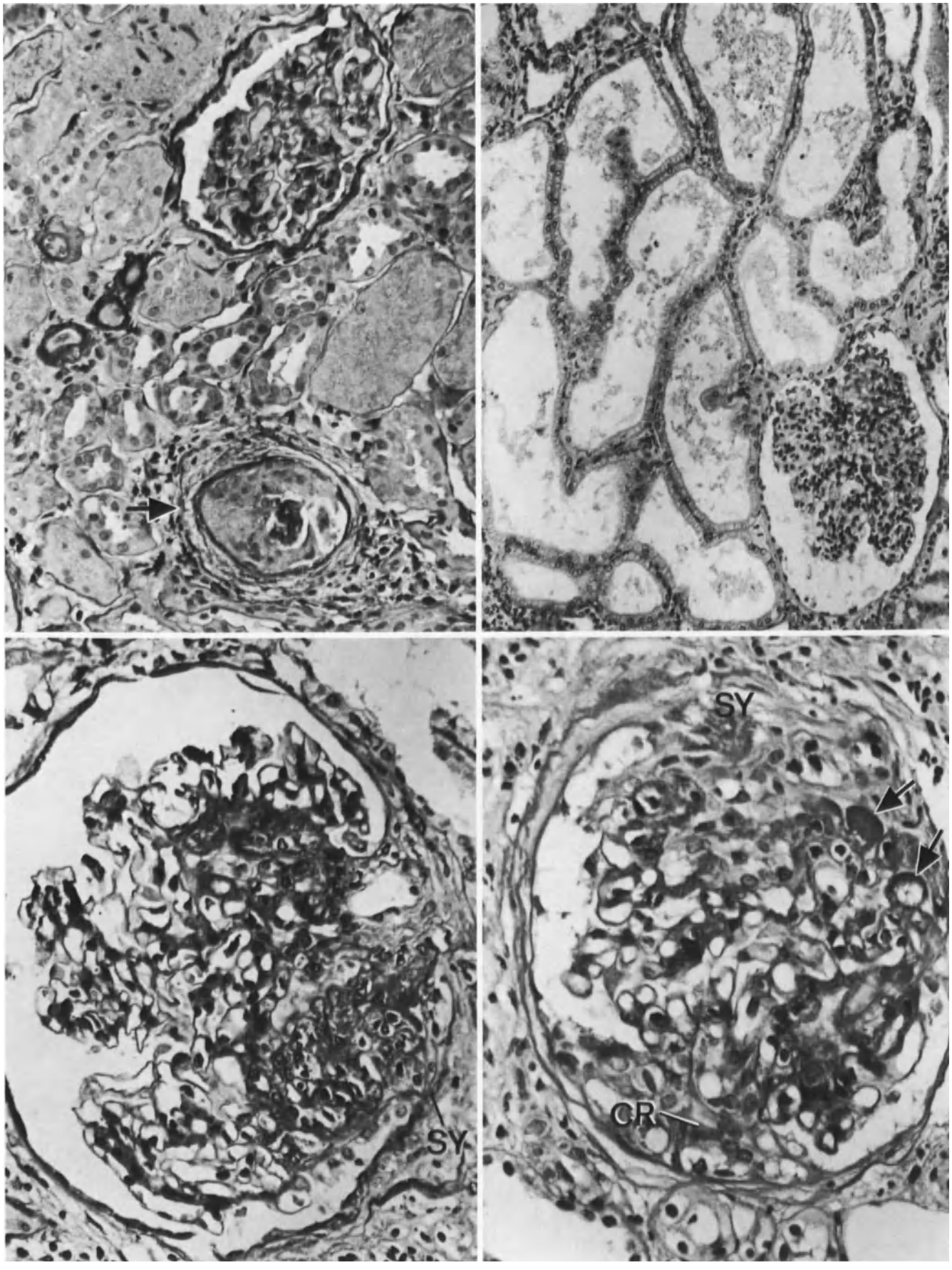


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15.41

loop collapse with obliteration [596, 1484] in which the subendothelial deposits are considered to arise from purely insudative processes [741] or as a primary podocyte change proceeding with degeneration and detachment from the BM [597]. Other investigators, however, hold that segmental-focal sclerosing FGN is an expression of prior diffuse GN which resolved with focal scarring [163, 281, 595]. Thus, sequential biopsies have shown that segmental sclerosis can develop from 6 months to 8 years after diffuse endotheliomesangial GN, as we have observed in one of our own cases (see also [621, 630]). Four of our patients with this lesion had a history of clinically acute GN (see Table 14.5; see also [409, 1791]).

Sclerosing FGN can arise with malaria (11 out of 27: [828]; 1 out of 73: [1732]; see also [1140]). It is also found associated with acute rheumatic fever ([130, 598, 1068, 1158; contra: [207]) and in heroin addicts (7 out of 11: [1554, 1018]; 20 out of 23: [579a]). Among our patients, sclerosing FGN was preceded once each by staphylococcal abscess, streptococcal angina, viral hepatitis, herpes virus infection, Schönlein-Henoch's purpura, and was encountered twice in SLE. But, in 92.6%, no etiologic factor could be found. On the other hand, observations of segmental-sclerosing changes following intravasal coagulation [1047], etc. show that other conditions besides immunocomplex GN can lead to this picture. Whether or not the lesion is progressive in these cases, however, is not known.

In our opinion, there is unequivocal evidence that some cases of segmental-focal sclerosing GN develop from diffuse or proliferative FGN. This is further substantiated by the fact that in some cases, IgG can be demonstrated intraglomerularly with IF. But the greater part may possibly be the result of metabolic or as yet other unknown factors injurious to the glomerulus. The main IF findings of IgM and C3 in these cases are possibly due to insudative processes and, as such, do not necessarily indicate an immunologic basis of the disease [1399, 1400, 1401]. The podocytic changes described are probably the result but not the cause of the disease [597]. The fact that relapses in renal transplants were observed (see p. 610) suggests the presence of a circulating humoral or cellular damaging factor.

The relationship between glomerular minimal change and segmental-focal sclerosing GN is not clear. It has repeatedly been observed in sequential biopsies that the first biopsy shows only glomerular minimal change whereas further biopsies exhibit segmental-focal sclerosing GN. This is no proof for the transition of the former into the latter even if serial sections are done, since segmental-focal sclerosing GN starts in the juxtamedullary zone, which is often not included in needle biopsy material, and even if it is, the initially rather scanty segmentally changed glomeruli could be missed (see also [630, 770]; contra: [596]; for literature: [621]). The hypothesis, that segmental-focal sclerosing GN develops after corticosteroid therapy of glomerular minimal change can probably also be discarded since there are more cases known without preceeding corticosteroid therapy than with [621].

◁ **Fig. 15.38.** Glomerular minimal change and incomplete glomerular obsolescence (→). Note periglomerular inflammation. Male, 6 years. PAS (×290)

**Fig. 15.39.** Hypertrophied glomerulus with a diameter of 320 µm surrounded by considerably hypertrophied tubules in a case of pyelonephritic contracted kidney with overload glomerulitis. Female, 8.5 years. PAS (×290)

**Fig. 15.40.** Same case as in Figure 15.39. So-called overload glomerulitis. Mesangium is highly segmentally enlarged and evidences very slight nuclear increase. Synechia (*SY*). Female, 8.5 years. PAS (×290)

**Fig. 15.41.** Same case as in Figure 15.39. Overload glomerulitis in pyelonephritic contracted kidney. Segmental crescent (*CR*), and a large synechia (*SY*) are present as are a few peripheral glomerular capillary loops which evidence giant deposits (→). PAS (×300)

## Focal-Global Sclerosing Glomerulonephritis

### Definition

The lesion is characterized by the presence of more than 10% of obsolescent glomeruli—predominantly in the juxtamedullary zone—without a determinable vascular or pyelonephritic cause. Many investigators—at least temporarily—differentiated this lesion from segmental-focal sclerosing GN [43, 621, 651, 888, 1399, 1400, 1401, 1732]. We do not consider focal-global sclerosing GN as a separate disease entity but as a stage in the development of segmental-focal sclerosing GN since serial sections often evidence—beside obsolescent glomeruli—those with segmental changes (see also [630, 827b, 1055]).

***Synonym:*** Focal-global fibrosis ([621]; see also Table 13.2).

### Incidence and Clinical Findings

The reported incidence is 1.7% [621, 635] which is the same in our GN biopsies and in 24% of those in pediatric focal nephritis [621]. The condition usually appears in children somewhat later than sclerosing FGN [1184b]. Boys are more frequently afflicted than girls (1.28:1. Z). The clinical findings do not differ significantly in our patients or those of others from segmental-focal sclerosing GN [630]. In another series, pure nephrotic syndrome predominates in focal-global sclerosing GN [1184b].

### LM Findings

The pronounced affliction of the juxtamedullary zone is typical for this lesion [1055] in which an increased number of glomeruli show global sclerosis (fibrosis: [621]). The other glomeruli evidence findings of glomerular minimal change. Perifocal inflammation is rarely seen (Fig. 15.38).
The tubules are surprisingly severely atrophic in relation to the relatively mild glomerular changes. As in sclerosing FGN, focal interstitial fibrosis is quite severe.

### IF Findings

According to the only reference in the literature [630] the findings—with the exception of unspecific deposition of IgM and complement—are negative. The same holds true for our 5 IF-investigated cases. EM findings are not available.

### Differential Diagnosis

A few obsolescent glomeruli may be encountered in normal kidneys of all age groups. They predominate in the subcapsular region (see Table 6.1, p. 107). When the number of obsolescent glomeruli comprises more than 10% of all glomeruli and the juxtamedullary region is afflicted, the diagnosis of focal-global sclerosing GN is strongly suggested [621]. This diagnosis requires exclusion of significant vascular and pyelonephritic changes. In vascular or pyelonephritic diseases, however, the obsolescent glomeruli occur in groups, and predominantly in the outer cortex. In doubtful cases, clinical data will prove helpful in the differentiation. Congenital glomerulosclerosis [1791] never shows more than 10% of obsolescent glomeruli (see p. 28).
Finally, we wish to point out that obsolescent glomeruli associated with other significant glomerular changes such as sclerosing FGN, marked proliferation, etc., should not be classified as focal-global sclerosis.

### Prognosis

The prognosis in focal-global glomerular sclerosis is said to be not as bad as for sclerosing FGN [630]. Thus, 17 patients with this lesion are still alive after 5 years, whereas 11 out of 35 patients with sclerosing FGN have died [630]. In 13 cases under our control, 3 died, 1 from uremia, 2 from unrelated causes. Other investigators [1184b] even found prognosis and responsiveness to corticosteroid therapy as good as in idiopathic glomerular minimal change with nephrotic syndrome.

### Pathogenesis and Etiology

Initially, focal-global sclerosing GN was viewed as a consequence of glomerular minimal change [621]. This view was subsequently rejected by its proponents [630]. Segmental-focal sclerosing GN can develop into focal-global sclerosing GN as has been demonstrated by different investigators [621, 630, 1055]. Thus, pathogenesis and etiology of focal-global sclerosing GN should be identical to that of sclerosing FGN (see also [1047]).

## Overload Glomerulitis
[1791]

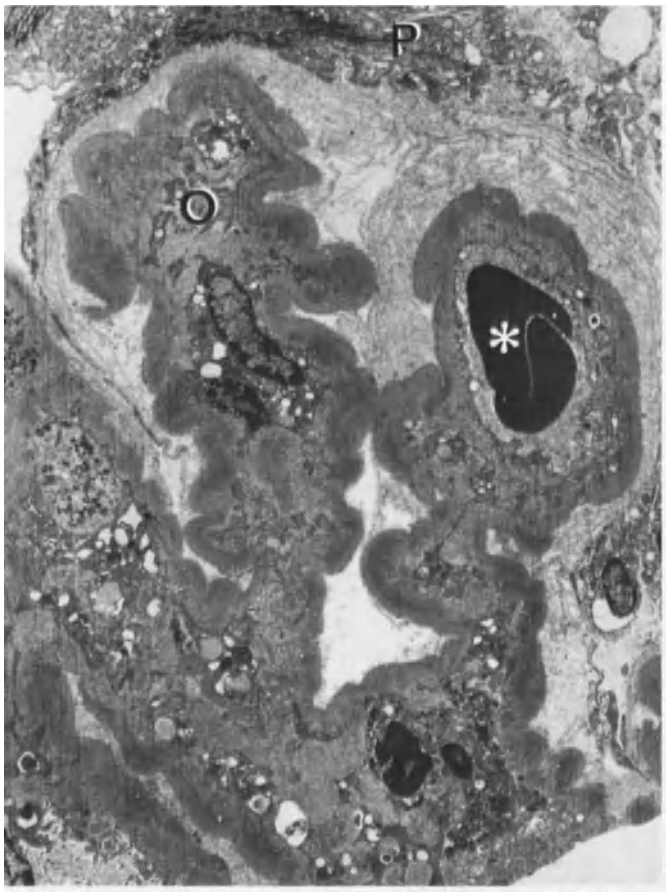
### Definition

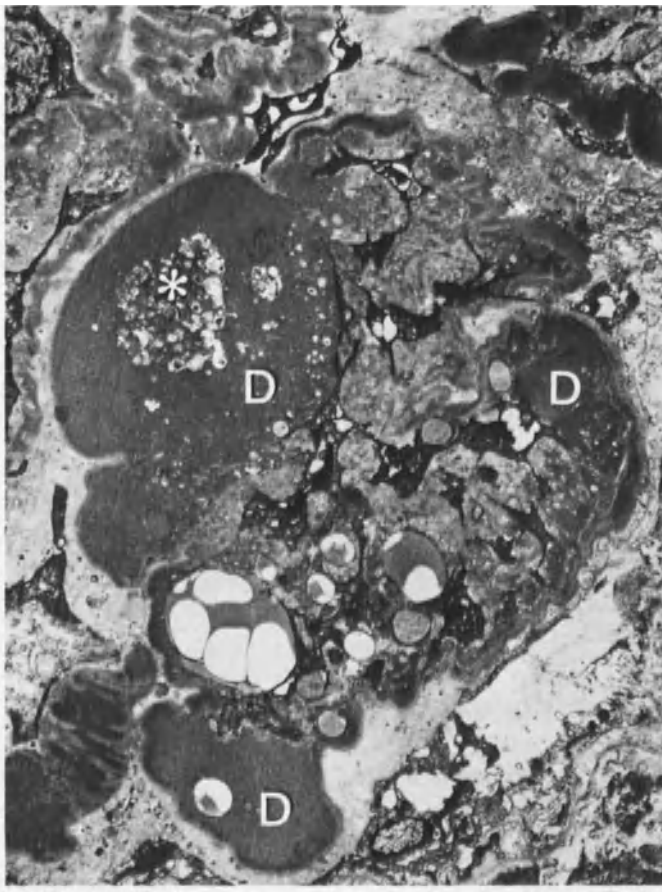
This lesion is a segmental-focal proliferative or sclerosing glomerular change associated with bilateral contracted kidney due almost exclusively to pyelonephritis.

**Fig. 15.42.** Overload glomerulitis in chronic pyelonephritis. One glomerular capillary loop is completely obsolescent (*O*) and a second one is obviously narrowed (*). Extensive fibrillar BM layers surround the thickened and wrinkled glomerular capillary loop BM and are covered externally by podocytes. Female, 54 years. EM (× 1460) ▷

**Fig. 15.43.** Same case as in Figure 15.42. Glomerular capillary loops are occluded by osmiophilic giant deposits (*D*) which exhibit lipid vacuoles (*). Other changes correspond to those seen in Figure 15.42. Female 54 years, EM (× 3800)

**Fig. 15.44.** Same case as in Figure 15.42. Peripheral glomerular capillary loops in overload glomerulitis. Note circumferential mesangial interposition (*M*) and new formation of a second subendothelial basement membrane (*BM*). Isolated, unclearly delimited osmiophilic deposits (*) are present in the considerably enlarged mesangium. Female, 54 years. EM (× 4330)

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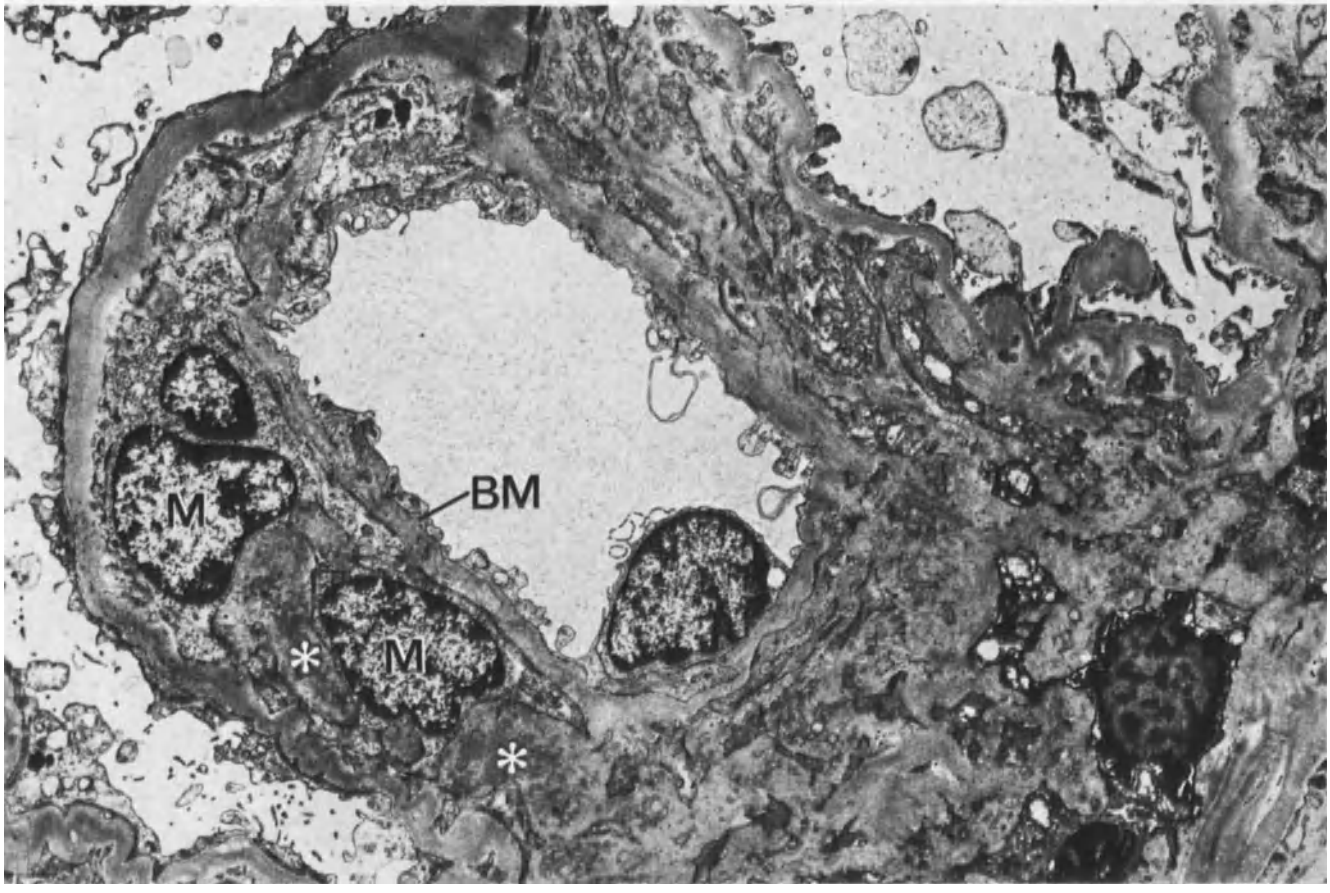


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### Incidence and Clinical Findings

The incidence in autopsy material is 0.15% (39 out of 25,000: Z) in our biopsy material 0.8%. The symptoms of uremia completely obscure those of overload glomerulitis.

### LM Findings

Numerous glomeruli are completely obsolescent. The intact glomeruli are greatly enlarged due to severe compensatory hypertrophy (Fig. 15.39). The other findings correspond to those of proliferative and, very commonly, of sclerosing FGN (Fig. 15.40). BM doubling with mesangial interposition, peripheral subendothelial deposits, and mesangial matrix increase (Fig. 15.41) as well as synechiae are frequently observed. Crescents are very rare.

### IF Findings

In our single case examined with IF we found only focal-segmentally distributed deposits of IgM and C3.

### EM Findings

In nearly obsolescent loops, some foam cells—presumably endothelial—were present (Fig. 15.42). The glomerular capillary loop lumens are often occluded by giant subendothelial deposits (Fig. 15.43). In addition, mesangial deposits and interposition (Fig. 15.44) may be found. BM thickening and new formation of a fibrillar layer between BM and podocytes are especially evident in progressive obsolescence.

### Differential Diagnosis

The chief difficulty lies in distinguishing overload glomerulitis in pyelonephritis from contracted kidney in sclerosing FGN. In the former, the concomitant severely destructive pyelonephritis is of great importance. Clinical data are often essential for definite differentiation.

### Pathogenesis

Some investigators stress the pathogenetic significance of ischemia [858, 1068]. We feel that there must be a relationship to the severe functional overload of the few remaining nephrons in the severely contracted kidney (see also [602]), since this change is absent even in contracted kidney as long as the contralateral kidney is functioning appropriately.

Furthermore, the lesion can be experimentally induced in rats by a five-sixths resection of their renal mass [677, 749, 1357a]. A similar lesion can be experimentally obtained by excessive protein feeding [426, 903, 1387] and by irradiation [426]; (see also p. 544). The lesion also occurs spontaneously in old rats [426].

Hypertension and old age can be excluded as the cause of the lesion arising experimentally after subtotal nephrectomy. The absence of analogous changes in chronic renal vein thrombosis excludes the assumption that the lesion is the consequence of loop dilatation [749].

We suppose that the lesion results from functional overload with concomitant impairment of mesangial function as well as from a decrease in resistance of hypertrophied glomeruli towards minimal bacterial dissemination, toxic influences, and immunologically induced lesions. Finally, it is conceivable that serum factors found after unilateral nephrectomy—which cause increased incorporation of thymidine and of uridine in nucleic acids, as shown in supravital renal slices [1295]—could be the cause of the proliferative inflammatory changes.

# 16. Glomerulonephritic Contracted Kidney (Nonclassifiable Glomerulonephritis, End-Stage Kidney)

## Definition

GN contracted kidney in biopsy is defined as renal tissue with more than 75% of obsolescent glomeruli—in the absence of any indications for a vascular or interstitial cause of the process—associated with chronic renal insufficiency. When only weight at autopsy is considered, contracted kidney is not necessarily present. Weight of both kidneys in GN with chronic uremia is $180 \pm 60$ g and in pyelonephritic contracted kidney $125 \pm 26$ g as seen in our material.

## Incidence

The incidence in biopsy material has been given as 2.1% (Z), 3.1% [277] and in children as 1.4% [621, 624]. Table 16.1 compares the relative frequency of GN forms, of deaths independent of cause and of deaths in uremia in a 10-year-period. It can be seen that among 100 deaths in uremia due to GN and glomerular minimal change, 34% (21% proliferative FGN, 13% sclerosing FGN) was accounted for by focally accentuated GN, 25% by membranoproliferative GN, 17% by extracapillary accentuated GN, 16% by epimembranous GN and less than 10% by the other forms. Comparison of the projected frequency with actual frequency in a series of 47 nephrectomies [1467a] prior to transplantation revealed good agreement with the exception of epimembranous GN.

## Clinical Findings

Chronic insufficiency—usually accompanied by hypertension, hematuria and proteinuria—is predominant. Nephrotic syndrome is more rarely observed. Primary chronic GN with insidious clinical onset is reported to be especially frequent [485].

Table 16.1. Relative frequency of GN and glomerular minimal change, and calculated relative frequency of deaths independent of cause and due to uremia

| No. | | Relative frequency | | | |
|---|---|---|---|---|---|
| | | of GN[a] | of deaths independent of cause[b] | of deaths due to uremia[c] | of GN forms in 47 nephrectomies prior to transplantation [1467a] |
| 1 | Glomerular minimal change | 33% | 15% | 2% | 28% (10%)[d] |
| 2 | Endotheliomesangial GN | 22% | 10% | 5% | |
| 3 | Proliferative FGN | 11% | 22% | 21% | 28% (including No. 5) |
| 4 | Epimembranous GN | 9% | 14% | 16% | 4% |
| 5 | Sclerosing FGN | 7% | 10% | 13% | see No. 3 |
| 6 | Membranoproliferative GN | 7% | 18% | 25% | 25% (including No. 8) |
| 7 | Extracapillary accentuated GN | 3,5% | 10% | 17% | 15% |
| 8 | Intramembranous GN | 1% | 1% | 1% | see No. 6 |
| | | 100% | 100% | 100% | 100% |

[a] Summated from 8 different series comprising 7520 cases (see Table 14.1).

[b] Deaths independent of cause in % of all deaths calculated on the basis of our own 10 year survival rates (from disease onset) presented in the corresponding chapters.

[c] Deaths due to uremia in % of all deaths in uremia calculated on the basis of our own 10 year survival rates and follow-up data presented in the corresponding chapters.

[d] Considering only patients with a reliable clinical history of GN.

Acute, reversible renal failure is seen in GN contracted kidney in association with interstitial nephritis due to drug allergy (furosemide, thiazide; [983]). In rare cases, acute renal failure may be due to superimposed pyelonephritis, systemic infection, and nephrotoxic antibiotics. The true state of affairs, however, is difficult to assess since renal biopsy is not usually done in the presence of chronic uremia.

The number of cases with nonclassifiable contracted kidney has perceptibly increased because of the progression of the changes during chronic hemodialysis and after transplantation.

## LM Findings

Obsolescent glomeruli with obliterated capsular spaces and thickened Bowman's capsules (Figs. 16.1, 16.2; see p. 107) are the predominant findings. There are no indications of focal destruction of parenchyma. Principal attention must be directed to the glomeruli with a more or less preserved blood supply (Fig. 16.3) in which synechiae are frequent as are sclerosed or proliferative crescents which occasionally show adenomatoid structures (Fig. 16.3).

When PAS, PASM and Masson's trichrome/AFOG stains are used, the underlying form of GN can quite frequently be suspected, e.g., sclerosing FGN (Fig. 16.4) or membranoproliferative GN with obliterated lipid-filled loops (Fig. 16.5).

The still intact glomeruli are severely hypertrophic and usually a very severe increase of the mesangial matrix is demonstrable (see also [62]).

In addition to the glomerular changes, those ascribable to ischemia are always encountered (see also [1068] and Table 6.1, p. 107). Small subinfarcts are present in rare cases.

Tubules belonging to the obsolescent glomeruli are severely atrophic and show thickened BM. Tubules belonging to intact glomeruli show cystoid transformation due to compensatory hypertrophy (Fig. 16.6) especially in early childhood cases (see p. 358).

The interstitium is considerably fibrosed, and has scanty lymphocytic infiltrates. The intertubular capillaries are often obliterated. The consequences of hypertension are usually evident in the vessels.

The large arteries—especially in cases with a history of long dialysis—show severe adaptive intimal fibrosis (see p. 151) superimposed on hypertensive arteriosclerosis.

## IF Findings

A comparative study comprising GN and non-GN end-stage kidneys has shown that the IF findings in all kidneys are very much alike. IgM, IgG, IgA, and various complement factors can be demonstrated in end-stage kidneys of different etiology [544, 730, 1659a].

In 3 out of 5 of our own GN cases, we exclusively found coarsely clumped IgM and C3 in glomeruli undergoing obsolescence and in preserved glomeruli. In two of these 5 cases, IgG was seen in the mesangium and in the periphery as well. These deposits are probably mainly due to insudative processes.

Completely obsolescent glomeruli are usually IF negative.

Only in two forms of GN—IgA mesangial GN and anti-BM-type GN—does IF of the contracted kidney enable definite diagnosis [1659a] insofar as all glomeruli are not obsolescent.

## EM Findings

In general, the findings are disappointing, i.e., only the picture of extensive glomerular obsolescence (Fig. 16.7) is seen (see p. 107). This renders the identification of the original form of GN exceedingly difficult. In fact, this is possible only in the region of intact loops (Fig. 16.8) where, according to our observations in 4 out of 19 cases, evidence reminiscent of primary membranoproliferative GN was found.

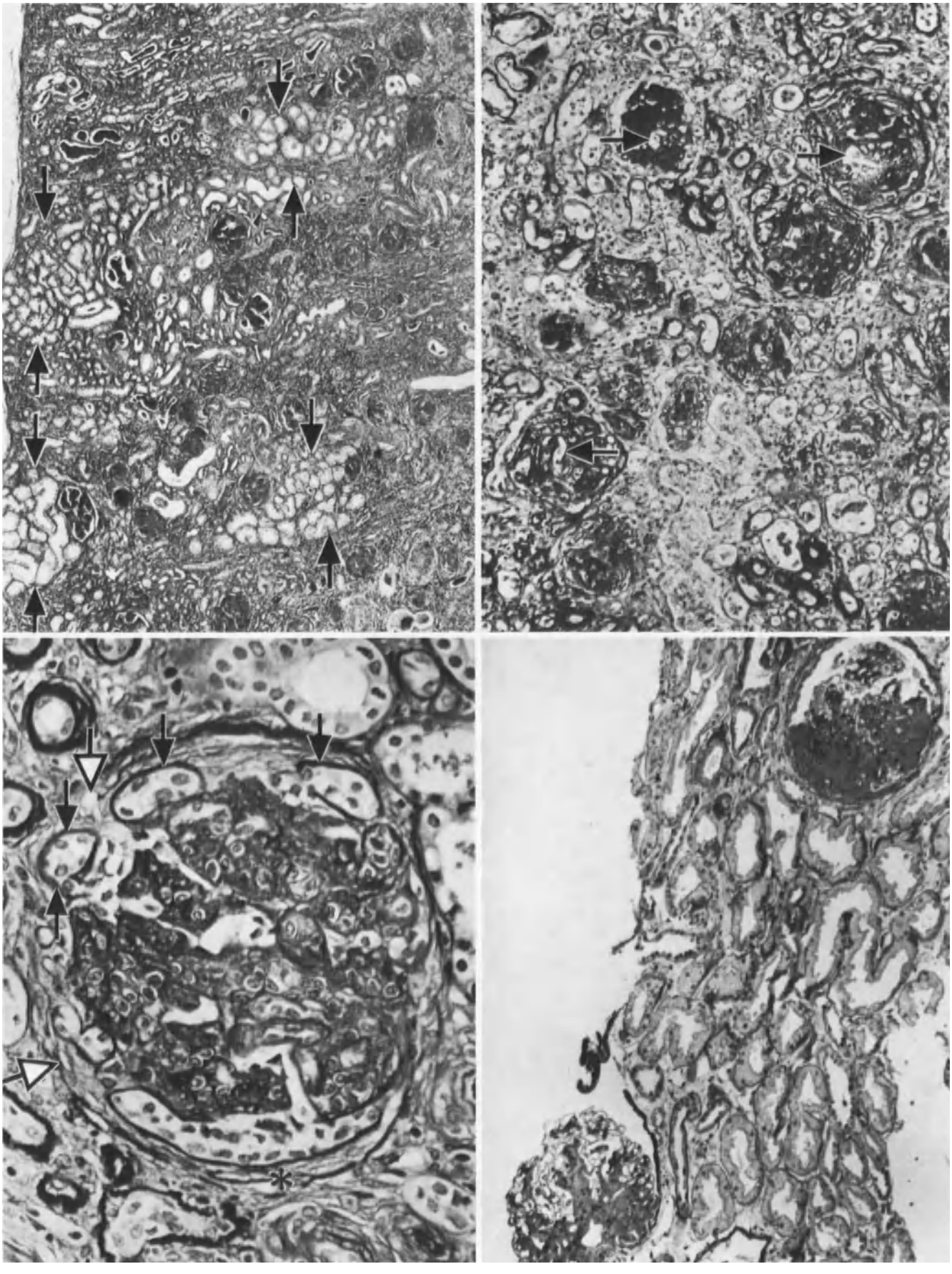
Often, extensive clearly delimited osmiophilic deposits in the subendothelial space are seen (Fig. 16.9) which are occasionally found in association with mesangial deposits (Fig. 16.10). Since osmiophilic deposits also occur however in blood vessels and in obsolescent glomeruli from other causes, we do not consider them as immunocomplexes but mainly as deposits arising from insudation.

**Fig. 16.1.** GN contracted kidney. Hypertrophied intact nephrons (→←) within scarred tissue. Majority of glomeruli are obsolescent. Male, 33 years. PAS (×100) ▷

**Fig. 16.2.** GN contracted kidney. There is almost total atrophy of the tubules. Glomeruli evidence thickened and almost completely obsolescent capillary loops and occasionally evidence shunt vessels (→). There are strikingly few proliferative changes in the region of glomerular capsule. Female, 45 years. PAS (×140)

**Fig. 16.3.** Same case as in Figure 16.2. There is practically complete proliferative obliteration of the glomerular capillary loops. In the capsular space are three adenomatoid structures—each surrounded by a BM (→). Capsular BM is partially split (*) and partially dissolved (⇨). Female, 45 years. PAS (×320)

**Fig. 16.4.** GN contracted kidney after clinically acute GN 10 years prior to biopsy. The two glomeruli present in the preparation were the best preserved, and they evidence sclerosing FGN. Male, 38 years. PAS (×210)



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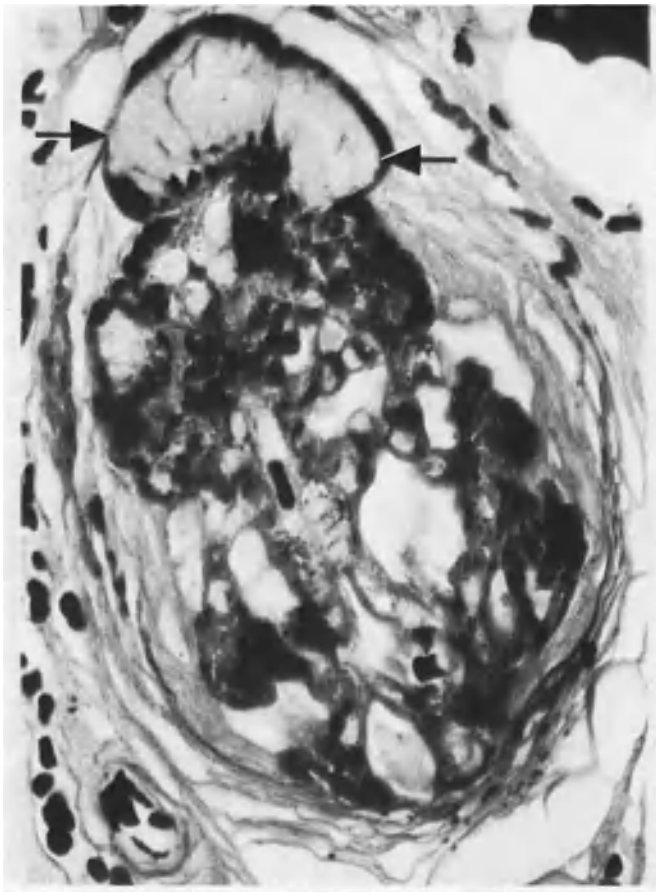

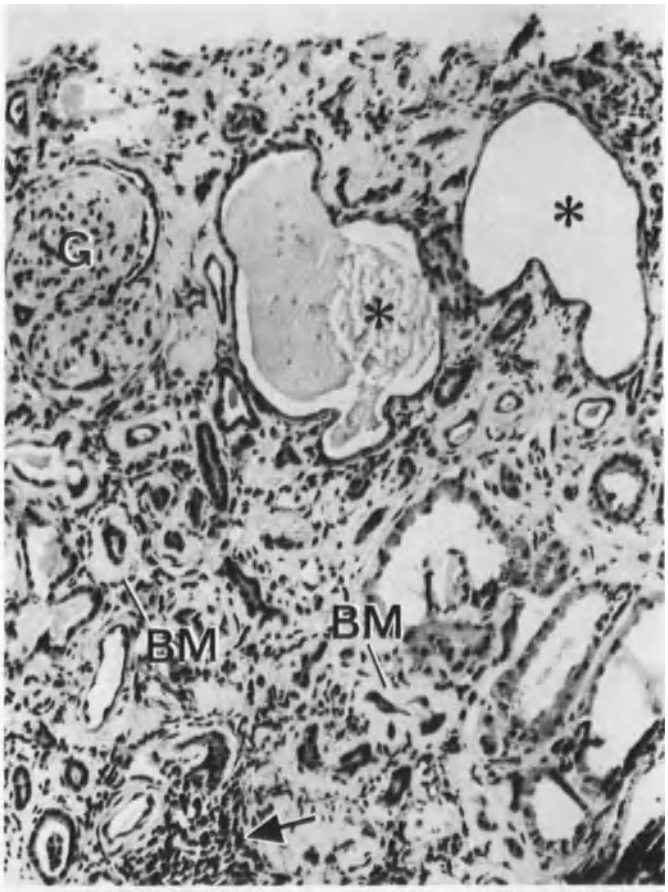


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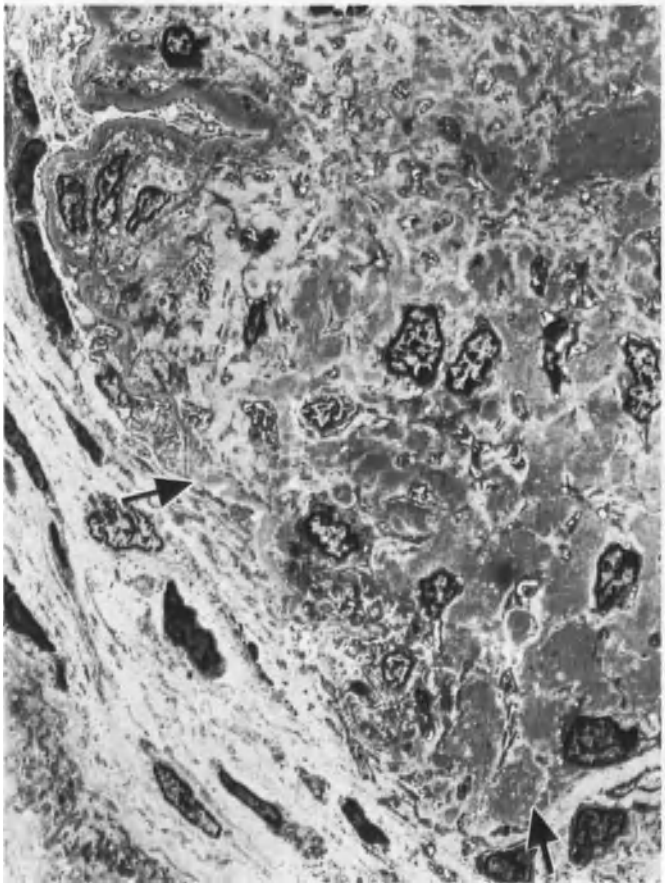
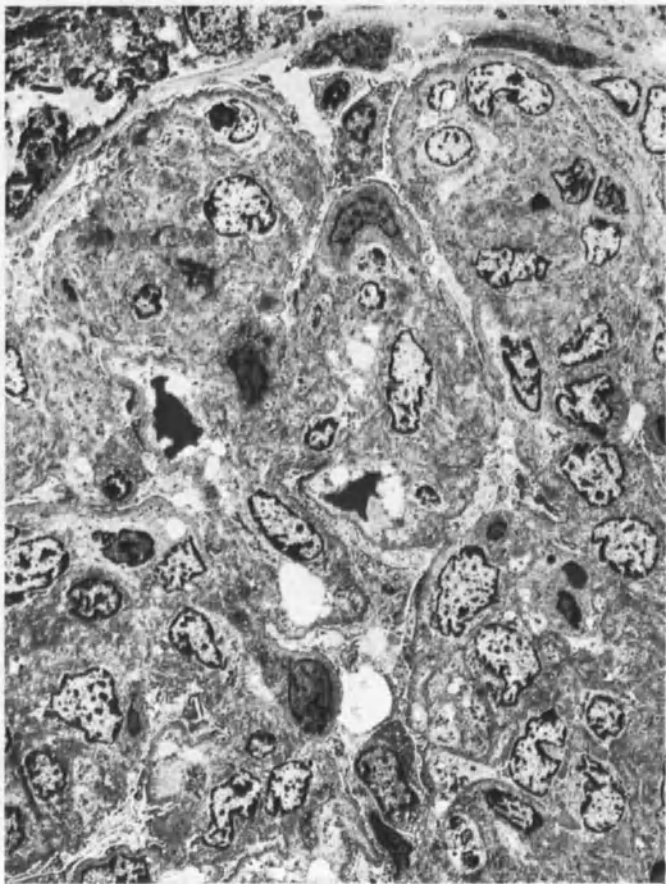




16.7
16.8

We have never seen humps in contracted kidney (contra: [128]). Glomerular loop collapse is common (Fig. 16.11). Sometimes the interstitial infiltrates indicate florid inflammation (Fig. 16.12).

## Differential Diagnosis

Differential diagnostic efforts consist of a two-step procedure: primarily, *differentiation from non-GN* disease and secondarily, the tentative diagnosis of the underlying *form of GN* whenever possible.

Differentiation of GN contracted kidney from that of pyelonephritis, diabetes mellitus, and chronic interstitial nondestructive nephritis can prove to be extraordinarily difficult even with LM, EM, and IF findings. After long-term hemodialysis, differentiation often becomes totally impossible.

Indicative for pyelonephritic contracted kidney in general is the presence of extensive tubular destruction, usually associated with considerable inflammatory interstitial infiltrates. Thyroid-like tubular changes are also indicative of—but not pathognomonic for—pyelonephritis. In pyelonephritic contracted kidney, the glomeruli frequently evidence findings of overload glomerulitis with extensive fibrinoid subendothelial deposits which are partly accompanied by pronounced mesangial proliferation and focal segmental mesangial interposition. In these cases, differentiation from GN contracted kidney (especially in FGN) may prove impossible. But a tentative diagnosis will often be realizable.

◁ **Fig. 16.5.** GN contracted kidney probably due to membranoproliferative GN. The completely obsolescent glomerulus shows extensive (PASM-negative) fibrinoid deposits (→←). Male, 23 years. PASM (×580)

**Fig. 16.6.** GN contracted kidney. Tubules demonstrate cystoid transformation (*) with extremely flattened epithelium. One glomerulus (*G*) is completely obsolescent. Moderately extensive patchy infiltrates are present (→). Majority of tubules are severely atrophic and evidence a much-thickened basement membrane (*BM*). Male, 22 years. HE (×190)

**Fig. 16.7.** GN contracted kidney. Glomerulus is nearly obsolescent and is broadly adherent to the capsule (→). Massive, probably mesangial, osmiophilic deposits and slight nuclear increase are recognizable. Capsule BM appears to be completely dissolved. Female, 54 years. EM (×1250)

**Fig. 16.8.** GN contracted kidney. Mesangial and endothelial proliferation predominate. When greater magnification is used, isolated instances of massive mesangial interposition and subendothelial deposits (undergoing dissolution) may be seen. It is striking that there are no signs of a capsular reaction whatsoever. Female, 40 years. EM (×1500)

Special difficulties are also encountered in distinguishing contracted kidney in Kimmelstiel-Wilson's nodular glomerulosclerosis from lobular membranoproliferative GN. This differentiation will be possible if clinical data are appropriately evaluated, and if the characteristic findings of nodular glomerulosclerosis are demonstrable, i.e., van Gieson red spheres in the mesangium, so-called exudative changes: subendothelial fibrinoid deposits, and capsular droplets. It is noted that the so-called exudative changes may be completely absent after long-term hemodialysis. For differential diagnosis from ischemic contracted kidney, see p. 510.

Differentiation with respect to chronic interstitial nondestructive nephritis, however, is not associated with great difficulties, even in contracted kidney. In these cases the dominant findings are extensive interstitial fibrosis, tubular atrophy, degeneration with scanty interstitial infiltrates, and extensive BM collapse in obsolescent and nonobsolescent glomeruli alike.

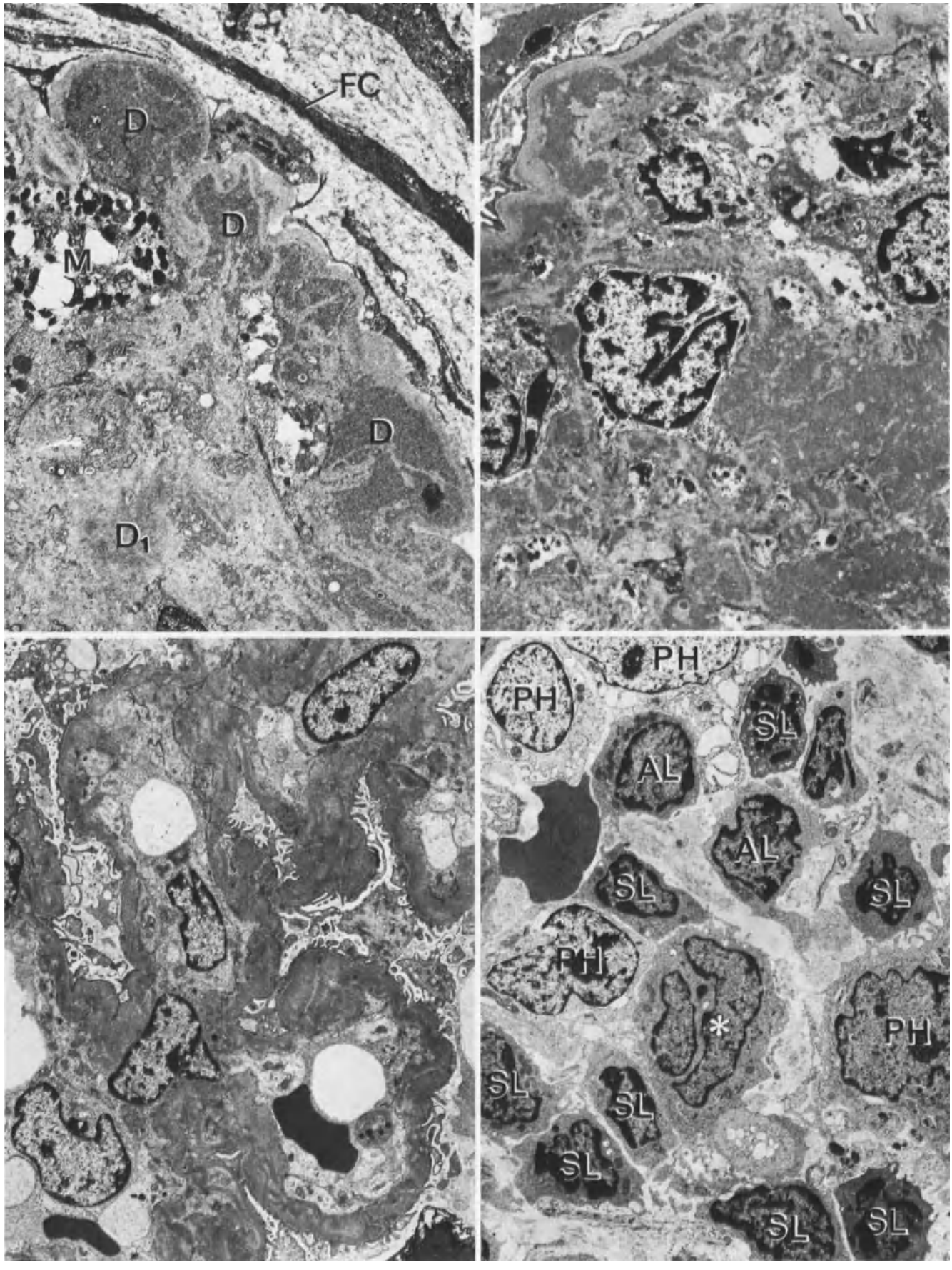
The second differential diagnostic step concerns *the GN form*. On the basis of Table 16.1 the following GN forms are to be expected in decreasing frequency: (see also [544, 911, 1068, 1541]): focally accentuated GN > membranoproliferative GN > extracapillary accentuated GN > epimembranous GN > other forms. Precise data on the incidence of IgA mesangial GN in contracted kidney are not yet available. Anti-BM-type GN and IgA mesangial GN can, in most cases, be identified by IF [1659a]. Intramembranous GN can probably—even in the end-stage kidney—easily be diagnosed, at least under EM, because of the unique character of the dense osmiophilic/fibrinoid material in the BM. Differentiation of all the other forms depends on the presence of some fairly well-preserved glomeruli but will, in any case, usually prove to be extremely difficult [1659a].

But despite the effort required, the time spent on the differential diagnosis of contracted kidney is justified in every case. This is especially true with regard to possible GN relapse in a transplant and to reliable evaluation of prognosis of the different forms of GN.

## Pathogenesis

From the pathogenetic viewpoint, an immunologic stimulus of many years' duration [544, 1068] and repeated infections [1068, 1630] should be considered. On the other hand, the possibility of a self-perpetuating destructive (sclerosing) reaction after a single severe immunologic damage should also receive attention.

In concluding, it is noted that nonimmunologic factors can also promote the development of contracted end-stage kidney, among which hypertension is probably the most important (see also [484a]), as well as other superimposed kidney disease (e.g., pyelonephritis; see p. 441).

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# 17. Special Forms of Glomerulonephritis

## Diffuse and Focally Accentuated Glomerulonephritis Associated With Systemic Disease

In this chapter we will discuss diffuse and focally accentuated GN occurring in systemic disease. We also include in this chapter IgA mesangial GN and early congenital childhood GN as further special forms.

### Glomerular Disease in Schönlein-Henoch's Purpura
[637, 1066, 1067]

***Definition:*** Acute allergic purpura with kidney involvement.

**Incidence**

Renal involvement has been reported in 34% of 1458 cases from the literature [136], (60%: 1661]; 96%: [793]), 44% in the first and 85% in the second month of the disease [1067].
Schönlein-Henoch's nephritis has been diagnosed in needle biopsy in 6% of GN in children [621] and in 15% of children with nephrotic syndrome [637]. Its incidence in FGN is stated as 23% [688] and 50% [620]. We observed it in 0.7% of all our biopsies and in 1.6% of our GN biopsies.
Boys are more frequently afflicted than girls [637, 737, 1578] and their illness is more severe [1578]. Typically, the disease occurs between the first and fifteenth year of life with a peak incidence between the sixth and seventh year [1577]; adult cases, however, have been described ([76, 136, 618]; see also Table 17.1). Renal involvement is supposedly greater in adults than in children [1067].

**Clinical Findings**
(Table 14.3)

The disease is rather frequently initiated by an infection of the upper respiratory tract (85%: [136]) often with streptococci (41%: [1067]; 6 out of 18: Z). The serum complement level remains normal (8 out of 9 cases: Z) and IgA containing cryoglobulins are present in active disease and disappear upon healing [1831].
In addition to the typical skin lesion (purpura and edema), joint (75%) and abdominal disturbances (52%: [1578]) with melena, diarrhea, nausea, and ileus have been described. Thrombocytes and the general coagulatory mechanism remain unchanged.
In case of renal involvement, both hematuria and proteinuria are practically always present. These symptoms may occur either independently or together and they may be so slight that they can only be identifed by regular examination of the urine. Among our patients (Table 14.3) isolated microhematuria was present in 5 out of 18 and microhematuria and proteinuria in 8 out of 18. Full blown nephrotic syndrome has been reported in about half of the cases (4 out of 18: Z; [637, 685, 1067]. Cases with nephrotic syndrome are said to be

◁ **Fig. 16.9.** GN contracted kidney. Numerous subendothelial deposits (*D*) are demonstrable, as are scanty mesangial deposits (*D1*), mesangial cell (*M*) (?) rich in protein droplets. Capsular BM has completely vanished. Interstitial fibrocyte (*FC*). Male, 22 years. EM (×5900)

**Fig. 16.10.** GN contracted kidney. With IF, only IgG was present in large amounts especially in the mesangium and less pronouncedly in the periphery. Peripheral deposits are scanty and lie subendothelially, whereas mesangial deposits are massive. Female, 10 years. EM (×4760)

**Fig. 16.11.** GN contracted kidney. Glomerular loops show only signs of collapse, as evidenced by the wrinkled and thickened BM. Endothelium is activated. Male, 39 years. EM (×3640)

**Fig. 16.12.** Same case as in Figure 16.7. There are extensive, unspecific inflammatory interstitial infiltrates in this case of GN contracted kidney. Phagocyte (*PH*), small lymphocytes (*SL*), medium-sized lymphocytes (*AL*), probably plasma cell (*). Female, 54 years. EM (×3910)

Table 17.1. Relative frequency (%) of different forms of glomerulonephritis in Schönlein-Henoch's purpura

| | Number of cases | Glomerular minimal change/ normal | Endothelio-mesangial GN without crescents | Endothelio-mesangial GN with crescents | Extra-capillary accentuated GN | Membrano-proliferative GN | Focally accentuated GN |
|---|---|---|---|---|---|---|---|
| Hurley and Drummond (1972) [1577] | 14 C | 14.3 | | 7.1 | | | 78.6 |
| Habib (1973) [622] | 60 C | 1.7 | 5.0 | 43.3 | 6.7 | 3.3 | 40 |
| Habib [1973) [621] | 93 C | | 4.3 | 51.6 | 4.3 | 1.1 | 38.7 |
| Meadow et al. (1973) [1067] | 88 C | 17.0 | 29.5 | 12.5 | 13.6 | | 27.3 |
| Bardare et al. (1975) [84] | 10 C | | | | 20 | | 80 |
| Bernhard (1968) [136] | 82 CA | 7.3 | ⊢——26.8——⊣ | | ? | 1.2 | 65.8 |
| Striker et al. (1973) [1578] | 16 CA | 12.5 | ⊢ | | 87.5 | | ⊣ |
| Zollinger and Mihatsch | 22 CA | 4.5 | 36.4 | | 4.5 | | 54.5 |
| Ballard et al. (1970) [76] | 7 A | 28.6 | | 42.8 | | | 28.6 |
| Kalowski and Kincaid-Smith (1973) [783] | 17 A | 5.9 | | | | | 94.1 |
| Total | 349 | ~8% | ⊢——~37%——⊣ | | ~5% | <1% | ~49% |

C = children; A = adult.

associated with more than 50% crescents ([1066]; 2 out of 4: Z). Pathologic urine findings may persist for months and even for years. Occasionally, nephrotic syndrome appears after the extrarenal signs have subsided [737]. Extrarenal symptoms do not parallel the severity of GN. Renal insufficiency and hypertension are less frequent in children than in the adults [136].

An attack-like course (relapses) is reported in 18–60% of the cases [136, 205, 622, 1067, 1578, 1645]; 3 out of 17: Z).

Isolated instances of pulmonary bleeding occur simultaneously with the skin lesions [1803], a finding which led to the incorrect diagnosis of Goodpasture's syndrome in two of our cases.

## LM Findings

The relative frequency of the different forms of GN in terms of modern classification is difficult to determine. Nevertheless, this was tentatively done and summarized in Table 17.1; the wide variation is partly due to the small number of cases. The overall picture of the different forms of GN does not differ from that as described in previous chapters.

The most frequent form in children and adults ([84, 136, 621, 783]; see also [685, 1102, 1484]) is *proliferative FGN* (Fig. 17.1) comprising about 50% of all cases.

Sequential biopsies have in some cases demonstrated a gradual transition from focal to diffuse glomerular involvement [866, 1645]. In some of our patients, it was striking to see a diffuse proliferation in all glomeruli and a specially pronounced accentuation in some glomerular segments (see also [1645]).

The relative frequency of *endotheliomesangial GN* (Fig. 17.2) with crescents (< 50%) and without crescents is about 37% (Table 17.1). There seem to be no obvious differences between children and adults.

*Extracapillary accentuated GN* (with crescents > 50%) (Fig. 17.3) is far more rare, comprising althogether only 5% of cases.

*Membranoproliferative GN* constitutes about only 1% of cases (see Table 17.1) but we believe that its true frequency is somewhat underestimated due to inclusion of these cases into the group of endotheliomesangial GN.

**Fig. 17.1.** Proliferative FGN (proliferative sclerosing stage) associated with Schönlein-Henoch's purpura of 2 months duration clinically. Segmentally accentuated mesangial proliferation is present (*). Segmental crescent (*CR*). Male, 8 years. PAS (×500) ▷

**Fig. 17.2.** Diffuse endotheliomesangial GN with 10% extracapillary involvement in a case of Schönlein-Henoch's purpura with acute clinical onset 6 months prior to biopsy. All three glomeruli present in this section exhibit segmental crescents (→). Female, 5.5 years. PAS (×130)

**Fig. 17.3.** Endotheliomesangial GN, with panmesangial involvement in the proliferative-sclerosing stage, in a case of Schönlein-Henoch's purpura. Segmental crescents are recognizable in all three glomeruli (→) (cf. Fig. 17.4). Female, 9 years. PAS (×170)

**Fig. 17.4.** Same case as in Figure 17.3 as seen 13 months later in which the findings are that of proliferative FGN (→). Note the delicate synechia (*SY*). A small artery is unchanged. A few scanty inflammatory interstitial infiltrates are still recognizable. Female, 10 years. PAS (×250)

*Glomerular minimal change* and *normal renal tissue* respectively also occur in about 8% (Table 17.1).
Overall, however, the focal character of the glomerular affection is by far the predominating element (see also [685, 1102, 1484]).
We have observed FGN with a few synechiae as early as 7 weeks after disease onset (Figs. 17.1, 17.4). The mesangial deposits are sometimes so massive as to be easily demonstrable by LM and, by IF, can be shown to consist mainly of IgA (Figs. 17.5, 17.6, 17.7).
FGN may be accompanied by fibrinoid loop necroses (Fig. 17.8), a finding which is considered typical for Schönlein-Henoch's nephritis [205, 544, 866, 1661].
Glomerulonephritis with vasculitis and arteriolonecrosis, which were previously considered as typical for Schönlein-Henoch's nephritis, are no longer considered a part of this disease (see also [244]). It is possible that confusion with respect to hypersensitivity angitis (see p. 536) occurred in former studies. With the exception of 2 cases with unspecific arteriolosclerosis (5 out of 22: [783]) we have only once seen a slight arteriolitis in EM (see p. 322). In none of our cases were perivascular polymorphonuclear leukocytic cuffing (2 out of 22: [783]) or leukoclasia (contra: [50]) present which are practically always demonstrable in the skin lesions. The occurrence of hematoxylin bodies has been described only once [405].

## IF Findings

All the glomeruli usually evidence granular IgG and C3 [125, 127, 486, 685, 1645, 1661, 621] as well as IgA [125, 127, 544, 637]; 83% of cases: [743]; linear: [50], IgM and fibrin(-ogen) [125, 127, 486, 637, 1577, 1644, 1645]; (see also Table 17.2). Properdin in combination with fibrin(-ogen) (6 out of 7: [84]) has also been reported [447] and it was suggested on the basis of IF studies of early and late complement factors that the complement activation follows the alternative pathway [452a].
IF findings are usually most pronounced in the mesangium [84, 128, 447, 544] and less so in the periphery but purely peripheral or mesangial deposits are also possible (see Table 17.2).
In the absence of clinical data, evaluation of the IF findings alone may very easily lead to misdiagnosis of IgA nephritis (2 our of 9: Z; see also [743]).
In one observation [128], IF was still positive 9 years after the disease. IF becomes negative following total remission of the glomerular lesion (15%: [621]). In two of our own IF negative cases, proteinuria of 0.5 g/day and microhematuria only were present.
No immunoglobulins were found in any of the blood vessels in our IF cases. This may explain the absence of vasculitis in the kidney in contrast to skin, where the vessels usually exhibit large amounts of IgA [452a].

Table 17.2. IF Findings in Schönlein-Henoch's purpura ($n=9$: 7 positive; 2 negative not considered in table)

| | IgG | IgM | IgA | C3 | Fibrin(-ogen) |
|---|---|---|---|---|---|
| Cases tested | 7 | 7 | 4 | 7 | 7 |
| Positive | 6 | 5 | 4 | 7 | 4 |
| Focal | 0 | 0 | 1 | 2 | 1 |
| Diffuse | 6 | 5 | 3 | 5 | 3 |
| Segmental | 1 | 1 | 1 | 3 | 2 |
| Global | 5 | 4 | 3 | 3 | 2 |
| Peripheral | 2 | 1 | 2 | 2 | 1 |
| Mesangial and peripheral | 4 | 3 | 2 | 4 | 2 |
| Mesangial | – | 1 | – | 1 | 1 |

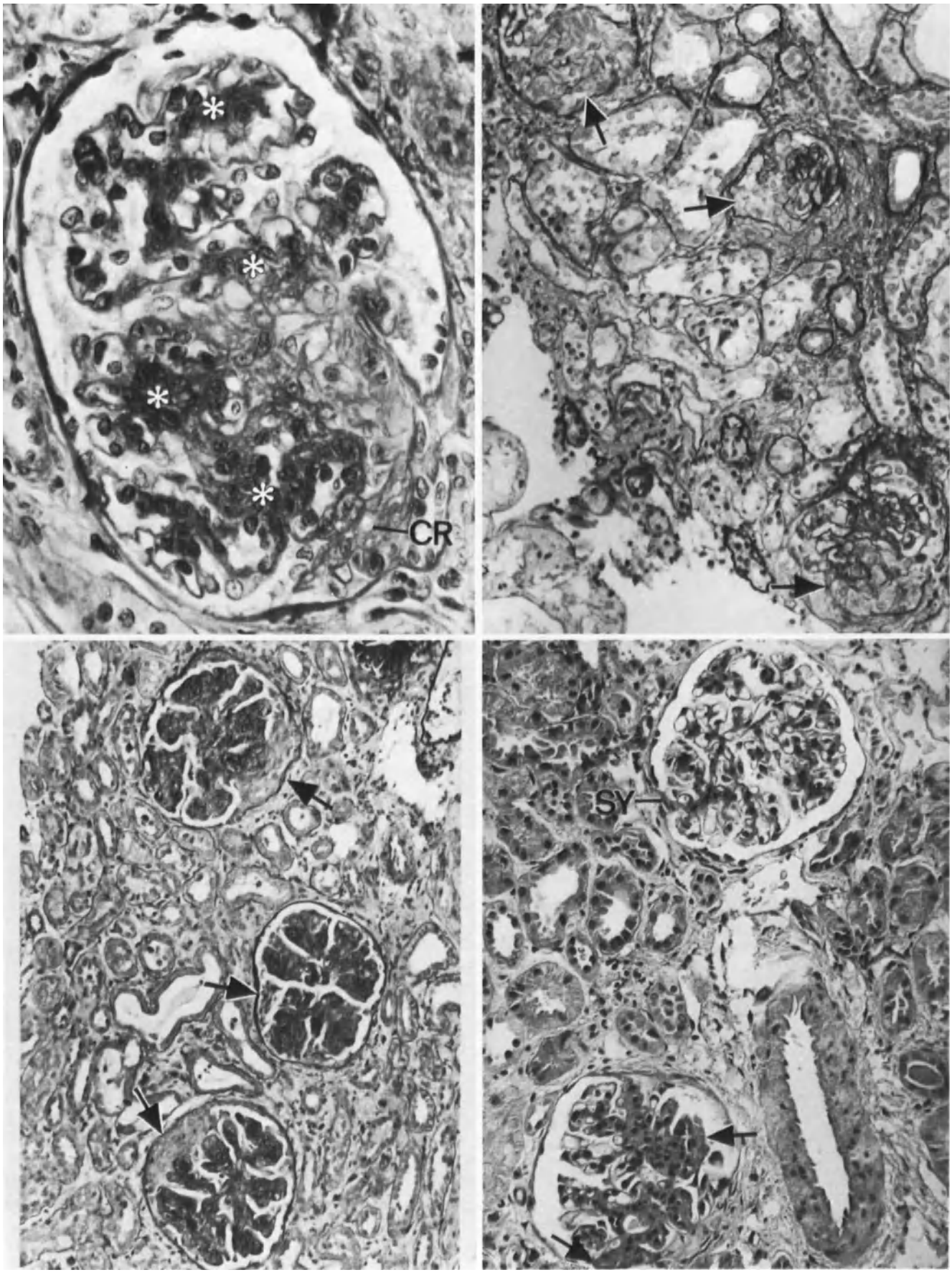
## EM Findings

No pathognomonic findings are seen with EM; the findings encountered correspond by and large to those of the underlying form of GN. Usually, however, the focally accentuated character of the lesion is evident. Thus, we observed segmental loop obliteration in half of our cases. The endothelium is hypertrophied and exhibits nuclear swelling and arcade formation. In all cases, podocytes show foot process fusion and a frequent increase of osmiophilic substance in the cytoplasm as well as formation of microvilli.
The most important changes affect the peripheral glomerular BM in a segmental fashion (15 out of 17: Z) which is characterized by focal, usually slight thickening of the total BM and by formation of osmiophilic deposits (Fig. 17.9). We saw these deposits subendothelially in 8 out of 17 cases (see also [205, 618, 866, 1645, 1819]) and subepithelially in 2 out of 17 but humps were always absent (contra: [618, 1819]; 4 out of 8 children: [621]). Additionally, we noted intramembranous deposits in 3 out of 17 cases (see also [1645]) and deposits along the mesangial BM in 6 out of 17. Finally, splitting of the lamina densa was present in 6 out of 17 cases, and BM interruption in 2 out of 17 (Fig. 17.10).

**Fig. 17.5.** Endotheliomesangial GN in Schönlein-Henoch's purpura of 2 months duration with extensive mesangial deposits (→). Male, 8 years. PAS (×910) ▷

**Fig. 17.6.** Same case as in Figure 17.5. There are heavy granular IgA deposits in the mesangium and fewer in the glomerular capillary loop periphery. Male, 8 years. IF (×250)

**Fig. 17.7.** Same case as in Figure 17.5. Numerous mesangial deposits (→) are present. There are swelling and activation of the endothelial cells besides three polymorphonuclear leukocytes (*PL*). Podocytes are slightly activated and foot process fusion is mild. Male, 8 years. EM (×5200)

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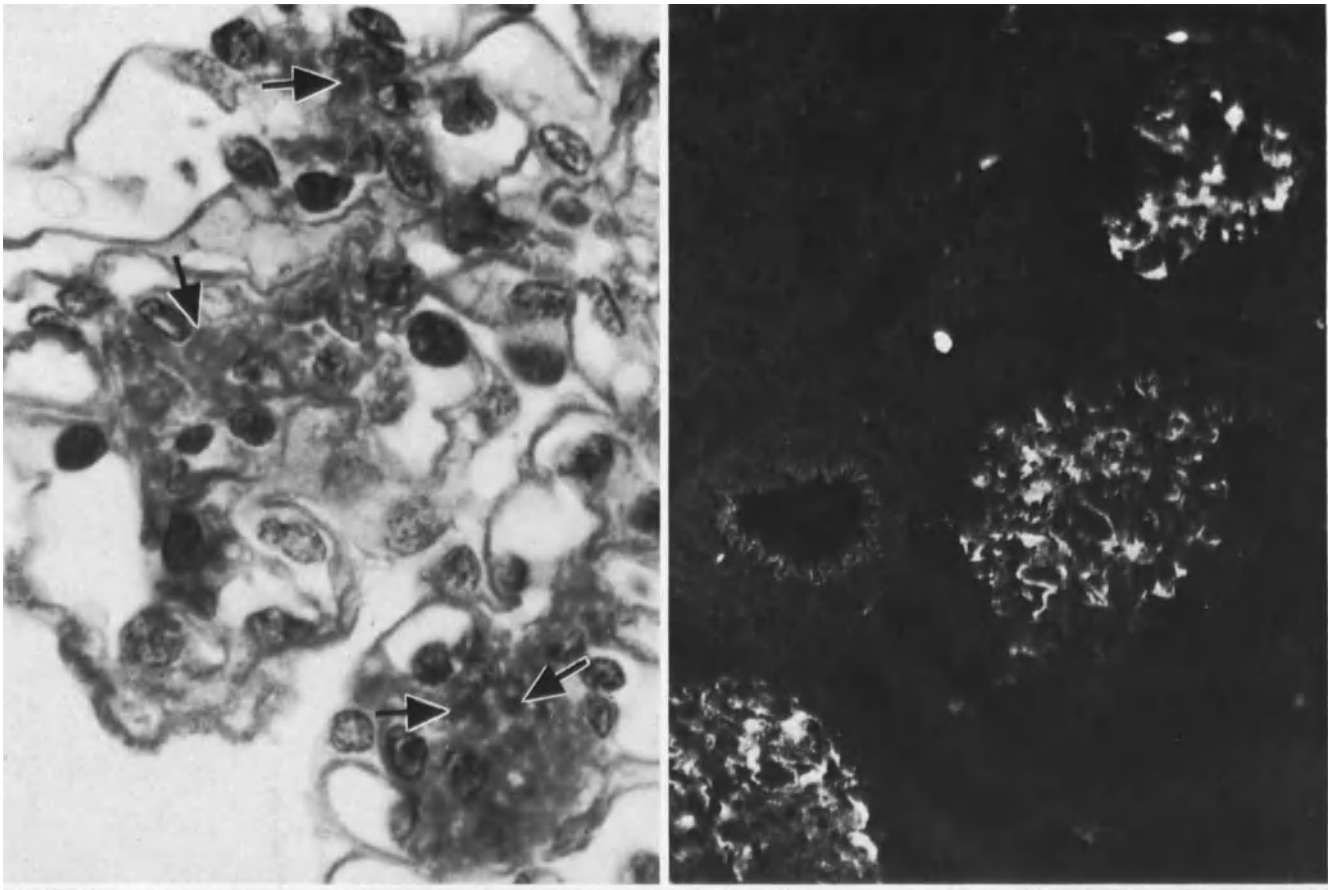

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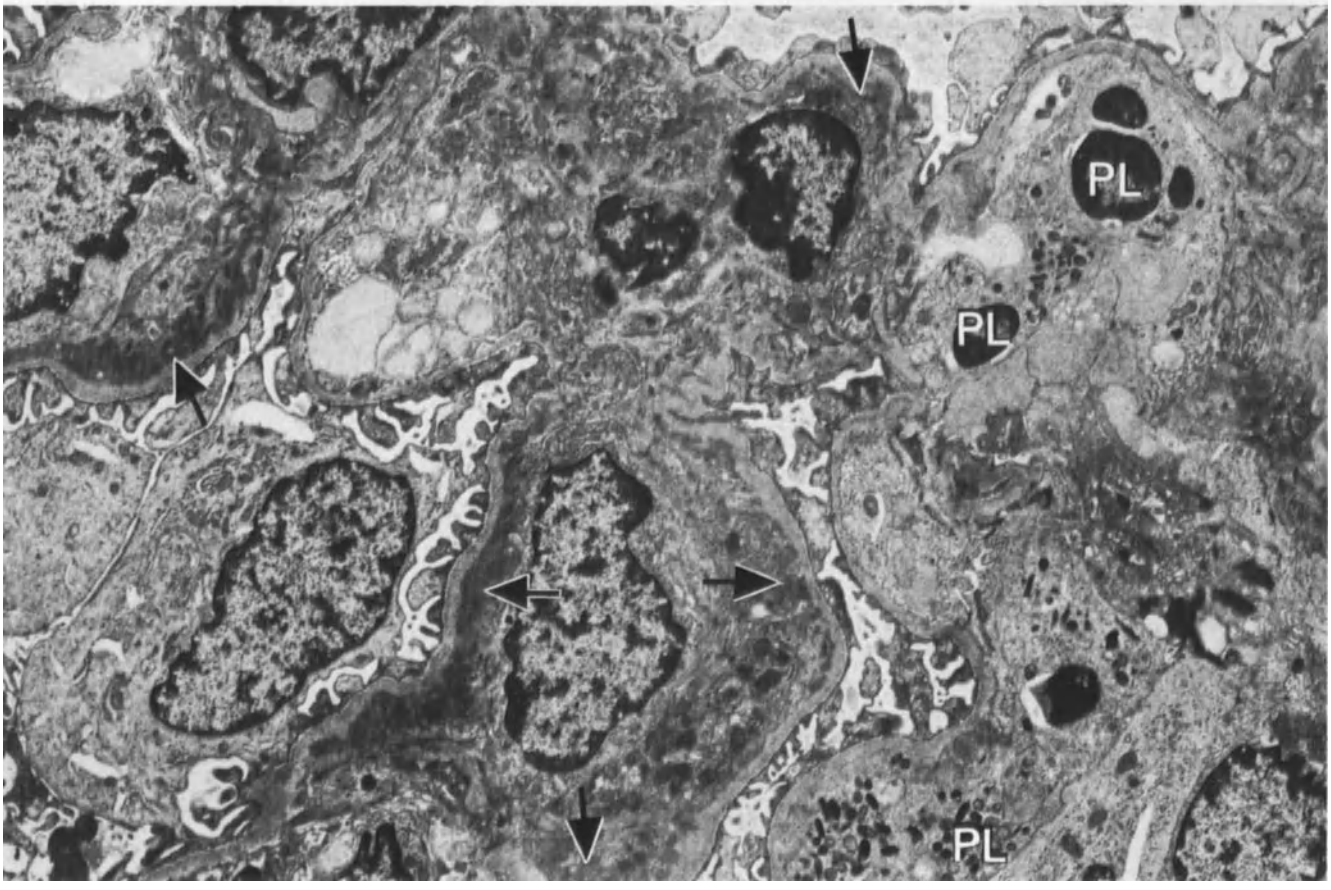


17.7

A peculiar change was found in 6 out of 17 cases consisting of subepithelial doubling of the glomerular BM with formation of a new thin densa layer which frequently surrounded deposits (Figs. 17.11, 17.12, 6.28). We found this change in 14.7% of all our GN biopsies irrespective of systemic disease. Thus, it appears very characteristic—but not pathognomonic—for Schönlein-Henoch's purpura.

The lamina rara interna was thickened in all of our cases. This was associated with formation of new lamina densa material in 8 out of 17 cases. Mesangial interposition was present in 2 out of 17 cases.

Virus-induced endothelial tubular structures were seen in 5 out of 17 cases (see also p. 96) and in 4 out of 17 cases, oval virus-like particles with a diameter of about 1200 Å were observed (Fig. 17.12).

Mesangial changes are chiefly characterized by the moderately severe increase of matrix (Fig. 17.13) associated with mild to moderate cell increase. The nuclei showed, in almost all of the cases, slight polymorphy accompanied by nuclear swelling in half of the cases. Mesangial matrix deposits were noted in 9 out of 17 of our cases (see also [621]).

In one observation, we noted proliferative arteriolitis with BM splitting along with an invasion of the media by histicytes and fibroblasts (Fig. 17.14).

**Fig. 17.8.** Proliferative FGN in Schönlein-Henoch's purpura of ▷ 1 week's duration. Two glomerular capillary loops are aneurysmatically dilated (→) and are filled with totally necrotic cells (glomerular capillary loop necroses?, mesangiolysis?). Male, 8 years. PASM (×400)

**Fig. 17.9.** Proliferative FGN in Schönlein-Henoch's purpura of 3 weeks' clinical duration. In addition to subendothelial deposits (*D*) massive new formation of subendothelial basement membrane (*BM*) is discernible. Virus-induced tubular structures are recognizable in the endothelium (*). Male, 12 years. EM (×25,400)

**Fig. 17.10.** Total interruption of BM (←→) in proliferative FGN in the course of Schönlein-Henoch's purpura. Cytoplasm of the severely hypertrophied podocyte (*P*) is projecting into the glomerular capillary loop (*). Endothelial cells are highly activated. Male, 7 years. EM (×7000)

**Fig. 17.11.** Same case as in Figure 17.5. There is severe, irregular thickening of lamina rara externa (*) which contains small, isolated osmiophilic deposits in dissolution (→). Subepithelially, new formation of a delicate densa layer is present (⊸▷). Glomerular capillary loop lumen (*CL*). Male, 8 years. EM (×11,100)

## Differential Diagnosis

On the basis of morphology, Schönlein-Henoch's nephritis may sometimes be suspected (but not proven) in the presence of proliferative FGN with loop necroses and marked fluorescence for IgA, as well as (in EM) by the demonstration of subepithelial BM-doubling. The occurrence of arteriolonecrosis and severe vasculitis are rather indicative of hypersensitivity angitis (see p. 536 and [244, 783]).

The pronounced destructive character of glomerulitis in Goodpasture's syndrome is not seen to occur in Schönlein-Henoch's GN. This is important to note since an eventual episode of pulmonary bleeding (and subsequent hemosiderosis) may easily lead to the erroneous diagnosis of Goodpasture's disease ([1790a], see also [907]). The decisive method for differentiation of Schönlein-Henoch's purpura and Goodpasture's syndrome is IF, which demonstrates an ultralinear immunoglobulin pattern in the latter.

We feel that IgA mesangial GN cannot always be distinguished from that of Schönlein-Henoch's with LM, EM, and IF (see also [743]). Loop necroses, which hardly ever occur in IgA-mesangial GN, are indicative of Schönlein-Henoch's GN.

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**Fig. 17.12.** Same case as in Figure 17.5. Massive nodular thickening of lamina rara externa with new formation of BM (→) is recognizable and, therein, unclearly delimited osmiophilic deposits which contain masses of round, virus-like particles (*). Lamina rara interna is also slightly thickened (⊸▷). Male, 8 years. EM (×30,200)

**Fig. 17.13.** Same case as in Figure 17.5. There is very pronounced enlargement of mesangium with matrix increase and vacuolar degeneration of mesangial cells. Isolated peripheral subendothelial and intramesangial deposits are recognizable (→). There is considerable foot process fusion. Capsule epithelium (*CE*) is atrophic. Severe periglomerular fibrosis (*FC*). Male, 8 years. EM (×4900)

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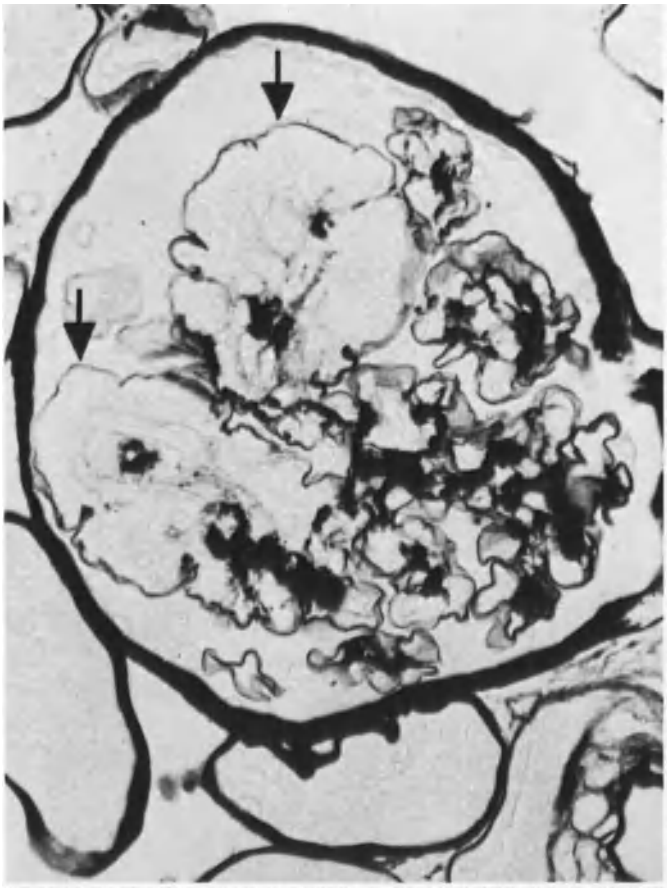
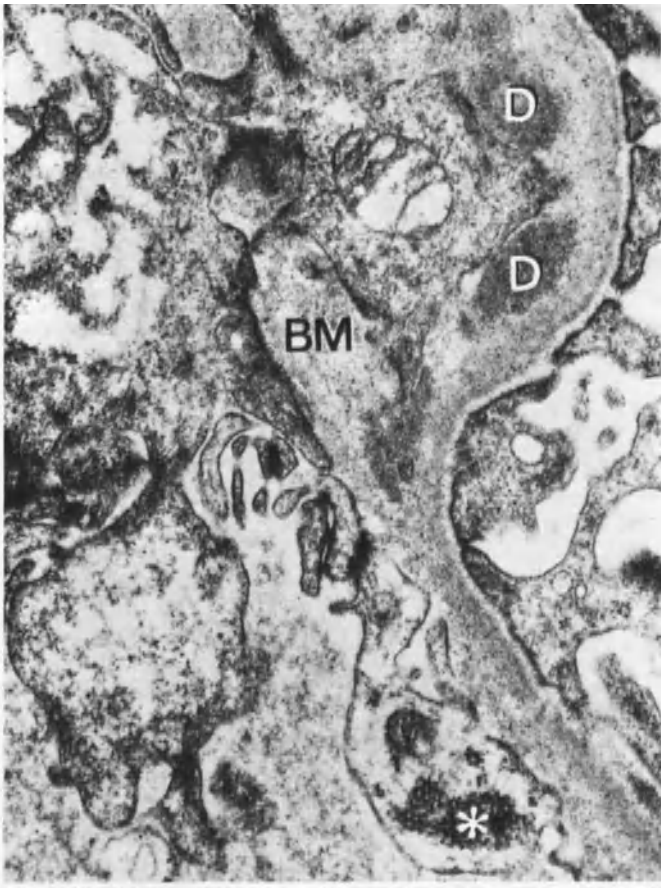
**Fig. 17.14.** Unique finding of arteriolitis in Schönlein-Henoch's purpura of about 6 weeks duration. Three leukocytes (*PL*) and a monocytoid cell (*MO*) are present in vessel lumen. Endothelial cells (*E*) are swollen. Myocytes in the media are severely degenerated (*MC*) and are usually not recognizable at all. The surrounding fibrous tissue is split, and between the layers, longitudinal, spindly cells—thought to be fibroblasts—with very severe cystoid-widened endoplasmatic reticulum are seen (*). In the outer zone numerous phagocytes and fibroblasts are present. Male, 7 years. EM (×3400)



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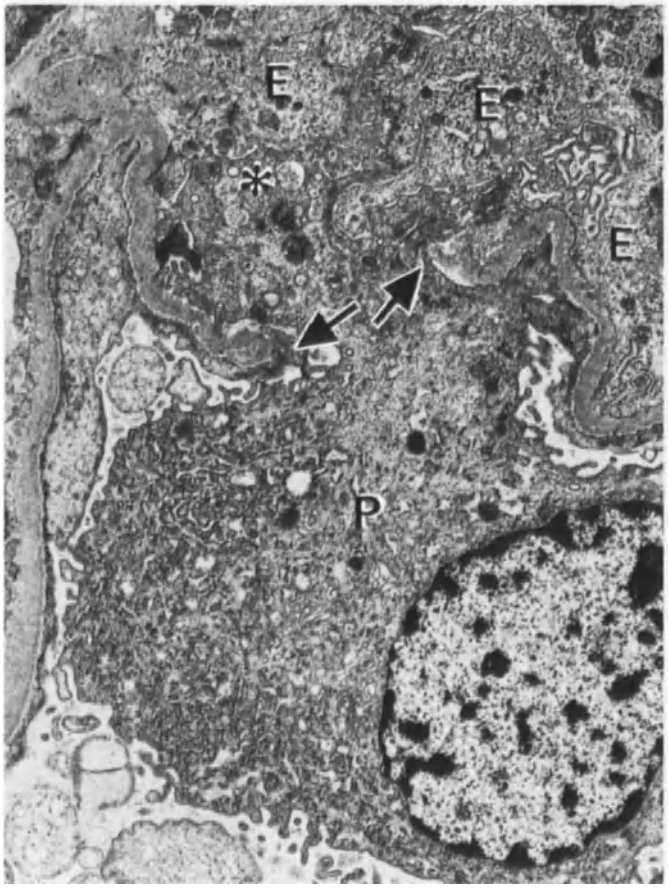


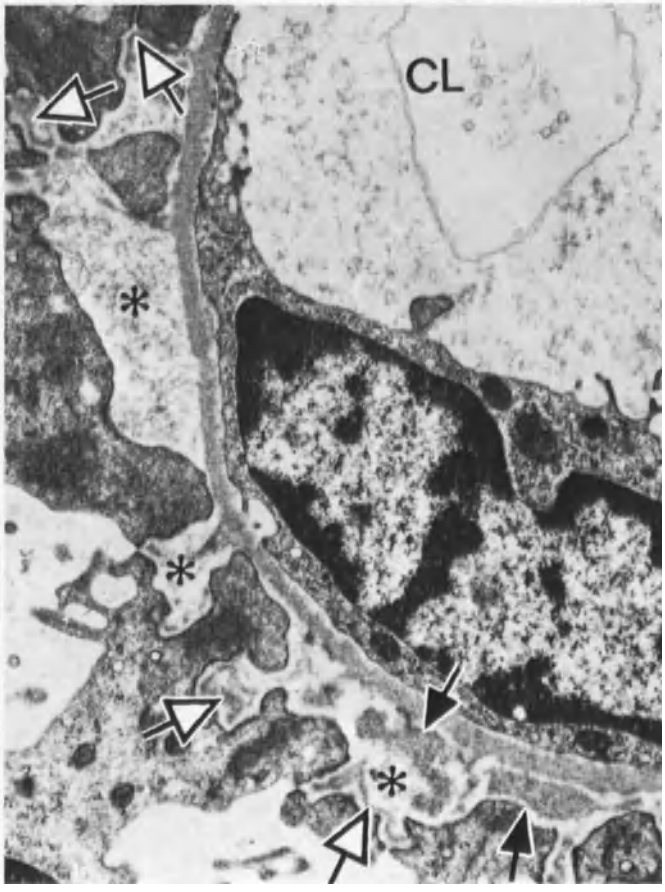


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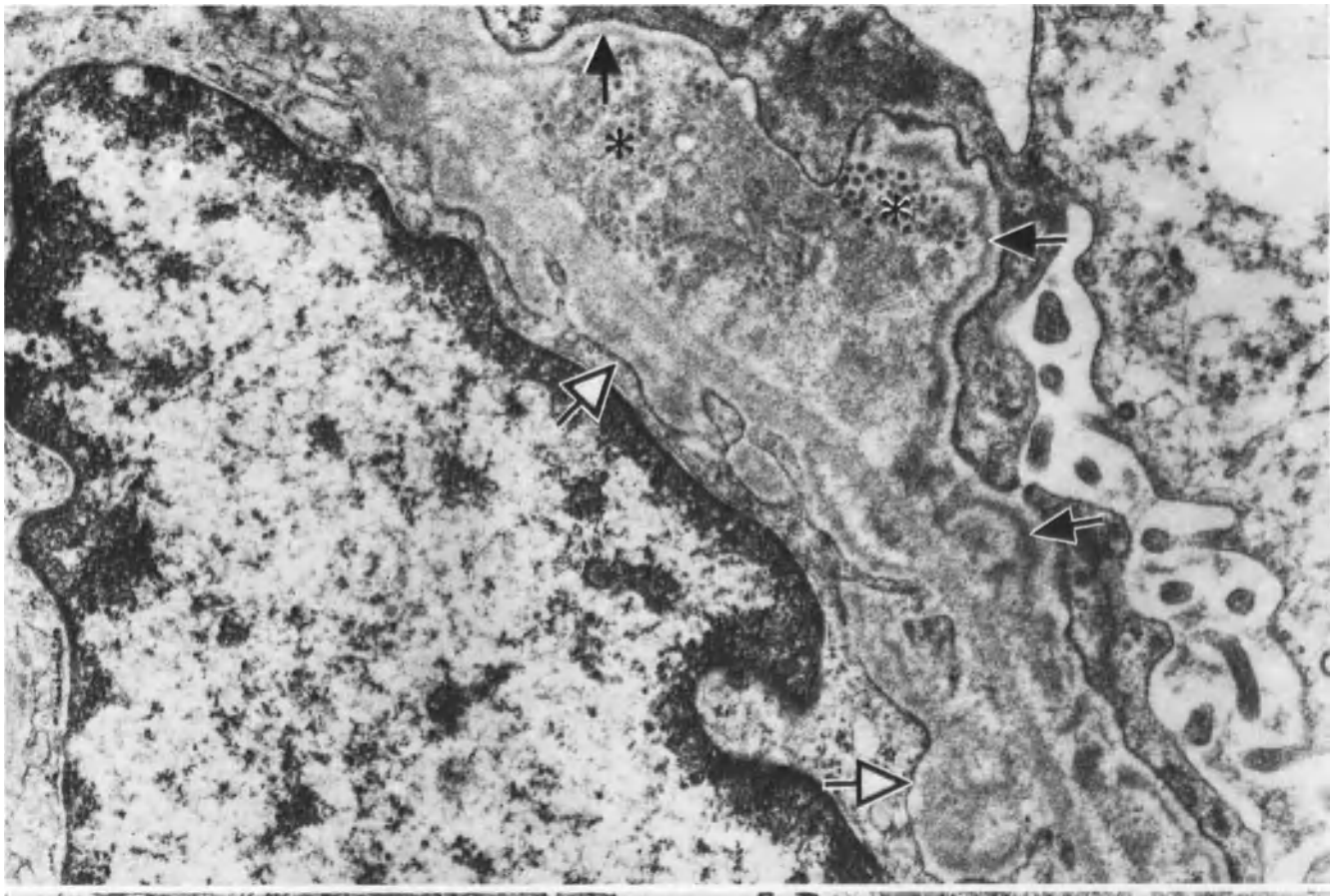

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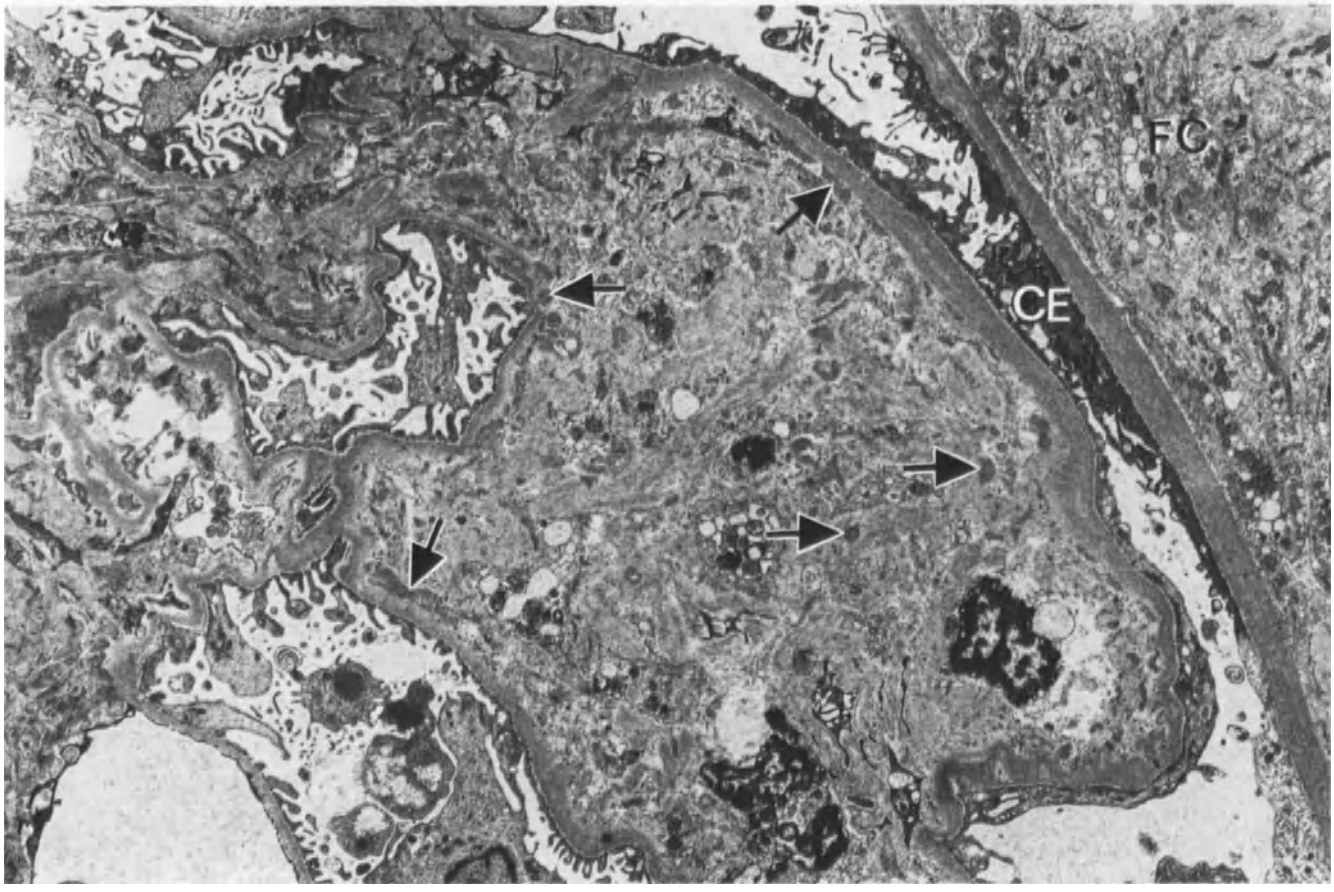


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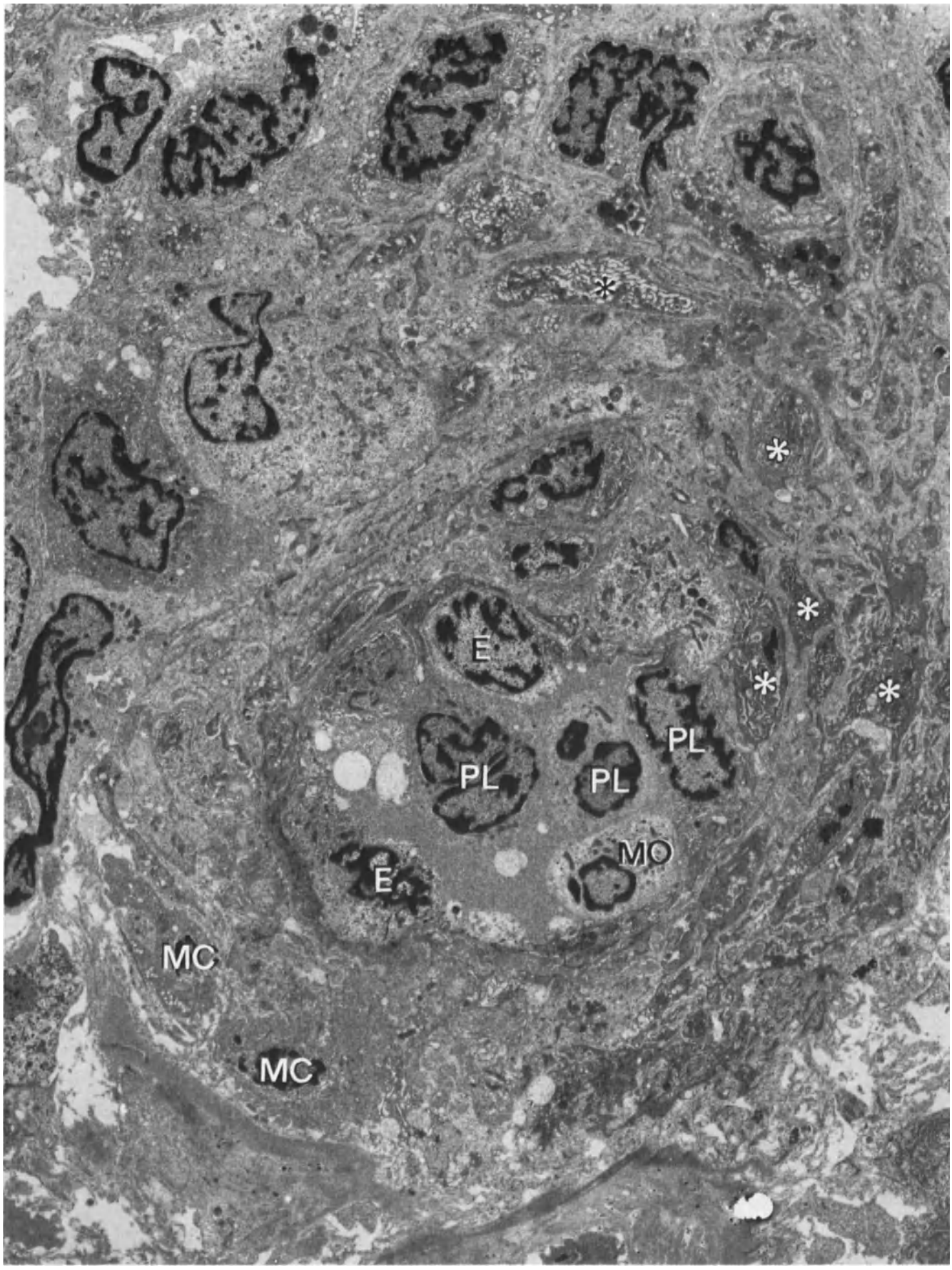



17.14

### Prognosis

Prognosis appears to be all the better the younger the patient. As a rule, boys evidence more serious renal affliction than girls (contra: [1577]). In the long run, the overall mortality rate in children is reported as ranging from 5% [1661] to 21% [621], and in adults from 10% [1067] to 36% [136] (15%: [783]; 28.5%: [76]; 36%: [136]). In our opinion, the prognosis corresponds to the form of GN present. When extracapillary accentuated GN is present, the prognosis is unfavorable [76, 637], but exceptions to this rule are probably more frequent (complete or incomplete remissions 6 out of 12: [1067]) than in the idiopathic form of extracapillary accentuated GN, which is also demonstrated by our own observations. Thus, the initial biopsy of a 10-year-old girl revealed extracapillary accentuated GN. One year later, biopsy showed proliferative FGN and, clinically, microhematuria and proteinuria (1.5 g/day) were present. After a 3-year observation period, the only pathologic clinical finding was a proteinuria of 1.3 g/day. In another case (not included in the clinical series), initial biopsy of a 21-year-old male revealed diffuse crescent formation in more than 75% of the glomeruli; 2.5 years later, nephrotic syndrome and hypertension were present, but renal function had improved. Persistent damage is reported present in 6–38% of patients [637, 685, 1067, 1644] and is again more frequent in adults than in children [76, 136].

### Pathogenesis

It is generally recognized that Schönlein-Henoch's purpura is an allergic process associated with generalized fibrinoid inflammation of the smaller blood vessels, especially in skin. It is presumed that poorly soluble immuncomplexes play the decisive role in the condition [520, 544, 1653]. It is possible that the alternative pathway of complement activation is involved. The variability of the morphological picture may be either an expression of repeated immunological insults and/or of the immunological reactivity of the host. The latter possibility is suggested by the fact that patients with congenital C2 deficiency are afflicted more frequently with Schönlein-Henoch's purpura [1589a].

### Etiology

Agents considered as causative factors in the lesion include drugs (13 out of 14 cases: [76, 325, 685, 1645, 1661]), bacteria causing upper respiratory tract infection (85%: [136]; 42 out of 74: [1066]; 12 out of 18:Z), streptococcal infections (in 33 out of 88: [1066]; 6 out of 18:Z), food stuffs [685], and insect bites [685].

## Glomerular Disease in Systemic Lupus Erythematosus

[71b, 485a, 1157, 1683]

### Definition

SLE is an autoimmune disease characterized by involvement of skin, joints, kidney, blood, etc. and the presence of antinuclear antibodies.

### Incidence

The kidney is reported afflicted in 50–80% of cases of SLE [1157, 1280, 1449, 1511a]. Renal involvement is probably even more frequent since, even in cases without urinary symptoms, morphological glomerular abnormalities may be present [485a, 707a]. We found SLE with renal involvement in 24 out of 25,000 autopsies, in 1.2% of all our biopsies, and in 2.7% of all our GN biopsies (21.6%: [544]; in children: 2.1%: [621]).

SLE usually occurs between 15 and 40 years of age (average: 29 years) however, even cases in the newborn are known. Females are considerably more frequently affected than males with a sex ration of about 8:1 (20:5: Z); 51:5: [1511a]; 45:5: [1576]; 45:4: [485a]; 77:15: [716]).

### Clinical Findings

The clinical picture of generalized lupus erythematosus is best portrayed with the criteria established by the American Rheumatism Association [296a] which clearly formulates the diversity of symptoms, i.e., butterfly-shaped facial exanthema, photosensibility, lupus discoides, alopecia, Raynaud's syndrome, ulcers of the mucosa of the mouth and/or nasopharynx, nondeforming arthritis (chiefly of the hand and elbow joints), pleurisy with and without effusion, psychoses, convulsions, massive proteinuria and cell (leukocytes, erythrocytes) casts in the urine, hemolytic anemia, leukopenia, thrombopenia, falsely positive serologic tests for syphilis, antinuclear factors in the serum, and the LE cell phenomenon. When at least four of the above-instanced criteria are fulfilled, the diagnosis of SLE can be made.

The LE cell phenomenon, which is positive in 82% of the patients [1511a], as well as the demonstration of antinuclear AB in high titers—positive in 89% of the patients [1511a]—are the most important laboratory findings for the diagnosis of SLE. Some investigators maintain the opinion that SLE may be diagnosed when the antinuclear AB evidences a titer greater than 1:160 in the simultaneous presence of a positive LE cell phenomenon, even in the absence of all other symptoms

[106, 544]. In one of our own cases, generalized lupus erythematosus with extremely severe skin manifestations developed 7 years after a single demonstration of a positive antinuclear AB titer and LE cell phenomenon. At that time, slight proteinuria and microhematuria associated with morphological findings of mild endotheliomesangial GN were already present.

Generally, a very high titer of antinuclear AB is especially characteristic. The antinuclear AB belong to the IgG or IgE class and, with IF examination, a peripheral nuclear fluorescence is typical. AB activity against native DNA and intense complement (C3) binding are further attributes of antinuclear AB in SLE [1367a]. Correspondingly, there is often a decrease of C3 in the serum. The frequent occurrence of cryoglobulins (see p. 169) is also noteworthy.

Renal symptomatology (Table 14.3 for own findings) is determined by the nature and extent of kidney involvement and comprises a large spectrum of symptoms ranging from isolated hematuria, proteinuria or nephrotic syndrome to a combination of these findings. Nephrotic syndrome is present in about 20% of the patients and is usually associated with diffuse proliferative (membranoproliferative) or epimembranous GN [1157, 1511a, 1683]. Morphologic renal involvement may even be present in the absence of urinary findings [485a, 707a]. Characteristic for SLE is the frequent absence or very tardy appearance of hyperlipemia within the framework, of nephrotic syndrome [1449]. Hypertension is usually present in cases evidencing a rapidly progressive course [1157]. Sudden occurrence of oligo-anuria is occasionally observed. Renal failure (6 out of 16 cases: [1576]; 19 out of 40 cases: [71b], CNS complications [1511a] and infections due to therapy (6 out of 7 cases: [485a]) are the commonest causes of death. (For mixed connective tissue disease, see [1822, 1823]).

### LM Findings

Renal involvement reveals a large spectrum of lesions none of which, however – with the exception of hematoxylin bodies – are specific for SLE [1157, 1683]. Since the individual lesions of this spectrum (Table 17.3) differ considerably with respect to prognosis of the disease, their individual consideration is wholly merited [75, 840, 1280].

***1. Normal glomerular findings*** are relatively rare (Table 17.3). If such glomeruli are examined with EM, however, osmiophilic deposits as well as a diffuse BM thickening are frequently found. IF studies occasionally reveal linear deposits of gamma-globulins along the glomerular BM or granular ones [485a, 869, 1449, 1511a].

***2. Glomerular minimal change.*** This form is also relatively rare (Table 17.3). As in cases with normal glomeruli, EM and IF study usually demonstrate deposits [71b, 485a, 544, 707a, 1280, 1484]. So-called mesangial lupus nephritis belongs in part to this group, to proliferative FGN and to endotheliomesangial GN without crescents [71b, 485a].

Table 17.3. Relative frequency (%) of different forms of glomerulonephritis in SLE

| | Number of cases | Normal | Glomerular minimal change | Focally accentuated GN | Membranoproliferative GN | Endotheliomesangial GN | Epimembranous GN |
|---|---|---|---|---|---|---|---|
| Baldwin et al. (1970) [74] | 52 | | | 26.9 | ← 46.2 → | | 26.9 |
| Dujovne et al. (1972) [401] | 40 | 5.0 | 12.5 | ← 77.5 → | | | 5 |
| Garancis et al. (1970) [530] | 15 | | | 33.3 | 40.0 | 26.7 | |
| Germuth and Rodriguez (1973) [544] | 41 | | 4.9 | 41.5 | 21.9 | | 31.7 |
| Ginzler et al. (1974) [554] | 69 | | 13.0 | 31.9 | ← 34.8 → | | 20.3 |
| Habib (1974) [624] | 13 | | | 30.8 | 23.1 | 46.2 | |
| Koffler et al. (1969) [869] | 19 | 42.1 | | | 5.3 | | 52.6 |
| Mery et al. (1974) [1085] | 28 | | | | 25 | 75 | |
| Morel-Maroger et al. (1973) [1139a] | 54 | | 37 | 29.6 | 25.9 | | 7.4 |
| Nanra and Kincaid-Smith (1973) [1184a] | 72 | | | 4.2 | 63.9 | 23.6 | 8.3 |
| Sinniagh and Feng (1976) [1511a] | 56 | 3.6 | 17.8 | 5.4 | 33.9 | 26.8 | 12.5 |
| Striker et al. (1973) [1576] | 50 | | | 20 | ← 64 → | | 16 |
| Zollinger and Mihatsch | 47 | | | | | | |
| Autopsy | | | | 4.8 | 57.1 | 38.1 | |
| Biopsy | | | | 50 | 19.2 | 11.5 | 15.4 |
| Total *n* | 556 | 12/556 | 46/556 | 108/516 | 122/345 | 74/345 | 82/556 |
| | – | ~10% | | ~20% | ~35% | ~20% | ~15% |

*3. Proliferative (and sclerosing) FGN* (Figs. 17.15–17.17) comprises about one fourth of the cases of SLE-GN (Table 17.3). In this form, subendothelial deposits are generally found, but they may be accompanied by subepithelial deposits (3 out of 46 children with FGN: [620]; 9%: [74]; see also [1484]). In the segmentally changed glomeruli polymorphonuclear leukocytes and mesangial cell proliferation are found. These findings are frequently associated with extensive capillary loop necroses with subsequent crescent formation [1671]. According to some investigators, focal GN is always present in the early disease stage [685].

*4. Membranoproliferative GN* (Figs. 17.18–17.20) is also seen in about one fourth of the cases of SLE (Table 17.3). It is characterized by particularly large subendothelial fibrinoid deposits [1068]. Initially, the lesion frequently demonstrates a segmental-focal character, but slowly progresses to a global and diffuse one. This form often terminates in uremia [1280, 1484]. Glomerular capillary loop necroses are occasionally observed.

*5. Endotheliomesangial GN with or without crescents* is observed in about one fifth of the cases of SLE-GN (Table 17.3). At disease onset, focal segmental accentuated glomerular affliction is also frequently noted as is subsequent slow development to a diffuse form with affliction of all glomeruli. In 9 out of 31 cases, sequential biopsy revealed initial focal mesangial changes and later diffuse glomerular affliction [554]. Accordingly, focal glomerular involvement appears to be only a transitory change. Crescent formation is found in 18% of endotheliomesangial and membranoproliferative GN [1511a]. So-called diffuse proliferative lupus GN comprises both membranoproliferative and endotheliomesangial GN.

*6. Epimembranous GN.* It is found in about 16% of all cases of SLE-GN [600, 1167, 1280, 1484, 1683]; Table 17.3). A few cases in which LM reveals normal glomeruli or those with only minimal changes would probably be included here following EM and IF examination.

In summarizing findings seen with LM, it is noted that in SLE, all forms of GN as well as glomerular minimal change and even normal glomeruli are encountered. A very characteristic feature of renal involvement is the frequently observed transition of FGN into diffuse GN or, under therapy, vice-versa. Even transition of diffuse or segmental-focal proliferative GN into epimembranous GN and vice-versa are reported, i.e., true mixed forms of (membranoproliferative and epimembranous) GN occur (see p. 279; 1 out of 26 cases: Z; Fig. 17.21; [71a, 74, 300, 485a, 554, 1086, 1280, 1820, 1830]).

Further LM characteristics, which may be found in different forms (3–6) of GN are fibrinoid (hyaline) thrombi which we observed in 5 out of 12 EM biopsy cases and in 14 out of 21 autopsy cases (Figs. 17.17, 17.19, 17.21) (contra: [74, 1068]).

The formerly used term "wire loops"—which were considered as typical for SLE-GN—, refers to a capillary wall thickening due to the extensive deposits in epimembranous and membranoproliferative GN [544, 599, 300, 1280, 1671].

The hematoxylin bodies (H-bodies, Figs. 17.22, 17.23) which are the only pathognomonic finding in SLE-GN [1460], are seen in EM to consist of aggregations of electron-opaque nuclear chromatin [454]. Large polymorphic phagolysosomes are found in the cytoplasm of H-body-containing cells [294]. The general view regarding these bodies is that they arise by injury to in situ cells by antinuclear-AB [73, 544]. Another suggestion is that the H-bodies are broken down leukocytic fragments which are phagocytized by mesangial cells [294]. The H-bodies are usually found in the glomeruli (4 out of 21 autopsy cases: Z) and less frequently in tubules [1460] and vessels [1791, 1460]. Unfortunately, the H-bodies are rarely demonstrable in biopsies (0 out of 26: Z; see also [300, 1068, 1280, 1484, 1671]) which is suggested to be due to the fact that H-bodies represent a post-mortem phenomenon [403a].

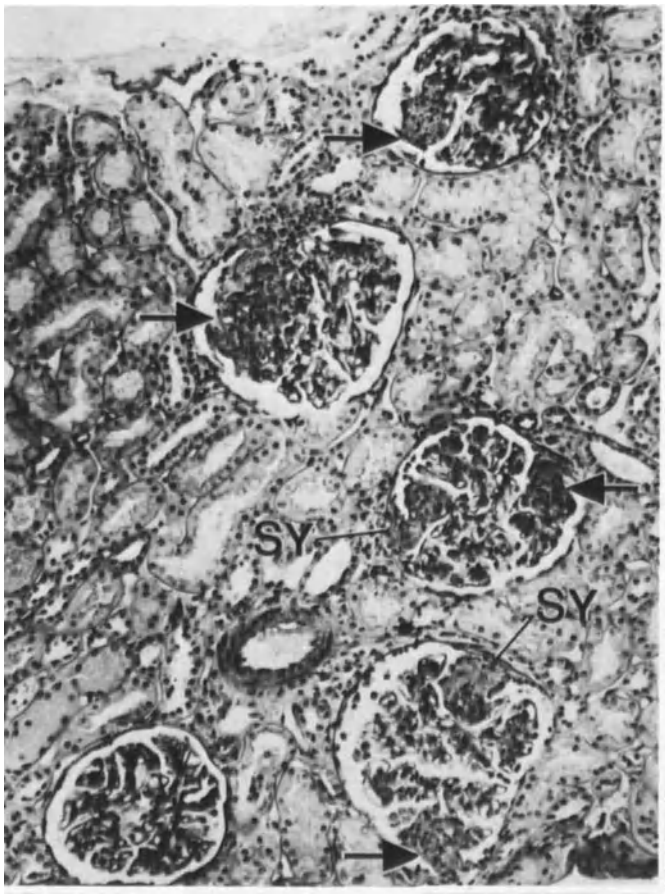
Lesion of the other renal tissue elements correspond to those of the type of GN involved. Interstitial lymphoplasmocytic infiltrates appear to be absent only in very slight forms and during stationary phases [1576]. It has been claimed that such infiltrates are not present in FGN as opposed to the diffuse form [1157]; we have not been able to substantitate this assertion.

**Fig. 17.15.** Proliferative FGN (proliferative stage) in SLE. In addition to glomerular capillary loop synechia (*SY*), a few of the loop segments have been totally occluded by cell proliferation (→). Note that one glomerulus shows no obvious changes (*bottom left*); the others are segmentally changed. Male, 12 years. PAS (×140)

**Fig. 17.16.** Proliferative FGN in SLE. Pseudolinear subendothelial deposits (→) are clearly recognizable in the glomerular capillary loop periphery. There is general mesangial hypercellularity. Note the artificially detached segmental crescent (*CR*). Female, 23 years. PAS (×400)

**Fig. 17.17.** Same case as in Figure 17.16. Numerous nuclear fragments (→) and a massive fibrinoid deposit (*D*) are recognizable. Female, 23 years. HE (×640)

**Fig. 17.18.** Same case as in Figure 17.16. Membranoproliferative character of the GN is clearly evident: BM doubling with mesangial interposition (tram-track picture) (→) in the peripheral glomerular capillary loop BM. There is severe enlargement and cell increase of the mesangium. Female, 23 years. PASM (×580)

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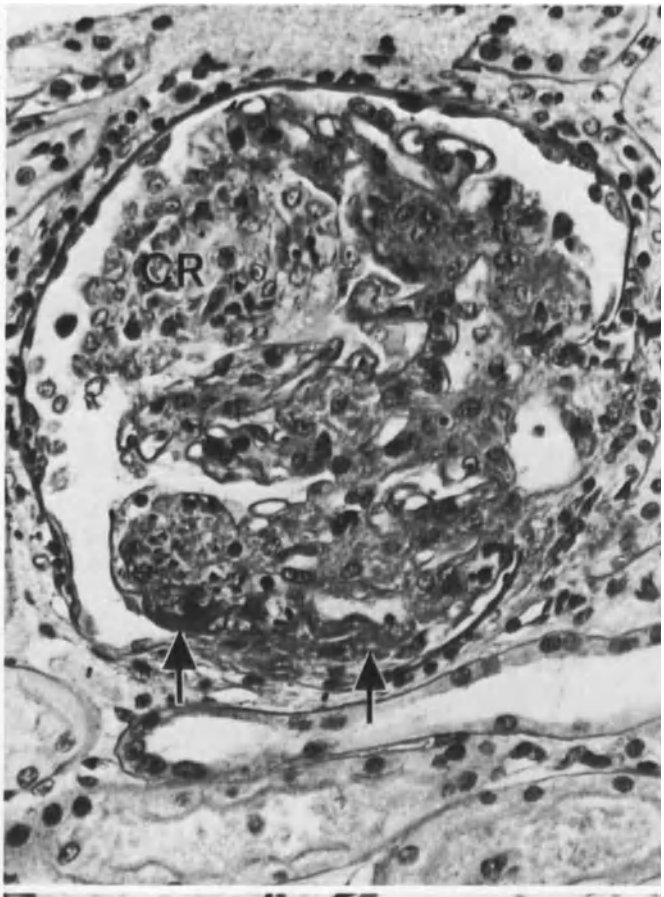


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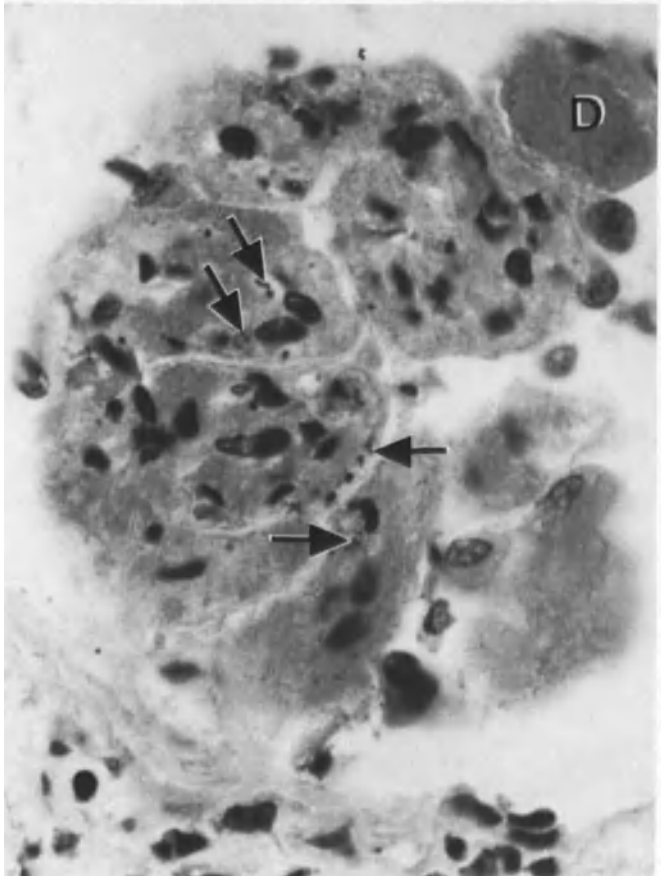


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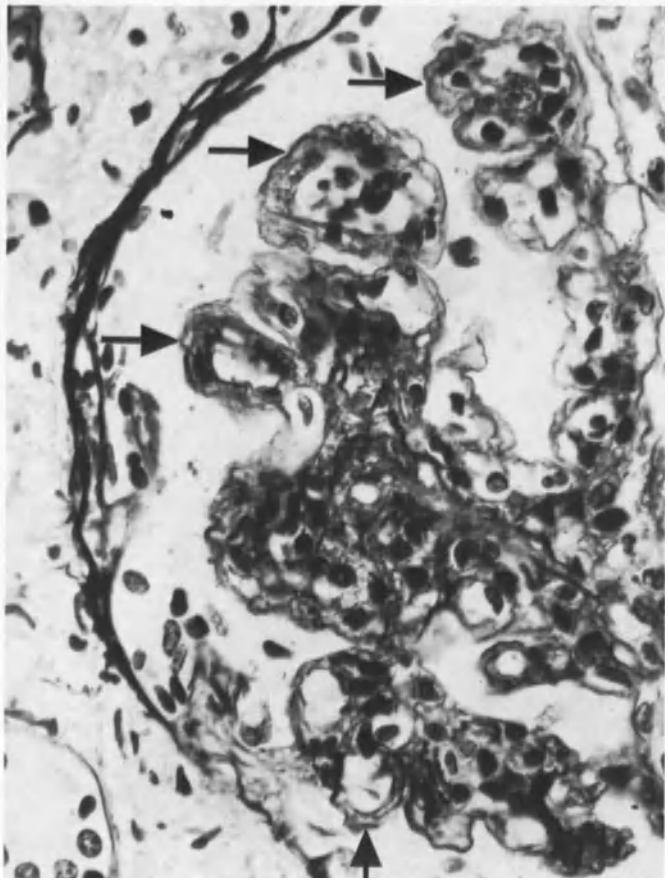

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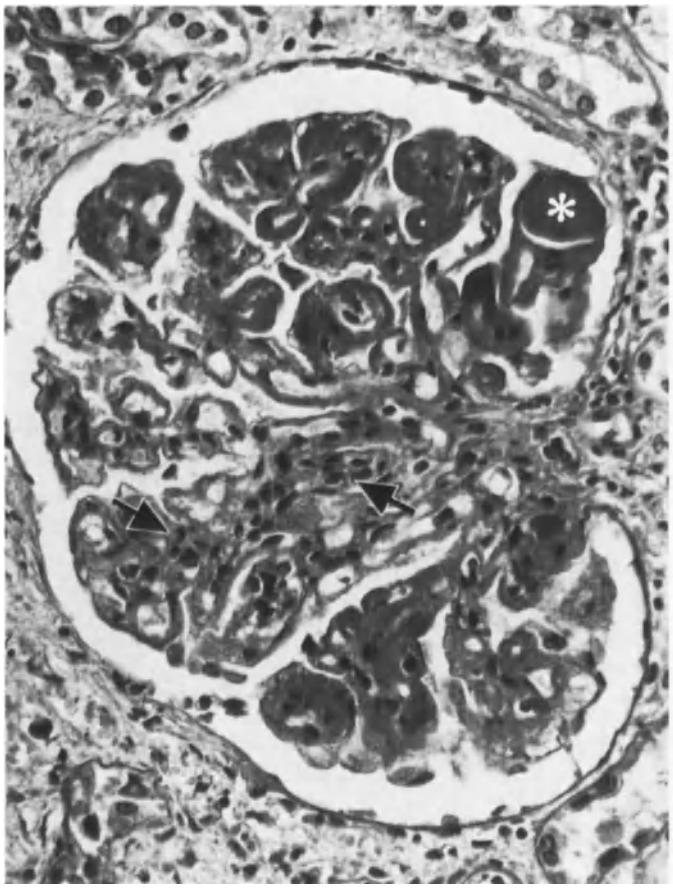

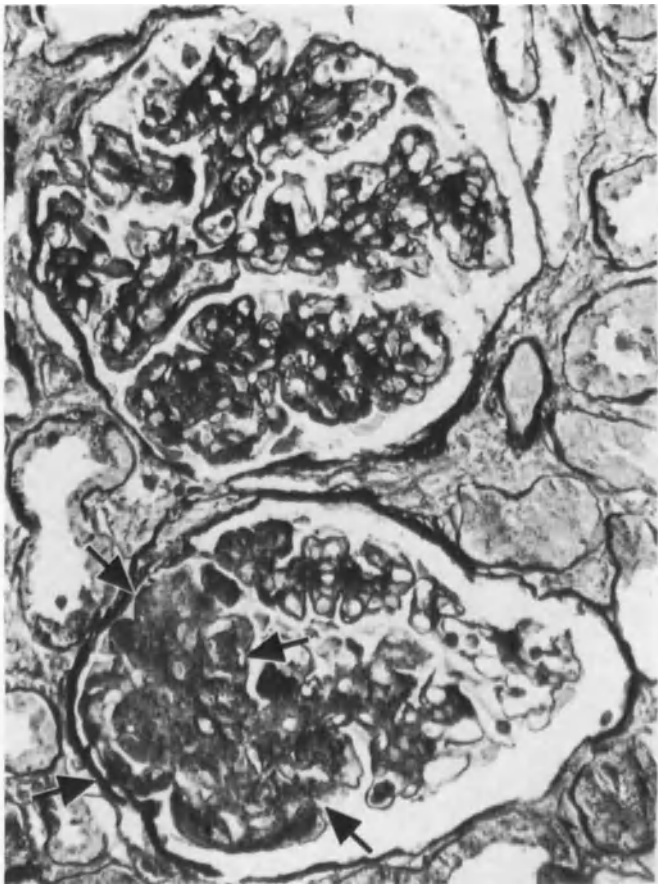

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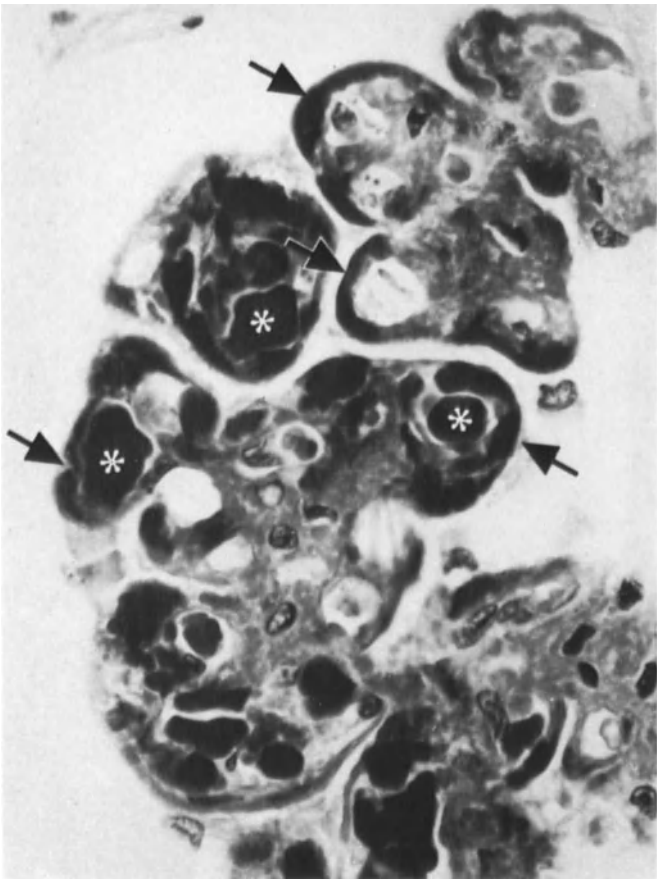

17.21

**Fig. 17.19.** GN in SLE. Homogenous thickening of glomerular capillary loops is suggestive of epimembranous GN. However, the unequal capillary loop affliction, mesangial cell increase—especially in the less seriously afflicted loops (→)—and large osmiophilic deposit (*) which appears to lie subendothelially, do not conform to epimembranous GN. There is rather severe inflammatory infiltration of the surrounding connective tissue. Cf. Figure 17.21. Female, 25 years. PAS (×400)

**Fig. 17.20.** Proliferative FGN in SLE with extensive glomerular capillary loop necroses (→). Female, 27 years. PASM (×340)

**Fig. 17.21.** Same case as in Figure 17.19. Clumpy deposits in glomerular capillary loop lumens (*) and coarse-clumpy fibrinoid subendothelial deposits in the peripheral BM can be recognized. Female, 15 years. Picro-Mallory (×890)

Interstitial edema and hyaline droplet storage or atrophy of the tubules are almost always present in severe cases of the disease. Focal fibrinoid vascular necrosis and inflammation (Fig. 17.24), frequently encountered in autopsy material (25–90%: [1791, 71b]), are late-appearing lesions and are hardly ever mentioned in biopsy material (we have not encountered them in our own biopsies).

### IF Findings

Summing up of the IF findings reported in the literature is difficult due to the wide variety of changes which may be present. Although under LM the kidney lesion often demonstrates the character of a primary—and often permanent—FGN, the IF findings (Table 17.4) are usually diffuse (Fig. 17.25; see [544, 620, 869]).

In cases with normal glomeruli or glomerular minimal changes, immunoglobulins, especially IgG, can usually be detected (17 out of 20: [1139a]. The deposition is often purely peripheral and in a smooth linear form (12 out of 17: [1139a]; see also [401, 869, 1280]). In other cases, granular mesangial IgG, IgM, and C3 deposits are found [485a, 707a, 1189a, 1511a]. Or, in still other cases, no immunoglobulins are present at all [1511a]. Apart from these smooth linear IF findings, ultralinear IgG deposition in SLE has rarely been reported to be associated with extracapillary accentuated GN [1408a]. In all other forms of GN, the immunoglobulin distribution pattern corresponds to that of the underlying form of GN. Among the immunoglobulins detected, IgG usually accompanied by C3 predominates [1139a, 1511a, 485a, 71b]. IgA and IgM, as well as IgE and IgD, are less frequently found (see Table 17.4; [127, 300, 544, 620, 1139a, 1511a]. Now and again, fibrin(-ogen), usually in trace amounts, only is seen especially in the subendothelial deposits [401, 620, 730, 743]; 60%: [1282; 43%: [485a]. Albumin and transferrin are also observed [1282], 1511a].

Nuclear IgG deposits in glomerular and tubular cells are characteristic of but not absolute proof for SLE [544], since nuclear fluorescence can also be found in other diseases in which antinuclear antibodies are present, e.g., chronic polyarthritis.

Nuclear fluorescence can exhibit different patterns, e.g., speckled, homogenous, membranous and nucleolar of which the membranous pattern is said to be most characteristic for SLE [1040, 1367a].

Recent reports described immunoglobulin deposition of IgG and/or C3 along intertubular capillaries, in the interstitium and along the tubular BM. These deposits are considered to be the cause of the accompanying interstitial nephritis [194]. In case of vasculitis, the vessels usually contain IgG and C3 [71b].

Proof of SLE lies in the detection of nuclear factors (DNA) as antigen within the immunocomplexes. We were able to demonstrate this only once (Fig. 11.1).

Table 17.4. If findings in SLE ($n=9$)[a]

| | IgG | IgM | IgA | C3 | Fibrin(-ogen) |
|---|---|---|---|---|---|
| Cases tested | 9 | 9 | 6 | 9 | 9 |
| Positive | 7 | 5 | 4 | 8 | 2 |
| Focal | 1 | 2 | 1 | 1 | 2 |
| Diffuse | 6 | 3 | 3 | 7 | 0 |
| Segmental | 0 | 0 | 0 | 1 | 2 |
| Global | 7 | 5 | 4 | 7 | 0 |
| Peripheral | 4 | 2 | 1 | 2 | 1 |
| Mesangial and peripheral | 3 | 3 | 3 | 4 | – |
| Mesangial | – | – | – | 2 | 1 |

[a] Proliferative FGN 6×; epimembranous GN 2×; endotheliomesangial GN 1×.

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**Fig. 17.22.** Numerous hematoxylin bodies (→) in SLE in the glomerular loop segment (we are indebted to Dr. Schürch, Zürich, for this preparation). Autopsy specimen. HE (×800)

**Fig. 17.23.** Hematoxylin bodies in the tubular lumen and epithelium in SLE-GN (Preparation from Dr. Schürch, Zürich). Autopsy specimen. HE (×710)

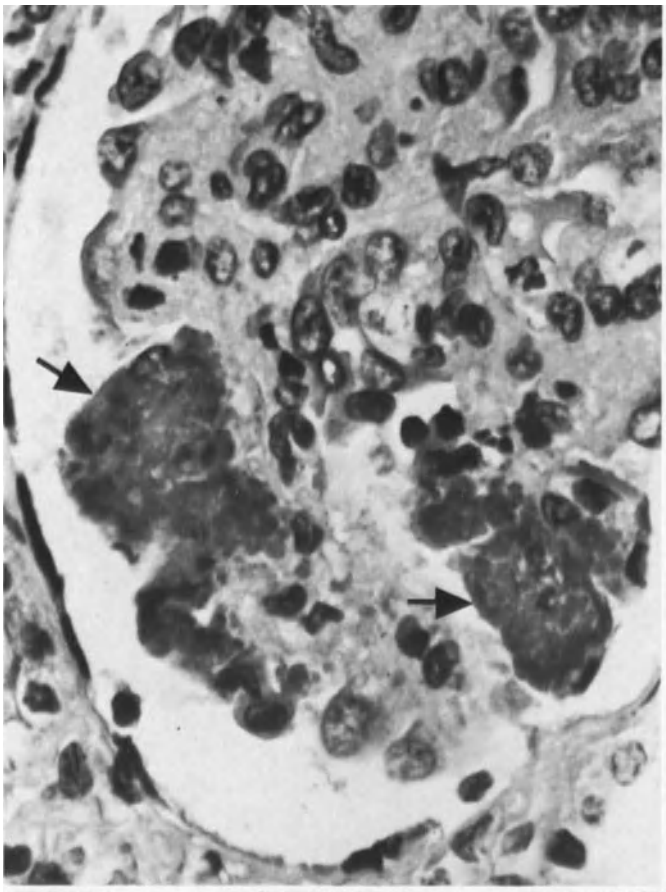
**Fig. 17.24.** Arteritis with fibrinoid necrosis (*N*) and severe periarterial inflammation in SLE-GN. Note isolated hematoxylin bodies (→) in a proliferatively thickened intima. Lumen (*L*). Autopsy specimen. HE (×110)

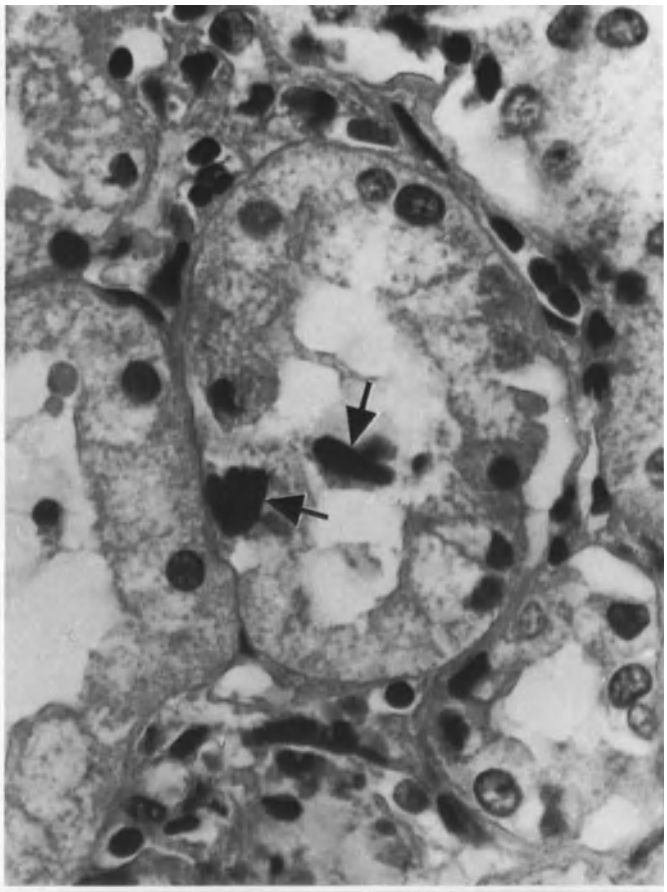
**Fig. 17.25.** Extensive coarse-granular and partly pseudolinear IgG deposits in the periphery of glomerular capillary loops in SLE-GN. Female, 23 years. IF (×680)

Page 333

**Fig. 17.26.** Endotheliomesangial GN (exudative-proliferative stage) in SLE. Glomerular capillary loop lumens are more or less occluded by activated and also possibly proliferated endothelial cells. Isolated polymorphonuclear leucocytes (*PL*). Osmiophilic deposits are not recognizable. Podocytes are highly swollen and occasionally demonstrate foot process fusion. Male, 12 years. EM (×3940)

**Fig. 17.27.** Mixed form of membranoproliferative and epimembranous GN in SLE. Extensive subepithelial deposits with spike formation (→) as well as massive subendothelial deposits (⇨) are present. Podocytes (*P*) demonstrate considerable hypertrophy and vacuolization and complete fusion of foot processes. Female, 14 years. EM (×4230)





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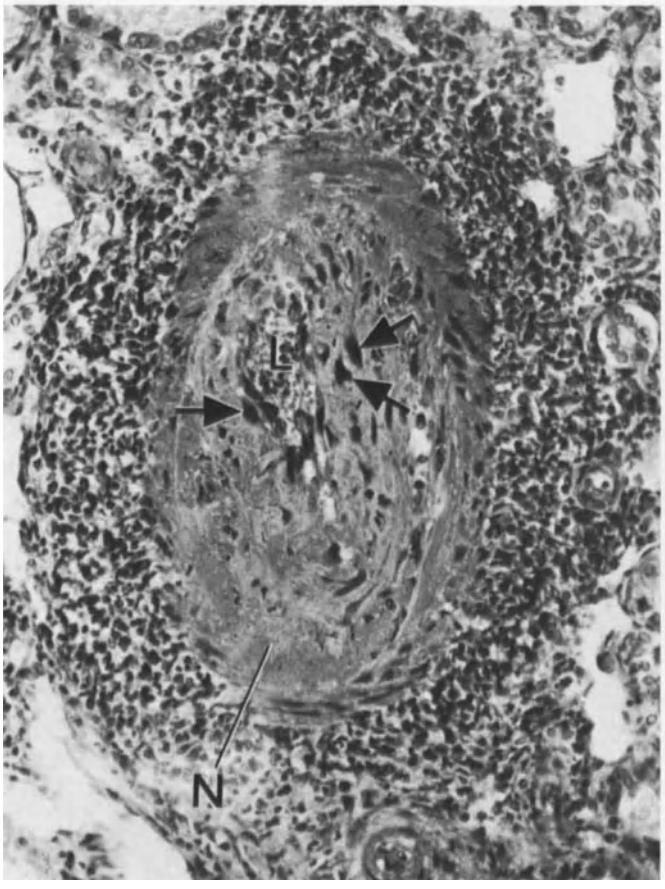


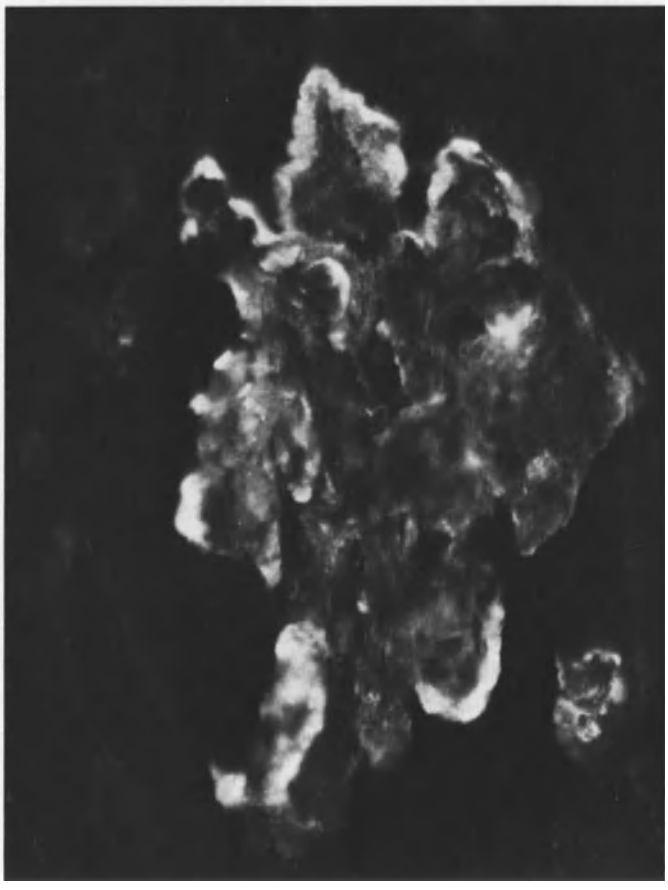

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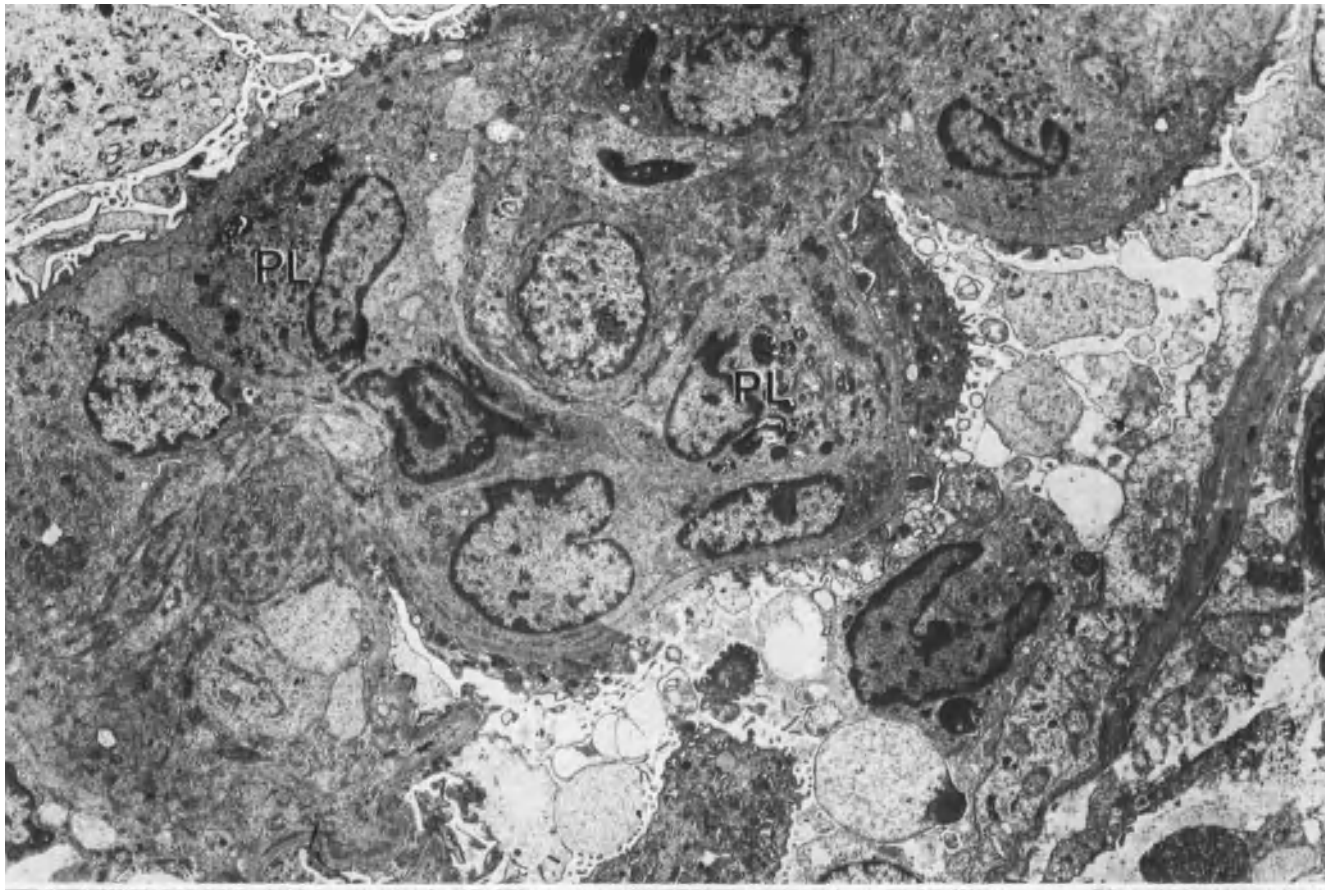


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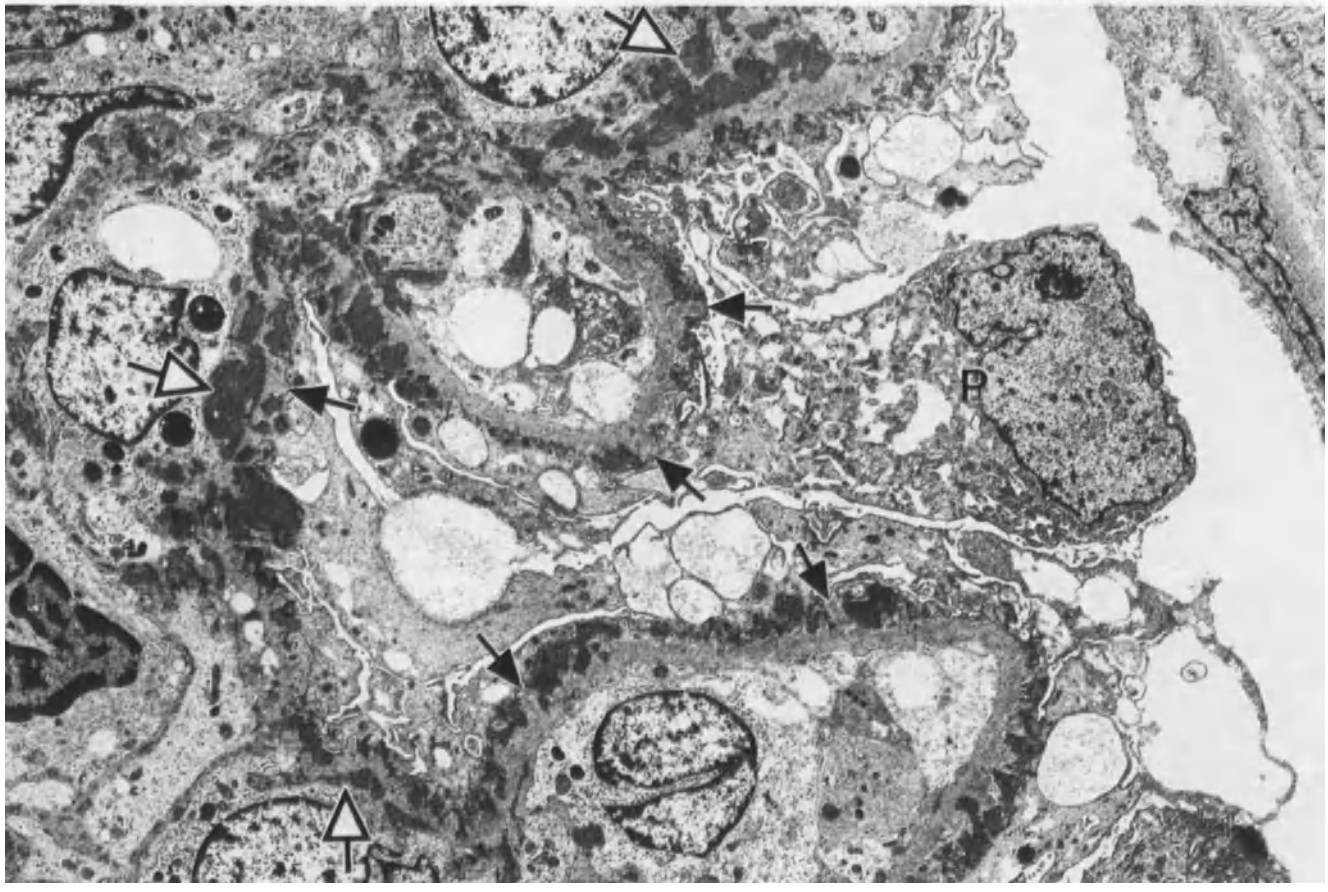



17.27

### EM Findings

Apart from the characteristic changes of the individual GN forms already described in previous chapters (Figs. 17.26, 17.27), the topography and extent of osmiophilic deposits—which are recognizable in LM as "fibrinoid"—are noteworthy findings (Figs. 17.26–17.31). It is highly probable that these deposits are mainly immunocomplexes partly containing cell constituents, e.g., nuclear factors [454].

The subepithelial deposits usually have a broad base (Fig. 17.28) as in epimembranous GN. In addition, we found hump-like subepithelial deposits in 4 out of 13 of our cases (Fig. 17.31). They are reported to persist for quite some time [401]. This observation is supported by the finding of spike formation and the occurrence of thread-like structures within the deposits (Fig. 17.29). Long-lasting spikes and subepithelial deposits in the absence of subendothelial deposits are supposedly indicative of a good prognosis and must not be interpreted as signs of the activity of the process [300, 401, 1282].

It has been proposed that the subendothelial deposits may possibly arise by secondary insudation of plasma components [401, 1282]. We do not accept this view. They are usually extraordinarily massive, as indicated previously in the section on LM (Figs. 17.27, 17.28) and they demonstrate signs of breakdown (Figs. 17.29, 17.30). With successful therapy, they are supposed to disappear much more rapidly by endothelial resorption [300] than subepithelial deposits [401]. Mesangial deposits (7 out of 13: Z) are rarely absent in the presence of subepithelial (8 out of 13: Z) and/or subendothelial deposits (9 out of 13: Z; Figs. 17.27, 17.31).

Subendothelial deposits often contain inclusions of spherical lipoid bodies. Additionally, 100–150 Å-wide cross-striated thread-like structures (see p. 96 and Fig. 17.29; [601]) as well as fingerprint-like crystalloid formations [1541] have been demonstrated.

Sometimes, deposits are completely absent. In these instances, proliferative changes are also missing. Such cases are supposed to have a relatively good prognosis (1 out of 5: [300, 1086]). We found loop necroses in 2 out of 26 cases (Fig. 17.32).

A further EM particularity of the kidney in SLE is the frequent occurrence of cytoplasmic microtubuli (with a diameter of 200–220 Å) mainly in the endothelium of the glomerular loops (Fig. 17.33; [619]; 89%: [93]; 93%: [1511a]; 7 out of 13: Z; see also [529, 1541]) and rarely of intertubular capillaries (Fig. 17.34).

Although some investigators consider the microtubuli to be specific for SLE [590, 1683], others have shown that they also occur in scleroderma, rheumatoid arthritis, idiopathic GN, etc. [529, 614, 619, 1613]. Although their form is reminiscent of myxovirus, they are interpreted as being a reaction product of the endoplasmatic reticulum to viral infection [544, 852].

Osmiophilic deposits may also be found along the intertubular capillaries and tubular BM and in the interstitium (Figs. 17.34, 17.35; see also [194]) as also demonstrated by IF.

### Differential Diagnosis

On the basis of LM or IF, the only diagnostic proof for SLE is the demonstration of hematoxylin bodies or nuclear factors (DNA) within immunocomplexes in the kidney. If both of these parameters are absent, which is usually the case in biopsies, the following morphologic characteristics are indicative of SLE: focally accentuated GN, mixed-form GN, extensive subendothelial deposits, fibrinoid (hyaline) thrombi (giant deposits), endothelial cytoplasmic microtubules in large amounts, deposits in the interstitium and along the BM of tubules and intertubular capillaries and demonstration of antinuclear antibodies with a membranous pattern under IF. But final proof for SLE is only possible in these cases through close cooperation with the clinician.

### Prognosis

The overall survival rates vary considerably in different series, e.g., 5-year survival rate of 78% [1184a], 66% (Z); the average 10-year survival rate of 9 different series is 57% (range 38–86%) as reported in [485a].

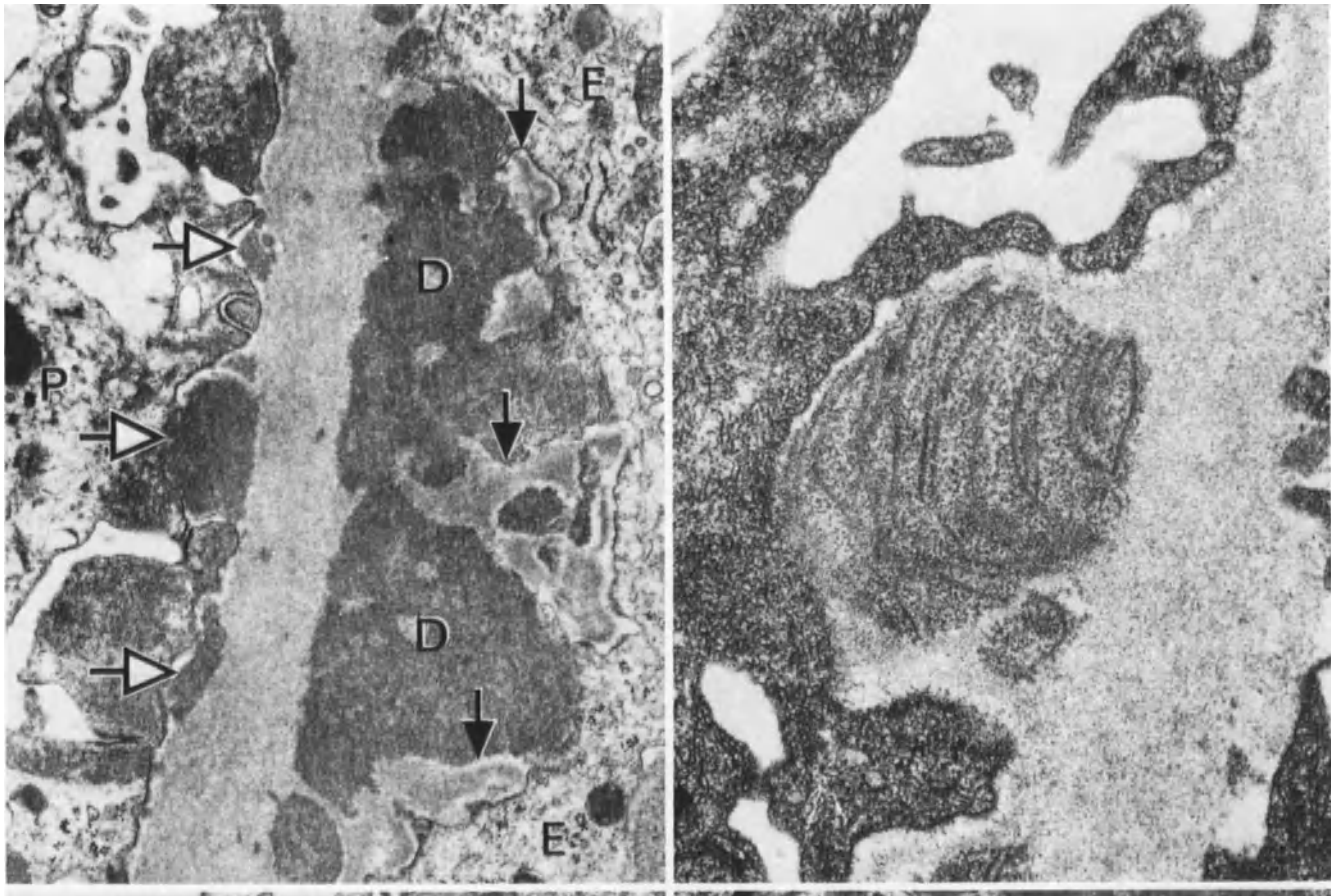
The prognosis as related to patient age is reported all the poorer the younger the patient; this finding has not been substantiated by others [485a].

**Fig. 17.28.** Membranoproliferative GN in SLE: pronounced subendothelial deposits (*D*) with subendothelial BM new formation (→). A few subepithelial deposits (⇾)—possibly the expression of an acute attack—are also present. Podocyte (*P*); endothelium (*E*). Female, 17 years. EM (×17,200) ▷

**Fig. 17.29.** Subepithelial deposit with peculiar striping which is thought to be due to decomposition of deposits in SLE-GN. Female, 21 years. EM (×47,800)

**Fig. 17.30.** Same case as in Figure 17.28. Many subendothelial deposits surrounded by translucent areas as result of dissolution of deposits. Female, 17 years. EM (×8230)

**Fig. 17.31.** Pronounced mesangial (*D*) and isolated intramembranous (*) deposits as well as a solitary hump (→) in a case of membranoproliferative GN in SLE. Female, 36 years. EM (×6600)

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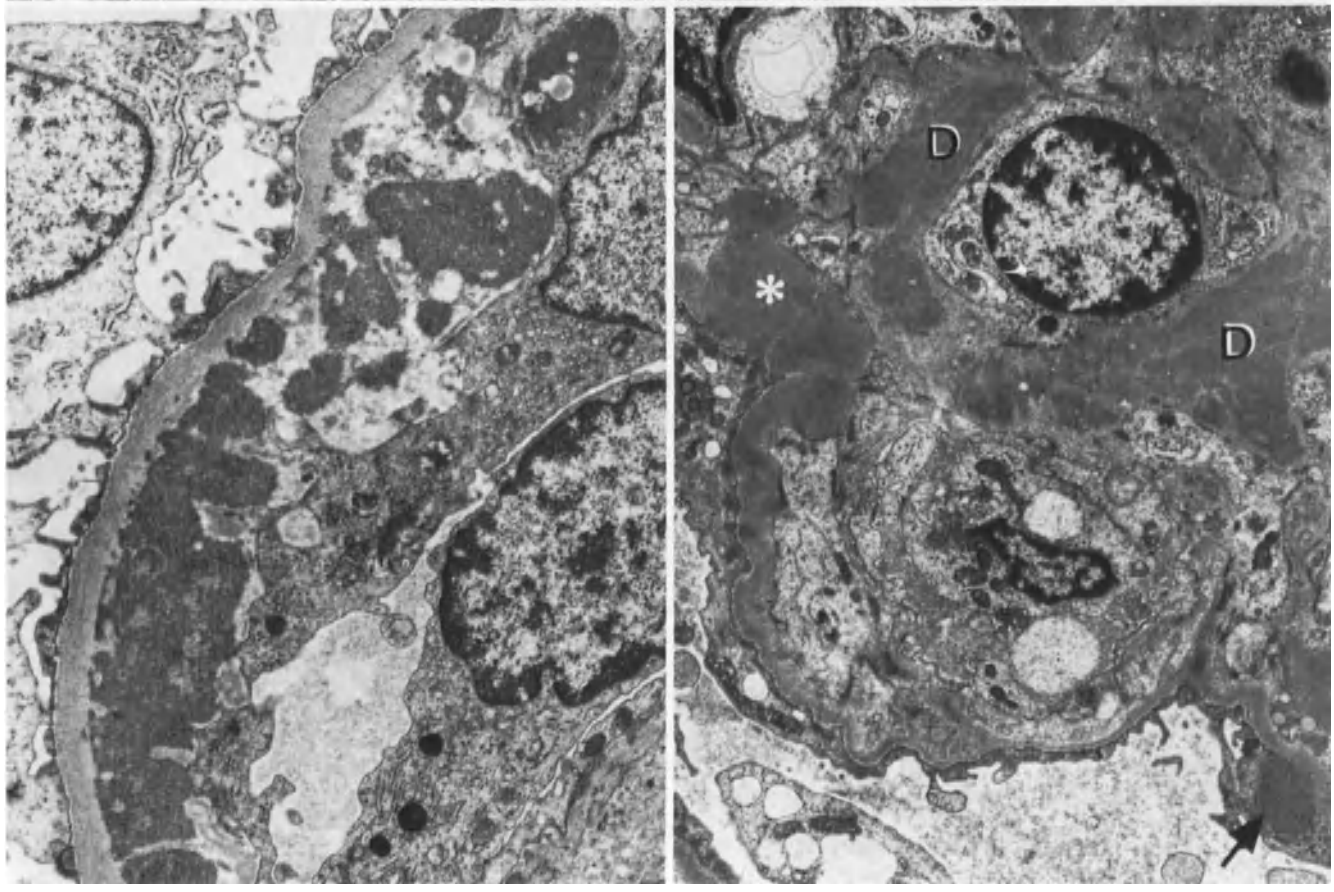


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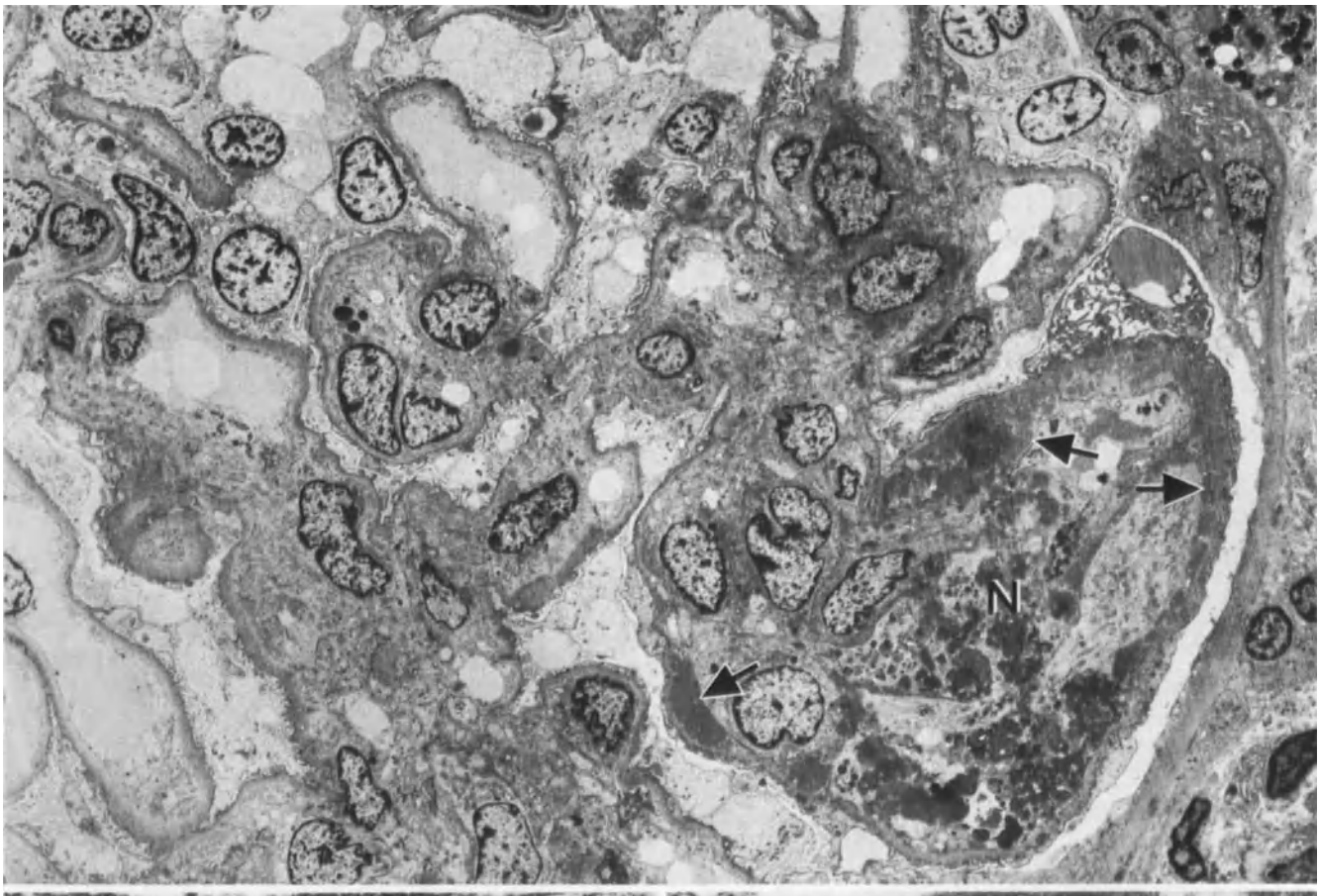


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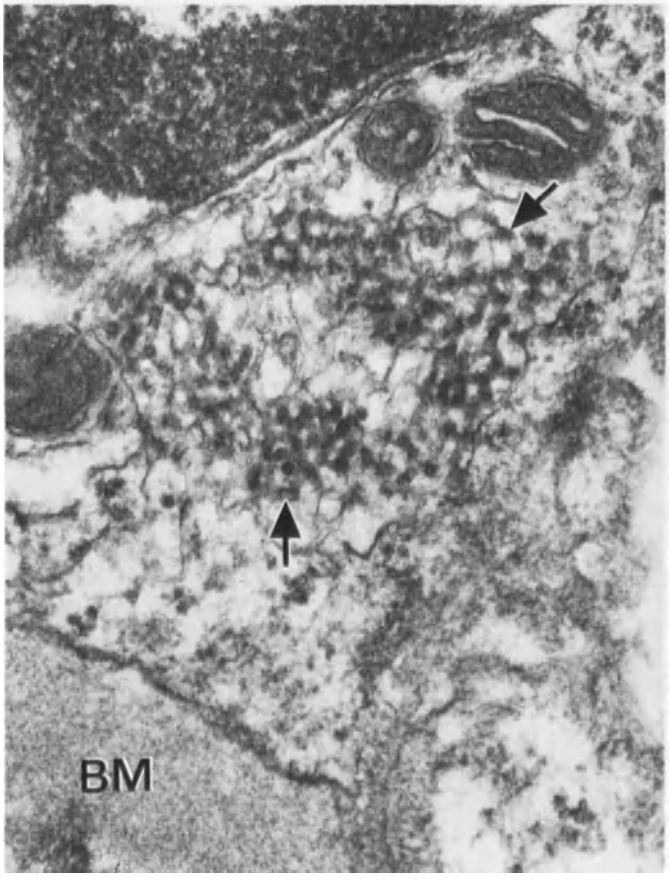
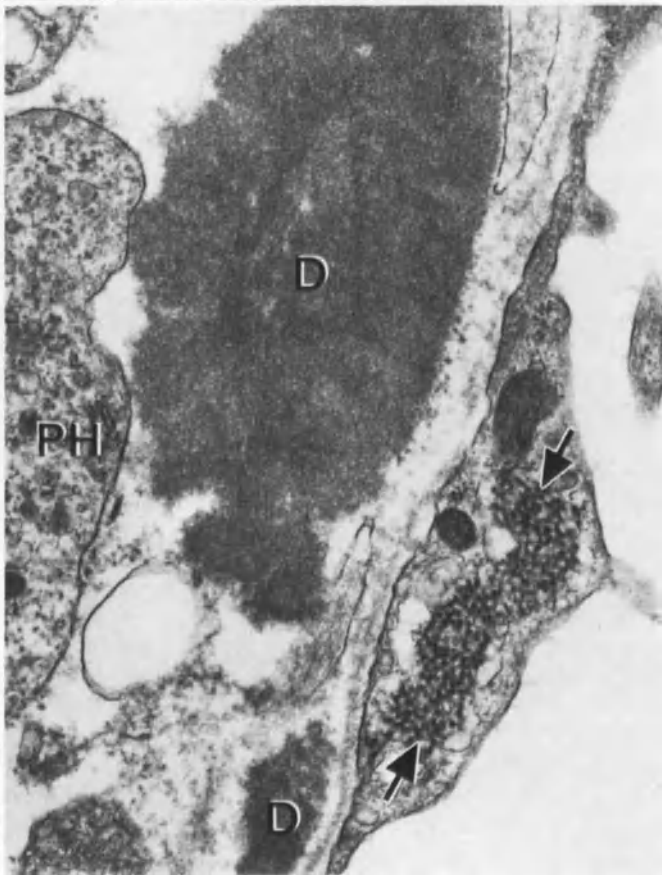



17.33
17.34

On the other hand, there is general agreement that the prognosis is intimately dependent on the form of GN present. The following 6-year survival rates for the individual GN forms are reported as follows [74, 1282]; see also [1511a]: normal glomeruli and glomerular minimal change without focal sclerosis: 90%, epimembranous GN 85%, proliferative FGN 60%, diffuse proliferative GN (including endotheliomesangial and membranoproliferative GN) 20%. In series from children and young adults, the correlation between morphology and survival rates is substantiated, i.e., epimembranous GN for 5 years: 100% [531a]; proliferative FGN for 5 years: 100% [531a], and for 10 years: 87% [485a]; mesangial lupus GN for 10 years: 100% [485a]; diffuse proliferative GN for 5 years: 60% [531a] and 10 years: 73% [485a].
In any event, adequate therapy can result in considerable improvement even in cases with diffuse GN [1085] which may regress into proliferative FGN [485a]. Under therapy a decrease of deposits is reported [360, 1163].
The relatively good prognosis of segmental-focal proliferative SLE-GN—even with up to 50% crescents (usually males: [1576])—is clouded by the quite frequent transition into the diffuse form (3 out of 7: [1085]; 29%: [554]). Additionally, a certain parallelness between the amount of subendothelial deposits and the activity of lupus GN is reported to be present ([401, 600, 601, 613, 1163, 1511a, 1824; contra: [372]).
The prognosis is considerably better in drug-induced SLE-GN. In the majority of the patients, the renal findings are reported to return to normal after withdrawal of the incriminating drug [1068]. Renal vein thrombosis is a unique complication of epimembranous GN in SLE [39].

### Pathogenesis

SLE is currently viewed as an autoimmune disease with formation of mainly antinuclear AB to native DNA. Immunocomplex formation occurs when cells disintegrate and thereby make the corresponding nuclear (and partially cytoplasmic) AG available to the AB. In this process, not only local H-bodies but also circulating, variously soluble complexes arise; it is this difference in solubility which explains the diversity of the glomerular reaction [544]. The particular affinity of glomerular BM and collagen for DNA indicates the possibility of glomerular fixation of liberated DNA with secondary deposition of antibodies [757a]. Denaturation of cellular components is decisive for triggering the autoimmune reaction.

### Etiology

A virus has been considered as the main etiological factor because of findings obtained in animal diseases—NZB mice, Aleutian minks—characterized by an SLE-like syndrome in which not only RNA C-type viruses, but also antinuclear antibodies have been demonstrated [265, 392, 614, 682, 958]. In man, there were—until recently—only indirect indications of a viral etiology as evidenced by the presence of endothelial tubular structures which are also found in NZB mice and Aleutian minks [29]. Further evidence for a viral etiology has recently been provided by the demonstration of C-type RNA virus antigen in the human glomeruli from patients with SLE [1073a, 1237a].
Drugs have also been frequently implicated as causative agents [1732a]. Cases unquestionably caused by drugs and, in most instances, healed by their withdrawal, have been reported following administration of hydralazine (150 cases: [10]), isoniacid, procainamide and the anticonvulsants hydantoin and trimethadion ([917, 1732a]; see also [544, 1068, 1613]).

◁ **Fig. 17.32.** Proliferative FGN in SLE: segmental glomerular capillary loop necrosis (*N*) and coarse subendothelial deposits (→). Female, 23 years. EM (×3590)

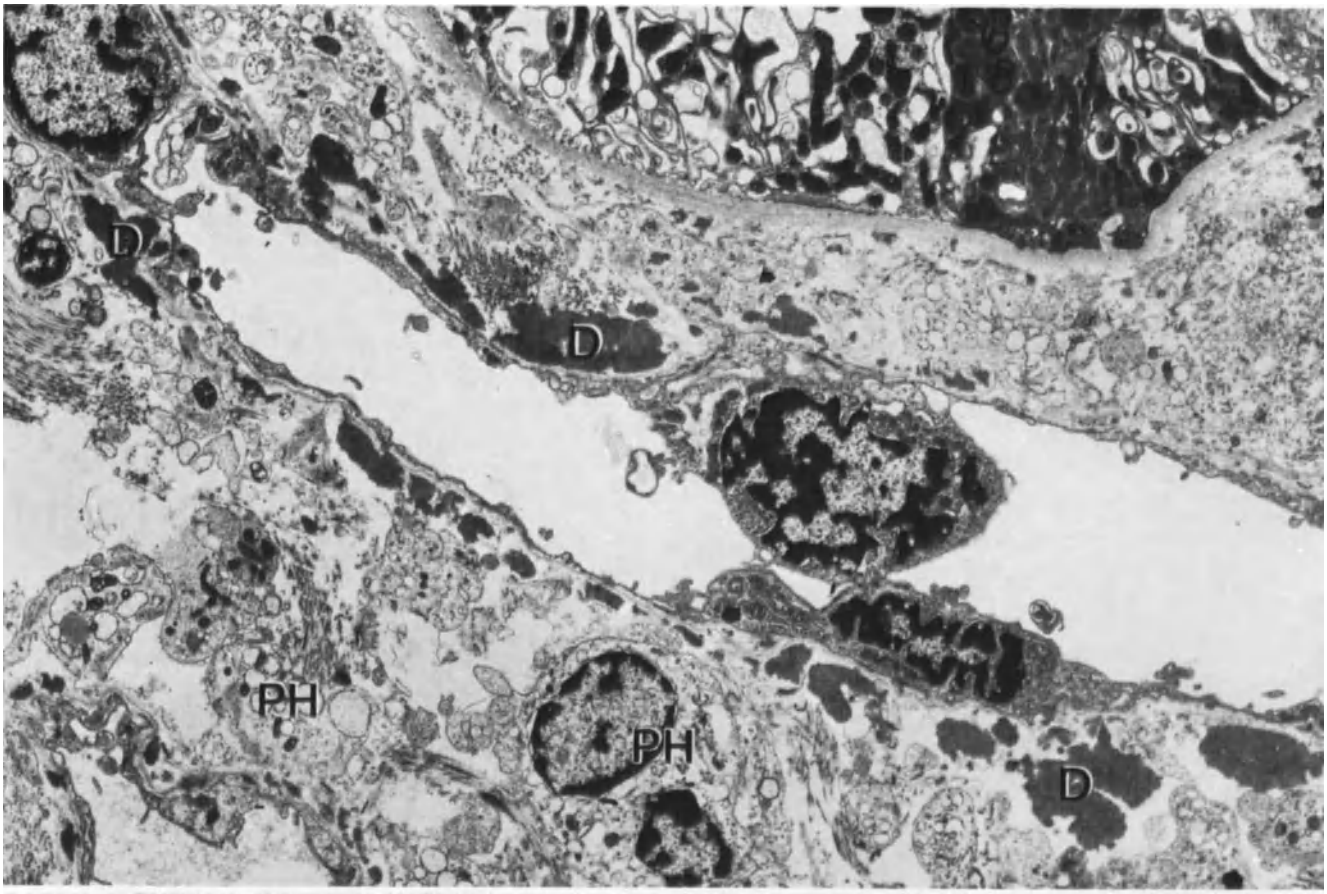
**Fig. 17.33.** Virus-induced tubular endothelial structures (→) in SLE. Basement membrane (*BM*). Female, 28 years. EM (×97,040)

**Fig. 17.34.** Same case as in Figure 17.33. Virus-induced tubular structures in endothelium (→←) of an intertubular capillary. Osmiophilic deposits (*D*) are present along the BM. Part of an interstitial phagocyte (*PH*). Female, 28 years. EM (×29,300)

## Renal Changes in Goodpasture's Syndrome
[685, 1293, 1300]

### Definition

This disease is characterized by recurring pulmonary hemorrhage followed by a highly destructive focally accentuated GN with marked crescent formation and IF demonstration of linear IgG deposits in the glomeruli (and lungs).

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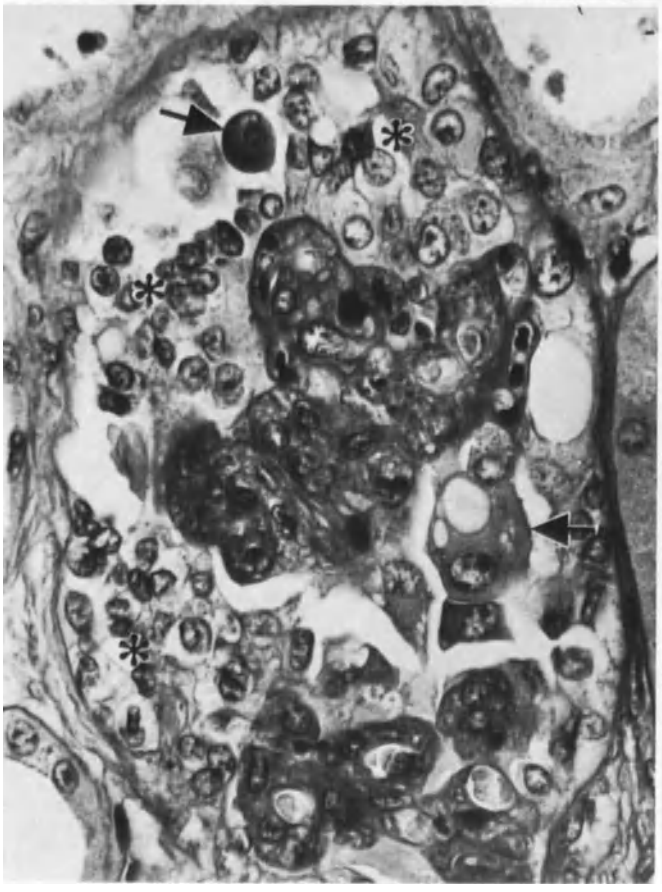
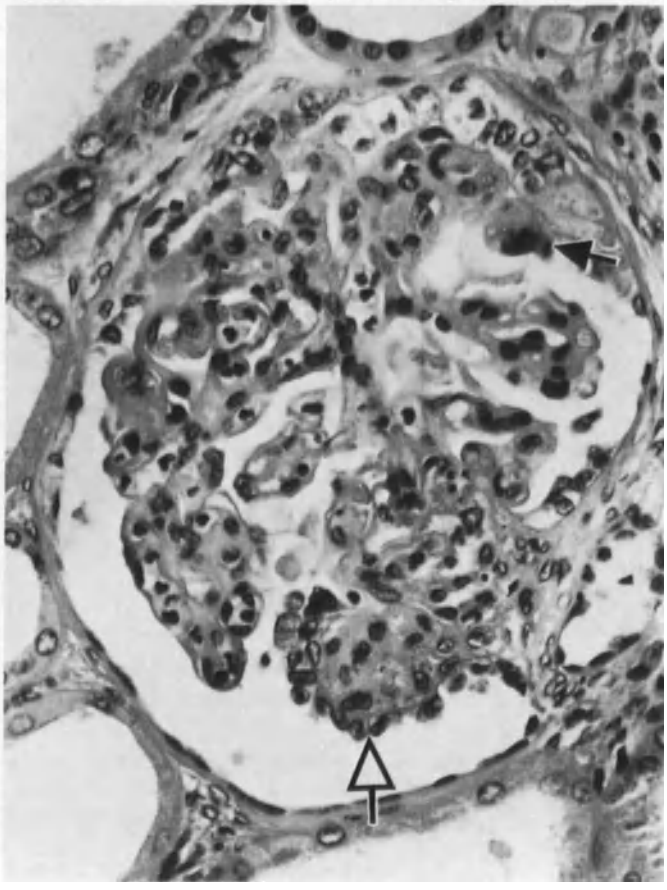




17.36
17.37

### Incidence

The lesion is rare. It has been reported in 4 out of 213 renal biopsies [544], 4 out of 1368 biopsies in children and in 2 out of 46 cases of focal nephritis in children [624], 4% of all needle biopsies with GN [1312], in 0.76% [904] and in our material in 3 out of 25,000 autopsies, 0.15% biopsies, and 0.3% biopsies of GN.
The disease occurs typically in younger adults between 15 and 35 years of age, but it also occurs in older patients [690] as well as in children [620]. Males are more frequently afflicted than females [1300].

### Clinical Findings

The disease [54, 1300] begins either with coughing, dyspnea, and bloody sputum or with massive, recurring lung hemorrhage which is accompanied by incommensurate anemia. X-ray films of the lungs show patchy, occasionally confluent infiltrates. Renal symptoms can develop days or even months after disease onset, in a few cases, concomitantly with the pulmonary symptoms or even before them. Initial renal symptoms consist of micro- or macrohematuria accompanied by slight proteinuria corresponding to the morphologic picture of FGN [685], which develops into diffuse GN after some months (less frequently after weeks or years) and is accompanied by increasing proteinuria and rapidly progressive renal insufficiency and, terminally, by hypertension. In one case series, renal insufficiency developed within 6 months in 5 out of 6 patients, whereas spontaneous remission occurred in the other subject [54]. Anti-BM-AB are usually first demonstrable in patients' serum following bilateral nephrectomy ([544]; contra: [750]). Lung hemorrhage often ceases following nephrectomy. Serum complement levels are normal and antinuclear AB are not present.

◁ **Fig. 17.35.** Same case as in Figure 17.33. Intertubular capillary with numerous osmiophilic deposits (*D*) which lie exterior to the capillary BM. Interstitial phagocytes (*PH*) evidence intense activation. Female, 28 years. EM (×5100)

**Fig. 17.36.** Proliferative FGN with severe extracapillary involvement in Goodpasture's syndrome. Glomerular capillary loops are completely compressed and can scarcely be evaluated. Crescent formation (*) and two podocytic giant cells (→) are present in the capsular space. Female, 70 years. PAS (×720)

**Fig. 17.37.** Same case as in Figure 17.36 as seen 5 weeks later. There are now extensive synechiae. A podocytic giant cell (→). General hypercellularity with loop obliteration due to cell proliferation (⇨). No significant periglomerular inflammation is present. Female, 70 years. HE (×500)

### LM Findings

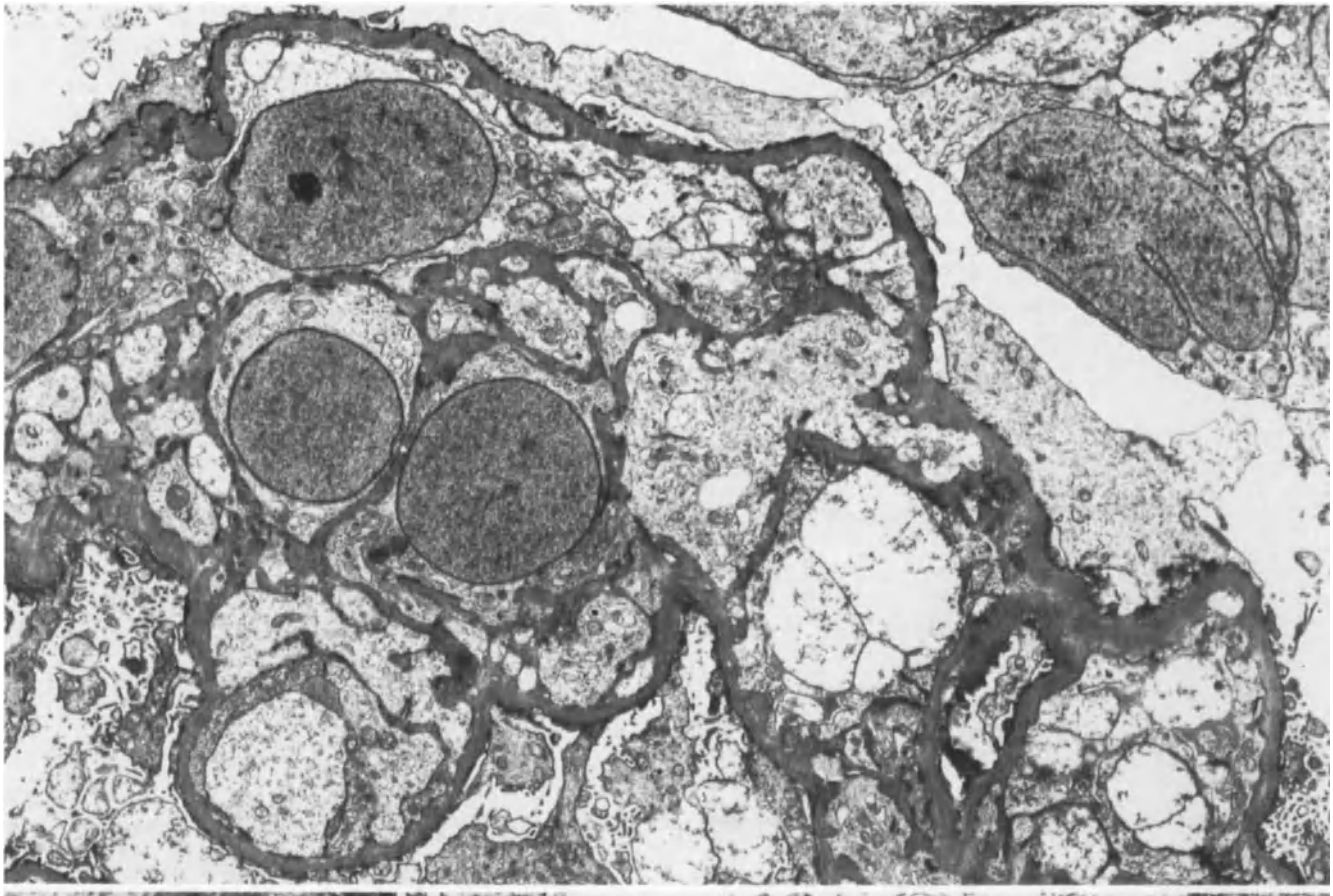
In the early stage of the disease, a severe, focally accentuated GN is present (Figs. 17.36, 17.37)—usually with considerable crescent formation (Fig. 6.91) [344, 750, 904, 954, 1353, 1484]. A particular highly characteristic feature is the occurrence of syncytial giant cells in the capsular space (Figs. 17.36, 17.37; 2 out of 3: Z; see also [904]). They are commonly associated with loop necrosis. They are not, however, pathognomonic, since they are, rarely, observed in amyloidosis [1715], extracapillary GN [1209, 1211] and in other types of focally accentuated GN associated with loop necroses (see Table 8.1). According to our observations, these giant cells are of podocytic origin (histiocytes: [904]). Fibrinoid loop necroses are relatively frequent and we found them already present during the early stage of the disease whereas other investigators encountered them only during the terminal attack [883]. The BM is often pronouncedly split and evidences mesangial interposition but without subendothelial deposit formation.
In the later stages, the glomeruli are often diffusely afflicted but segmental changes and various inflammatory stages of the lesions can still be identified side by side. We did not find arteritis as has been described by other investigators [954, 1068].

### If Findings

The IF findings are those of anti-BM-AB type GN with ultralinear deposition of IgG and more rarely C3 [1747]—which involves all glomeruli—also those which appear unchanged under LM ([620]; Fig. 11.3; see also [54, 344, 983, 544, 1101, 1293, 1484] and for granular deposits: [1211, 1825]). Other immunoglobulins are more seldom present (IgA: [620]). The absence of C3 within glomerular deposits, in some cases, can be explained by the fact that the glomerularly bound $IgG_4$ does not fix complement [954]. Furthermore, 2–5% of the glomeruli show coarse fibrin(-ogen) deposition peripherally [1197].
The same IF type is found now and again in lung biopsies along alveolar capillary BM [54, 883].

### EM Findings

In the late stage, the lesion is strongly reminiscent of membranoproliferative GN; massive deposits, however, are absent (Fig. 17.38; see also [1293, 1300, 1353]). Interposition and, above all, BM doubling are especially obvious (Fig. 17.39). Loop BM is focally considerably thickened, irregular and evidences cytoplasmic inclusions (Fig. 17.40); it may even be ruptured [544]. We were able to demonstrate very thin subendothelial osmiophilic deposits (Fig. 17.41) in a relatively fresh case (see also



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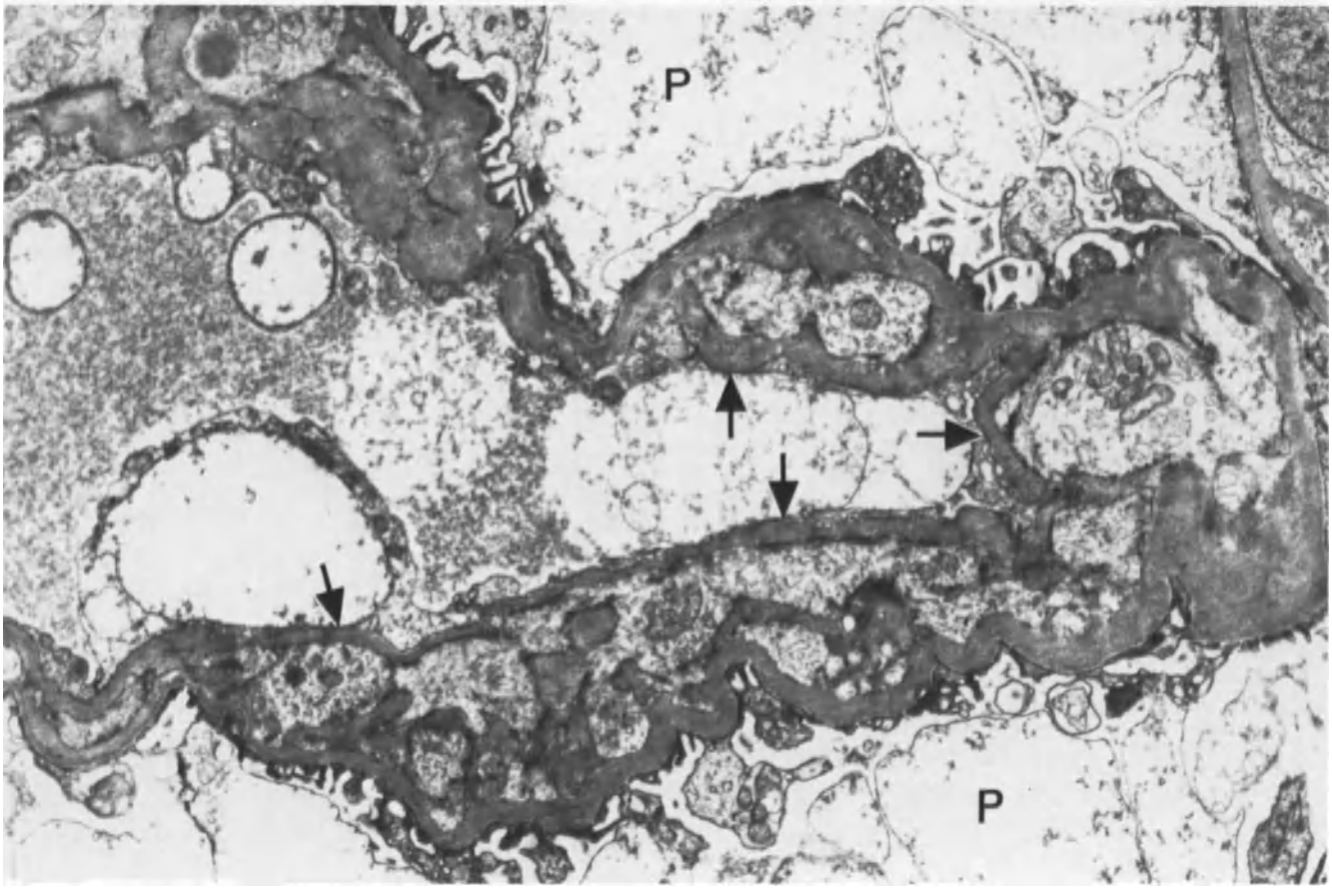


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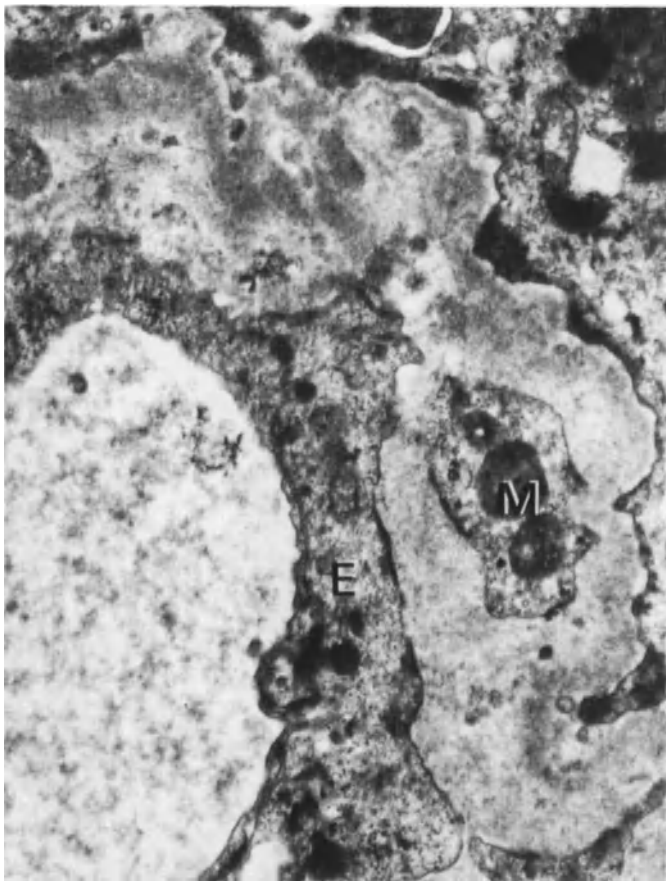


17.40

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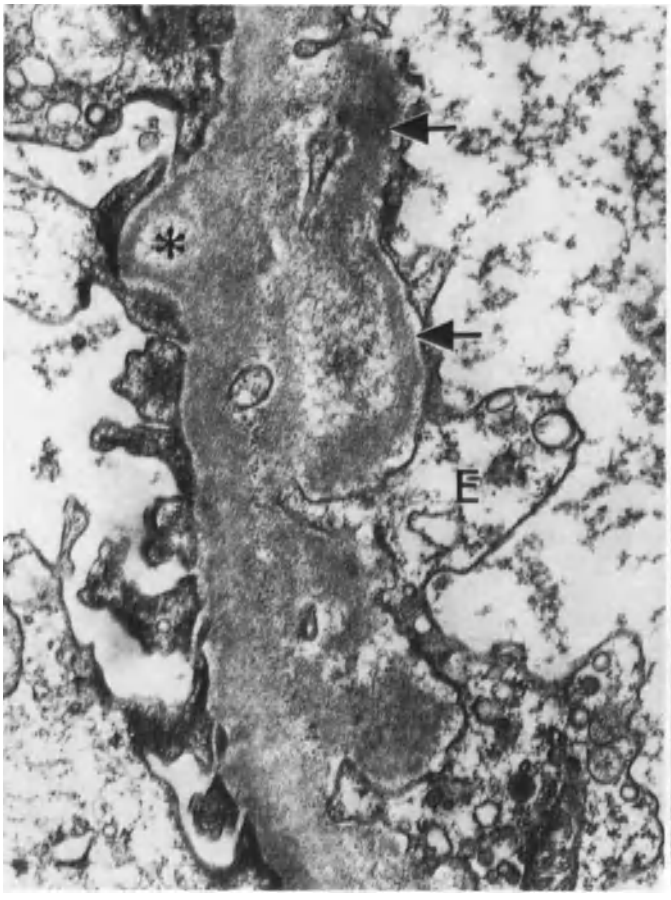
**Fig. 17.38.** Same case as in Figure 17.36. Goodpasture's GN: new formation of mesangial matrix, extensive activation of mesangial cells and occasionally mesangial interposition with new formation of a second, thin densa layer are present. Female, 70 years. EM (×4450)

**Fig. 17.39.** Same case as in Figure 17.36. Peripheral glomerular capillary loops demonstrate severe mesangial interposition and new formation of subendothelial BM (→). Massive ballooning of podocytes (*P*) is due to poor fixation. Female, 70 years. EM (×8750)

**Fig. 17.40.** Same case as in Figure 17.36. Severe degeneration of peripheral BM with mesangial interposition (*M*). Endothelial cells (*E*) are highly hypertrophied. There is complete fusion of podocytic foot processes and osmiophilic material is considerably increased. Female, 70 years. EM (×18640)

**Fig. 17.41.** Same case as in Figure 17.36. Peripheral BM in Goodpasture's GN: considerable thickening of the lamina rara interna and new formation of a thin densa layer (→) which is separated from the endothelium (*E*) by a new, uniformly narrow l. rara interna. Degradation particles are embedded in the BM. There is also subepithelial loosening (*) of the BM. EM (×26,400)

**Fig. 17.42.** Same case as in Figure 17.36. Extensive deposition of iron granules in mesangial and endothelial cells in Goodpasture's GN. Female, 70 years. EM (×17,340)

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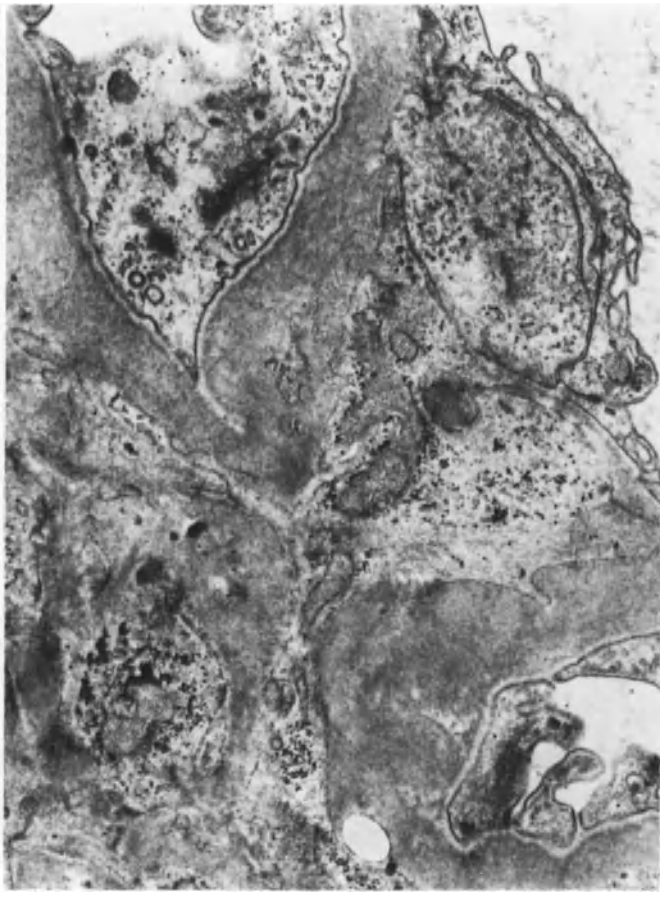


17.42

[750]) which were no longer present in a biopsy 3 years later, but which still showed frank mesangial interposition and considerable fine-granular thickening of the lamina rara interna as is the case in experimental anti-BM-GN [38, 1197]. Deposition of iron granules in and under podocytes and in the endothelium of the intertubular vessels (Fig. 17.42) can be shown in a few cases [1353]. The remaining findings correspond to those of proliferative FGN with severe extracapillary involvement. The fibrin content of capsular spaces filled with crescents as well as the (fibrinoid) loop necroses are especially pronounced.

### Differential Diagnosis

In the presence of lung hemorrhage and a progressive kidney disease, several possibilities must be considered. Above all, attention must be directed to Schönlein-Henoch's purpura ([1803]; 3 out of 25,000 autopsies: Z; 2 out of 22 biopsies of Schönlein-Henoch's purpura) in which, however, the recurring character of the lung hemorrhage typical of Goodpasture's syndrome is very rare.
Lung hemorrhage is also occasionally encountered in hypersensitivity angitis [1068] and in SLE [544] as well as in Wegener's syndrome, apart from chance association of pulmonary hemorrhage and renal symptoms.
Idiopathic pulmonary hemosiderosis of children is not accompanied by renal involvement and its prognosis is good [1068, 1526].
Because of these differential diagnostic problems, renal biopsy is of primary importance for diagnosis, especially so with IF investigation. When IF investigation is not done, segmental-focal proliferative GN with marked crescent formation, capillary loop necroses, numerous podocytic giant cells, and the absence of EM-demonstrable osmiophilic deposits are indicative of but not proof for Goodpasture's syndrome.

### Prognosis

The prognosis is very poor. Among 100 patients reported in the literature, 90 succumbed after an average of 10 months following diagnosis (36 from pulmonary changes and 54 in uremia: [1562]). There are only a few cases described where healing (with defects) has occurred [685, 1682]. The efficacy of treatment with immunosuppressives and corticosteroids is questionable [1505].
Transplantation is usually successful ([1197, 1505]; contra: [422]) after bilateral nephrectomy and complete disappearance of serum anti-BM-AB, otherwise, a relapse of the GN in transplant must be expected [1293]. The favorable, usually immediate effect of bilateral nephrectomy on lung hemorrhage is not yet completely understood.

### Pathogenesis and Etiology

Goodpasture's syndrome represents the prototype of anti-BM-AB GN (experimental findings: [641]). The chain of events leading to anti-BM-AB formation is poorly understood.
Both a cross-reaction against streptococcal membranes (see p. 183; [544]) and a viral infection (influenza-$A_2$ virus: [1748]) have been proposed as causative.
A further etiologic factor is supposed to be hydrocarbon solvent poisoning which is injurious to lung BM [107].
Recently, it has been demonstrated that the glomerularly bound IgG corresponds to $IgG_4$ which does not fix complement. Thus, it has been suggested that the glomerular lesions are due to a cell-mediated immune response [954].

## Renal Changes in Wegener's Syndrome
[130, 714, 1697, 1791]

### Definition

This lesion is characterized by a pronouncedly destructive FGN with proliferative periglomerulitis and vasculitis associated with chronic, granulomatous inflammation of the respiratory tract, and coarse, nodular granuloma in other organs as well.

### Incidence

We found this rare disease in 6 out of 25,000 autopsies and in 0.35% of our biopsies (0.7% of GN biopsies). Males are afflicted slightly more frequently than females. The onset of disease is usually during the fourth to fifth decades of life (see also Table 14.3).

### Clinical Findings

The disease (Table 14.3) usually begins with ozena and/or rhinitis, otitis media, sinusitis, or pneumonia. Biopsy provides the characteristic findings, i.e., chronic inflammation of the mucosa with severely proliferative and occasionally necrotizing vasculitis. Eye symptoms (uveitis, keratoconjunctivitis, exophthalmus) are also described [984]. An interesting laboratory finding is an increase in serum IgE [301a].
In one of our own cases, purpura initially occurred and led to the diagnosis of Schönlein-Henoch's syndrome [824]. Disease onset may be so insidious that diagnosis is first achieved during the subsequent phase of massive granuloma formation, chiefly in the lung. Lung biopsy reveals destructive tuberculoid granulomas [256, 824], which are often misinterpreted as tuberculosis, meta-

stases, or fungal pneumonia. In one of our own cases, granulomas were restricted to the breast and led to the wrong diagnosis of lipophagic granuloma. Observation of the severe vasculitis in this case would have permitted the correct diagnosis which was then achieved with subsequent renal biopsy.

In general, significant renal symptoms already occur in the early disease stage. Renal involvement is usually attack-like. Lack of renal involvement has also been reported [256]. The existence of this "limited form of angitis and granulomatosis of Wegener's type" [255] has been challenged [714]. Renal affliction is generally associated with proteinuria in 88% and hematuria in 81% of the cases ([1687]; see also Table 14.3). Not infrequently, patients present with oligo-anuria (5 out of 6: Z) unaccompanied by any indications of the underlying disease. Diagnosis was made in 3 out of 6 of our cases by renal biopsy (extrarenal manifestations were first demonstrated later).

The disease may last for months or even years. Death is due to renal insufficiency in 80% of the lethal cases and to lung and vascular involvement in the other 20%. In 24% of the patients, hypertension occurs terminally.

If therapy with steroids and cytostatics is commenced in the early disease stage, the course of the illness is reported to be considerably protracted [984].

## LM Findings

Strikingly severe destructive GN (Fig. 17.44) with very pronounced *periglomerulitis* is present (Fig. 17.43) which is best demonstrated with PASM stain (Figs. 17.45, 17.46). The focal character of the lesion is immediately apparent in autopsy material, but may be difficult to recognize in biopsies even though relatively numerous glomeruli are present. The various inflammatory stages of the process in the different glomeruli are always clearly evident and emphasize the attack-like course of the disease (Figs. 17.43, 17.44, 17.47).

In freshly afflicted glomeruli, capillary loop necroses and thrombi (Fig. 17.46) are frequently seen [781]. Peculiar holes of up to 0.2 μm in size in tangential BM sections may represent residues of dissolved immunodeposits [714]; see also [1628a]). Fibrinoid glomerular and vascular deposits are present in about one third of the cases [714]. Furthermore, pronounced mesangiolysis which may lead to the finding of ballooned loops has been described [1498]. In addition, intense capsular epithelial proliferation occurs with formation of segmental or global crescents. In the early stages, the latter contain numerous polymorphonuclear and scattered eosinophilic leukocytes (Fig. 17.47), is rich in fibrin, as in Goodpasture's syndrome, and finally contains completely destroyed glomerular loops (Figs. 17.46, 17.47). Destruction of Bowman's capsule by cells of the periglomerular granuloma and development of severe periglomerulitis (5 out of 6: Z), which spreads considerably into the surroundings, are typical for the lesion (contra: [65]) even though not pathognomonic (Fig. 17.43; [1791]). This capsular proliferation with inclusion of loop residues and pronounced destruction of capsular BM (Fig. 17.43) are the characteristics we encountered in 5 out of 6 of our cases. Collapse glomeruli are also observed when the vessels are severely afflicted.

In the interstitium, there is always a very severe, predominantly plasmocytic inflammation (Fig. 17.48) with a variable number of eosinophilic leukocytes. Wegener's granulomas themselves are rarely observed in the kidney (1 out of 6 autopsies; 0 out of 6 biopsies: Z).

Page 344

**Fig. 17.43.** GN in Wegener's syndrome. Two glomeruli (*G*) have been completely destroyed and replaced by granulation tissue which extends far into the surroundings. There is a massive perifocal lympho plasmocytic infiltration. Males, 62 years. HE (× 150)

**Fig. 17.44.** Wegener's syndrome: severe destruction of a glomerulus (→) and arteriolitis with extensive fibrinoid necroses (⇨). Female, 63 years. HE (× 250)

**Fig. 17.45.** Severe mantle-like periglomerulitis (→←) in Wegener's GN. The glomeruli (*G*) themselves are partly destroyed. Female, 45 years. PASM (× 85)

**Fig. 17.46.** Wegener's glomerulitis and periglomerulitis. Glomerulus depicted is only identifiable on the basis of the BM fragments (→) which are surrounded by extensive periglomerulitis. Female, 64 years. PASM (× 190)

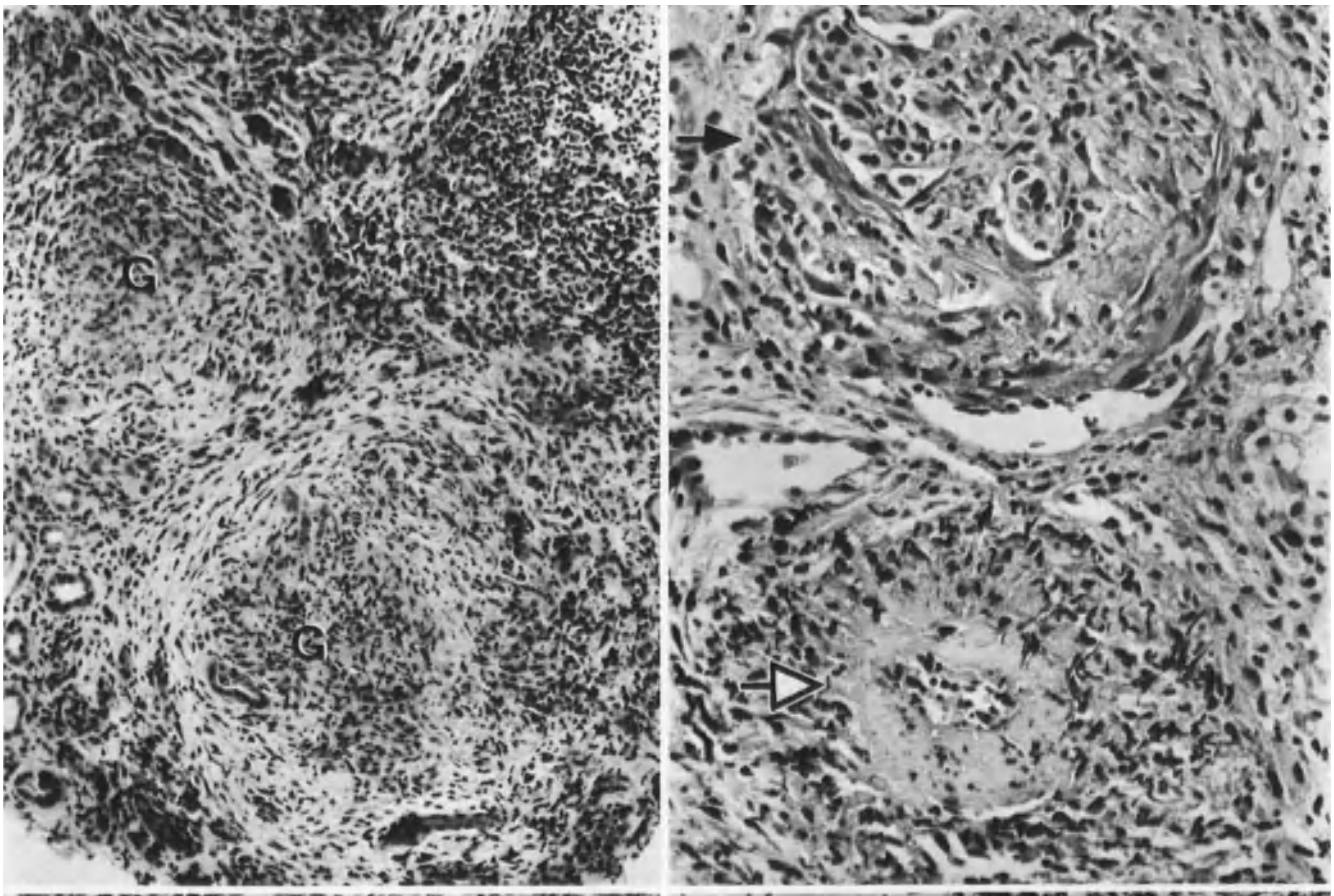
Page 345

**Fig. 17.47.** Same case as in Figure 17.43 showing pronounced segmentally accentuated GN with segmental crescent (*CR*). Striking extension of the inflammation to the interstitium is again present. Male, 62 years. HE (× 390)

**Fig. 17.48.** Same case as in Figure 17.43. Severe accompanying interstitial nephritis in Wegener's syndrome. Male, 62 years. HE (× 95)

**Fig. 17.49.** Severe fibrinoid necrotizing arteritis in Wegener's syndrome, a finding corresponding to that encountered in hypersensitivity angitis. Male, 35 years. PAS (× 70)

**Fig. 17.50.** Same case as in Figure 17.43. Scarified arteritis is seen with pronouncedly sector-like vessel involvement. Glomerulus depicted is unchanged. HE (× 110)

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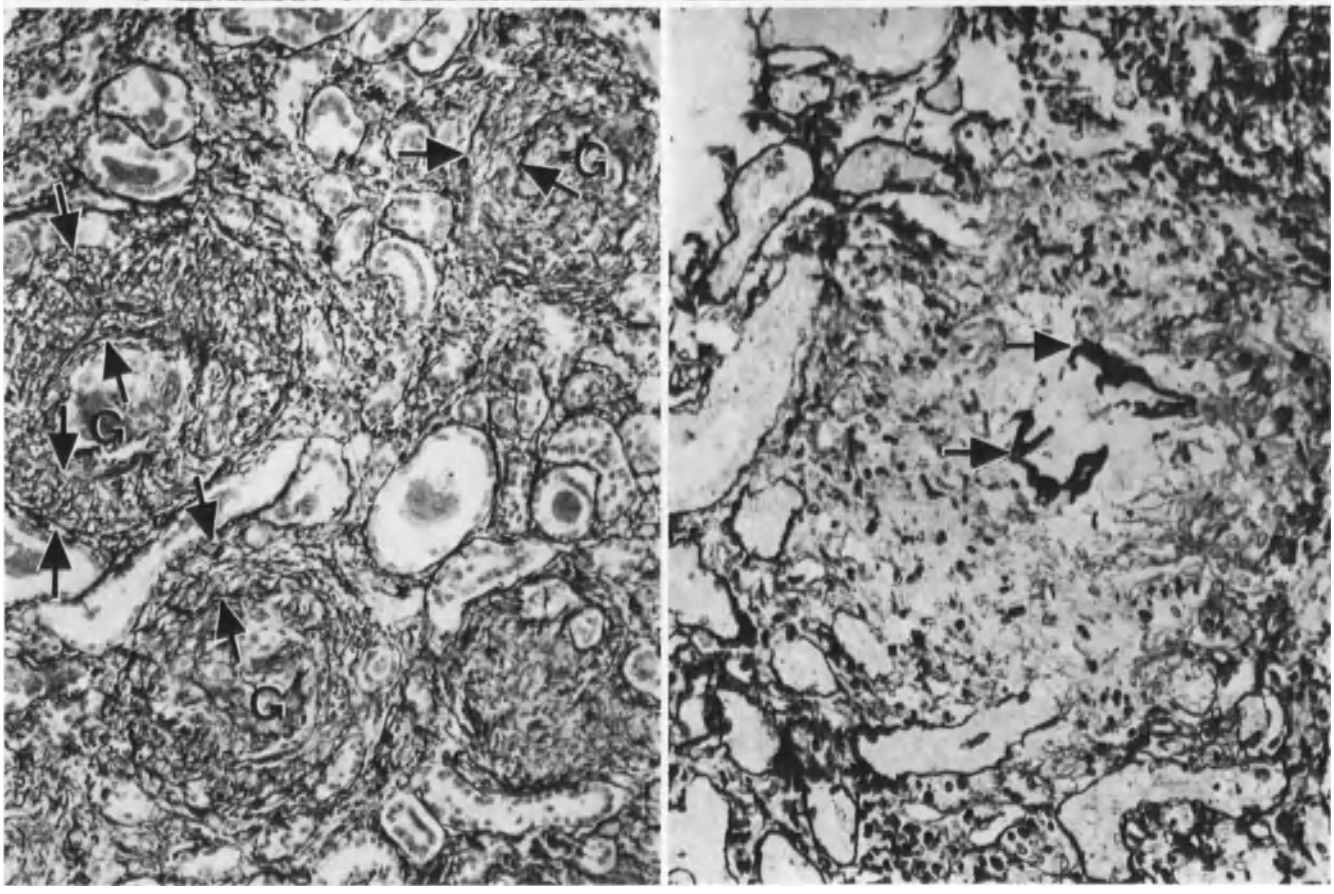


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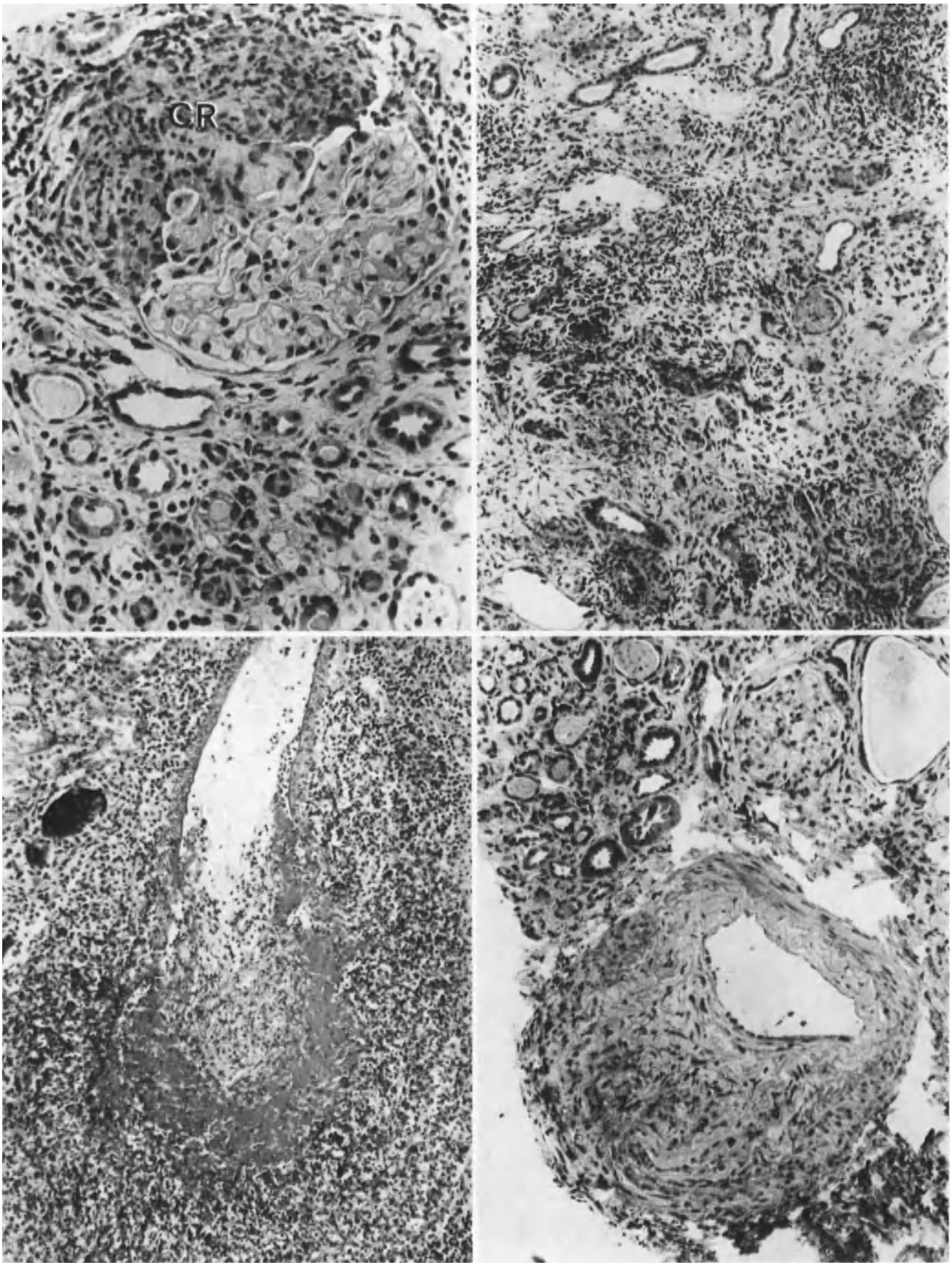



17.47
17.48
17.49
17.50

A severe destructive-proliferative arteriolitis was present in 6 out of 6 of our own autopsies and 4 out of 6 biopsies (Figs. 17.49, 17.50). The vascular changes cannot be differentiated from hypersensitivity angitis [685, 789].

### IF Findings

Currently, the available data are scanty. In one report, IgA, IgM, IgG, and C3 were observed in focal-segmental distribution in glomeruli and in arterioles [743]. In two of our own cases, we observed IgG and IgM in focal-segmental distribution in the mesangium and along the peripheral glomerular BM as well as C3 in the same intraglomerular but diffuse intrarenal distribution and in periglomerular granulomas (Fig. 17.51). In a third case, only complement was present in focal-segmental mesangial distribution. Fibrin(-ogen) was negative in arterioles. In one case only, C3 was found in a small artery.

### EM Findings

Severe obsolescence of glomerular capillary loops was the predominant feature in three of our own EM cases. In one instance, numerous leukocytes were demonstrable in the capillary lumen. Hypertrophy of the endothelium was always present. Except for slight fusion of foot processes, no significant epithelial cell lesions were noted (Fig. 17.52). The BM of a few isolated loops was focally thickened and, in 2 out of 3 cases, deposits were located subendothelially (Fig. 17.53) and 1 out of 3 also subepithelially (Fig. 17.52). In 1 out of 3 cases, we noted humps (2 out of 7: [714]). With the exception of slight, focal increase of the mesangial matrix, there were no further constant BM or mesangial changes. In all our cases, we found severe focal segmental crescent formation.
Massive fibrin deposits were not only present in the glomeruli (Fig. 17.53) but also in the capsular space in the walls of the intertubular blood vessels and, very massively, in the interstitium (Fig. 17.54).
The interstitial infiltrates were predominantly composed of plasma cells (Fig. 17.55). Finally, necroses of myocytes, a severe histiocytic and a slight polymorphonuclear leukocytic infiltration as well as fibrin deposition are reported in afflicted vessels [781].

### Differential Diagnosis

Differentiation from Goodpasture's FGN, except in IF, may be difficult, but according to our observations, Goodpasture's FGN is not as destructive and does not exhibit massive periglomerulitis.

All the other forms of GN can be excluded on the basis of the same criteria. We consider genuine granulomatous periglomerulitis to be specific for Wegener's FGN (contra: [65]). Allergic granulomatous arteritis does not cause such severe destructive glomerulitis (contra: [1068]) and the lung granulomas observed thereby are much smaller (see p. 538).

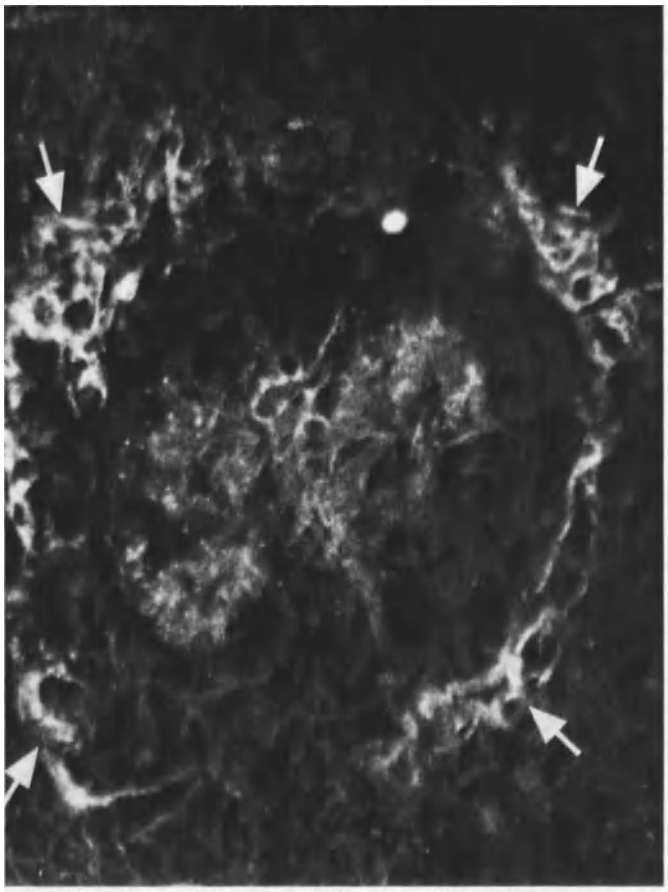
### Prognosis

Formerly, prognosis was extremely poor. Good results have been reported recently with cytostatic therapy which is supposed to cause the glomerular changes to undergo sclerosis [714, 984].
Among our patients (Table 14.3) at the time of biopsy, 5 out of 6 were already on hemodialysis, four of whom later either died or became permanently dialysed.
In one patient following hemodialysis of 1 month, administration of azathioprine and prednisone led to striking improvement of creatinine clearance, which, after 1 year's observation, has been now stabilized at 27 ml/min. In yet another patient, clearance improved with these two drugs from 62 to 108 ml/min. In both cases, extrarenal affliction in bronchial and nasal mucosa has been demonstrated.
Transplants in patients with complete remission after bilateral nephrectomy showed no relapses 10–28 months after transplantation [466].

**Fig. 17.51.** Same case as in Figure 17.43. Wegener's glomerulitis. ▷ Fine-granular IgM deposits, which are scanty in the glomerulus, are massively present in the periglomerular ganuloma (→). Male, 62 years. IF (×350)

**Fig. 17.52.** Same case as in Figure 17.43 of Wegener's glomerulitis. Three humps (*H*) are recognizable, one of which has been tangentially sectioned and therefore does not appear to be continuous with the BM. Male, 62 years. EM (×6030)

**Fig. 17.53.** Same case as in Figure 17.46. Peripheral glomerular capillary loop in Wegener's syndrome demonstrating subendothelial deposits (*D*) and massive intraluminal fibrin deposits (*D 1*). Fibrin deposits (*) are present in the periglomerular interstitium which is considerably broadened by connective tissue. Female, 64 years. EM (×4580)



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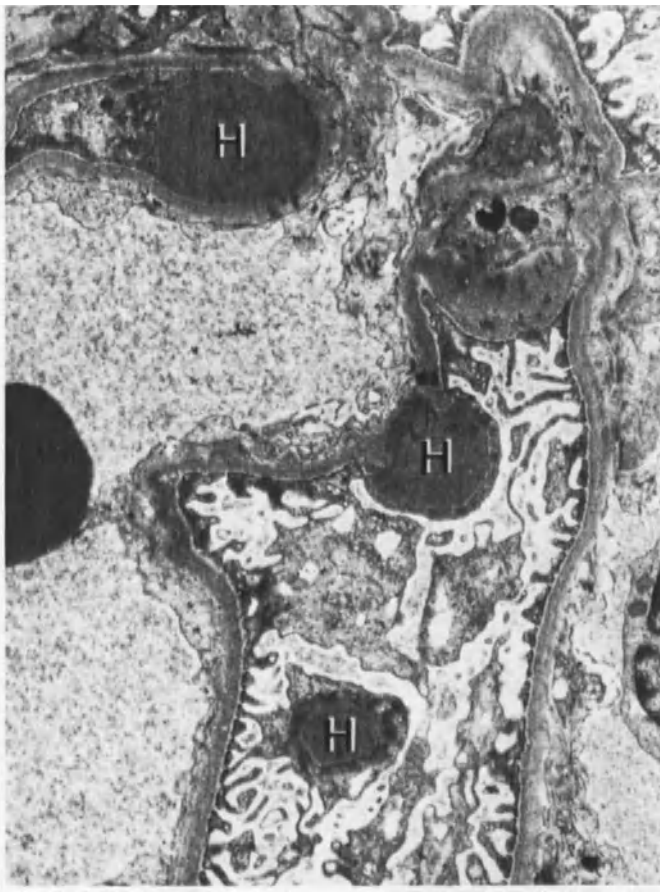


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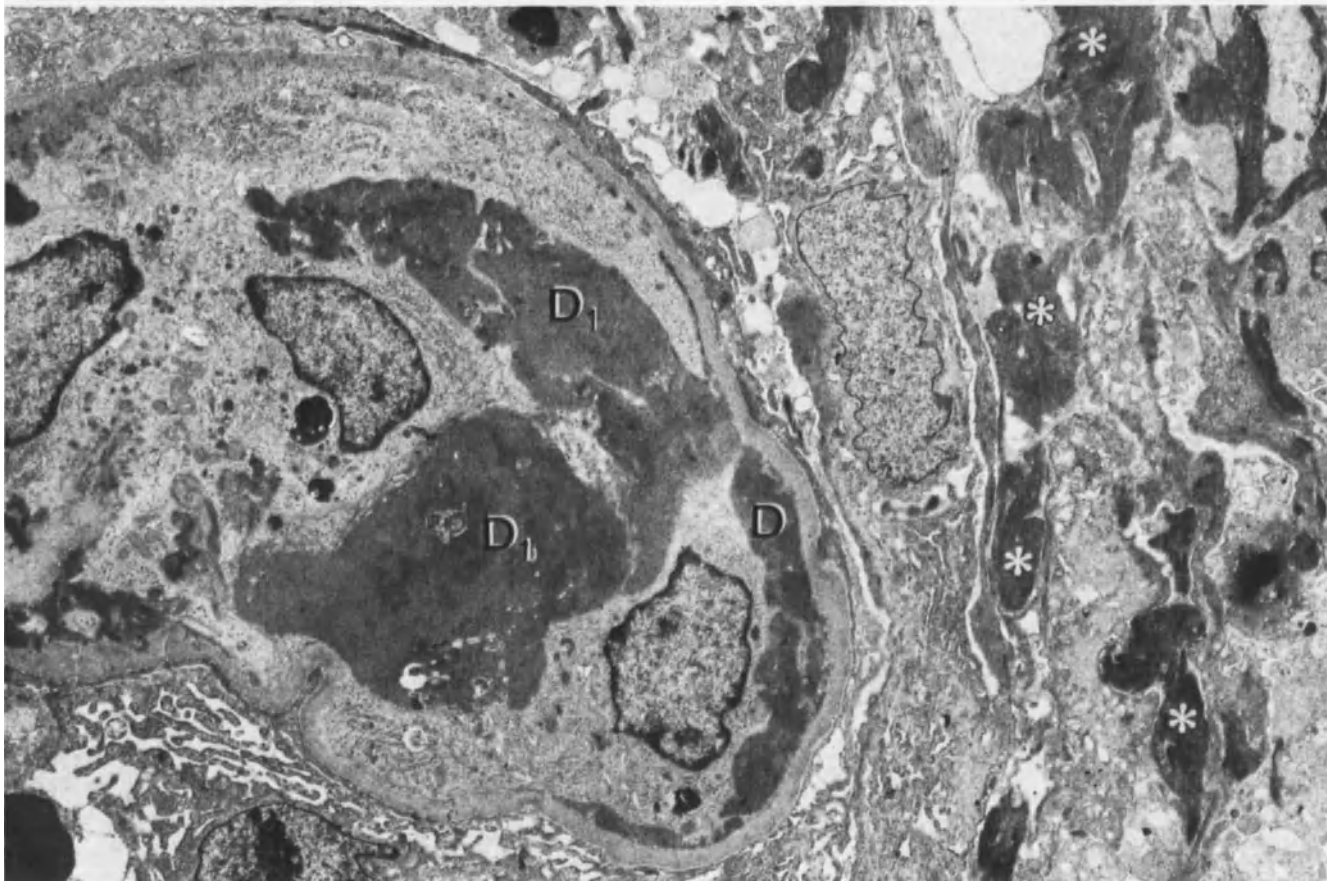


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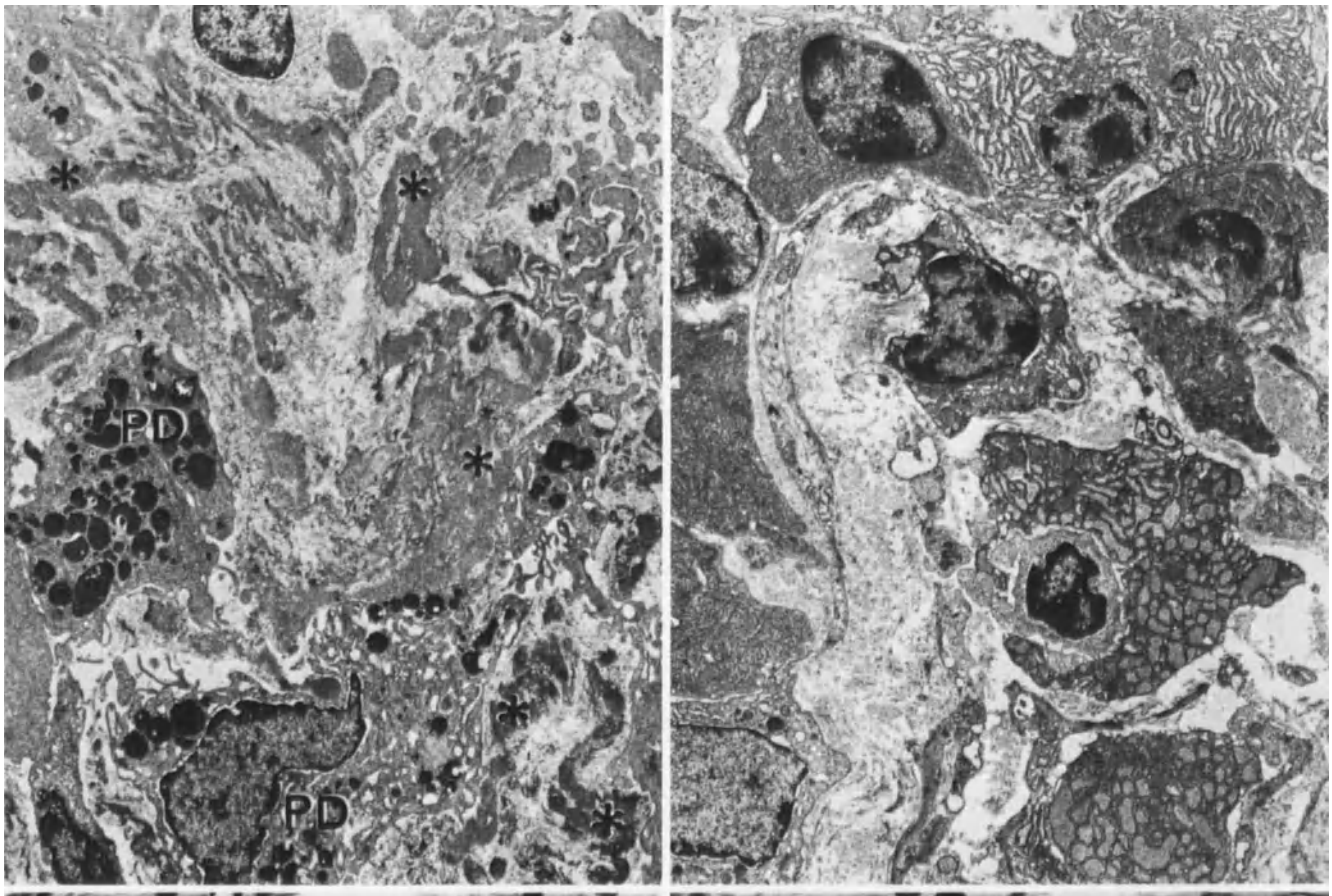


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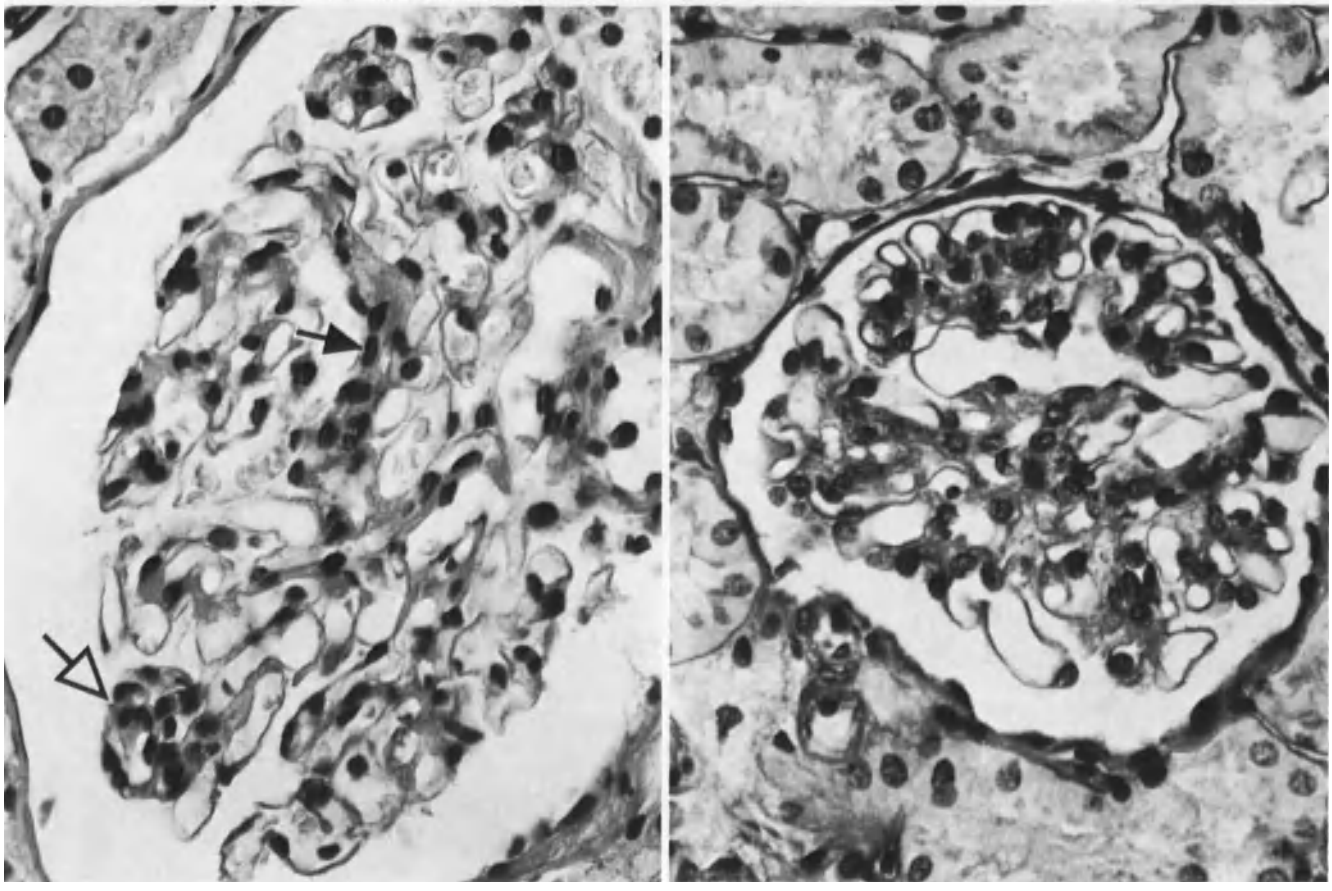


17.56
17.57

**Pathogenesis and Etiology**

Pathogenesis and etiology are unknown. Pathogenetically, it may be assumed that an immunocomplex mechanism is involved ([1500]; contra: [389a]). On the other hand, a cell-mediated immune deficiency is suggested due to delayed hypersensitivity skin reaction and reduced lymphocyte transformation by different antigens [1500]. Simultaneous formation of AB (against smooth muscle demonstrated in 4 out of 10: [1500]; in 3 out of 6 rheumatic factor, and in 1 out of 1 antimitochondrial AB: Z) possibly represents a reaction secondary to tissue breakdown. Finally, a combination of a humoral (vascular fibrinoid necroses) with a cellular immune reaction (epitheloid granulomas and giant cells) has been assumed [698].

Unambiguous demonstration of a causative agent has not been possible in either autopsy or biopsy material [256]. Wegener's syndrome is closely related to allergic, granulomatous arteritis and hypersensitivity angitis (see also [284]).

## Glomerulonephritis in Hypersensitivity Angitis (Microform of Periarteritis Nodosa)

GN occurs in about one-third of the cases of hypersensitivity angitis [130, 199, 794a, 1151, 1791]. It is characterized by extensive microthrombi and severe fibrinoid loop necrosis and is usually of diffuse extracapillary accentuated or proliferative FGN type ([130, 624, 794a]; see p. 536 for detailed discussion).

◁ **Fig. 17.54.** Same case as in Figure 17.46. Interstitial change in Wegener's GN with pronounced fibrin deposits (*) and macrophages with protein droplets (*PD*). Female, 64 years. EM (×3680)

**Fig. 17.55.** Same case as in Figure 17.46. Exclusively plasmocytic infiltrates in the interstitium in Wegener's GN. Rough endoplasmatic reticulum of plasma cell is cystoidally widened. Female, 64 years. EM (×3360)

**Fig. 17.56.** IgA nephritis after clinically acute GN 18 years prior to biopsy. Proliferative FGN restricted to a single glomerular capillary loop (↠). Glomerular minimal change is present in the mesangium (→). In IF, only mesangial IgA deposits were observed. Male, 36 years. PAS (×500)

**Fig. 17.57.** IgA nephritis: proliferative-sclerosing stage of endotheliomesangial GN with axial mesangial involvement. IF revealed typical mesangial deposits chiefly of IgA. Male, 12 years. PAS (×400)

## IgA Mesangial Glomerulonephritis
[1826, 1827]

### Definition

IgA nephritis is characterized by the constant presence of predominantly mesangial IgA deposits. With LM/EM, it is seen to be associated with different forms of GN as well as glomerular minimal change [123, 743].

***Synonym:*** Mesangiopathic GN [544], IgA-nephritis, IgA-IgG nephropathy [1821], IgA-nephropathy [1827].

### Incidence

It has been reported in 3.8% (Z); 4% [1513]; 4.3% [1043]; 5.6% [654]; 7.7% [1139] of all biopsies, and in 7.7% [654]; 10% [974]; 10.8% (Z); 19.3% [1139a]; 22% [393] of GN biopsies.
Summarizing the data from the literature, the male:female ratio in 268 cases is 3.5:1 [354, 393, 950, 1043, 1513, 1720, 1778a].
The age of onset of the disease is difficult to evaluate since the history of renal disease is quite often longer than 5 years (32%: [1720]) and may even last for decades [123, 1720]. This is best illustrated by one of our own patients with a 22-year history of 28 relapses of macrohematuria. The age of presentation with renal disease is usually that of the young adult (19 years: [1043]; 28 years: [1778a]; 20 years: [354]; 28 years: [1513]; 33 years: [393]) but it is also observed in children between 3–8 years of age [950].

### Clinical Findings
(Tables 14.3, 14.4, Fig. 17.58)

IgA nephritis is frequently discovered fortuitously when routine urine examination reveals microhematuria and/or proteinuria of slight degree [393, 1511b, 1720]. In other cases, the disease manifests itself in the form of macrohematuria which often lasts only for a few hours or days and then decreases to microhematuria or vanishes completely (Fig. 17.58).
In about 43% of the cases, respiratory infection [1052] precedes disease onset (Table 17.5). In other cases, extreme physical stress or immunization [1720] may immediately precede disease manifestation. Typically, hematuria is observed after only a few hours (at the most, 1–2 days) following infection or stress [544, 950, 1720]. In rare cases, the disease sets in as typical acute GN ([393]; 2 out of 15: Z).
After disease onset, the illness exhibits an attack-like course ([1720]; see also Fig. 17.58). Individual attacks are again also characterized by micro- or even macrohematuria. Single or multiple episodes of macrohematuria have been noted in 48% of patients (Fig. 17.58). Complete remission is frequently observed between the attacks (14 out of 36: [950]; 22 out of 96: [1720]).
At the time of bioptical diagnosis (Fig. 17.58), patients usually present the following findings: proteinuria and hematuria are present in more than 50% of the cases. Proteinuria is usually only slight. A nephrotic syndrome is present in less than 10% of the patients. One-fourth of the subjects evidence isolated hematuria. Isolated proteinuria as well as isolated nephrotic syndrome are highly unusual. Despite a disease course which may span years or even decades, hypertension (17.8%) and hyperazotemia (11%) are infrequent. Decrease of complement (C3) is rare (14.8%) and usually of low grade. Increase of antistreptolysin titer is also seldom.
The frequent—but not constant—increase of the serum IgA level is a striking feature of the lesion [354, 483, 974, 1720, 1778a] as is the pronounced incidence of familial cases (5 out of 25: [1513]; 9 out of 96: [1720]; 2 out of 18: [1778a]; 1 out of 15: Z).

### LM Findings

LM findings in IgA nephritis are not essentially different from those observed in idiopathic GN forms. Table 17.6 presents their relative frequency. The only striking feature in IgA nephritis is the often-noted discrepancy between the staining results with PASM and PAS stain. In PAS stain, there appears to be an obvious increase of mesangial matrix which cannot be demonstrated with the PASM stain [1052]. This is explained by the fact that the PAS stain also colors the LM-demonstrable deposits (Masson's trichrome/AFOG stain). It is noted, however, that the deposits cannot be demonstrated with LM in all cases (41 out of 96: [1720]). Normal glomeruli under LM are rarely observed. Those with glomerular minimal change (16.4%) are more frequently encountered (Fig. 17.56). In endotheliomesangial GN, axial enlargement of the mesangium is usually present (Fig. 17.57).

Table 17.5. Relative frequency of different forms of glomerulonephritis in 200 cases of IgA-mesangial GN from the literature [393, 950, 1139] including our own cases

| | |
|---|---|
| Normal glomeruli | 1% |
| Glomerular minimal change | 16.4% |
| Endotheliomesangial GN | 26.9% |
| Proliferative FGN | 54.2% |
| Unclassified | 1.5% |

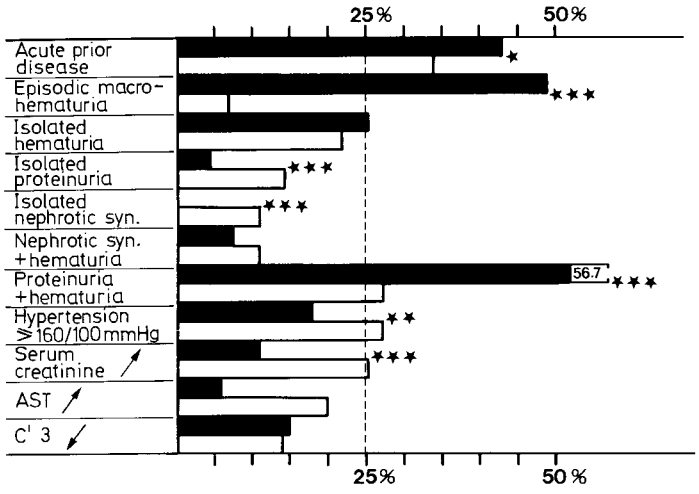



**Fig. 17.58.** Profile of symptoms and clinical findings in IgA-mesangial GN
*White columns:* Relative frequency of symptom/finding in all GN
*Black columns:* Relative frequency in IgA-mesangial GN (data collected from the literature; see Table 14.3)
Asterisks indicate characteristic findings for IgA mesangial GN:
*: characteristic
**: very characteristic
***: highly characteristic

Mesangial IgA nephritis manifests itself in more than half the cases in LM as a proliferative FGN (Table 17.5, Figs. 17.56, 17.58, 17.59). But the relative frequency of this form varies considerably in individual series: 17 out of 36 [950], 11 out of 20 [1043], 85 out of 89 [1139] and in one it is not a characteristic finding: 3 out of 52 [393] (see also [123, 128, 654]). We found proliferative FGN in 4 out of 15 cases.
The number of obsolescent glomeruli is reported as increased (7 out of 15: [974]) which we cannot confirm (0 out of 15: Z). Crescents are rare (8 out of 96: [1720]; 3 out of 15: [974]; 3 out of 15 (in less than 10% of the glomeruli): Z). Glomerular capillary loop necroses with fibrin deposition have been described exceptionally [128].

Table 17.6. IF findings in IgA nephritis ($n=12$; positive = 12)

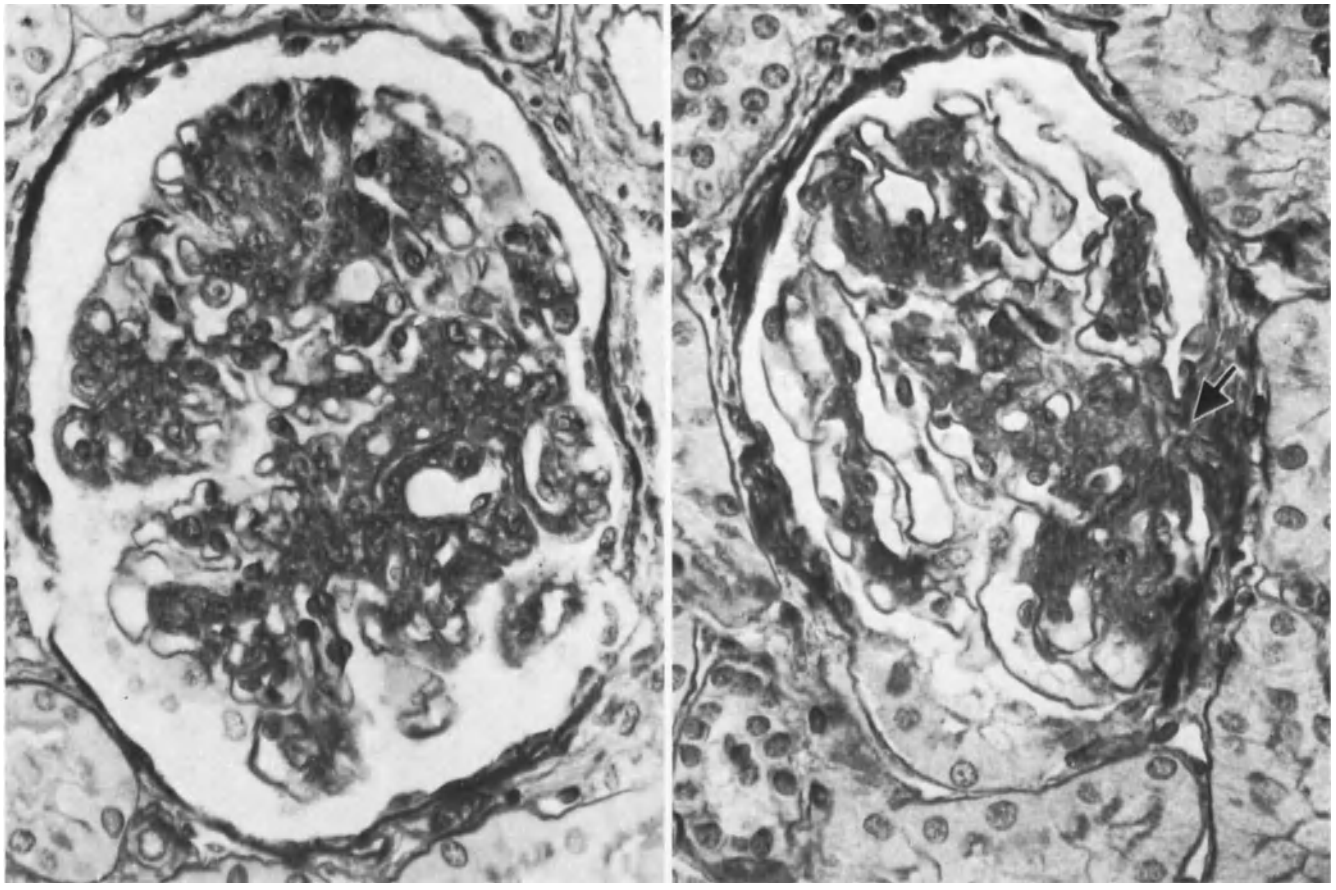
| | IgG | IgM | IgA | C3 | Fibrin(-ogen) |
|---|---|---|---|---|---|
| Cases tested | 12 | 12 | 12 | 12 | 12 |
| Positive | 10 | 8 | 12 | 12 | 1 |
| Focal | 3 | 4 | 0 | 1 | 0 |
| Diffuse | 7 | 4 | 12 | 11 | 1 |
| Segmental | 3 | 4 | 0 | 2 | 1 |
| Global | 7 | 4 | 12 | 10 | 0 |
| Peripheral | — | | | | |
| Mesangial and peripheral | 5 | 7 | 6 | 6 | 1 |
| Mesangial | 5 | 1 | 6 | 6 | — |

### IF Findings

The predominant feature is massive IgA deposition. IgA is mainly located in the mesangium but may occasionally extend to the peripheral BM (Fig. 17.61; [1052, 950, 1139]) as we encountered in half of our cases (see Table 17.6). The deposits also contain IgG and C3 [128, 393, 1002, 1052, 1139, 1513]. The absence of mesangial IgM deposits has been especially emphasized by some investigators [1052, 1139]; contra: [1513]). In our own material (Table 17.6), we encountered IgM in 8 out of 12 cases, half of which in focal-segmental distribution. Fibrin(-ogen) is rarely present (see also [1139]).
The early complement components (C1q and C4) were not, as yet, demonstrable in our material as in the series of others [1043, 1513], a finding which suggests possible C3 activation via the alternative pathway supported by the almost constant presence of properdin [1043]. In further series, C3 and C4 were found almost constantly, while Clq was always absent [452a].
In our cases, IgA was not found in renal vessels, but recent reports indicate that, as in Schönlein-Henoch's purpura, massive IgA deposits are present in skin vessels [452a].

### EM Findings

Segmental obliteration of glomerular loops was observed in 3 out of 14 of our cases. Furthermore, there was only slight endothelial and podocytic hypertroOhy or edema with formation of microvilli and arcades (Fig. 17.62). A usually insignificant foot process fusion was present in all cases as was an increase of osmiophilic substance in podocytes in 4 out of 14 (see also [950]).
Very dense osmiophilic deposits were present along the mesangial BM and in the mesangial matrix in 10 out of 14 of our cases (Figs. 17.62, 17.68) and in 4 out of 14 cases, they were present exclusively along the mesangial BM. Furthermore, osmiophilic deposits—occasionally undergoing dissolution—were found in the peripheral glomerular BM in 7 out of 14 cases (see also [393]; Fig. 17.64).



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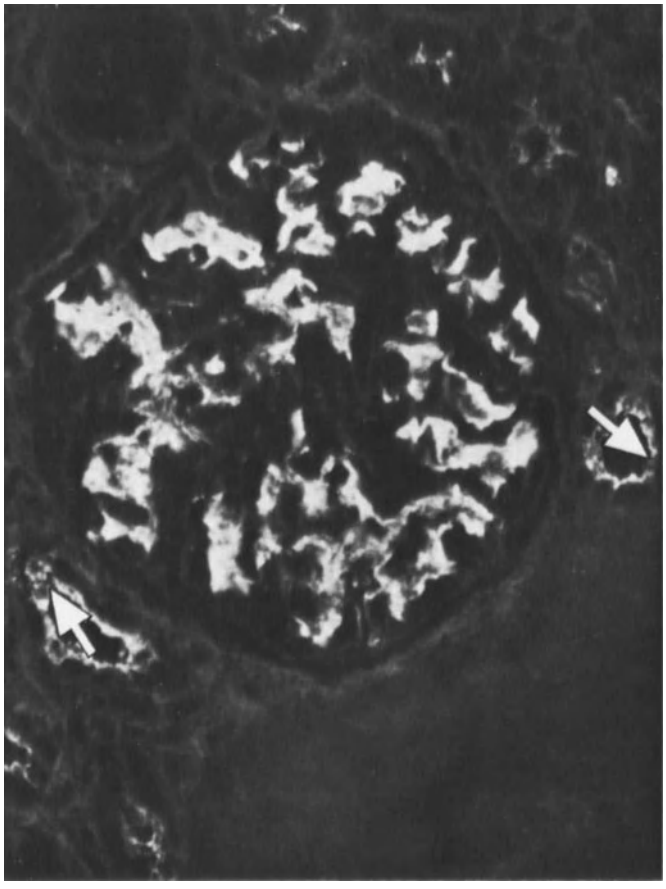


17.61

**Fig. 17.59.** Severe proliferative FGN (proliferative-sclerosing stage). In IF, masses of IgA deposits were found in the mesangium. Note isolated thickened glomerular capillary loops. Female, 14 years. PAS (×500)

**Fig. 17.60.** Same case as in Figure 17.59. Segmental accentuation of glomerular involvement is now obvious. Note also the synechia (→). Female, 14 years. PAS (×500)

**Fig. 17.61.** Same case as in Figure 17.59 showing massive IgA deposits in the mesangium here and there slightly extending to the peripheral BM and on the epithelial surface of several tubular cells (→). Female, 14 years. IF (×350)

In 5 out of 14 cases we noted a few isolated subendothelial deposits (10 out of 19: [950]; see also [354, 393]). Subepithelial deposits and humps were seen each in 1 out of 14 (see also [950]). We observed intramembranous deposits in 4 out of 14. In a further biopsy, osmiophilic deposits could be demonstrated exclusively in the periphery with EM, but not in the region of the mesangium in the presence of otherwise typical IF findings.
The BM was focally thickened in 9 out of 14 of our cases; this was predominantly caused by thickening of the lamina rara interna (Fig. 17.64). In three patients there occurred a slight splitting of the lamina densa and thickening of the lamina rara externa with formation of new BM which, in one case, was associated with the occurrence of a virus-like particles. Segmental mesangial interposition was noted in 3 out of 14 cases.
With the exception of the previously mentioned deposits, the findings in the region of the mesangium were restricted to a generally slight cell increase and hypertrophy in 12 out of 14 cases (8 out of 19: [950]) as well as to moderately severe to severe matrix increase.

### Differential Diagnosis

The diagnosis of IgA nephritis is based on IF findings showing dominant IgA affliction of the mesangium. They are not conclusive proof of the disease, since identical IF patterns are also observed in Schönlein-Henoch's syndrome and SLE (see also [354]) or liver cirrhosis [241]. LM and EM diagnosis of the disease can at best be suspected by the demonstration of extensive fibrinoid Masson's trichrome/AFOG positive and osmiophilic mesangial deposits but not on the basis of the presence of segmental-focal GN alone since typical IgA nephritis may appear in different forms of GN as well as in glomerular minimal change in LM (see also [393, 950]; Table 17.5). Recent findings of IgA deposits in skin vessels [452a] in IgA nephritis may be helpful retrospectively in all cases with predominant mesangial deposits in LM or EM when no IF investigation was done, but further substantiating evidence is needed.

### Prognosis

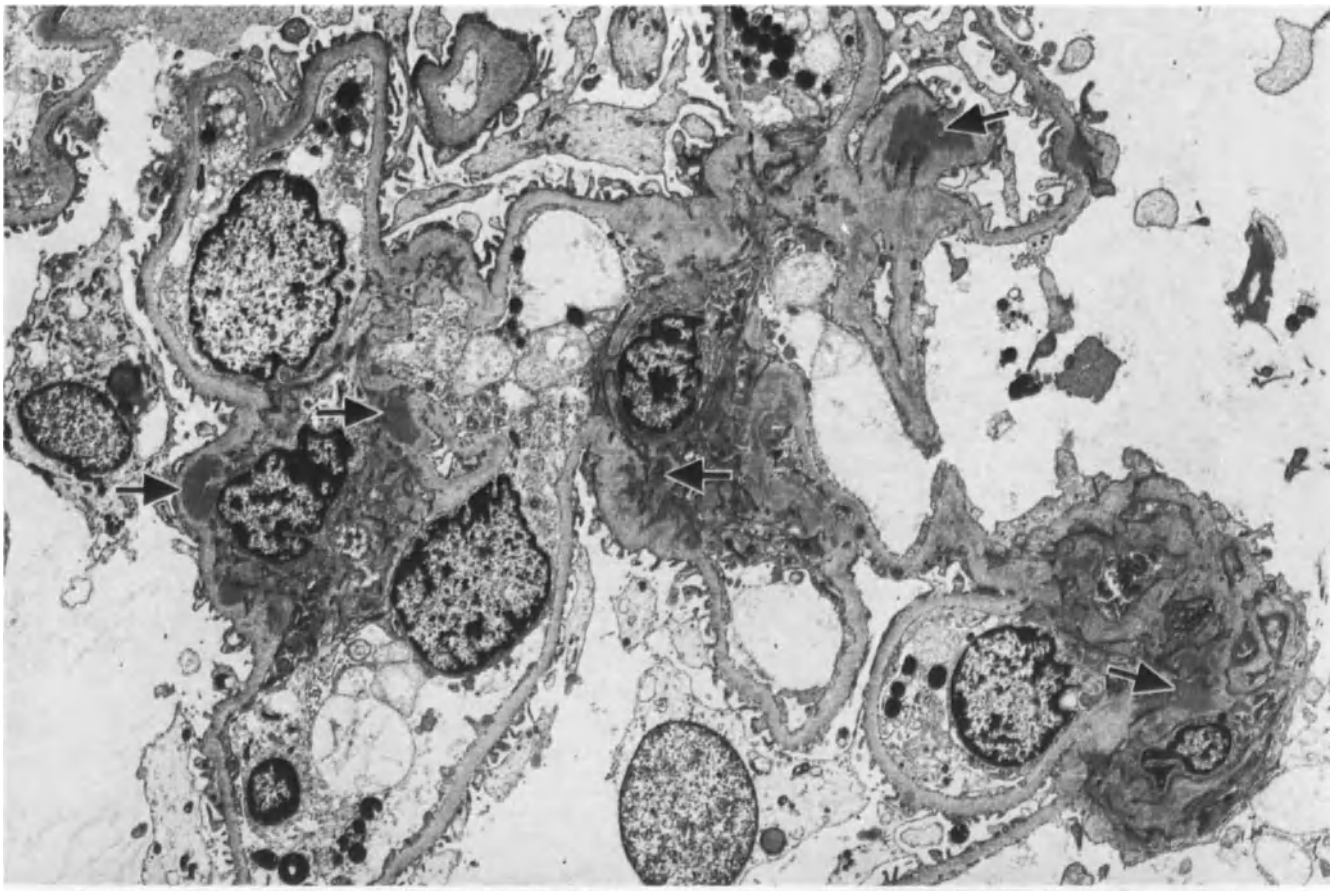
The disease appears to run a very protracted course and the duration of illness before biopsy may be one of years or even decades [123]. Complete remission for many years also appears to be typical [393, 950, 974, 1052, 1720]. Furthermore, serial biopsies have shown no essential progression of the lesion [128, 1052]. Terminal renal insufficiency is extremely rare and only reported in isolated instances [129, 1513, 651].
Patients with glomerular minimal change were reported to have complete disease remission in 8 out of 12 cases between the attacks of macrohematuria, those with proliferative FGN in only 5 out of 17 cases, while in those with other GN forms, intermittent or constant microhematuria and/or proteinuria were present [950]. In our own material, 6 out of 7 patients with permanent proteinuria of $>1$ g/day revealed findings of diffuse endotheliomesangial GN as was shown by 5 out of 6 patients with a decrease of creatinine clearance ($<90$ ml/min) and by the only hypertensive patient. Our IgA-nephritis patients with glomerular minimal change or FGN respectively showed only hematuria and, at the most, minimal proteinuria.
Recurrence was observed in four cases after transplantation [651].

### Etiology and Pathogenesis

Etiology and pathogenesis of IgA nephritis are unknown. Three possibilities must be considered to explain the deposition of IgA in the mesangium:

1. The deposits represent filtered, aggregated IgA
2. The IgA represents the antigen of an immunocomplex
3. The IgA is the antibody of an immunocomplex.

The first possibility—excessive filtration of aggregated IgA—has been proposed [974]. In favor of this assumption is the fact that it has been shown experimentally that aggregated globulin can be deposited in the mesangium [1026, 1027]. In the case of IgA nephritis, it must be assumed that IgA is either altered physicochemically as to aggregate, or that aggregation occurs spontaneously as a result of the increased serum IgA levels which have been observed in numerous patients [483, 974, 1720, 1778a]. Further support is lent by the fact that IgA may be the only immunoglobulin present in the glomerulus [974, 1043, 1720, 1778a]. The often simultaneous presence of C3 may be interpreted as C3-binding by aggregated IgA [582]. Nevertheless, we feel that the concomitant occurrence of IgA in skin vessels [452a] and the frequent prescence of other immunoglobulins in the mesangium, like IgG and IgM, are insufficiently explained by this hypothesis.
The second possibility, i.e., that the mesangial IgA is the antigen, is hardly probable, at least for secretory IgA. Thus, various investigators have shown that only minute amounts of secretory IgA—or none at all—are present in the mesangium [974, 1043, 1720].
The most likely hypothesis, accordingly, is that IgA is the antibody component of an immunocomplex. In this case, either the mesangial matrix acts as the antigen or one unknown, e.g., virus, bacterium or toxin. The possibility that the mesangial matrix may be acting as antigen is indicated by the as yet unconfirmed finding that eluted IgA binds specifically to the mesangium of control kidneys [974].



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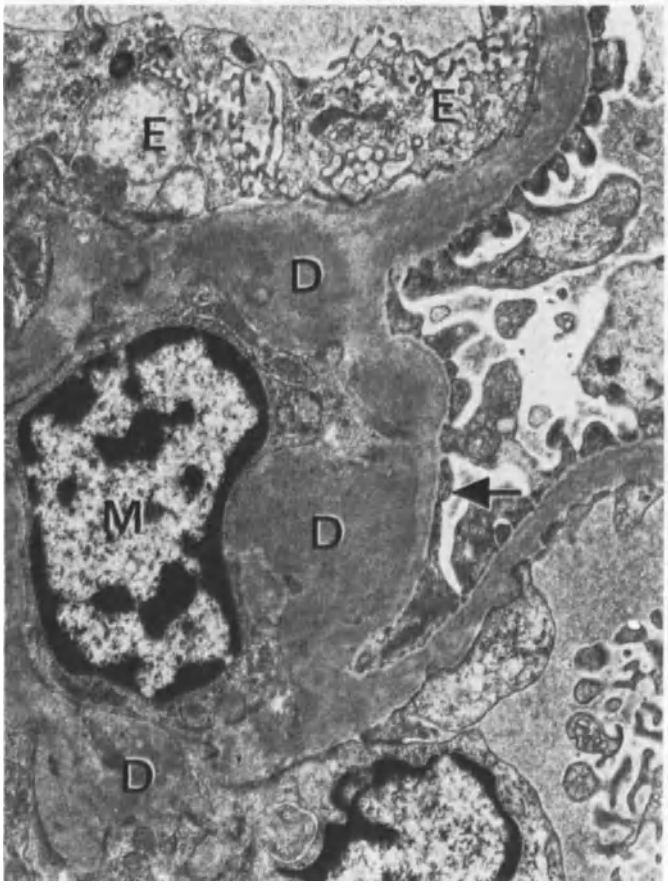
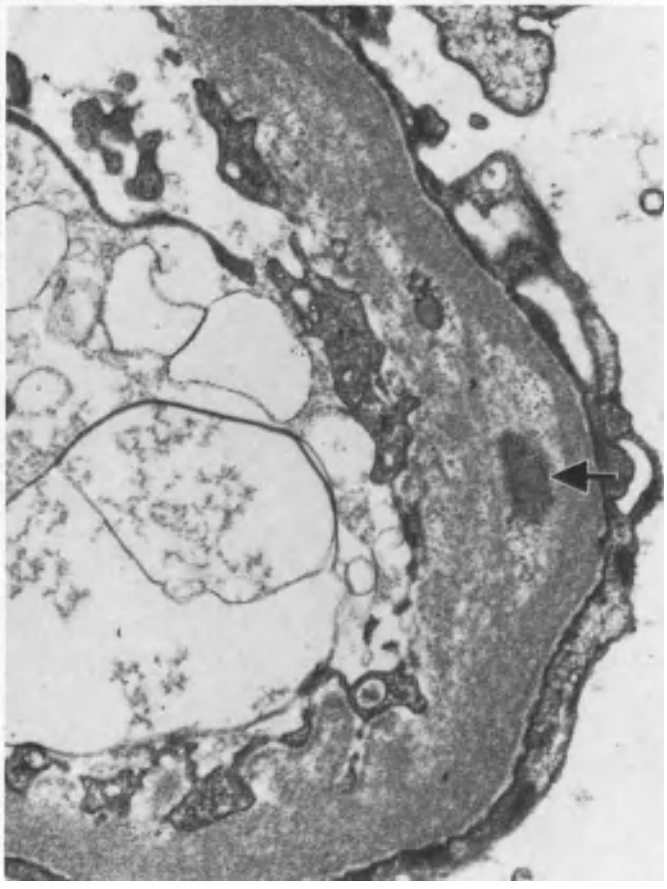


17.63
17.64

The common occurrence of IgA in the mesangium in such different lesions as Schönlein-Henoch's purpura [1720, 1778a], "hepatic glomerulosclerosis" [241], familial thrombopenia [1778a] and in IgA-nephritis, in all of which serum IgA may be increased, may indicate a shared pathogenetic pathway and etiology. Etiology and pathogenesis await further clarification as well as the increased incidence of familial cases of IgA-nephritis, [1513, 1720, 1778a]. The increased incidence of familial IgA-nephritis could be an indication of genetic disturbance. It is interesting to note in this context that patients with congenital C2 deficiency are more prone to suffer from Schönlein-Henoch's purpura [1589a].

One investigator group [483] proposed that all GN with IgA, independent of type and localization of deposits, should be classified as IgA nephritis. On clinical and prognostic reasons, we do not recommend such an extension of the definition of IgA nephritis at the present time.

◁ **Fig. 17.62.** IgA-nephritis. There is moderately severe enlargement of the mesangium with numerous mesangial osmiophilic deposits (→). Activation of the endothelium—which contains isolated protein droplets—is also present as is swelling of podocytes. There is no significant foot process fusion. Male, 22 years. EM (×3770)

**Fig. 17.63.** Same case as in Figure 17.59 showing the mesangial deposits (*D*). There is intense activation of endothelial cells with arcade formation (*E*). Foot process fusion is scarcely recognizable (→). Mesangial nuclei (*M*) are activated. Female, 14 years. EM (×9100)

**Fig. 17.64.** IgA nephritis. Peripheral BM damage with isolated intramembranous deposits (→) and loosening of the lamina rara interna. There are numerous intraluminal endothelial balloons. Slight foot process fusion is present. Male, 20 years. EM (×14,370)

## Early Infantile Glomerulonephritic Contracted Kidney, Congenital (Infantile) Nephrotic Syndrome

### Early Infantile Glomerulonephritic Contracted Kidney (So-Called Oligonephronia) [1146, 1393]

#### Definition

Diffuse GN during the first year of life and its subsequent development into contracted kidney.

***Synonyms:*** Oligonephronia [628, 1393] and oligomeganephronia [428, 1146].

#### Incidence

The disease is very rare. Only 40 cases have been described in the world literature. Boys are considerably more often afflicted than girls (male: female, 16:5 [1393]).

#### Clinical Findings

Symptoms of renal disease are rarely present at birth (6 out of 21: [1393]). They usually develop between the first and twenty-fourth months of life (7 out of 21: [1393]) or between the second and twelfth years of life [1393]. The symptoms consist of slight proteinuria in the absence of hematuria, leukocyturia and hypertension.
Decrease of creatinine clearance is observed very early. In 15 out of 21 cases, chronic renal insufficiency developed which evidenced a stable course for a considerable period of time without concomitant hypertension [1393]. The terminal phase is characterized by progressive uremia. The disease is not familial. Acral growth retardation may occur [428]. Only isolated reports of associated malformations are present [1393, 593].

#### LM Findings

Glomerular findings differ from those in diffuse GN acquired in later life. Glomerular obsolescence in infancy is usually followed by dissolution of the obsolescent glomeruli. This process is far more pronounced in infants than in older children. At the end of the process, only 30–60 μm-sized, spider-like coils of PAS-positive membranes (spider scars) are found in place of the obsolescent glomeruli (Fig. 17.65). The spider scars are easily overlooked unless attention is specifically directed to their identification (Fig. 17.66). Thus, there is a strong temptation to assume a numerical glomerular deficiency and, accordingly, of the entire nephron, i.e., an oligonephronia [628].
In material kindly placed at our disposal by Mrs Habib (Paris), we found a large number of such glomerular residues ([1797]: Fig. 24 and Fig. 11; see also [636]).
The number of glomeruli per 1 $mm^2$ of tissue was increased and not decreased with respect to the norm, a finding reflecting parenchymal shrinkage (contra: 11 glomeruli instead of 56.7: [1393]).
In general, a pronounced mesangial-sclerosing from of GN appears to predominate in the still more or less intact glomeruli [1791]. Intact or only slightly afflicted glomeruli are enlarged up to 320 μm due to compensatory hypertrophy. Microdissection has shown the nephrons to be reduced in number but considerably enlarged in size [593]. This is not surprising since obsolescent glomeruli and atrophic tubules can no longer be isolated by microdissection.
A further prominent difference from the usual findings of GN contracted kidney is the presence of very severe cystoidal widening of the intact straight parts of the proximal tubules (Fig. 17.67) referred to as "microcystic dysplasia" [477, 1206]. We interpret this finding as a secondary reaction to the overload of the few nephrons which are still functioning [412, 1791, 1797]. We have observed the same changes in rabbits in whom pyelonephritic destruction was produced in the immediate postnatal period [8].
The interstitium is severely sclerosed and exhibits lympho-plasmocytic infiltrates. Destructive tubular and vascular changes which differ from those of ordinary GN are not present. — We are unaware of any IF findings.

#### EM Findings

According to published microphotographs [1146] collapse glomeruli appear to occur very frequently. The intact glomeruli show a significant mesangial thickening with cell increase and an irregularly formed BM without, however, either lamellation or osmiophilic deposits. In addition, fusion of foot processes with slight increase of osmiophilic material in podocytes was noted.

#### Differential Diagnosis

The form of renal inflammation under discussion is relatively easy to distinguish from early childhood pyelonephritis (see p. 437) — which is also designated as segmental renal hypoplasia [1393] — since it is not sector-like but diffuse, demonstrates no thyroid-like foci, and evidences no destruction of tubules but only their severe atrophy in addition to hyperplasia of intact nephrons. Hypertension, which is typical for early childhood pyelonephritis (see also [1393]), is lacking and interstitial

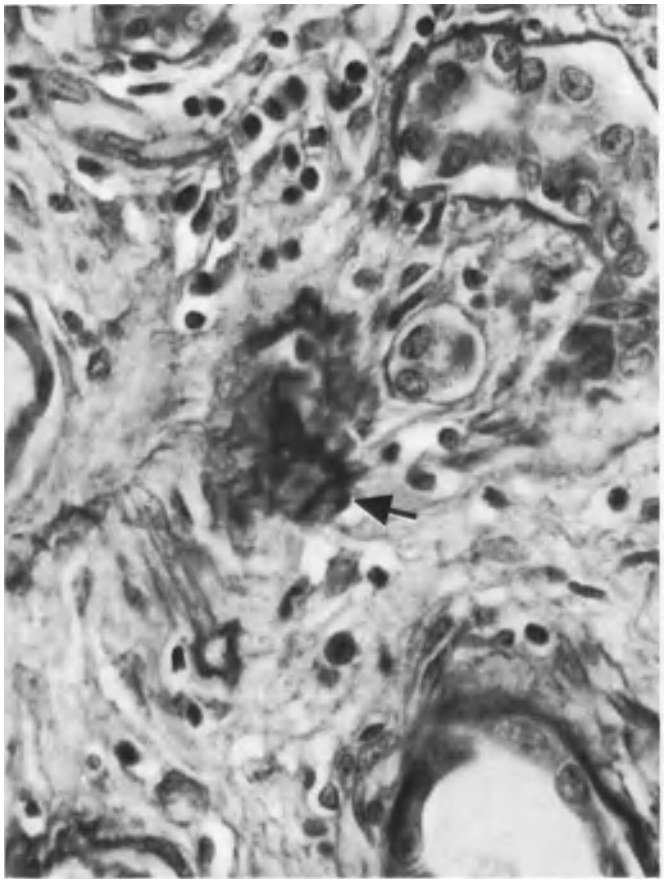


**Fig. 17.65.** Early infantile GN, so-called oligonephronia. PAS positive spider scar of a glomerulus = fetal and early infantile type of glomerular obsolescence (→). Surrounding stroma is infiltrated with loosely distributed lymphocytes. We thank Mrs. R. Habib, Paris, for this preparation. PAS (×310)

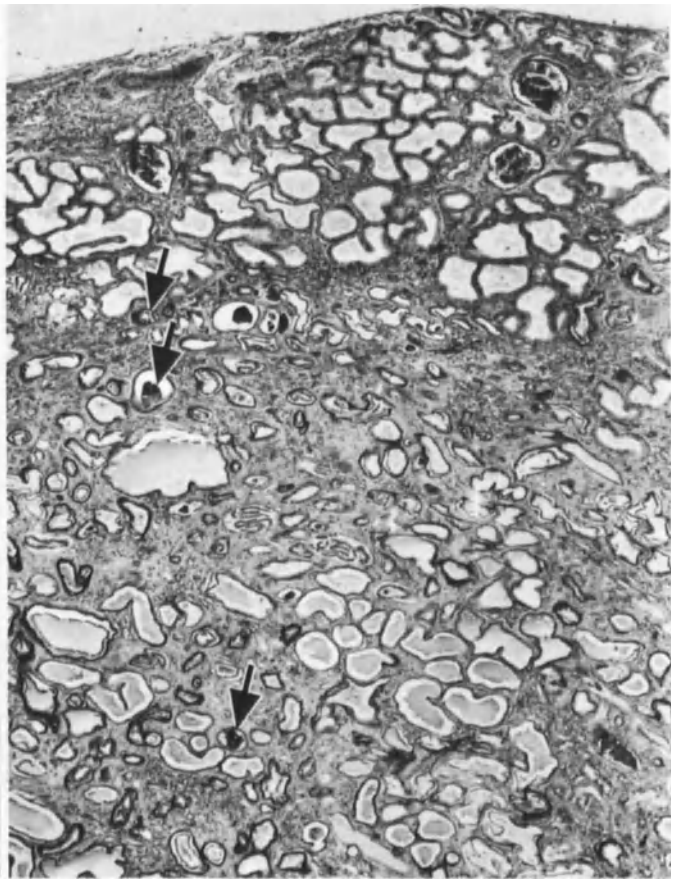


**Fig. 17.66.** Same case as in Figure 17.65. Severe atrophy as well as cystoid widening of the tubules, side by side, are striking. Careful inspection of the section is necessary for identification of the numerous very small obsolescent glomeruli (→). There are only slight inflammatory infiltrates in the interstitium. PAS (×28)

inflammation is far less extensive than in pyelonephritis.

Glomerular changes can be clearly differentiated from those in nephronophthisis in which only glomerular collapse is present. Spider scars and symptom-free interval between birth and disease onset are absent in nephronophthisis ([1433]; contra [1393]).

### Prognosis

Prognosis appears to be poor in the presence of contracted kidney. In one case series, 11 out of 21 patients succumbed [1393].

### Pathogenesis and Etiology

Pathogenesis and etiology are obscure.

A few investigators assume a malformation [477, 1206] or an oligonephronia [636, 1393] or an oligomeganephronia [1146] respectively.

Others propose progressive mesangial sclerosis [428] as also suggested previously [625]. We believe [1592, 1759, 1791, 1797] that the disease represents glomerular inflammation acquired early in life – possibly before birth – which causes subtotal destruction of glomeruli as we encounter in pyelonephritis of early childhood.

Three cases in the literature demonstrated agenesis of the contralateral kidney so that the observed glomerular changes in the kidney present were interpreted as overload glomerulitis [593].

## Congenital (Infantile) Nephrotic Syndrome

[539, 645, 646, 625, 1759, 1779]

### Definition

Nephrotic syndrome (NS) which is present at birth or which develops during the first year of life (up to 3 months of age: [412]).

## Nosology

Several morphologic types of congenital NS can be distinguished:

1. Finnish type, ("microcystic renal disease") [625, 645]
2. Infantile diffuse mesangial sclerosis [621, 625, 646]
3. Glomerular minimal change [625, 1728]
4. Segmental-focal sclerosing GN [625, 1430, 1734]
5. Epimembranous and possibly other forms of GN [625]
6. *Others:* syphilis, Hg-poisoning, cytomegalovirus infection, renal vein thrombosis, etc. [645].

The types 1–4 are often familial [625, 645, 646, 1126, 1430, 1728].

The Finnish type and that of infantile diffuse mesangial sclerosis merit separate discussion (all other forms do not essentially differ from those seen in older age groups: [1430]).

## Incidence

***The Finnish type*** has a far greater incidence in Finland (85 out of 137 cases: [219]) than elsewhere. It accounts for 30% of congenital nephrotics outside of Finland [625] and for 55% of congenital familial nephrotic syndrome [1728]. Boys are nearly as often afflicted as girls [645].

***The infantile diffuse mesangial sclerosis type*** is also very rare and has been reported in 16% of congenital nephrotic syndrome [625] and in 0.7% of glomerular nephropathies in children [625]. Boys are more often afflicted than girls.

In our material, cases of congenital nephrotic syndrome comprise 0.32% of all GN.

## Clinical Findings

***The Finnish type*** of congenital nephrotic syndrome [645, 646] is frequently familial and shows autosomal recessive inheritance [646, 719]. Diagnosis of the Finnish type is now possible before birth by the demonstration of alpha fetoproteins which are highly increased in maternal serum and in the amniotic fluid [1482a].

The apparent intrauterine disease onset is typical for the Finnish type. The placenta is abnormally enlarged and the children are usually born prematurely (underweight). The newborn usually appear clinically healthy, but the symptoms of steroid-resistant NS become manifest shortly after birth, usually within the first 3 months of life [625, 645]. In the further course of development, disturbances in ossification (especially of the skull), and occasionally aminoaciduria and glycosuria [646] become apparent. Of these children, 81% die from infections or other complications during the first year of life.

***Infantile diffuse mesangial sclerosis*** also frequently occurs familially [625]. Nephrotic syndrome becomes manifest during the initial months of life (4 out of 6 after the fourth month: [625]) and progression to renal insufficiency procedes slower than in the Finnish type, so that the children first demonstrate terminal renal insufficiency at the age of 3–4 years [625]. Hematuria is only rarely encountered (1 out of 6: [625]).

## LM Findings

In the ***Finnish type*** [645, 646], the "microcystic" transformation of the straight parts of the proximal tubules is immediately apparent. They are as wide as 400 μm, irregularly formed, and contain varying amounts of protein (Fig. 17.67). Frozen sections stained with Sudan demonstrate rich amounts of neutral fats and lipoids in the tubular epithelium.

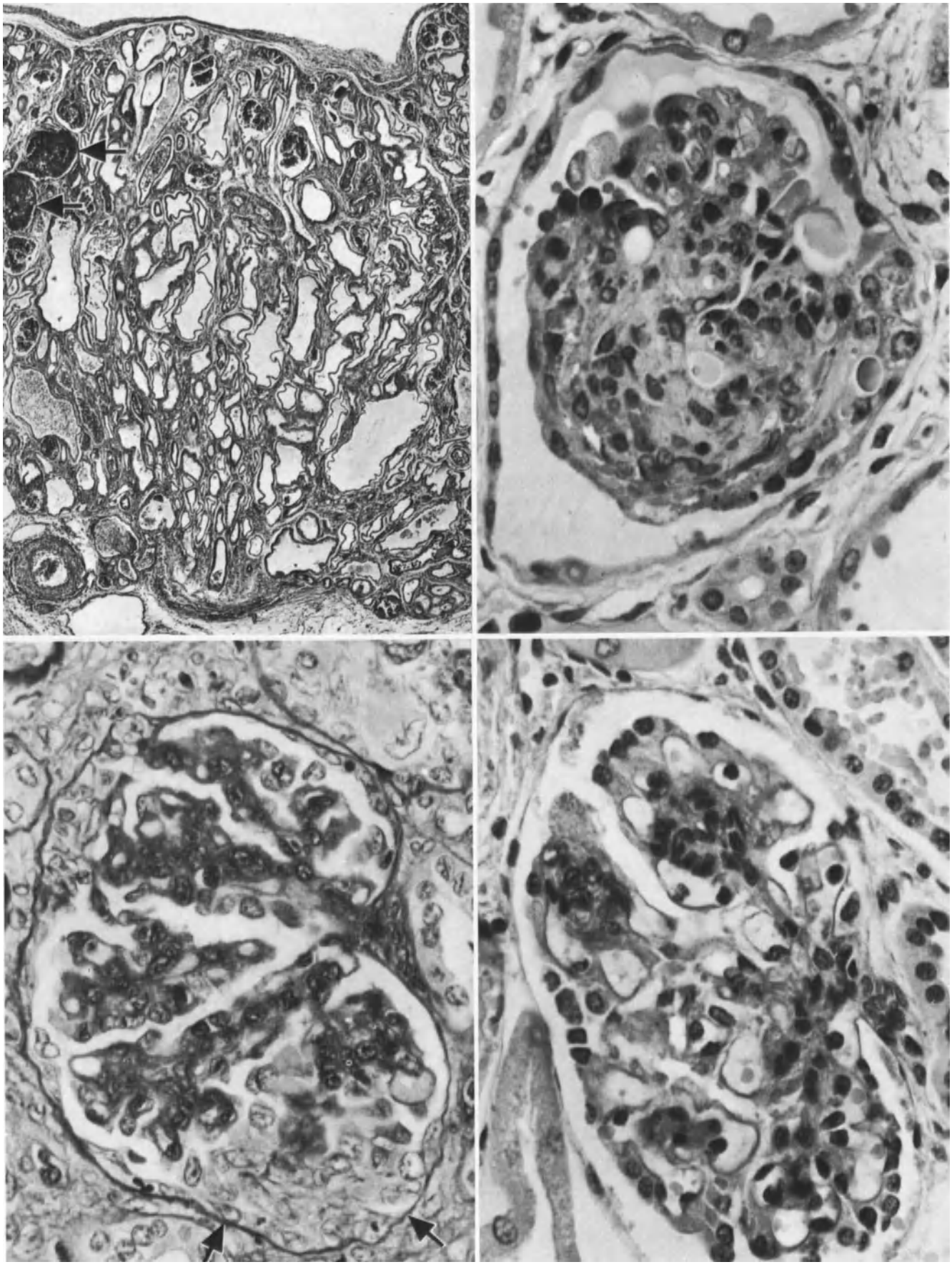
Between the hypertrophic tubules, careful examination also reveals the presence of severely atrophic and often completely solid tubular cords. Microdissection shows cystoidal widening of the proximal convoluted tubules and, in 14 out of 20 of the cases, a narrow neck segment [1234]. Slight dilatation of a few distal tubules was also noted [1234]. The interstitium is edematous, and scantily infiltrated with lymphocytes and histiocytes. Immature-looking glomeruli with a collapsed tuft have a widened capsule space. The mature glomeruli exhibit mesangial hypercellularity and mesangial matrix increase. The latter becomes more pronounced with progression of the disease and is accompanied by a simultaneous decrease of mesangial cells. In advanced stages, some small segmental crescents and synechiae may also be present [645, 646].

**Fig. 17.67.** Congenital GN in a 20-day-old boy: Entire cortex ▷ is clotted with numerous irregularly formed and pronouncedly cystoid widened tubules. Obsolescent glomeruli (→) are scanty. Note almost complete absence of interstitial changes. PAS (×27)

**Fig. 17.68.** Congenital GN in a 13-day-old girl. Proliferation and cell increase with almost complete occlusion of glomerular capillary loops. No polymorphonuclear leukocytes are present. Podocytes are swollen. HE (×800)

**Fig. 17.69.** Congenital nephrotic syndrome: diffuse endothelio-mesangial GN with axial mesangial involvement in the proliferative-sclerosing stage is present. Note small segmental crescent (→). Male, 6 months. PAS (×370)

**Fig. 17.70.** Same case as in Figure 17.67. Congenital nephrotic syndrome with mesangial enlargement and cell proliferation. Male, 20 days. PAS (×430)



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In the ***infantile diffuse mesangial sclerosis*** type, a microcystic transformation of the proximal tubules is also observed but is less pronounced than in the Finnish type [625]. Severe increase of PASM positive mesangial matrix without significant cell increase in the shrunken glomeruli is reported to be characteristic for the lesion [625].

All glomeruli are equally afflicted. In advanced cases, the glomerular tuft is completely sclerosed and covered by swollen podocytes forming an epithelial halo. No specific changes are noted in the interstitium or blood vessels.

*In six patients of our own,* we have found the glomeruli to fundamentally demonstrate the same picture as is observed in endotheliomesangial GN in later age. The mesangium shows severe enlargement due to intense cell increase in both early and later stages (Fig. 17.68). The mesangial cell increase is accompanied by a mesangial PASM positive matrix increase of variable extent (Figs. 17.69, 17.70) which may finally be the dominating feature (Figs. 17.71, 17.72; see also [719]). Segmental crescents are pronouncedly rare (Fig. 17.69).

In the terminal stage, very small 'hyaline' spheres—which appear to lie free in the capsular space—represent the dominant finding (Fig. 17.73). Large podocytes form a halo around the more or less obsolescent glomeruli. A few investigators describe a late-occurring focal and segmental sclerosis and hyalinosis [219, 719, 1126]—which was present in one of our cases—besides a diffuse proliferative sclerosing change in the other glomeruli. We did not encounter spider scars in our cases as are present in the contracted kidney of early childhood. Loop thrombi are extremely rare (Fig. 17.74).

The number of fetal-like (immature) glomeruli is supposed to be increased [719].

The interstitium shows no significant changes—only a very slight interstitial fibrosis with a few scattered lymphocytes. A microcystic transformation of tubules of variable but usually slight degree is seen in all but one of our cases (Fig. 17.67).

## IF Findings

In the ***Finnish type,*** contrary to earlier reports [645, 913], the IF studies were entirely negative in 10 patients [646]. In another report [719] of three cases of congenital NS, at least one of the Finnish type, the initial biopsies were negative except for slight deposits of IgM and once for IgG in the mesangium, whereas at the time of nephrectomy, IgG, IgM, and C3 were segmentally distributed in the mesangium.

In ***infantile diffuse mesangial sclerosis,*** only one report is known to us describing IgM and C3 in granular form mesangially and subendothelially [1478].

**Fig. 17.71.** Same case as in Figure 17.67. Endotheliomesangial ▷ GN with obvious axial enlargement of the mesangium. Note tubular polymorphism and cystoid distention. Male, 20 days. PASM (×120)

**Fig. 17.72.** A 6-month-old boy with congenital nephrotic syndrome showing sclerosing stage of endotheliomesangial GN. There is severe nodular enlargement of the mesangium. PASM (×410)

**Fig. 17.73.** Congenital GN in a 26-day-old boy. There is complete obsolescence of four glomeruli the capsular spaces of which however, are unaffected apart from one synechia (→). PAS (×220)

**Fig. 17.74.** Same case as in Figure 17.67 illustrating a fresh attack in a case of congenital GN. Extensive fibrinoid thrombi are present in the glomerulus. The other glomerular segments show intense cell proliferation. Male, 20 days. HE (×610)

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**Fig. 17.75.** Endotheliomesangial GN (proliferative stage) in congenital nephrotic syndrome. The findings are similar to those in the corresponding GN in adults. There is intense, general cell proliferation and activation of mesangium and endothelium. Intense podocytic microvilli formation (*) and complete fusion of foot processes. Male, 4 months. EM (×2250)

**Fig. 17.76.** Severe mesangial enlargement without significant cellular increase in congenital nephrotic syndrome since birth. Glomerular capillary loop BM is slightly thickened and somewhat loosened in the region of lamina rara interna. Crown-like arrangement of podocytes is indicated (→). Male, 2.5 years. EM (×2360)

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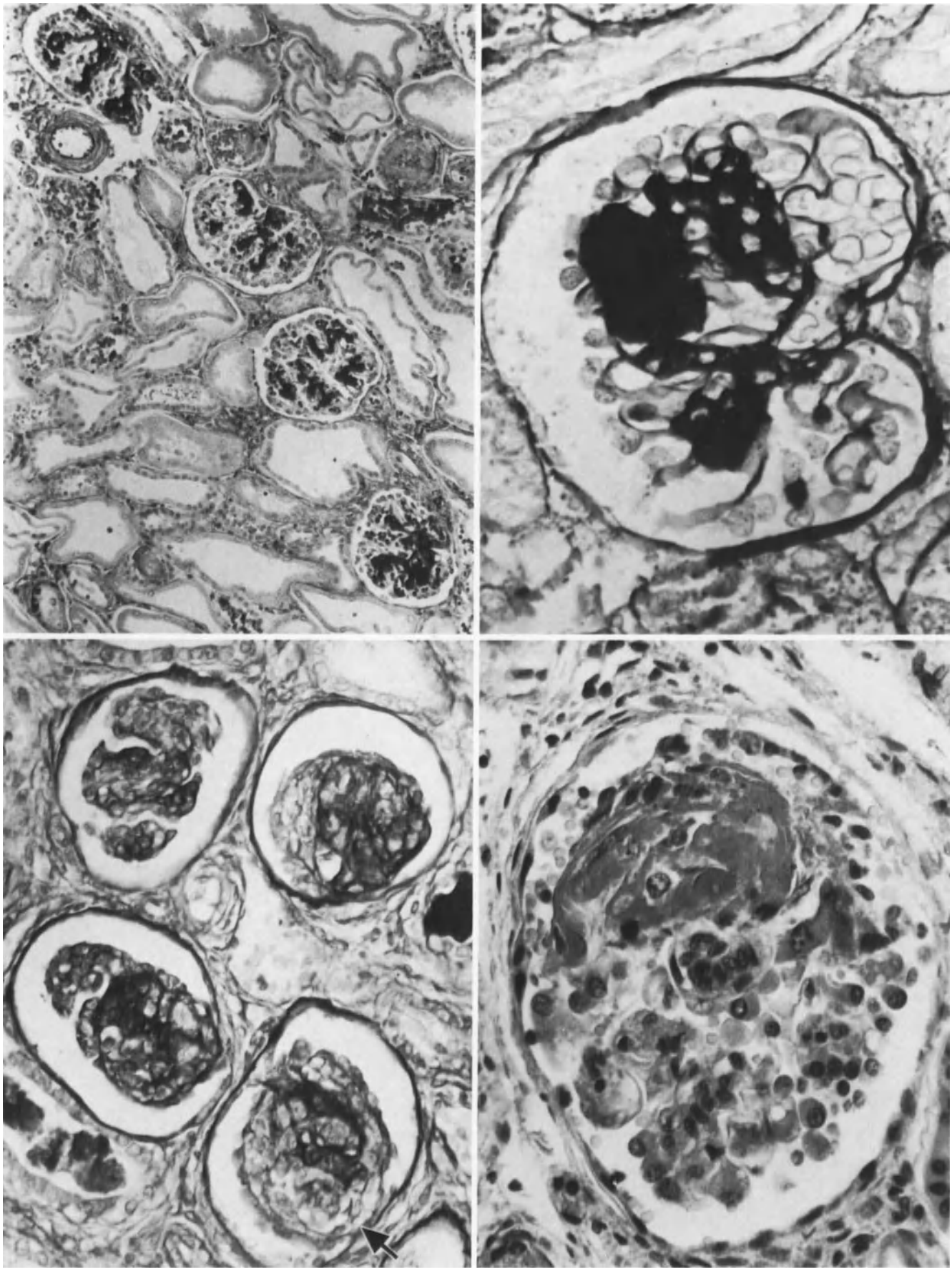
**Fig. 17.77.** Congenital GN in a 20-day-old boy (same case as in Figure 17.67). Peripheral BM is unchanged (→). Massive mesangial enlargement by very coarse mesangial bars and by pronounced mesangial cell increase are the dominant findings. Autopsy material. Formalin fixation EM (×2210)

**Fig. 17.78.** Same case as in Figure 17.76 with predominant mesangial sclerosis. Subepithelial deposits (*D*) are fairly numerous. Lamina densa (*LD*) is irregular and thinned. Rara interna is very irregularly widened (*). Osmiophilic substance is increased in podocytic foot processes. Male, 2.5 years. EM (×33,300)

**Fig. 17.79.** Same case as in Figure 17.76 now evidencing extensive subendothelial deposits (*D*) and very pronounced widening of lamina rara interna. Endothelium is highly activated. Podocytes show slight foot process fusion. Male, 2.5 years. EM (×9460)



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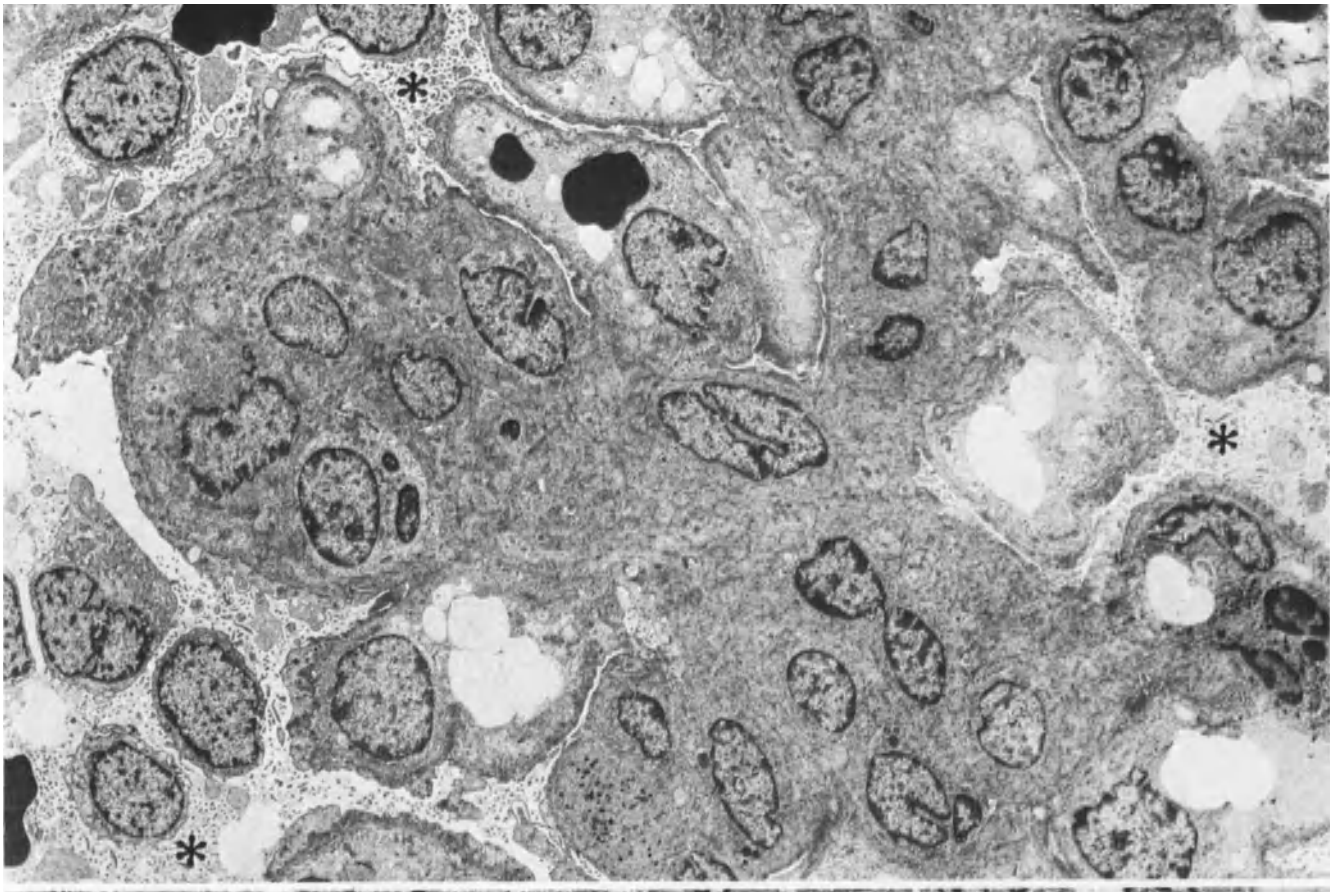

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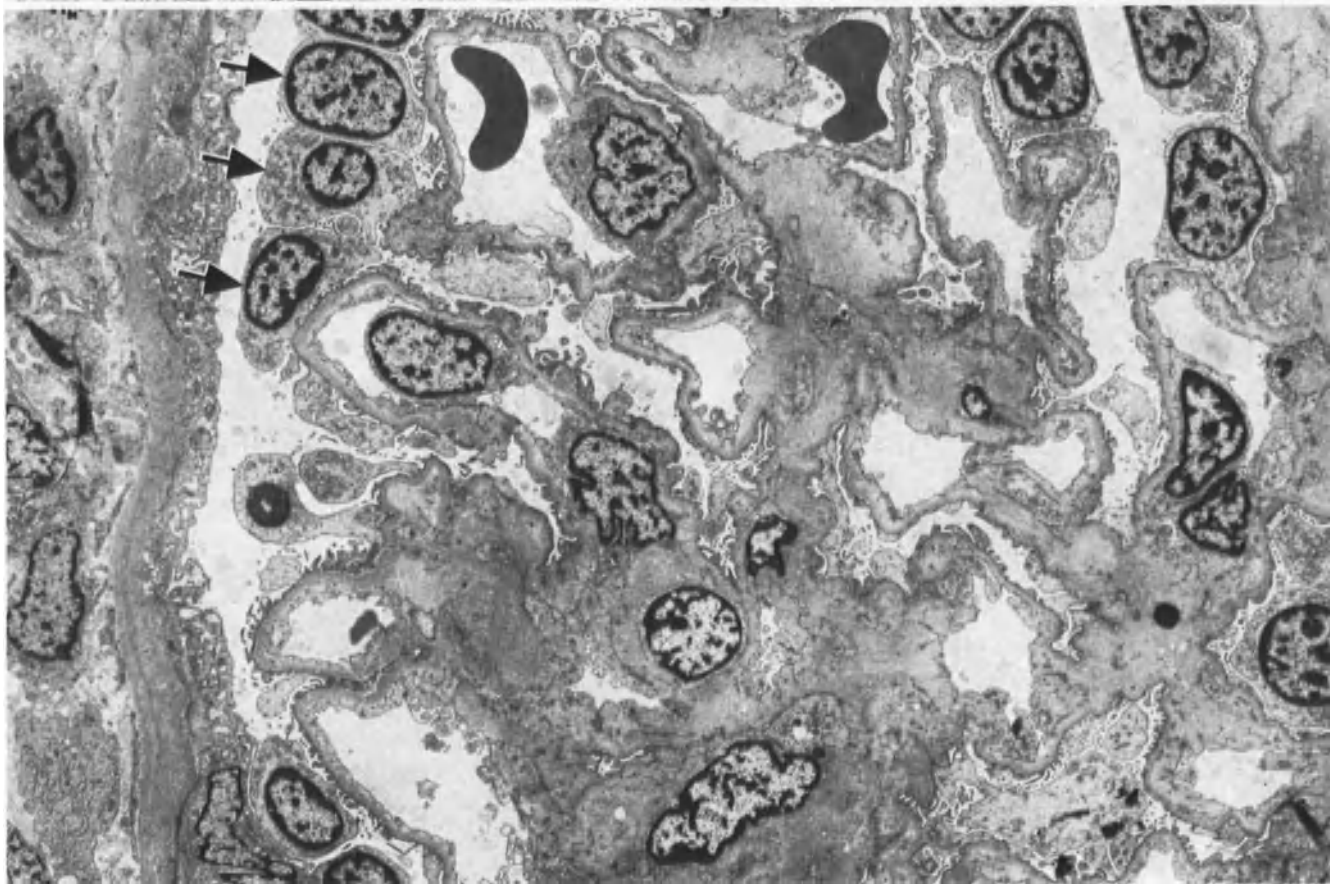

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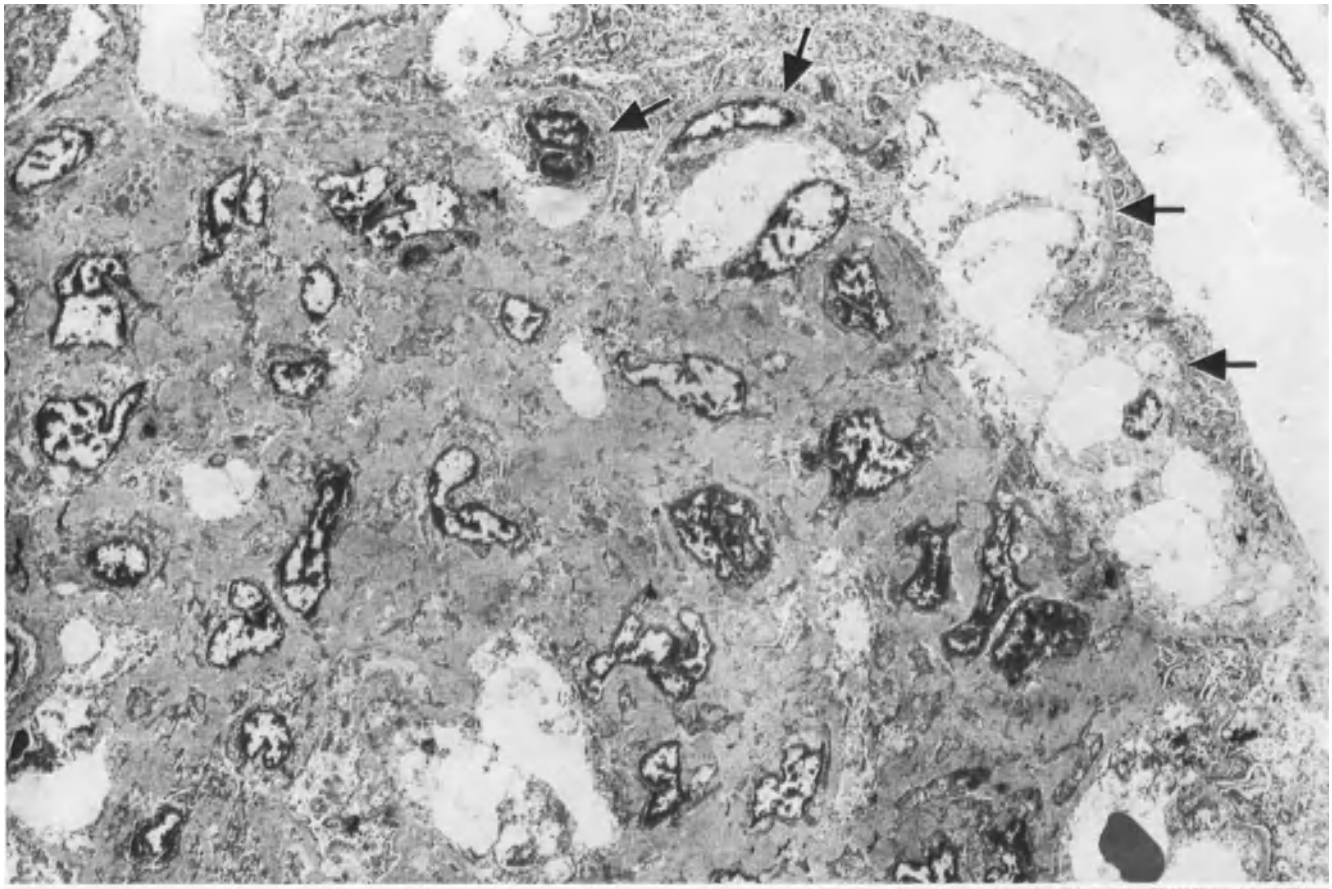

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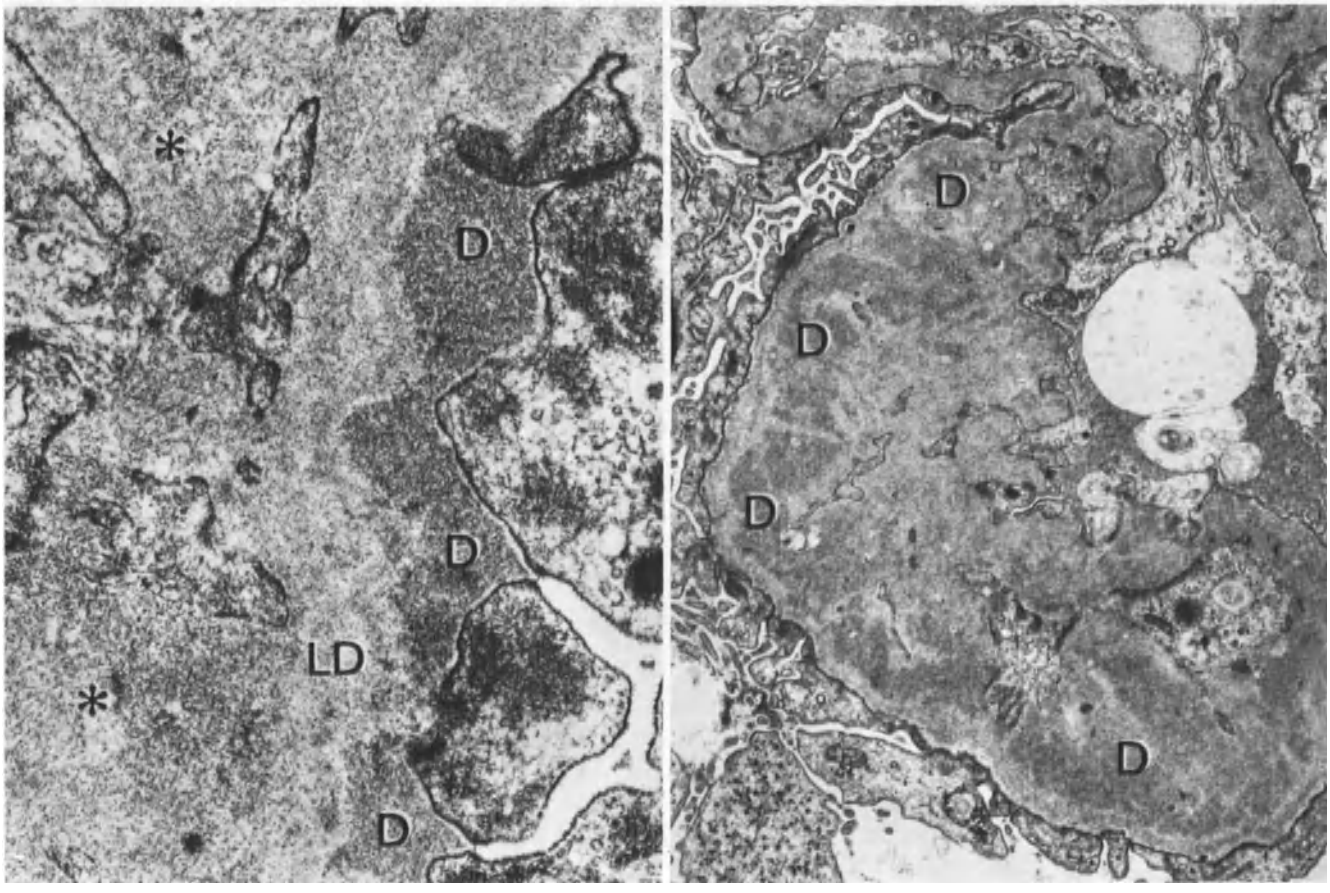


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17.79

*In our cases,* one was entirely negative. Another showed slight granular deposits of IgM and C3 peripherally and, mesangially, of C3 only. The third case demonstrated slight peripheral granular deposits of IgG, C3, and fibrin (-ogen).

### EM Findings

EM reports—which are entirely lacking in the *infantile diffuse mesangial sclerosis type*—are scanty in the *Finnish type*. In addition to the morphologic changes seen by LM, the BM shows, under EM, a slightly diffuse, uneven BM thickening, especially of the lamina rara interna [645]. Osmiophilic deposits are not mentioned by this author nor evidenced in the EM micrographs [645].

*In our six cases* studied with EM, we noted findings of endotheliomesangial GN in various stages. The GN was either predominantly proliferative (Fig. 17.75) or, at a later period, sclerosing, characterized by a very severe increase of the mesangial matrix (Fig. 17.76) which was the outstanding feature in a boy only 20 days old (Fig. 17.77). In 3 out of 6 cases, deposits were present in the region of the peripheral glomerular BM, in 2 out of 6, they were found subepithelially (Fig. 17.78) and in only 1 out of 6 subendothelially (Fig. 17.79). Overall, deposits were extraordinarily rare. Humps and mesangial deposits were not present.

Virus-induced endothelial tubules (Fig. 6.76) were found in large numbers in 3 out of 6 of our cases (see also [346]). In a further case of an 8-month-old boy, round, usually osmiophilic, solid, virus-like particles with a diameter of 200–500 Å were found subepithelially (Figs. 17.80, 17.81) and also, at times, subendothelially next to 800–1200 Å-sized vesicular particles (Fig. 17.81). In 3 out of 6 cases, a severe, diffuse thickening of the peripheral glomerular BM, upon which podocytes lay crown-like, was present (Fig. 17.76). In 1 out of 6 cases, an irregularity of the inner aspect of the BM—partly with nodular thickening of the lamina rara interna and new formation of a thin densa lamella (Fig. 17.82)—was observed. Finally, in a 4-month-old child, there was extensive new formation of a densa lamella, a finding suggestive of BM splitting and reminiscent of Alport's syndrome (Fig. 17.83). The original lamina densa, however, has maintained its continuity, but is obviously thinned (Fig. 17.83). The endothelium was frequently activated and hypertrophied and evidenced numerous arcades. Podocytic foot processes were usually completely fused.

### Differential Diagnosis

Demonstration of microcystic tubules is unspecific and does not prove the presence of idiopathic congenital nephrotic syndrome since they may also occur in other renal diseases of early childhood.

Differentiation between the Finnish and infantile diffuse mesangial sclerosis types is said to be possible in view of the massive increase in PASM positive mesangial matrix without cell proliferation [625] in the latter. A more essential difference, in our opinion, is the later onset and the longer disease course in diffuse infantile mesangial sclerosis as well as the more frequent uremia [625] which is said never to occur in the Finnish type [645]. Our own experience has led us to believe that morphologically, a differentiation between these two forms of congenital (infantile) NS is not possible and that the infantile diffuse mesangial sclerosis type represents a late stage of evolution of a nephropathy which is fairly identical to endotheliomesangial GN of later age. Thus, the main attention must be directed to excluding other glomerular nephropathies as summarized under Nosology, p. 358.

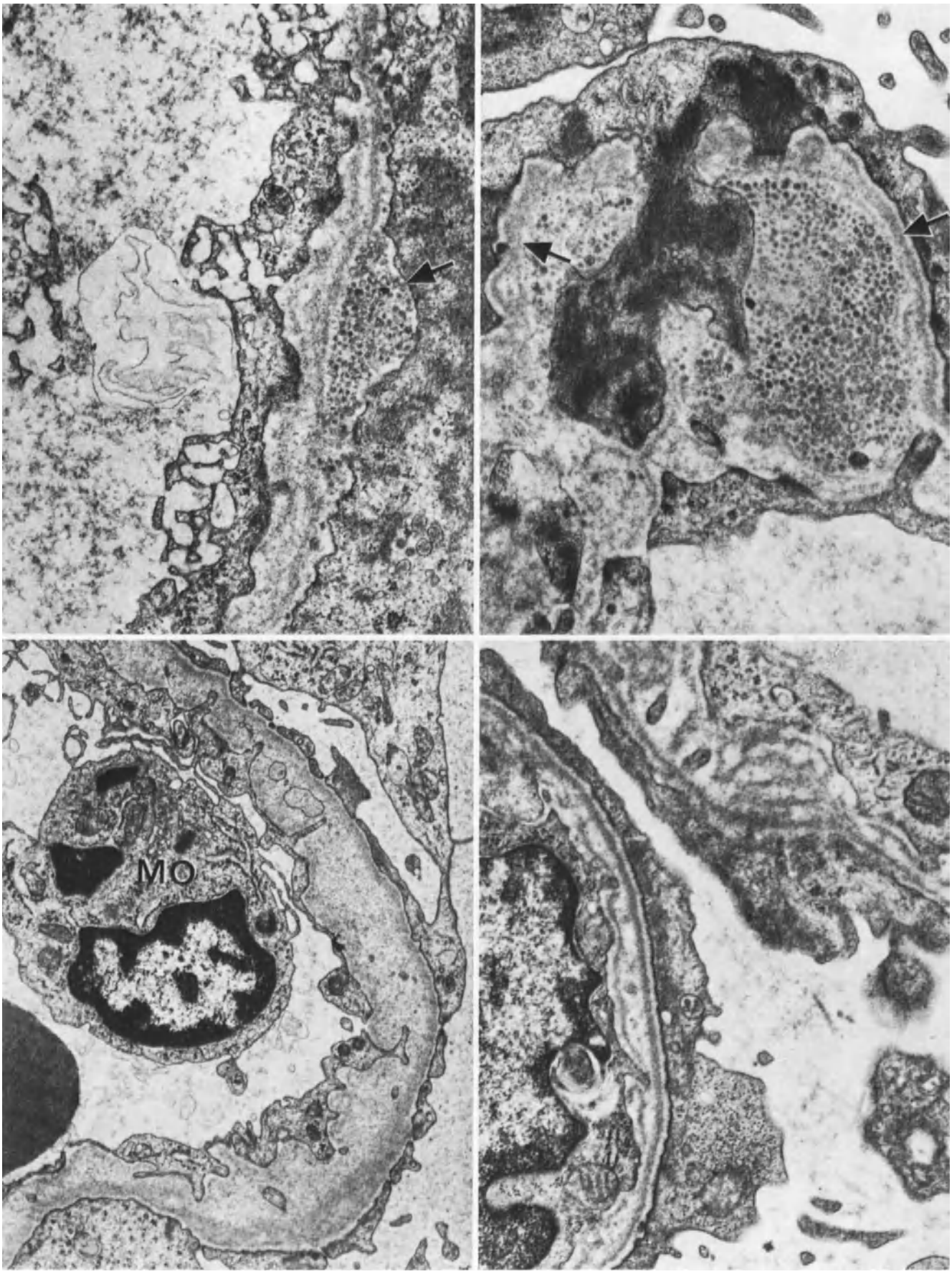
Exclusion of epimembranous GN—which can also occasionally occur during the first year of life [625]—is important and may prove very difficult. Early infantile (congenital) epimembranous GN in congenital syphilis [810, 1217b] may exhibit a more pronounced mesangial matrix and cell increase. Synechiae and crescents are present more often than in later life. Accordingly, the LM picture can easily be mistaken for endotheliomesangial GN. Under EM, a peculiar, coarse-granular, bulb-like and vesicular desintegration of subepithelial deposits is seen after penicillin treatment of congenital syphilis [810]. The glomerular deposits contain T. pallidum AG in congenital syphilis as demonstrated by IF [1217b]. Further, differentiation of glomerular minimal change, sclerosing FGN [625, 1126, 1728] as well as cytomegalovirus infection (own case: Z; [645]) and renal vein thrombosis [606] should not present difficulties.

**Fig. 17.80.** Congenital nephrotic syndrome: same case as in Figure 17.69. There is irregular thickening of the lamina rara externa which contains numerous round virus-like particles (→). Lamina densa is split and lamina rara interna is irregularly thickened. Endothelium evidences obvious arcade formation. Male, 6 months. EM (×25,300) ▷

**Fig. 17.81.** Same case as in Figure 17.69. Masses of virus-like structures are present in the tangential section of peripheral BM in which original lamina densa is not visible; only newly formed densa is seen (→) in broadened lamina rara interna. Podocytes are again rich in osmiophilic material. Male, 6 months. EM (×26,150)

**Fig. 17.82.** Same case as in Figure 17.56. Injury of peripheral glomerular BM. Lamina rara interna is very irregularly thickened. Monocytoid cell in capillary lumen (*MO*). Male, 2.5 years. EM (×11,020)

**Fig. 17.83.** Congenital nephrotic syndrome. There is pronounced splitting of peripheral BM of glomerular capillary loops. Total foot process fusion is present. Male, 5 months. EM (×23,200)




17.80
17.81
17.82
17.83

## Prognosis

***Finnish Type.*** The prognosis is hopeless. The children die after a few weeks or months, usually within the first year of life [621, 645, 646], of infections, electrolyte disturbances, or other complications but never, as it is stated, of uremia [645, 646].

***Infantile Diffuse Mesangial Sclerosis.*** In one report all patients developed uremia during the third year of life [625] and in another report on this form [539], 4 out of 6 patients survived.

No relapse was noted in three transplant cases of congenital nephrotic syndrome at least one of which was of the Finnish type [719].

## Pathogenesis and Etiology

***The Finnish type*** congenital nephrotic syndrome shows autosomal recessive inheritance whose pathogenesis is unclear. The various immunopathogenetic theories which have been proposed, such as a disturbance in the cellular immune response (as suggested by the accelerated rejection of maternal skin transplants by the afflicted child) or a humoral reaction (i.e., AB against placental tissue and renal tissue of children), have been rejected [645, 646, 1371]. The observation of complete remission of nephrotic syndrome (probably of the Finnish type: [719]) following renal transplantation could—as is the case in Alport's syndrome—indicate a genetic disturbance of the BM structure and its formation (see also [646]). The increased excretion of glomerular BM fragments in the urine would be in agreement with this concept [646].

We consider our own cases of congenital nephrotic syndrome described in this chapter as endotheliomesangial GN in which we also include ***diffuse mesangial sclerosis*** ([625]; see also [1478]) as the end stage. In favor of this assumption is the demonstration of deposits and the occasionally positive IF findings as well as the virus-induced endothelial tubules and virus-like particles (see also [346]). The possibility of a viral etiology has been alluded to previously [1205]. Toxoplasmosis has also been proposed as an etiologic agent. Recently, toxoplasmosis AG has been demonstrated in the kidney [553, 1485]. Due to the many questions which remain to be answered, a definitive formulation of pathogenesis and etiology of congenital nephrotic syndrome in question is currently not possible.

# 18. Glomerular Minimal Change

## Definition

Our definition is based primarily on morphology, e.g., glomerular minimal change is a discrete insular mesangial glomerular lesion (see below) associated with proteinuria and/or hematuria. It constitutes a syndrome rather than a unique disease entity. Any other definition which is based on pathogenesis, etiology, or clinical findings is, in our opinion, at the present time unsatisfactory. A few investigators have denied that the change exsists at all [273].

***Synonyms:*** Genuine lipoid nephrosis, acute membranous GN [161, 1703]. No change nephrotic syndrome, nil disease, foot process disease [538a], minimal change GN [403a]. For further synonyms, see Table 13.2.

## Nosology

This primarily morphologic concept of glomerular minimal change encompasses various diseases of diverse pathogenesis and prognosis such as Alport's disease, epimembranous GN, IgA nephritis, and the idiopathic form of glomerular minimal change (see Table 18.1).

Table 18.1. Nosology of glomerular minimal change

A. *Familial forms*
   1. Alport's disease (including sporadic cases)
   2. Benign (essential) hematuria (including sporadic cases)
   3. Familial nephrotic syndrome

B. *Non-familial forms*
   1. Idiopathic (IF negative)
   2. Symptomatic (predominantly IF positive)
      a) Endotheliomesangial GN
      b) Epimembranous GN
      c) IgA mesangial GN
      d) In systemic diseases such as SLE, Schönlein-Henoch's syndrome
      e) In focal lesions (when these are not found in biopsy material)
      f) Unspecific accompanying phenomenon in amyloidosis, arteriolosclerosis, etc.

Differentiation of the various forms of glomerular minimal change, which is often not unequivocally possible clinically and with LM alone, requires EM and IF investigation. Attentive study of complete sequential sections of the biopsy material is helpful in avoiding classification of focally accentuated GN as glomerular minimal change. But even then, such false classification of a few cases of focally accentuated GN evidencing very discrete renal involvement and the absence of juxtamedullary zones in biopsy material cannot be avoided.
We suggest classification of only those forms of the disease as idiopathic glomerular minimal change which are IF negative, have no EM-demonstrable deposits, and which evidence no specific glomerular changes, e.g., BM changes in Alport's syndrome. On the basis of these criteria, 95 cases of glomerular minimal change under LM and with a complete set of information (clinical data, EM, IF) could be classified into the subgroups as presented in Table 18.2. Only 23 out of 95 cases belong to the group of idiopathic glomerular minimal change.

Table 18.2. Reclassification of glomerular minimal change under LM using IF, EM and a complete set of clinical data ($n=95$)[a]

| No. of cases | Disease entity |
|---|---|
| | Familial forms |
| 15 | Alport's syndrome |
| 4 | Benign hematuria |
| 0 | Familial nephrotic syndrome |
| | Non-familial forms |
| 23 | Idiopathic (IF negative) |
| 36 | Endotheliomesangial GN |
| 18 | – IF: IgM/C'3 |
| 18 | – IF: IgG, etc. (without IgA mesangial GN) |
| 8 | Epimembranous GN (stage I) |
| 8 | IgA mesangial GN |
| 0 | In systemic disease |
| 1 | Unspecific accompanying phenomenon in amyloidosis (other disease not considered) |

[a] Including many recent cases not referred to in further discussion. The urinary findings in these cases were: proteinuria (nephrotic syndrome) and/or hematuria.

On the basis of IF findings, 36 cases (Table 18.2) are summarized tentatively under the heading of endotheliomesangial GN.

Whether it is justified to ascribe glomerular minimal changes positive for IgM and/or C3 only to endotheliomesangial GN or whether these cases should constitute a group of its own cannot as yet be decided with certainty. In any of these three groups—IF negative, IF positive with IgM/C3; with IgG, etc.—patients exhibiting clinically pure proteinuria (nephrotic syndrome), only hematuria or hematuria and proteinuria (nephrotic syndrome), were present in the same frequency. Because of this finding, we reject a classification of glomerular minimal change based on LM and clinical data only.

In most series of other investigators, the diagnosis of glomerular minimal change has been based exclusively on LM study so that it is quite conceivable that these series as well as our own LM series of 211 patients (Table 14.3) contain cases which should be classifed elsewhere. "The main interest of the finding of minimal glomerular lesion is that it excludes other types of glomerular lesions" [621] which can be identified under LM with certainty. In the following discussion, we refer to our crude LM series, from which all those cases are excluded in which EM or IF investigation disclosed Alport's syndrome, benign hematuria, epimembranous GN or amyloidosis, so that the bulk of cases belongs to the idiopathic or endotheliomesangial group of glomerular minimal change.

The concept of *lipoid nephrosis* is, in our opinion, outdated. It was used to describe a large pale-yellow smooth kidney demonstrating microscopically massive lipoid deposition which is more pronounced in the proximal than in the distal tubules. Additionally, clusters of lipoid-containing cells are found in the interstitium and lipoid can also be demonstrated within rejected tubular cells and in casts. The lipoid nature of the fatty substances can be shown by demonstrating their birefrigence. In all of our own cases, we found a few nephrons that were fat-free.

It has long been known that lipoid nephrosis is a syndrome—and not a unique disease entity [1788, 1791]—which may arise in conjunction with inflammatory, toxic, dysorotic (amyloidosis, etc.) and anoxic processes. Since, as indicated above, the concept of lipoid nephrosis has been used to include the most diverse kinds of disease, we suggest that the term be discarded.

## Incidence

The change is found very frequently in needle biopsy material and especially so in association with nephrotic syndrome in childhood.

In biopsies of children, the incidence varies between 22% and 65% (see Table 18.3). The incidence in children with nephrotic syndrome has been given as 53.6% [621] and 76.5% [1731]. On the other hand, in 10–43% of all patients with nephrotic syndrome, glomerular minimal change is found [168, 616, 661, 671, 1484]. In biopsy material including that from adults, the overall frequencies vary between 17.3% and 42.9% (see Table 18.3). Boys are more frequently afflicted than girls (1.5:1: Z; [163, 1544, 1731]). The maximum age at which the disease is manifested is between 3 and 5 years [1731].

Table 18.3. Relative frequency of glomerular minimal change

| Pediatric GN biopsies | | Total GN biopsies | |
|---|---|---|---|
| 22% | Bohle et al. (1974) [163] | 17.3% | Churg and Duffy (1973) [277] |
| 42% | Zollinger and Mihatsch | 20.9% | Hamburger et al. (1971) [654] |
| 44% | Churg and Duffy (1973) [277] | 22.1% | Morel-Maroger et al. (1973) [1137a] |
| 49.1% | Habib (1973) [621] | 23.5% | Zollinger and Mihatsch (1975) |
| 56% | Cameron (1968) [242] | 32.8% | Germuth and Rodriguez (1973) [544] |
| 65% | Seymour et al. (1971) [1484] | 35.5% | Seymour et al. (1971) [1484] |
| | | 35.9% | Cameron (1973) [242b] |
| | | 42.9% | Bohle et al. (1976) [163a] |

In our material, the pediatric age group is significantly more frequently affected (Fig. 18.1) but isolated cases may be encountered at any age (Table 14.3; see also [658]).

## Clinical Findings

(Tables 14.3, 14.4, 14.5; Fig. 18.1)

Often, nothing is known anamnestically about these patients in whom urinary symptoms are found fortuitously [1511b]. In a large series of cases, the disease manifested itself subsequent to pharyngitis in 31% of the patients, and after immunization in 6% [632].

In 23.2% of our patients (Fig. 18.1), acute prior disease was present in two-thirds of whom as an infection of the upper respiratory tract. Typical acute GN is rarely present in the case history (Table 14.5; 4.5% of our cases). In another series consisting of 34 cases of acute GN, later biopsy revealed glomerular minimal change in nine patients [658].

The further course of the disease is often strikingly attack-like ([916]; 30%: Z).

Highly selective proteinuria is usually the predominant clinical finding. It occurs in 70–90% of the patients [163, 621, 1731] and is generally so pronounced as to constitute

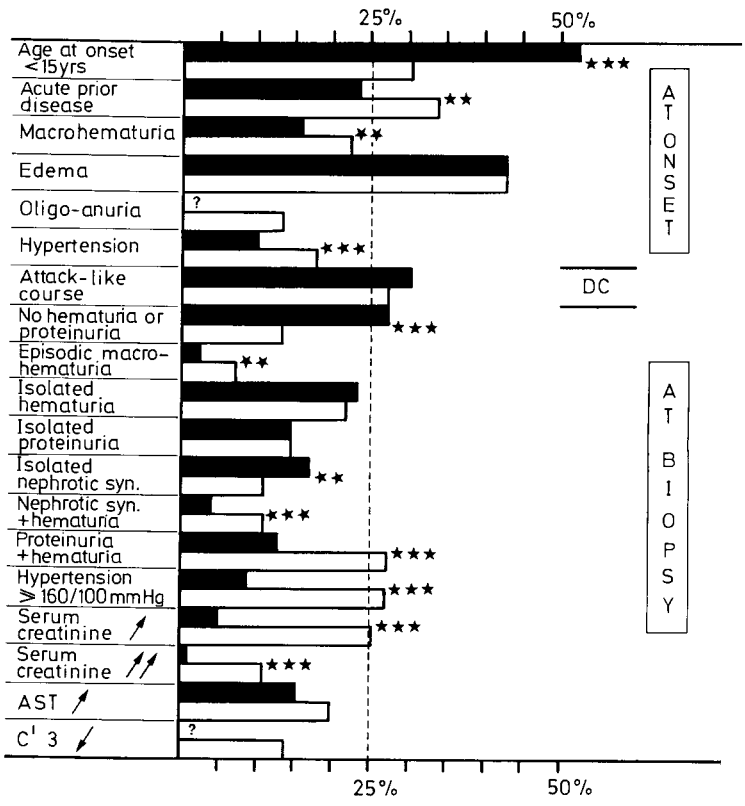



**Fig. 18.1.** Profile of symptoms and clinical findings in glomerular minimal change
*White columns:* Relative frequency of symptom/finding in all GN
*Black columns:* Relative frequency in glomerular minimal change
Asterisks indicate characteristic findings for glomerular minimal change:
*: characteristic
**: very characteristic
***: highly characteristic; DC: disease course

an nephrotic syndrome which occurs in 73% of pediatric cases [621]. Proteinuria was present in 76.2% of our patients and led to nephrotic syndrome in 46.4% which, at the time of biopsy, had undergone remission in 27.5%.

Hematuria is reported in 31.2% [620] and in 41% [163] of the patients. In our patients, proteinuria was accompanied by hematuria in 17.1%. Of our cases 23.8% evidenced isolated hematuria (see also [1544]). Hematuria may be the only persisting symptom following remission of nephrotic syndrome. Initial (15.7%; Table 14.3, 14.4) or episodically occurring macrohematuria (2.6%; Table 18.4) is an uncharacteristic finding as is hypertension (3.5%: [620]; 9%: [1731]; 8.8%: Z; contra: 30%: [163]).

Increase in urea and creatinine (19%: [1731]; 5.2%: Z) or reduction of creatinine clearance (4%: [1731]) are also infrequently encountered. Acute renal failure is extremely rare and occurs chiefly in elderly patients. We observed an increase of the antistreptolysin titer in only 15.9% of our cases.
The duration of the disease varies between a few months to 50 years.

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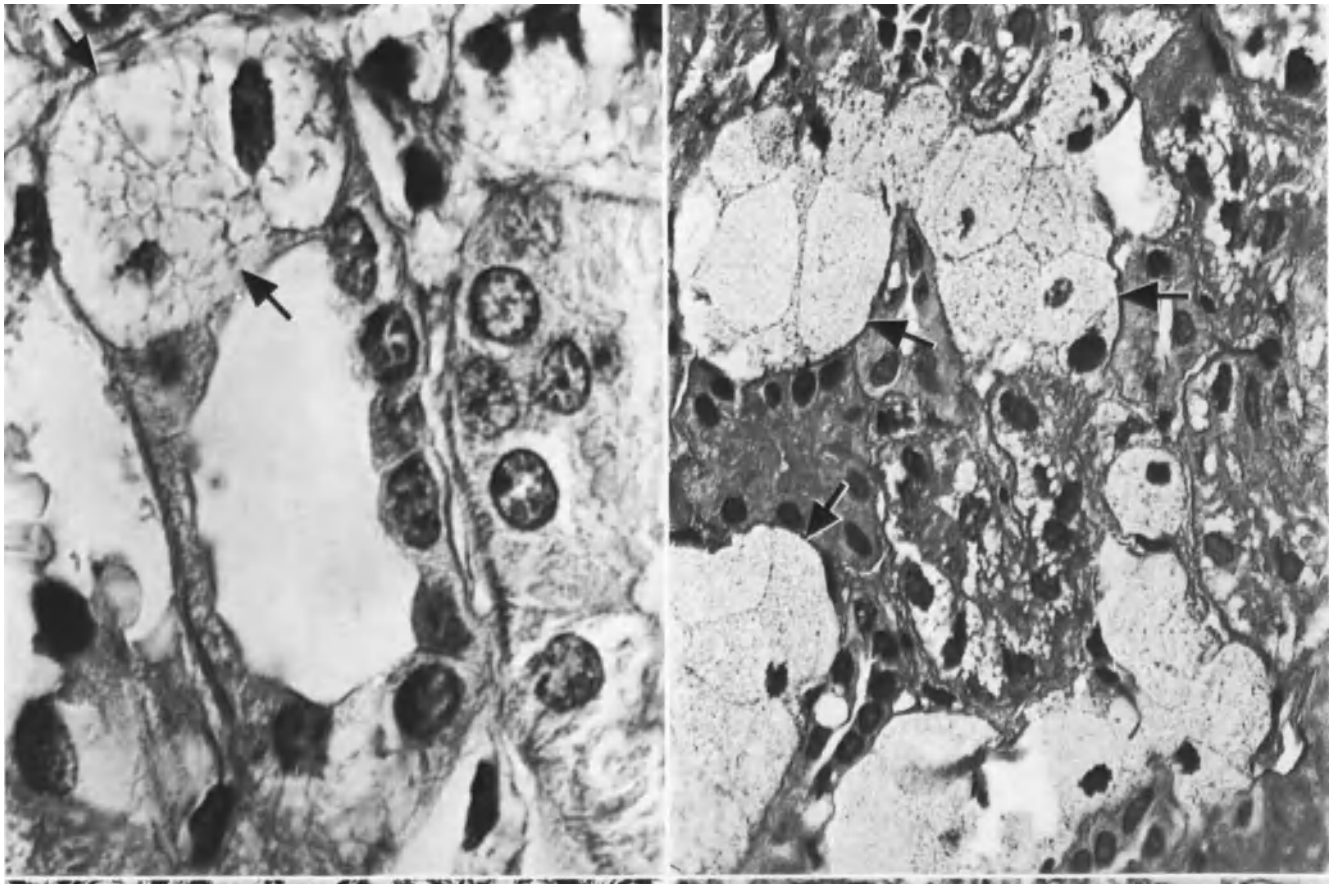
**Fig. 18.2.** A solitary foam cell is seen in the distal tubule (→) in a case of glomerular minimal change. Male, 3 years. PAS (×920)

**Fig. 18.3.** Groups of foam cells in glomerular minimal change. Tubular nature of foam cells can be recognized from the tubular BM which is partially visible (→). Female, 10 years. PAS (×420)

**Fig. 18.4.** Secondary focal lipoid storage in severe arteriolosclerosis. There is extensive lipoid deposition in the slightly atrophic proximal tubules. Severe narrowing of the lumen and fatty change of the arterioles is seen (→). Autopsy specimen. Sudan (×110)

**Fig. 18.5.** Glomerular minimal change with nephrotic syndrome following acute poststreptococcal GN 4 months prior to this biopsy. There is an insular mesangial enlargement and minimal cell increase. BM of tubules and glomerular capillary loops are entirely unchanged. Male, 6.5 years. PAS (×110)



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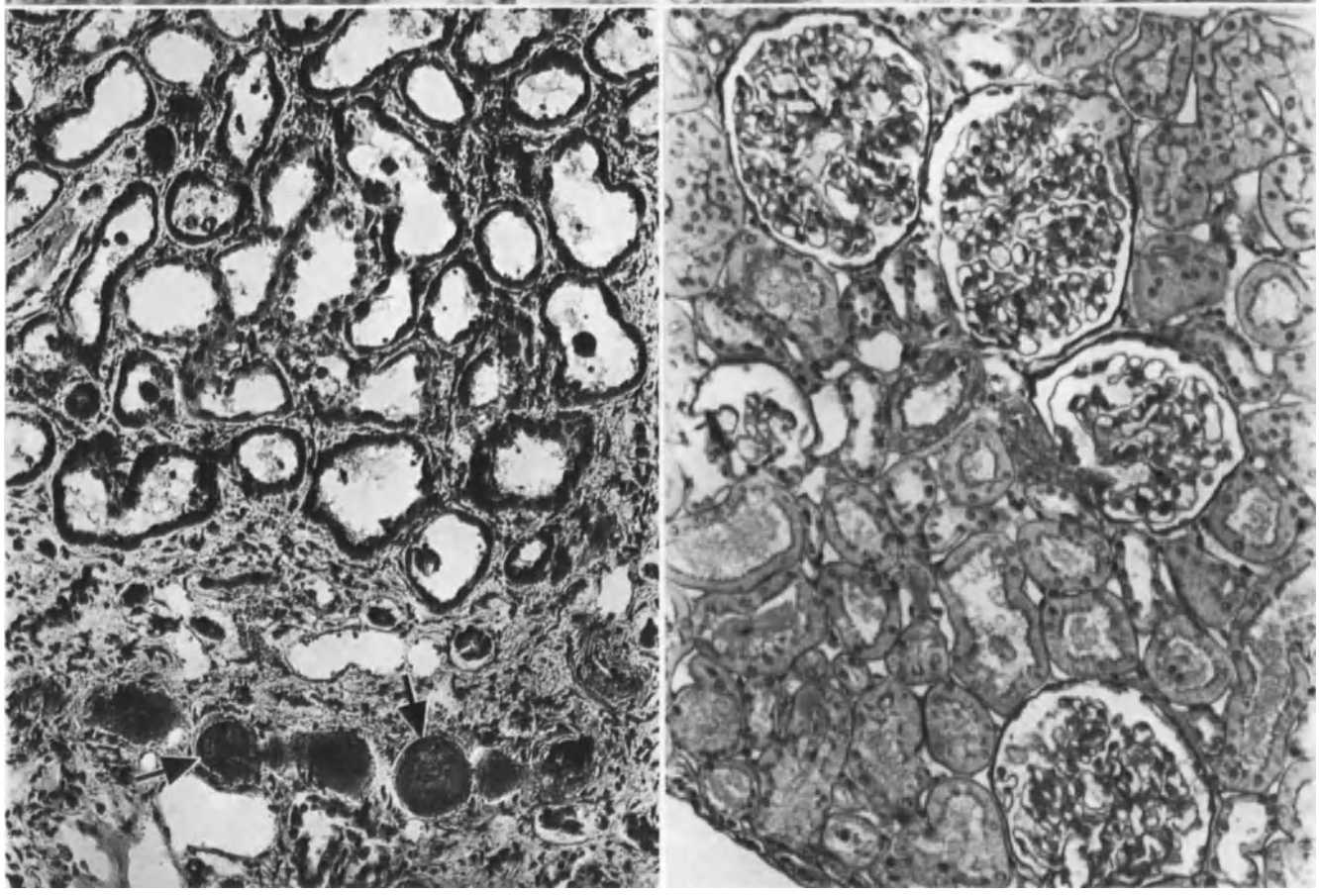

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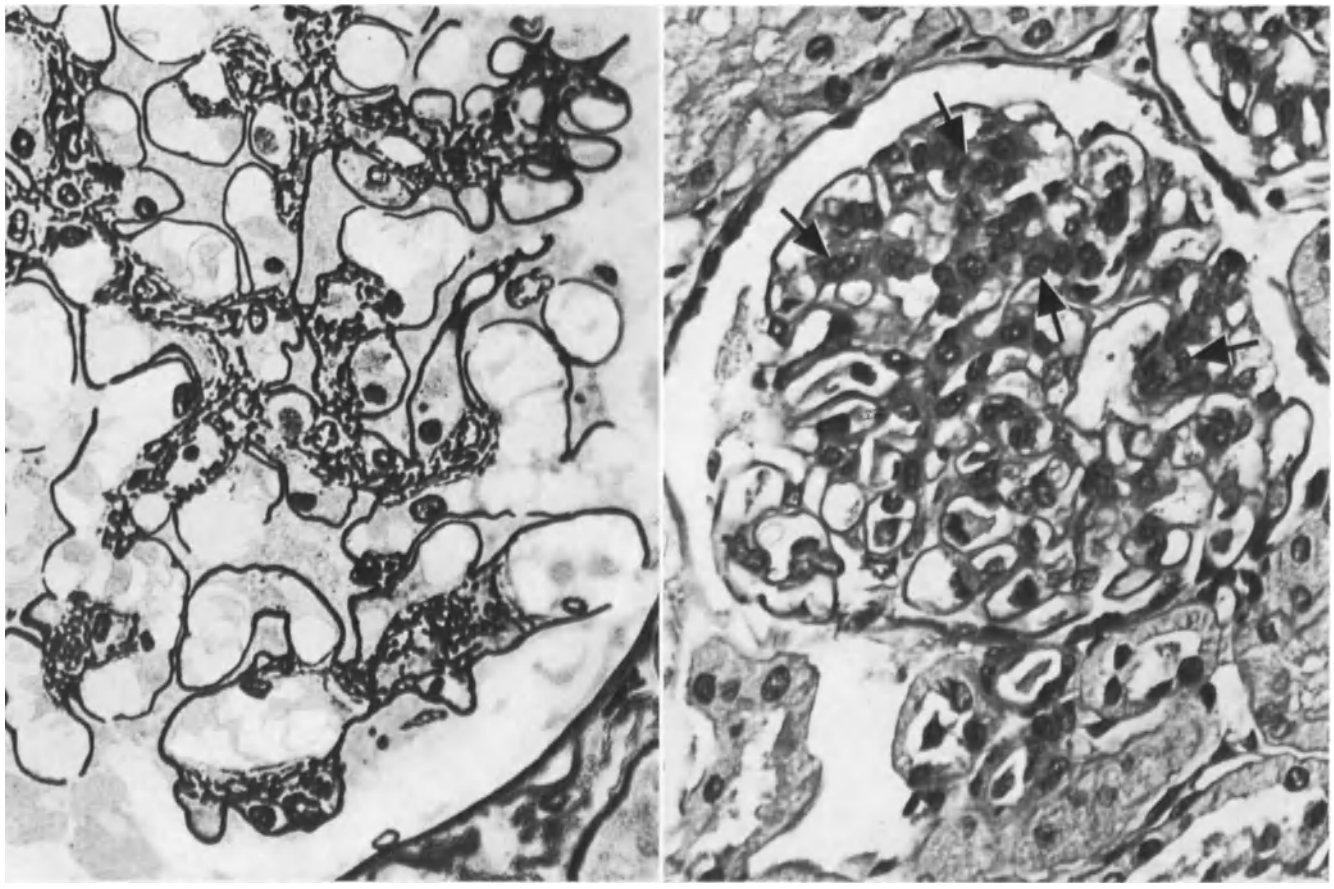

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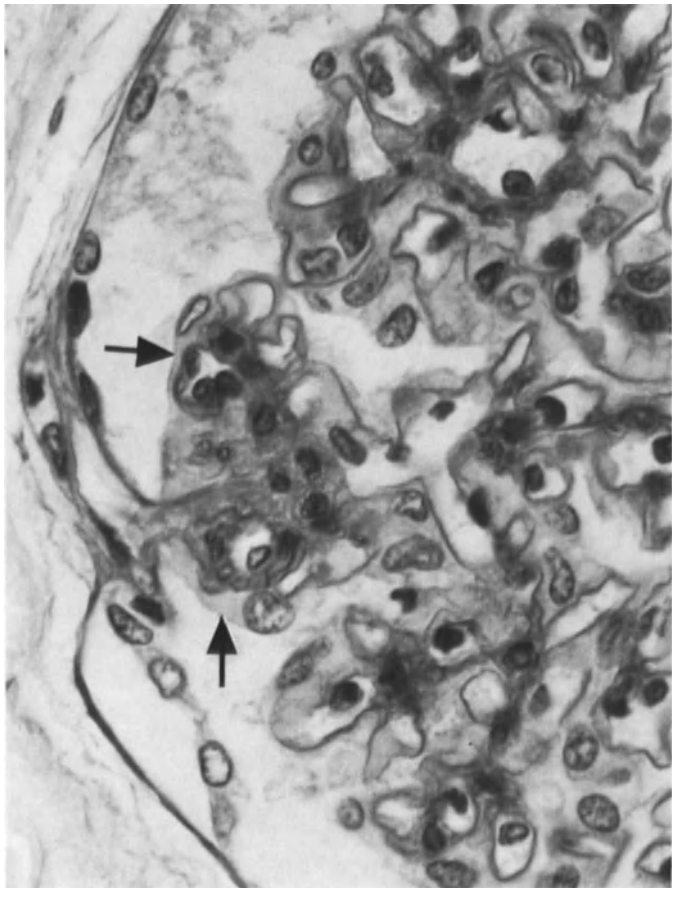


**Fig. 18.6.** Glomerular minimal change with nephrotic syndrome. Obvious but slight mesangial matrix increase, less so of cells. Male, 8 years. PASM ( × 110)

**Fig. 18.7.** Glomerular minimal change with hematuria. Four mesangial areas are slightly enlarged and contain increased number of cells (→). Male, 7 years. PAS ( × 400)

**Fig. 18.8.** Glomerular minimal change in all but one glomerulus in a kidney biopsy 1 year after acute poststreptococcal GN. Two glomerular capillary loops adhering to each other (→) show a synechia with the capsule. Mesangial regions of afflicted loops evidence a cell increase. Male, 31 years. PAS ( × 600)

## LM Findings

At low power magnification, the kidney often shows no changes at all [672], especially in isolated hematuria, or, in nephrotic syndrome, only foam cells. The foam cells are found singly (Fig. 18.2) or in groups (Fig. 18.3) in the interstitium and tubules. They may be scanty or even entirely lacking in a biopsy due to their focal distribution (Fig. 18.4).

However, if one compares the glomeruli in cases with glomerular minimal change with those from age-matched controls, the former show insular mesangial thickening (Figs. 18.5, 18.6) and occasionally 4–5 nuclei (Figs. 18.7, 18.8) per mesangial area. In general, we have encountered this mesangial change in less than 10% of the glomeruli in normal kidneys and in more than 10% (but rarely as much as 50%) in cases with glomerular minimal change. The mesangial changes do not demonstrate the finger-like (axial) configuration, but rather the insular one [777, 1791]. Qualitatively, similar changes have been described earlier by other investigators, but usually in only a small percentage of the cases, e.g., mesangial thickening in 9.2% and cellular increase in 5% [636], and 3 out of 40 cases [766] and cell and matrix increase in 50% of cases with EM [596]. Morphometric evaluation of our cases of glomerular minimal change revealed no statistically significant mesangial matrix and cell increase in comparison to controls of similar age ([1624b]; contra: [658, 1705]). This discrepency between qualitative and quantitative findings may be explained by the limitations imposed by morphometric technique.

It is also important to note that the juxtamedullary glomeruli are generally more severely afflicted than those of the outer cortex [1329, 1395, 1484, 1795, 1796]. We found a few (< 10%) isolated obsolescent glomeruli in 16 out of 211 cases. The presence of more than 10% of obsolescent glomeruli as well as the finding of segmental glomerular sclerosis do not belong to glomerular minimal change, and are discussed on p. 296).

## IF Findings

Our IF findings in 80 cases are summarized in Table 18.4 of which 35 were entirely negative. Among the remaining 45 cases, IgA mesangial GN was present once. In the other 44 cases, C3 was most frequently observed (33 out of 44), partially accompanied by IgM in 21 out of 44 cases and IgG in 20 out of 44 cases (see Table 18.4). A focal and segmental distribution of slight amounts of immunoglobulins and C3 predominated. A comparison of these findings with those of other investigators is not possible since these investigators obviously use a different system for classifying IF positive cases, or consider weakly positive cases as virtually negative, apart from one investigator summarizing these cases in a group with doubtful lesions [840a].

We consider IF positive cases tentatively as probably belonging to the symptomatic forms. (For IgE see p. 162.)

Table 18.4. IF findings in glomerular minimal change ($n=80$; 35 negative)[a]

| | IgG | IgM | IgA | C3 | Fibrin(-ogen) |
|---|---|---|---|---|---|
| Cases tested | 44 | 44 | 29 | 44 | 44 |
| Positive | 20 | 21 | 6 | 33 | 2 |
| Focal | 10 | 9 | 6 | 20 | 0 |
| Diffuse | 10 | 12 | 0 | 13 | 2 |
| Segmental | 13 | 16 | 6 | 17 | 2 |
| Global | 7 | 5 | 0 | 16 | 0 |
| Peripheral | 11 | 10 | 4 | 12 | 2 |
| Mesangial and peripheral | 6 | 4 | 2 | 13 | 0 |
| Mesangial | 3 | 7 | 0 | 8 | 0 |

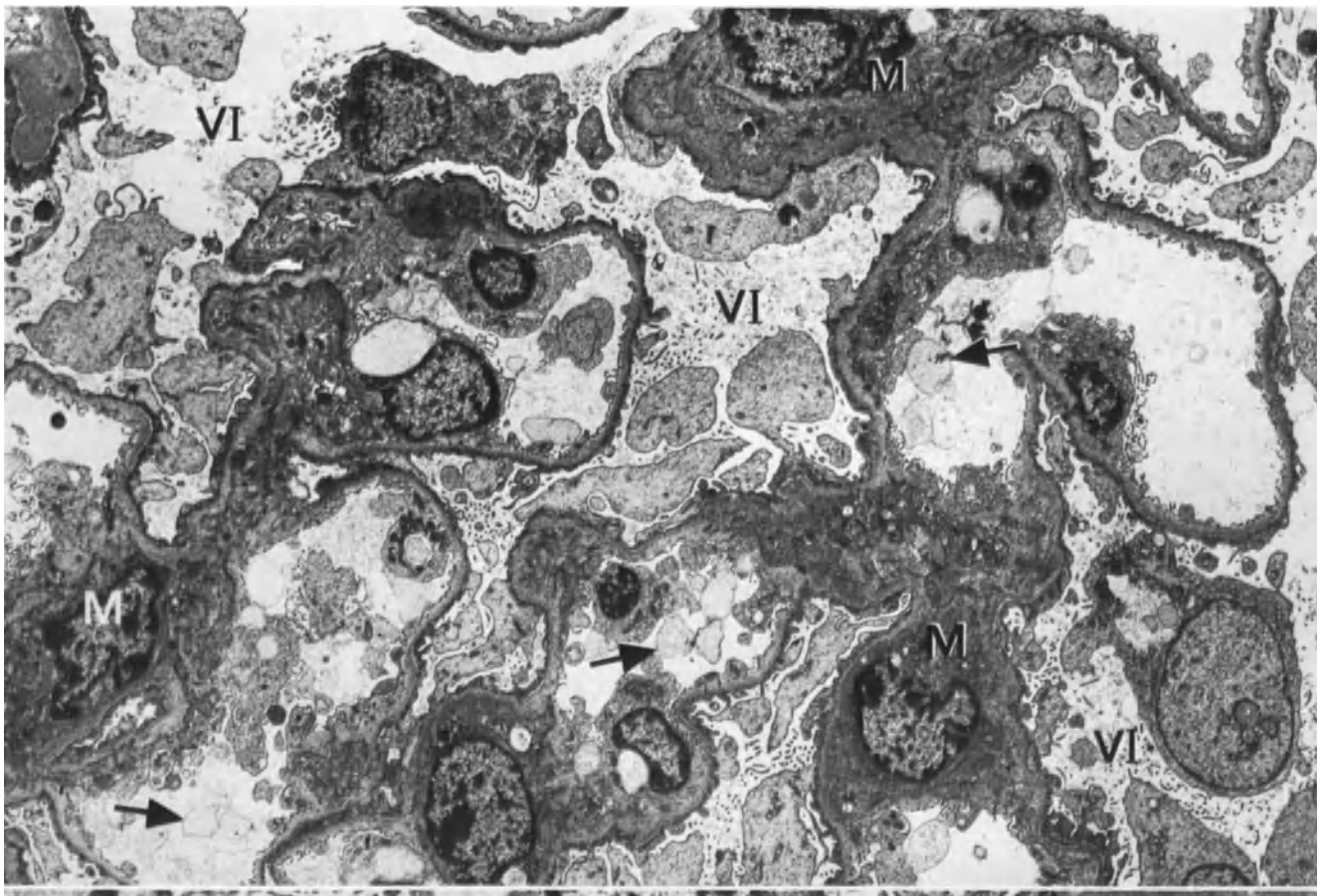
[a] 1 case of IgA nephritis is not considered.

Without consideration of fibrin(-ogen), the following combinations—listed in decreasing order of frequency—were found:

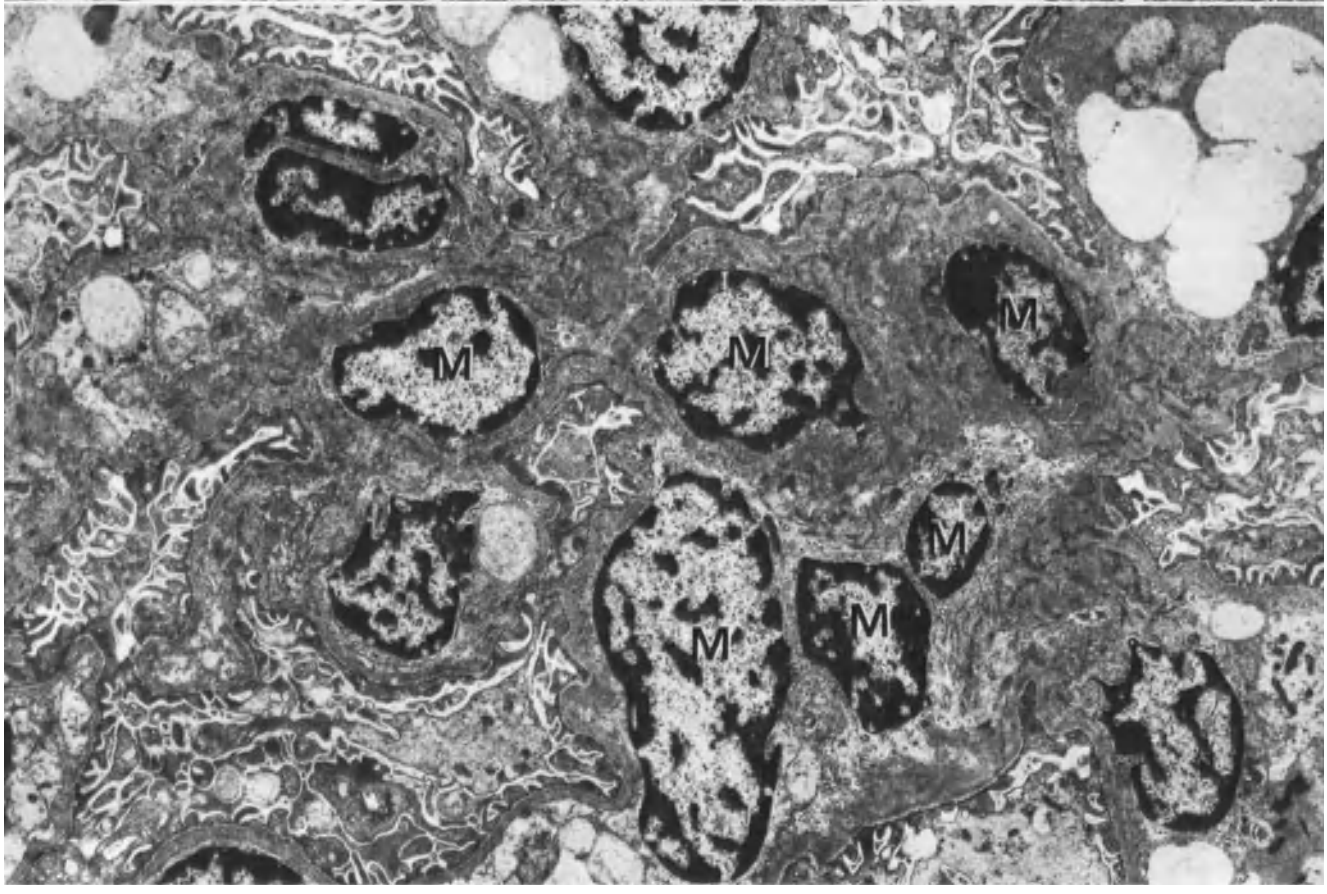
| Excluding IgA | | Including IgA | |
|---|---|---|---|
| C3 | 12 | IgG, A, C3 | 3 |
| IgG, C3 | 7 | IgG, M, A, C3 | 1 |
| IgM, C3 | 7 | IgG, M, A | 1 |
| IgG, M, C3 | 6 | IgM, A | 1 |
| IgG, M | 4 | | |
| IgG | 3 | | |
| IgM | 4 | | |

**Fig. 18.9.** Same case as in Figure 18.5. Enlarged mesangial areas (*M*) are clearly recognizable. There is intense activation and swelling of podocytes which evidence numerous microvilli (*VI*). Endothelial cells are slightly activated and demonstrate numerous ballooned processes (→). Pronounced foot process fusion is present. Male, 6.5 years. EM (×29,000) ▷

**Fig. 18.10.** Glomerular minimal change. Increase of mesangial cells (*M*) is far more obvious than in Figure 18.9. There is only moderately severe increase of matrix bars. Foot process fusion is slight. Podocyte activation, however, is again intense. Male, 6 years. EM (×5940)




18.9




18.10

### EM Findings

In the histograms (Fig. 6.9, etc). cases of idiopathic glomerular minimal change (in EM and IF, no demonstrable deposits) are contrasted to 24 probably symptomatic cases (IF positive or EM deposits). The comparison shows that no significant differences exist between the two forms with the exception of deposits which are always–by definition–absent in the idiopathic form.

Slight insular mesangial matrix increase associated with scanty cellular increase is demonstrable in all the abovementioned 41 cases (Figs. 18.9, 18.10). The matrix is pronouncedly coarse and the bars are irregularly shaped (Fig. 18.11). In the symptomatic cases, the cell increase was occassionally (3 out of 24 cases) more intense than in the idiopathic form. It is again pointed out that the mesangial changes—especially in EM—were not present in each glomerulus nor in each glomerular section. A comparison of idiopathic glomerular minimal change with proteinuria/nephrotic syndrome or hematuria or a combination of both, disclosed, semiquantitatively, no significant morphological differences except for a milder foot process fusion in cases with pure hematuria.

The endothelium is usually slightly hypertrophied and shows arcade formation. The pronounced fusion of foot processes—which was taken as pathognomonic for glomerular minimal change in the early days of EM study [460]—is currently viewed as the consequence and not the cause of proteinuria. The presence of foot process fusion is not a reliable criterion since it may be absent in complete remission of urinary findings (contra: [1484]). Equally questionable is the hypothesis that foot process fusion, viewed teleologically, is supposed to hinder proteinuria [1592].

In almost every case, small or large numbers of circumscribed thickenings, mainly of the lamina rara interna, and to a lesser extent of the lamina densa of the BM of the capillary loops, can be recognized with EM (Fig. 18.12; see also p. 64). A focal thickening of all BM layers has been reported by others [460, 596, 1582, 1647]. Slight irregularities (Fig. 18.13) with thinning and loosening of the lamina densa [387] or splitting (Fig. 18.14) are far more rare. A direct relationship between duration of proteinuria and thickness of BM has been proposed [1592], a finding we have not been able to confirm. Very typical, however, is thickening and unclear delimitation of the BM along the mesangium (Fig. 18.13).

Deposits, which are always absent in the idiopathic form (under EM and IF) can even be lacking in true symptomatic cases. This can be explained by the extensive ability of podocytes, among other structures, to remove the deposits [111].

In a few cases, however, deposits have been reported in the BM and subendothelially [1484] as we have observed them in our symptomatic cases (3 out of 24 subendothelially; 4 out of 24 intramembranously, 7 out of 24 along the mesangial BM; 2 out of 24 humps, and 3 out of 24 in the mesangial matrix: Z). Rarely, subtotal interruptions of the BM with deposit remnants (Fig. 18.15), loop obliteration (Fig. 18.16) and periglomerular infiltrates (Fig. 18.17) are found. These latter findings are especially frequent in cases with a clinical history of GN. Thus, they should be considered as symptomatic cases even in the absence of positive IF findings. A surprising but very questionable communication in relation to glomerular minimal change has reported fibrin deposition in 100% of the cases, platelet aggregation in 80%, and subendothelial deposits in 90% [399].

### Differential Diagnosis

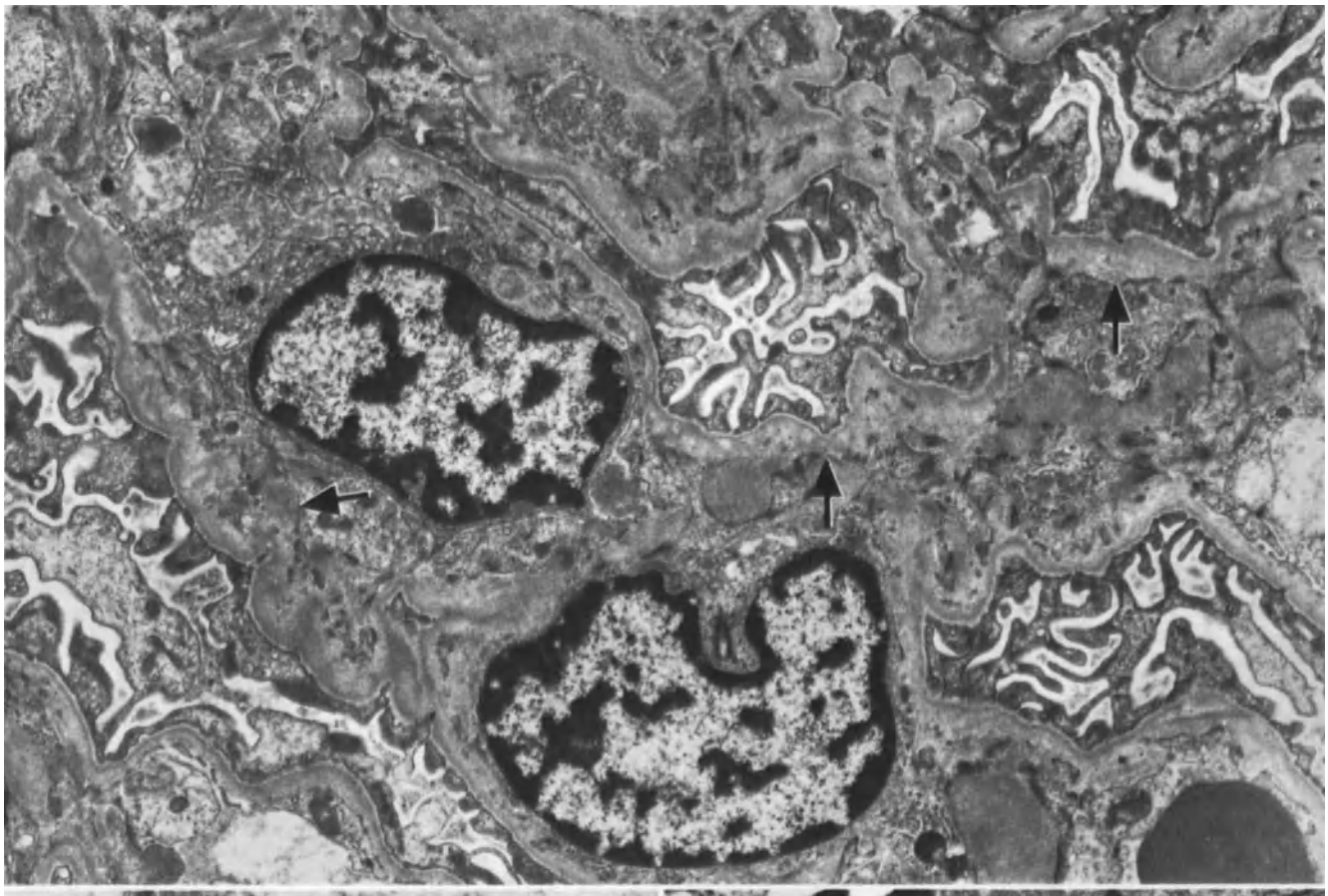
The differential diagnosis can be directly derived from the nosology (see p. 367). There is scarcely a glomerular change which is more dependent on the availability of meticulous clinical data and on LM, EM, and IF technical prowess than glomerular minimal change.

Among the familial forms, differentiation of Alport's disease—especially in sporadic cases—from benign recurrent hematuria and from the familial nephrotic syndrome is possible with EM alone, which demonstrates in Alport's disease the specific BM changes (see p. 475). In nonfamilial cases, study with LM alone (even using semi-thin sections) may result in confusing epimembranous GN in stage I with idiopathic glomerular minimal change (see also [160]). In this situation, as in differentiation of other symptomatic forms such as endotheliomesangial GN and IgA mesangial GN, only IF may prove to be of further help. If facilities are not available for IF and/or EM study, rebiopsy after several months of disease latency in therapy-resistant cases with nephrotic syndrome may be tried as a last resort for clarification. If necessary, EM study may be attempted on formalin-fixed material embedded in paraffin or paraplast.

**Fig. 18.11.** Glomerular minimal change with nephrotic syndrome. Patient had acutc poststreptococcal GN 5 years prior to this biopsy. There is intense activation of the two mesangial nuclei and cytoplasm appears to be strikingly rich in organelles. Glomerular BM is loosened along inner side of mesangium (→). Mesangial matrix is incrcased. Female, 10 years. EM (×8140) ▷

**Fig. 18.12.** Glomerular minimal change with nephrotic syndrome in complete remission. There is focal loosening of lamina rara interna in a peripheral glomerular capillary loop (→). No foot process fusion is present. Female, 5 years. EM (×27,900)

**Fig. 18.13.** Same case as in Figure 18.12 in which, however, loosening of lamina densa is recognizable. Female, 5 years. EM (×16,730)



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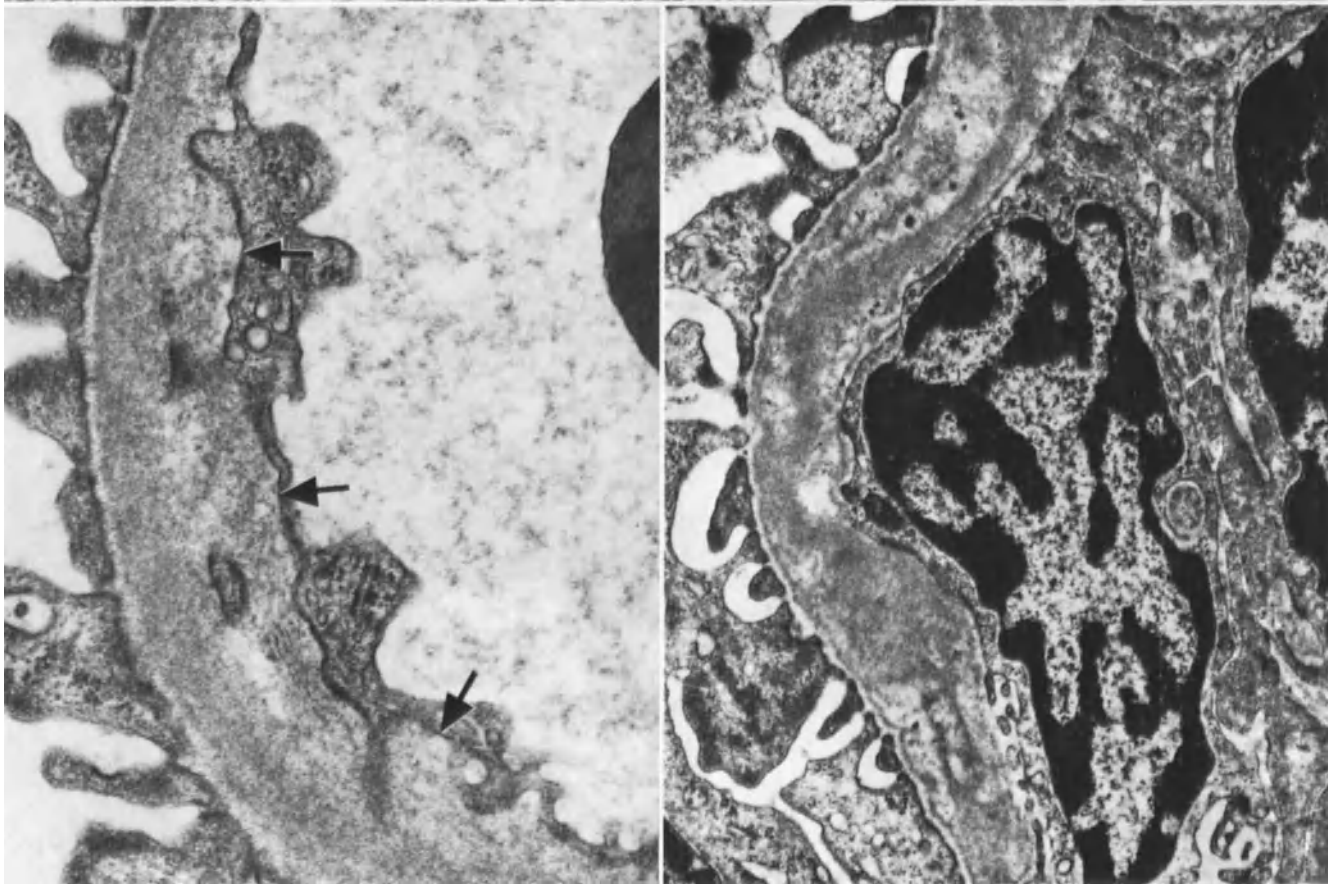

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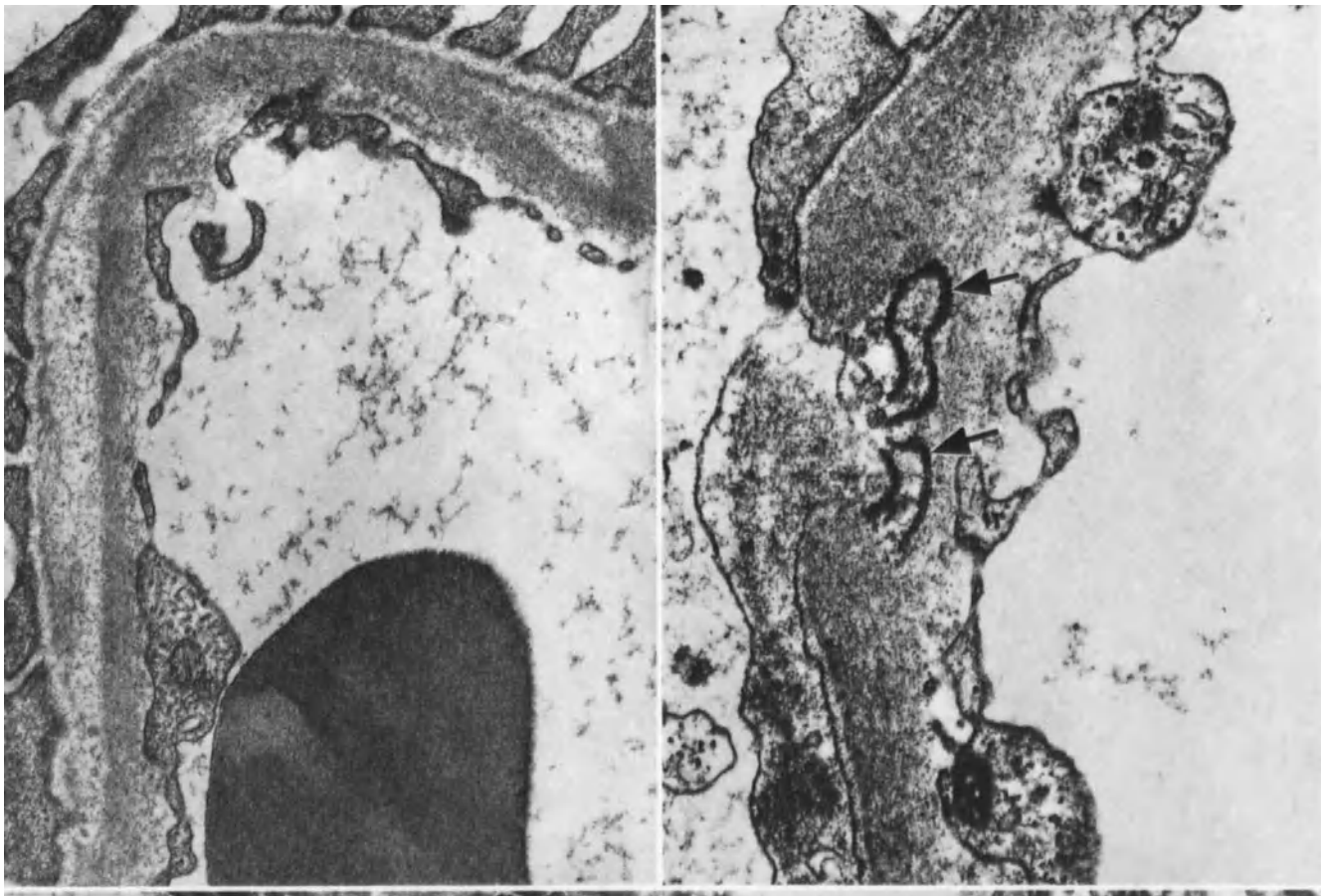

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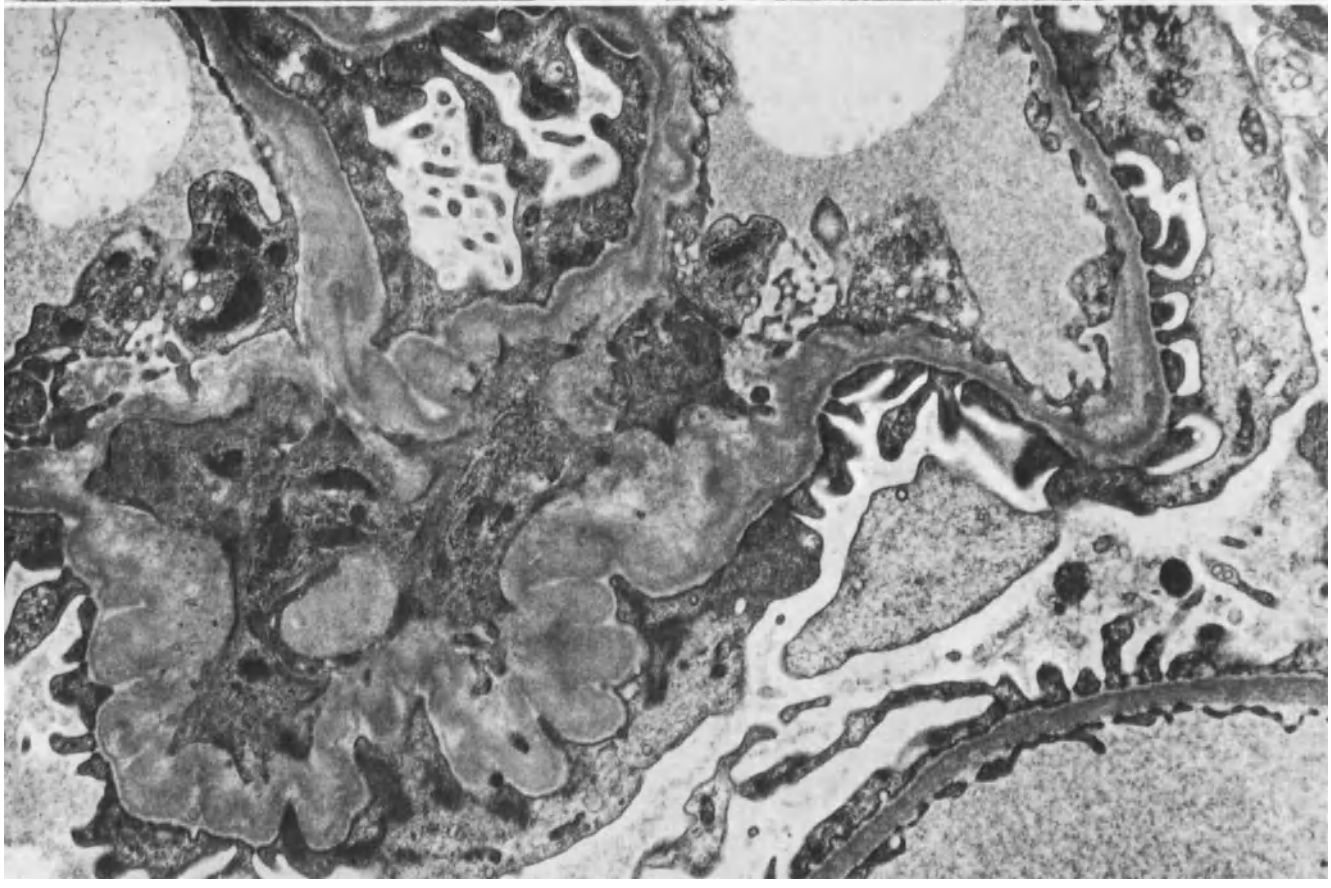

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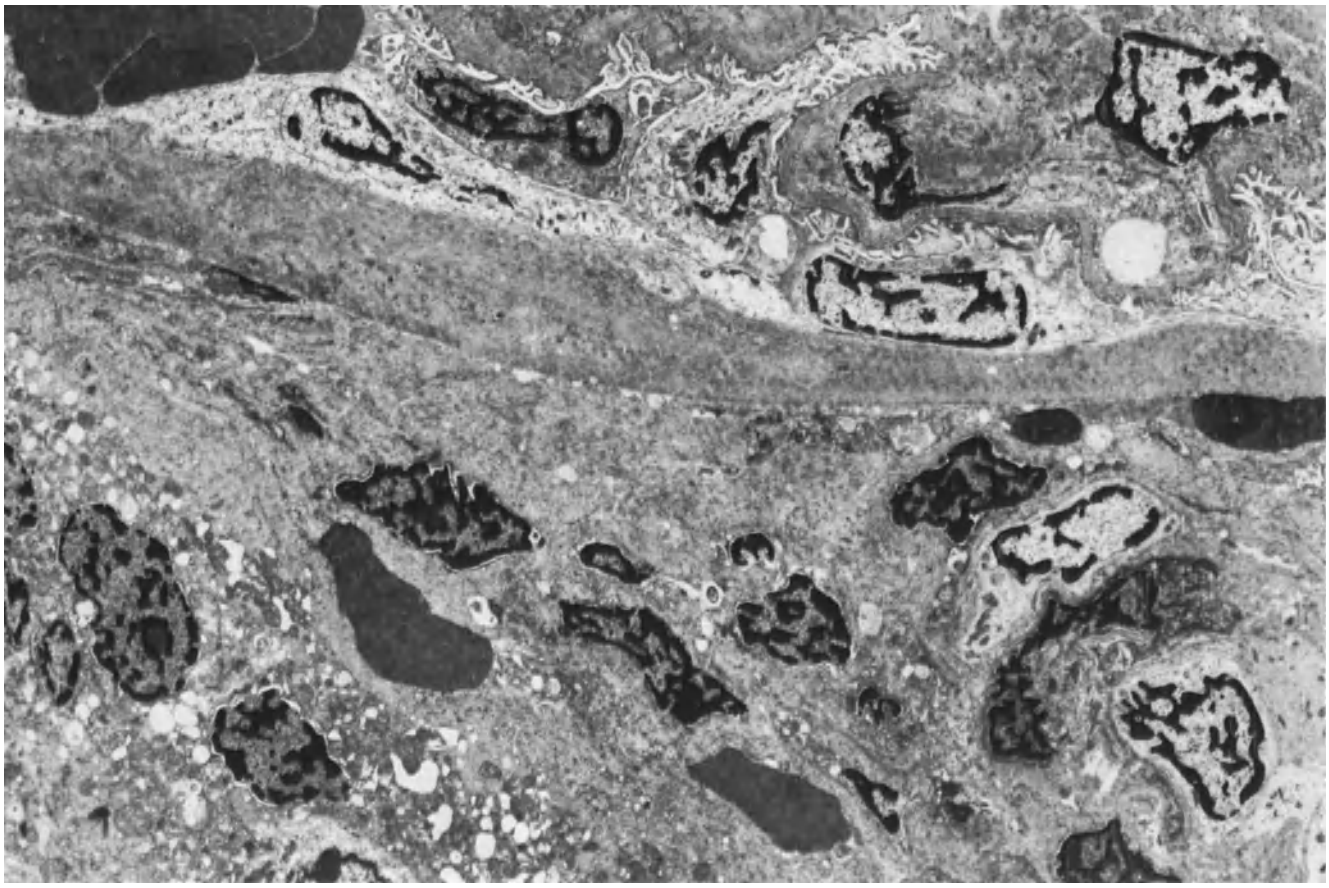


**Fig. 18.17.** Thickening of glomerular capsular BM and periglomerular infiltrates consisting of small lymphocytes and phagocytes. Male, 6 years. EM (×3960)

◁ **Fig. 18.14.** Peripheral BM injury in glomerular minimal change. Irregular thickening of lamina rara externa with new formation of a thin densa lamella subepithelially. Male, 11 years. EM (×26,000)

**Fig. 18.15.** Indentation of peripheral BM with thread-like structures (→) which are suggestive of dissolved osmiophilic deposits. Male, 36 years. EM (×39,460)

**Fig. 18.16.** Segmental glomerular loop obsolescence in glomerular minimal change. There is total foot process fusion over obsolescent loops. The severely wrinkled and partially loosened BM is thickencd. Male, 11 years. EM (×9750)

Demonstration of synechiae is indicative of a post-GN form of change (Fig. 18.8; see p. 188) and such biopsies should not be included in the group of glomerular minimal change.

A further difficulty lies in the differention from sclerosing FGN which is viewed by many investigators as a special form of minimal change (see p. 296). Since, in sclerosing FGN, the most severe changes occur chiefly in the region of the juxtamedullary glomeruli—which are almost the only ones developed prenatally and in the very early postnatal period—the decisive changes may not be in tissue obtained at biopsy. However, if they are present, they are decisive for the diagnosis of sclerosing FGN (see p. 296).

Finally, it is often impossible to differentiate glomerular minimal change from the different forms of glomerulosclerosis or glomerulonephrosis, at least in the beginning (see p. 382). In our material, there was one case classified as glomerular minimal change by LM, which turned out, with EM, to be one of very slight amyloidosis.

## Prognosis

With respect to survival, prognosis today is not bad as such, which represents considerable improvement over past decades. In some instances, improvement is attributable to antibiotic therapy since death was due earlier to a complicating infection of which pneumococcal peritonitis was especially prominent and later, in others, to corticosteroid administration. Cure probability in conjunction with corticosteroid therapy has been reported as being 50–90% [45, 636], 77% in adults and 90% in children [242, 248, 896]. In our series (Table 18.5), none of the patients less than 15 years of age died, but it was astonishing to see that only 16% were considered as cured, whereas in the majority, the disease course was considered as uncertain. On the other hand, among adults the 15-year survival rate was 82% from the onset of disease and 77% from biopsy onwards. But only 2 out of 78 patients with complete follow-up died from uremia. Reviewing the slides of both patients, no indications for sclerosing FGN—which is known to procede to uremia more frequently [595, 1484, 1731]; (see p. 296)—were present.

Disease onset in earliest childhood or familial cases indicate a considerably worse prognosis [1126]. In three cases which required transplants, proteinuria recurred within hours after operation [651].

Table 18.5. Prognosis and outcome in glomerular minimal change

| Prognosis | Survival rate (%) | | | |
|---|---|---|---|---|
| | 5 years | | 10 years | 15 years |
| Age: | < 15 years | > 15 years | > 15 years | > 15 years |
| From disease onset | 100 | 94 | 88 | 82 |
| SE[a] | | 2.4 | 4.1 | 5.5 |
| From biopsy | 100 | 88 | 80 | 77 |
| SE[a] | | 3.7 | 5.1 | 6.1 |

[a] Standard error in %.

*Outcome* (after minimal follow-up of 1 year)

| | Age < 15 years | > 15 years |
|---|---|---|
| Case number | 44 | 78 |
| Died | 0% | 16.6% |
| Died in uremia | 0% | 2.5% |
| Cure | 15.9% | 26.9% |

## Pathogenesis and Etiology

In discussing the pathogenesis of glomerular minimal change, differentiation must be done between cases with predominant proteinuria (nephrotic syndrome) and those with pure hematuria.

Idiopathic glomerular minimal change with predominant proteinuria is, in our opinion, a unique disease entity about which practically nothing is known regarding its pathogenesis. Four observations merit special consideration (see for survey: [1829].

1. Manifestation of glomerular minimal change in diseases associated with disturbance of T-lymphocytes. Thus, the remission of nephrotic syndrome during measle virus infection, the increased incidence of pneumococcal peritonitis and the response of the nephrotic syndrome to therapy with prednisone and cyclophosphamide all suggest an abnormality in T-lymphocyte function [1486]. This is further supported by an obviously deficient conversion of IgM-AB synthesis to IgG-AB synthesis after antigen stimulation [550a]. Furthermore, the relatively high incidence (see Table 14.8) of malignant lymphoma of Hodgkin's type associated with idiopathic glomerular minimal change lends further support to the hypothesis of disturbed T-lymphocyte function [52, 317, 1131]. The injury to the glomerular BM is said to be mediated via (abnormal) lymphokines [1216] (see also [1828]).
2. Immediate relapse following transplantation may indicate the absence of a permeability-regulating factor or the presence of a permeability-enhancing agent in the serum of afflicted patients [651].
3. It is a remarkable fact that among patients with familial nephrotic syndrome there occurs a large number of bioptically confirmed cases of glomerular minimal change (20 out of 50: [1728]; 4 out of 15 familial cases: [1126]; see also [625] and Table 14.3). In 5 of our own patients with familial nephrotic syndrome, 4 demonstrated glomerular minimal change of which 3 corresponded to the idiopathic from as revealed by EM study. The relatively frequent familial occurrence may either suggest a genetic determination of one of the above-mentioned pathogenetic factors or indicate structural impairement of the BM, which cannot be demonstrated with current techniques.
4. It must not be forgotten, however, that even the most severe endotheliomesangial GN may heal with the most discrete residual structural changes [1582] and become IF negative (see also [1389, 651]). Whether these disease residues may be the structural basis for the clinical symptoms is not known with certainty, although this concept is lately being shared by other investigators [163, 164, 1312, 1806]. In this respect it is also profitable to note that in some cases, diseases which may also lead to GN do cause glomerular minimal change, e.g., in malaria (17 out of 77 cases [828],

Table 18.6. Etiology of glomerular minimal change (predominant proteinuria and/or [isolated] hematuria) ($n=185$)

| | |
|---|---|
| 1.6% | Streptococcal angina |
| 1.6% | Scarlet fever |
| 1.1% | Viral hepatitis |
| 0.5% | Infectious mononucleosis |
| 0.5% | Chicken pox |
| 0.5% | Schönlein-Henoch's syndrome |
| 1.3% | IgA-nephritis (of IF investigated cases) |
| 93.4% | Unknown |

5 out of 63 cases [1728]), in Hodgkin's disease and malignant lymphoma in general [52, 317], in systemic disease: SLE [613, 401, 1484]; Schönlein-Henoch's disease [205, 637] (see Tables 18.6, 17.1, 17.3). Finally, there is experimental evidence that an immunocomplex GN may be present without demonstrable immunocomplexes in the glomeruli [1649a].

It is too early to give preference to any of the above-mentioned pathogenetic factors of glomerular minimal change with predominant proteinuria.

Even less is known about the pathogenesis of idiopathic glomerular minimal change associated with isolated hematuria. To what extent these cases represent only sporadic cases of familial idiopathic benign hematuria (see p. 476) or residual changes following subclinical GN (see Table 18.6) is not clear (see also [1544] and p. 188). Beyond that, there are transitions between both groups of idiopathic glomerular minimal change. One of our cases presented at first with pure nephrotic syndrome after whose complete remission persistent microhematuria developed.

The pathogenesis of the symptomatic forms is presented in the corresponding chapters.

Wether it is justified to include glomerular minimal change with IgM and/or C3 alone in the symptomatic group is not established since this IF pattern is unspecific and may be either the result of immunocomplex deposition or merely of insudation. The main reason for this tentative classification is to establish morphologically defined groups.

We cannot, in common with other investigators [816], support the assumption that glomerular minimal change is a form of focal nephritis. We do not include here the so-called minimal change with focal sclerosis (sclerosing FGN), since every focally accentuated GN shows glomerular injury in the sense of minimal change (at least when studied with EM).

Minimal glomerular change of the type described above can unquestionably occur as an unspecific secondary reaction to other renal diseases such as chronic mercury poisoning, renal vein thrombosis, amyloidosis, Alport's disease, Fabry's disease, hydronephrosis, anoxia, vascular disease, etc. The most meticulous judgement is required to avoid inclusion of these cases into the group of idiopathic glomerular minimal change.

# 19. Glomerulonephrosis and Glomerulosclerosis

[1357a]

## Definition

Operatively, we define glomerulonephrosis (GNo) [1624] as a glomerular change not caused by inflammation or anoxia (contra: [1065]), characterized by intra- or extracellular deposition of material which is quantitatively or qualitatively pathologic. The chronic form of GNo may be designated as glomerulosclerosis (GS: glomerulonephrosis, sclerosing form).

For purposes of simplification, we allocate enzymopathies—which partially belong to GNo and GS—to a separate group. GNo and GS are not recognized as entities by numerous other investigators since, among other elements, secondarily proliferative changes, and changes often interpreted as primarily inflammatory, are not too infrequently observed in GNo and especially in GS (e.g., amyloidosis).

## Nosology

The following subclassification of GNo and GS has proven useful in histopathology:

*Unspecific GNo and GS*

1. Idiopathic, unspecific GNo/GS also designated infectious, toxic [1791, 1065] GNo/GS.
2. Symptomatic, unspecific GNo and GS with known basic disease, e.g., plasmocytoma, diabetes mellitus, eclampsia, hyperthyroidism without [373] and with perchlorate therapy [936], chronic carbon disulfide poisoning [753], massive corticoid therapy [1791], and mercury poisoning without allergy [1788].

*Specific GNo and GS*

1. Specific GNo and GS due to pathologic extracellular deposition resulting in glomerular impairment (disturbances at the capillary interface) e.g. amyloidosis, diabetes mellitus, and foreign substances such as polyvinyl pyrrolidon [497, 1624].
2. Specific GNo and GS due to pathologic intracellular deposition, e.g., foreign substances such as silver, etc. [1771].

# Idiopathic Unspecific Glomerulonephrosis and Glomerulosclerosis

## Clinical Findings

The clinical findings in 16 of our own cases of idiopathic unspecific GNo were, by and large, insignificant: proteinuria of less than 1 g/day in one case and microhematuria in another. In two patients with GS resulting from carbon disulfide exposure, one evidenced proteinuria of less than 1 g/day and one a blood pressure of 150/115 mm Hg (the only case of hypertension encountered).

## LM Findings

Widening of the mesangial space, in GNo chiefly caused by swelling of mesangial cells (Fig. 19.1) and in GS by increase of the mesangial matrix (Fig. 19.2) is common to both forms. Although mesangial cellular increase does not belong to the basic picture of GNo and GS, it can occur as a reaction in GS as shown morphometrically [1624].

**Fig. 19.1.** Unspecific glomerulonephrosis associated with sepsis. ▷ Glomerular tuft appears to be enlarged. No hypercellularity present. PAS (×500)

**Fig. 19.2.** Unspecific diffuse diabetic glomerulosclerosis. Obvious mesangial matrix increase without accompanying cell increase. Glomerular capillary loops are not narrowed. Male, 73 years. PAS (×625)

**Fig. 19.3.** Unspecific glomerulosclerosis, possibly caused by ischemia. Mesangium is clearly broadened and demonstrates coarse mesangial matrix bars (*MM*) but no cell increase. Mild thickening of lamina rara interna, no foot process fusion or activation of endothelium. Female, 45 years. EM (×4700)

### IF Findings

Examination of three cases of idiopathic unspecific GS from our material revealed a diffuse, global mesangial fluorescence of slight intensity for C3 in one case, and a diffuse, global mesangial and peripheral distribution of IgM and C3—along with focal-segmental mesangial and peripheral IgG distribution—in another case. The third case showed a diffuse, ultralinear BM staining with IgG of slight intensity along with granular mesangial and peripheral focal-segmental distribution of IgM.

### EM Findings

In addition to swelling of mesangial cells and nuclei in GNo, which is partially accompanied by nuclear polymorphy in GS, there also occurs a thickening and increase of the mesangial matrix (Fig. 19.3) and, more rarely, a slight cell increase. The endothelium demonstrates slight edema or hypertrophy with arcade formation and nuclear swelling. Podocytes are also edematous and often demonstrate nuclear swelling. An insignifiant fusion of foot processes and formation of microvilli sometimes occur. Segmental thickening of the BM with participation of the lamina densa and thickening of the lamina rara interna are more frequently observed [373, 1800], see also Figures 6.9, 6.21, 6.34, 6.57, 6.65, 6.79, 6.88.

### Prognosis

The prognosis of idiopathic unspecific GNo/GS is good and the lesions probably regress if the inducing condition can be eliminated [753, 936, 1791]. In 10 of our patients with a follow-up of 1–6 years, only 1 female patient, long addicted to phenacetin, has a clinically demonstrable nephropathy. In 2 cases with chronic carbon disulfide exposure, no kidney changes are present after follow-up lasting 6 and 8 years respectively, while hypertension in one patient remains at 150/100 mm Hg.

### Differential Diagnosis

Differential diagnosis is, practically, of significance only in relation to the idiopathic unspecific form. It is of prime importance to exclude diffuse endotheliomesangial GN in axial and possibly minimal proliferative or sclerosing stage. Of help is the qualitatively nonobvious mesangial cell increase (a slight cell increase is, to be sure, usually only demonstrable by morphometry) as well as the absence of synechiae with LM.
Inflammatory glomerular disease is more or less improbable if IF findings are negative and if no osmiophilic deposits can be found with EM. If, however, positive IF findings or EM demonstrable deposits are encountered in the mesangium or along the mesangial BM, correct interpretation may be almost impossible on purely morphologic grounds as is the case for the differentiation from resolving GN. Differentiation from ischemic glomerulopathy is easy with EM, but may be difficult in LM since the needle biopsy may not contain the corresponding vascular lesions; or if they are present, they may be misinterpreted.

## Amyloid Nephrosis

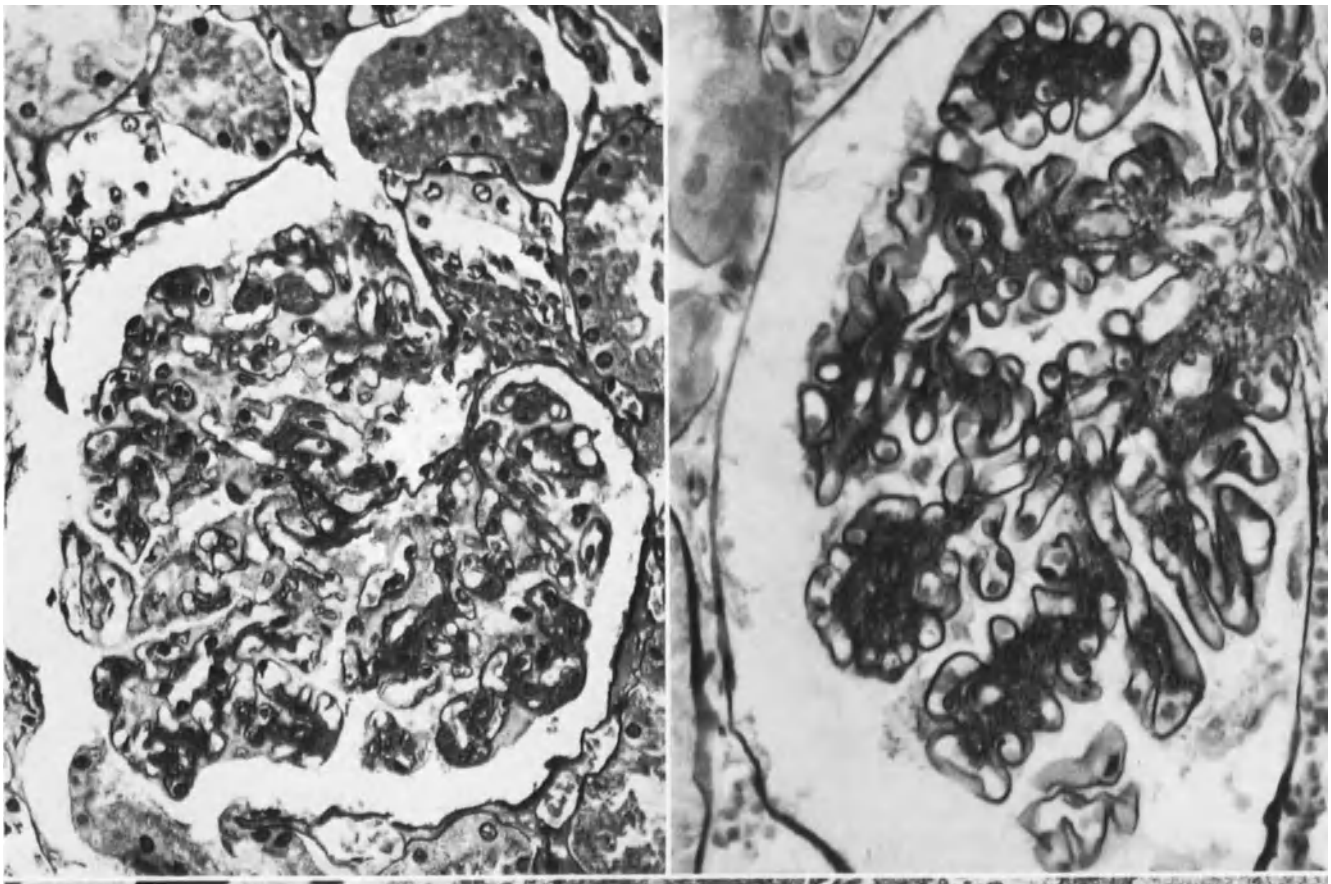
[112, 565, 785a, 1484, 1694, 1832]

### Nosology

Amyloidosis can be classified into three basic forms: (1) idiopathic (no known underlying disease) with relatively seldom renal involvement, (2) a rare familial form [12], and (3) an acquired form with known underlying disease which demonstrates frequent renal involvement. Of little importance for renal histopathology is the amyloid occuring in the aged and in its tumor form. The idiopathic form is by and large identical to paramyloidosis, although one may also occasionally encounter an atypical staining pattern in the acquired form, and especially in plasmocytoma [60] since, among other factors, old amyloid responds similarly as collagen [939].
A further classification of amyloidosis according to histologic findings recognizes a perireticular (better: BM) and a pericollagenous (better: vascular) form [1111]. The acquired perireticular form develops in conjunction with chronic inflammation, rheumatoid arthritis, and neoplasia, and the acquired pericollagenous form in conjunction with SLE (often both forms), plasmocytoma and Waldenström's disease [296]. These two forms cannot, however, readily be differentiated in the kidney. A recent tentative classification is based on the immunochemical composition of amyloid fibrils [785a, 1832]: AL=amyloid of light chain origin, AA=amyloid of unknown origin.
This classification shows a certain parallelness to the histologic one i.e. AL is found in plasmocytoma and in pulmonary tumor form and the AA in familial Mediterranean fever and in secondary amyloidosis due to chronic infections.
Tinctorial distinction is provided by the potassium permanganate Congo red stain [1833].

### Incidence

The frequency of amyloid nephrosis in autopsy has been variously reported: Z: 1.9%=49 out of 25,000; 4.5%:



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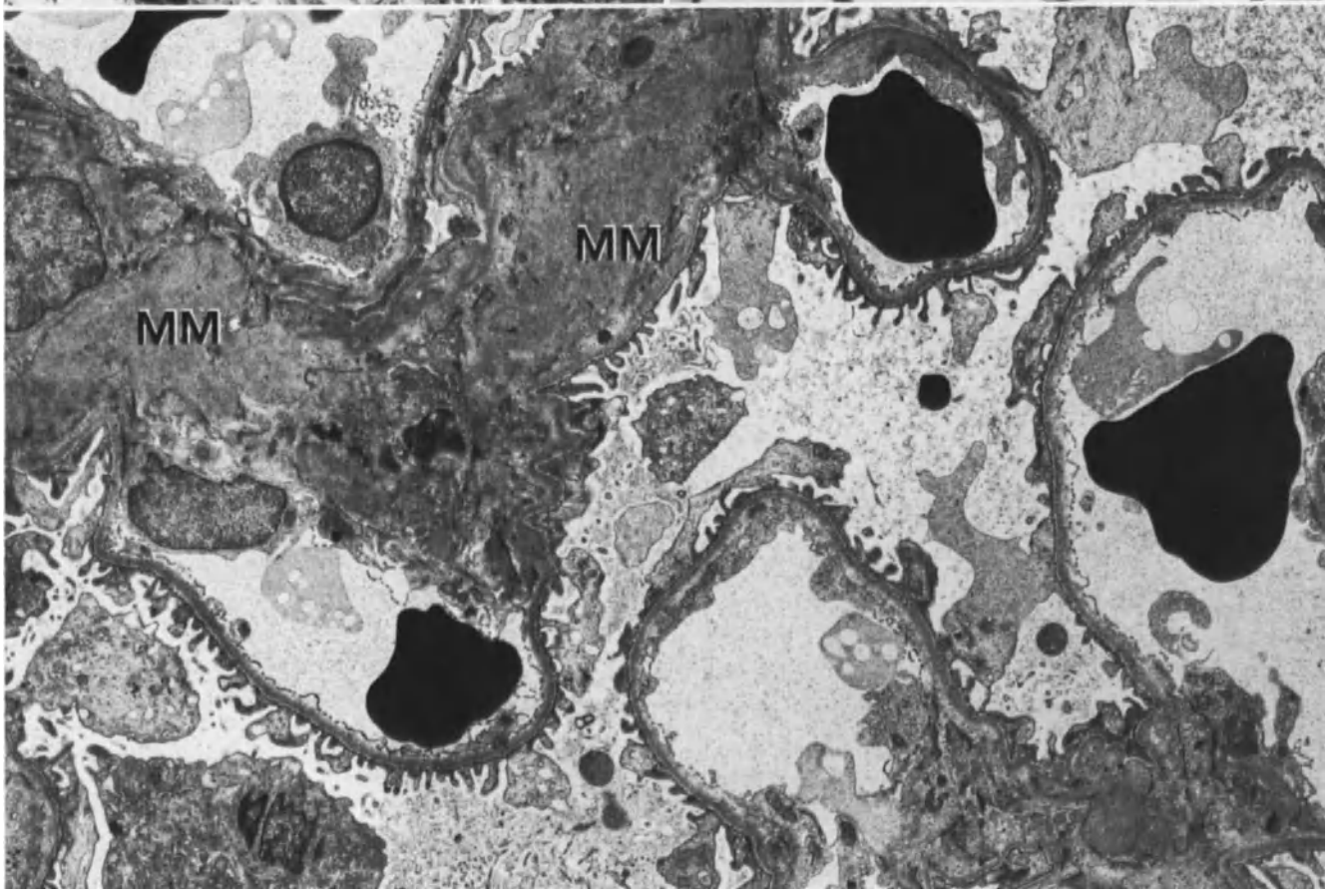



19.3

[1683]. In our biopsies, we encountered it in 1.25% of 2080 cases. The disease is most frequent in the middle and older age groups (70% between 30 and 60 years [1694]; see also Table 19.1). In children, the lesion has only been reported in 9 out of 1368 biopsies [624]. The sex ratio of males:females is 3:1 [1694]; 1.4:1 (Z).

## Clinical Findings

The predominant features of the clinical findings—as studied essentially on the basis of acquired amyloidosis occurring in conjunction with familial Mediterranean fever [1527]—consist of persistent proteinuria of as long as 10 years' duration and often of a nephrotic syndrome which has been reported as occurring in 18.2–83.3% [112]; (3 out of 4: [1694]; 11 out of 14: [1013]; 10 out of 20: Z), partly accompanied by microhematuria and leukocyturia (Table 19.1).

Various incidences have been reported for progressive renal insufficiency, e.g., 11 out of 49 autopsies and 9 out of 20 biopsies (Z), and in 10% [1013, 1683] of a series of cases.

Polyuria or true diabetes insipidus [82, 253] from amyloidosis of BM in the region of collecting ducts and the vasa recta are rare (1 in 26: Z) but may be the initial symptoms.

Oliguria—if it occurs at all—is a terminal symptom. Hypertension is said to occur in 36–50% of the severe cases [112, 1683] and in 21% of all cases of amyloid nephrosis [1694], 2 out of 17: Z; Table 19.1. We found unequivocal renal hypertension only in association with amyloid-contracted kidneys (3 out of 49 autopsies: Z).

Biopsy of rectal mucosa is often positive for amyloid in the vessels (25% of cases: [643a]). Serum gamma globulins are increased. The Congo red test is positive in generalized amyloidosis (loss of over 40% of the dye from the serum after 1 h) but can be negative in the early stage of the disease (4 out of 8: Z).

In a considerable number of cases (even in nonplasmocytoma patients), Bence Jones protein occurs in the urine [1228]. The disease course is usually slow, i.e., lasting years, rarely months.

Table 19.1. Clinical findings in amyloid nephrosis in 26 biopsy cases

1. Sex ratio ♂:♀ 1.4:1
2. Age at Biopsy

| Age Group | Incidence |
|---|---|
| <40 years | 4 |
| 40–60 years | 14 |
| >60 years | 4 |

3. Duration of disease at time of biopsy

| Duration | Incidence |
|---|---|
| <1 years | 7 |
| 1–2 years | 3 |
| >2 years | 6 |

4. Increase of serum urea/creatinin in 9 out of 20 patients
5. Total serum protein

| Protein | Incidence |
|---|---|
| >6 g% | 2 |
| 5–6 g% | 5 |
| <5 g% | 10 |

6. Hyperlipidemia: 10 out of 15 patients
7. Proteinuria

| g/day | Incidence |
|---|---|
| 0 | 1 |
| <1 | 1 |
| 1 3.5 | 8 |
| >3.5 | 10 |

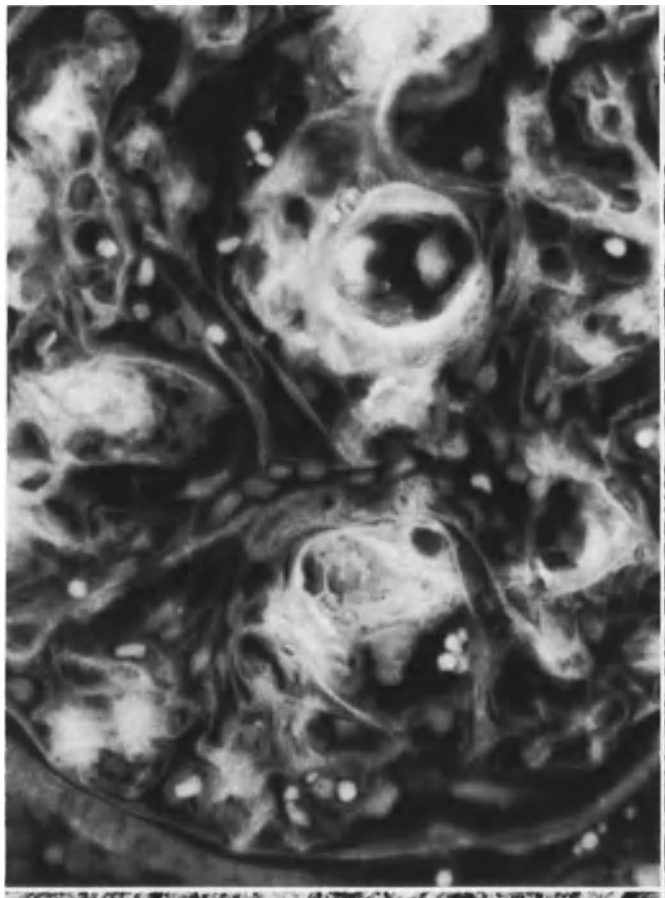
8. Microhematuria: 6 out of 18 patients
9. Leukocyturia: 9 out of 18 patients
10. Blood pressure ≧160/100 mm Hg:2 out of 17 patients
11. Clinical diagnosis

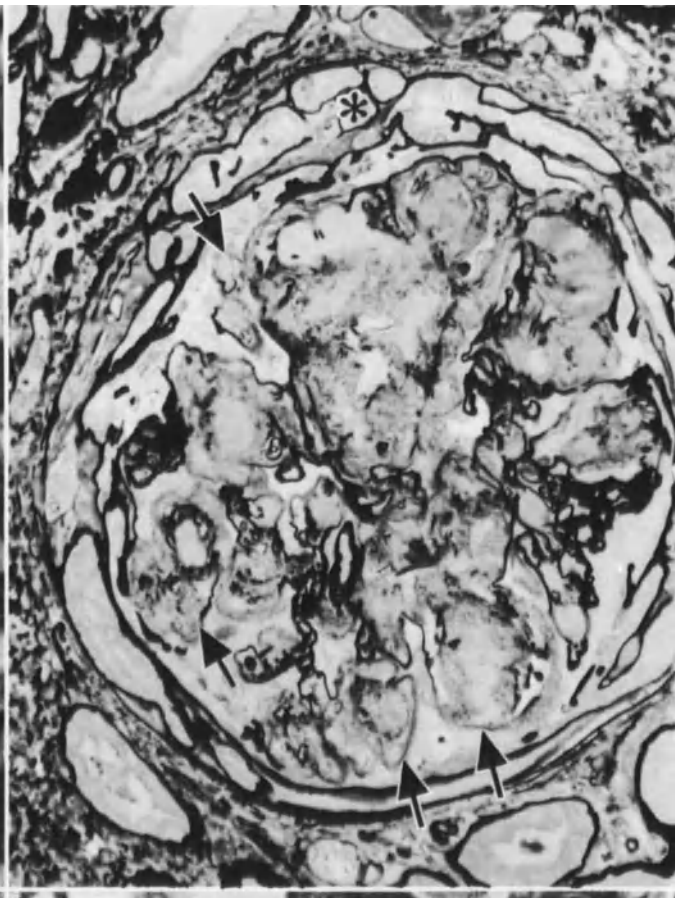
| Diagnosis | Incidence |
|---|---|
| GN | 4/20 |
| Amyloidosis | 16/20 |

## LM Findings

The simplest demonstration of amyloid is by means of the Congo red stain which, under polarized light, shows a brilliant green colour (Fig. 19.4; [308a]; for false positive results see [857]). Metachromasy is obtainable with the methyl violet stain. Intense fluorescence with the thioflavin stain [1756] (for phlorwhite BBU, see [1817, 1832]) and EM demonstration of fine fibrils are very sensitive methods for demonstrating amyloid.

In very mild cases of the disease, annular, oval, or spindle-shaped homogenous deposit which in HE stain pale pink and yellowish in van Gieson stain, are demonstrable peripherally or mesangially in scattered glomeruli. Amyloid deposits are weakly PAS positive and lie between endothelium and BM and also occasionally entirely within the mesangium. With PASM stain, the deposits appear as cut-out spaces. In the region of BM amyloid





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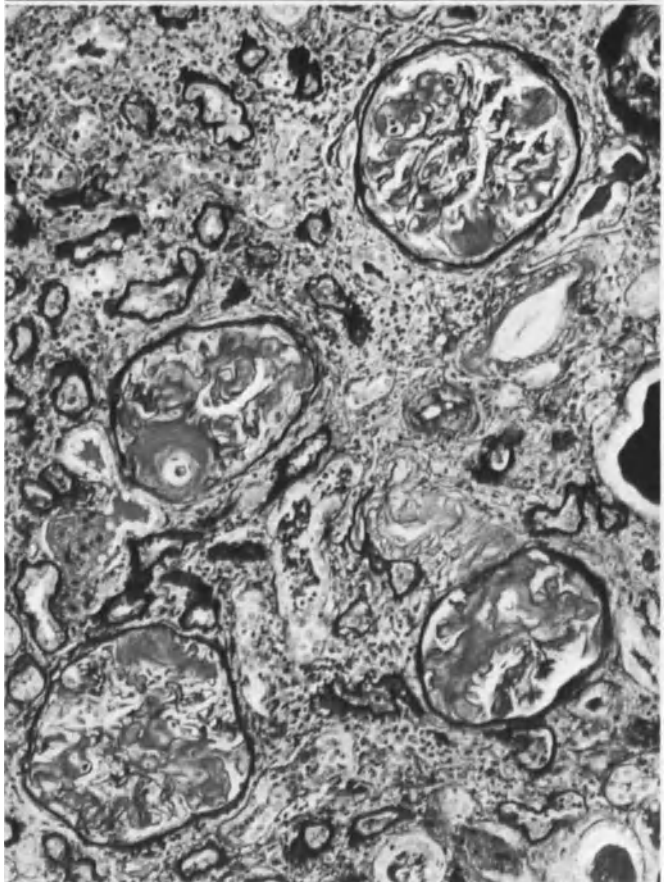
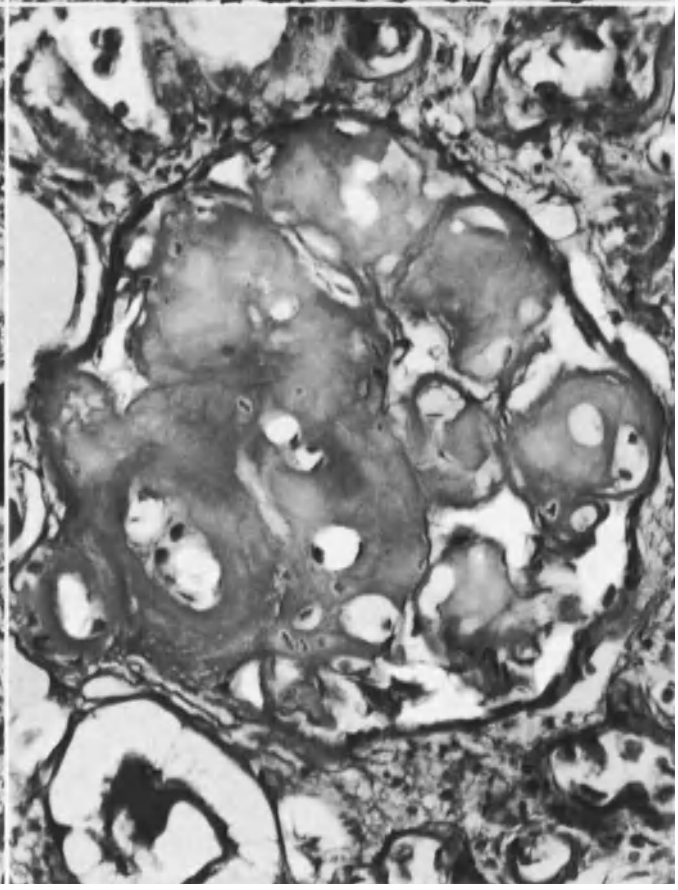




19.6
19.7

deposits, the BM is difficult to demonstrate (Fig. 19.5). In the AFOG stain, some of the amyloid stains red.
Relatively severe concomitant involvement of large blood vessels indicates idiopathic amyloidosis. However, histologic study of biopsy material does not permit differentiation between the idiopathic and acquired forms. With slight disease, the tubules usually demonstrate minimal protein droplet change whereas the interstitium is unaffected.
In the advanced cases, numerous, seemingly obsolescent glomeruli—which, however, are yellow with the van Gieson stain—are present.
In the more or less intact glomeruli, a considerable narrowing of capillary loop lumens is caused by amyloid deposits (Fig. 19.6). In the center of cross-section of glomerular capillary loops with large amyloid deposits, a crown of endothelial cells may be recognized (Fig. 19.7) even in loops without discernable lumen.
The pronounced lack of cells in the homogenous masses is always a good indication for the diagnosis. Here and there, local capsular epithelial proliferation (segmental crescents) over more or less obliterated capillary loops may be present. We have observed overload glomerulitis (see p. 308) in glomeruli free of amyloid in only one case of amyloid contracted kidney.
Amyloid deposition in the afferent glomerular vessels and in the arteries is usually always present in advanced stages. Proximal tubules of severely damaged glomeruli often show storage of neutral fats and lipoids (secondary lipoid nephrosis). Tubular and vascular BM—especially in the medulla—are thickened and infiltrated with amyloid in about 50% of the cases.
The numerous hyaline casts occasionally yield positive reactions to amyloid stains. Tubular atrophy is frequent when the glomeruli are severely damaged. In the absence of plasmocytoma, impacted medullary casts surrounded by syncytial giant cells and inflammatory cells are extremely rare. We have very seldomly seen amyloid deposits free in the interstitium [1503] but we have encountered them in the walls of intertubular capillaries. Interstitial groups of foam cells are commonly observed (Fig. 19.8).

### IF Findings

In general, immunoglobulins and complement (C3) with mesangial and peripheral distribution are found in the glomeruli in both idiopathic and acquired amyloidosis [228, 1074, 1651]. More rarely, complement alone may occur in the amyloid deposits [895].
We have found IgM and C3 and, less pronouncedly, IgG and IgA in the mesangial and peripheral amyloid deposits. Additionally, IgM and C3 could be demonstrated in afflicted vessels.

### EM Findings

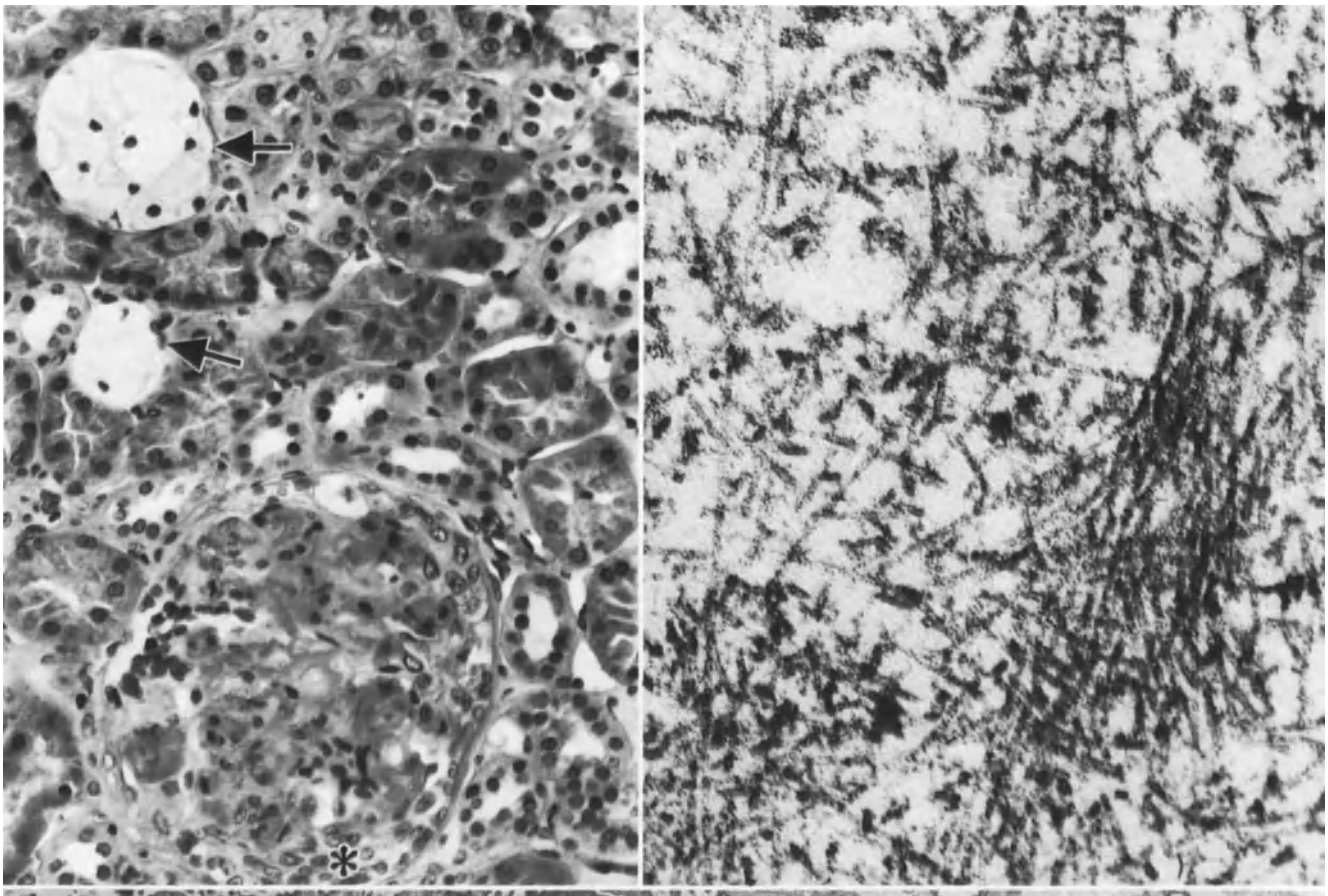
Fundamentally, amyloid consists of two components: (1) 30–35 Å-wide fibrils demonstrable with EM (Fig. 19.9) and (2) collagen-like rods with a periodicity which cannot be demonstrated in biopsy material [112]. Deposition of fibrillar amyloid masses is said to start in close contact with BM [767]. The amyloid is initially deposited along the BM in the mesangium (Fig. 19.10) and later subendothelially [1694]. Later on, the amyloid more or less spills out of the mesangium along—and sometimes within—the BM (Fig. 19.11) into the periphery and can finally come to lie subepithelially. The BM itself is usually well preserved for a considerable period of time; it is, however, thickened, and, at first, mainly the lamina rara interna and externa are permeated with amyloid fibrils while the lamina densa is thinned (Fig. 19.12). In a few cases, the amyloid fibrils form spike-like bundles subepithelially (Fig. 19.13).
We have never found fibrils intracellularly, nor could we confirm their emergence into the capsular space [767]. In very severe cases, capillary loop destruction occurs. Capsular BM is often thickened and fragmented, but, in our experience, was never found to contain amyloid.
Amyloid fibrils can often be demonstrated in peritubular BM and vessels as well as between interstitial cells (Figs. 19.14, 19.15). Massive amyloid deposits occur in the BM of collecting ducts.

◁ **Fig. 19.4.** Amyloid glomerulonephrosis as seen with the thioflavin T stain under ultraviolet light. There are extensive light-appearing amyloid masses in the mesangium which occasionally extend towards the glomerular capillary loop periphery. Male, 61 years. (×800)

**Fig. 19.5.** Amyloid glomerulonephrosis. BM in the region of the amyloid infiltration is either not argyrophilic or only poorly so (→). Old sclerosed segmental crescent (*). Female, 62 years. PASM (×600)

**Fig. 19.6.** Severe amyloidosis of the kidney with uremia. Extensive occlusion of glomerular capillary loop lumens by amyloid. Tubules evidence atrophy and BM thickening. Accompanying interstitial nephritis is present. Autopsy specimen. PAS (×187)

**Fig. 19.7.** Same case as in Figure 19.6. Only a few glomerular capillary loop lumens are still patent. Except for some endothelial cells, all other have disappeared. Extensive synechiae with capsular BM are present. Autopsy specimen. PAS (×500)



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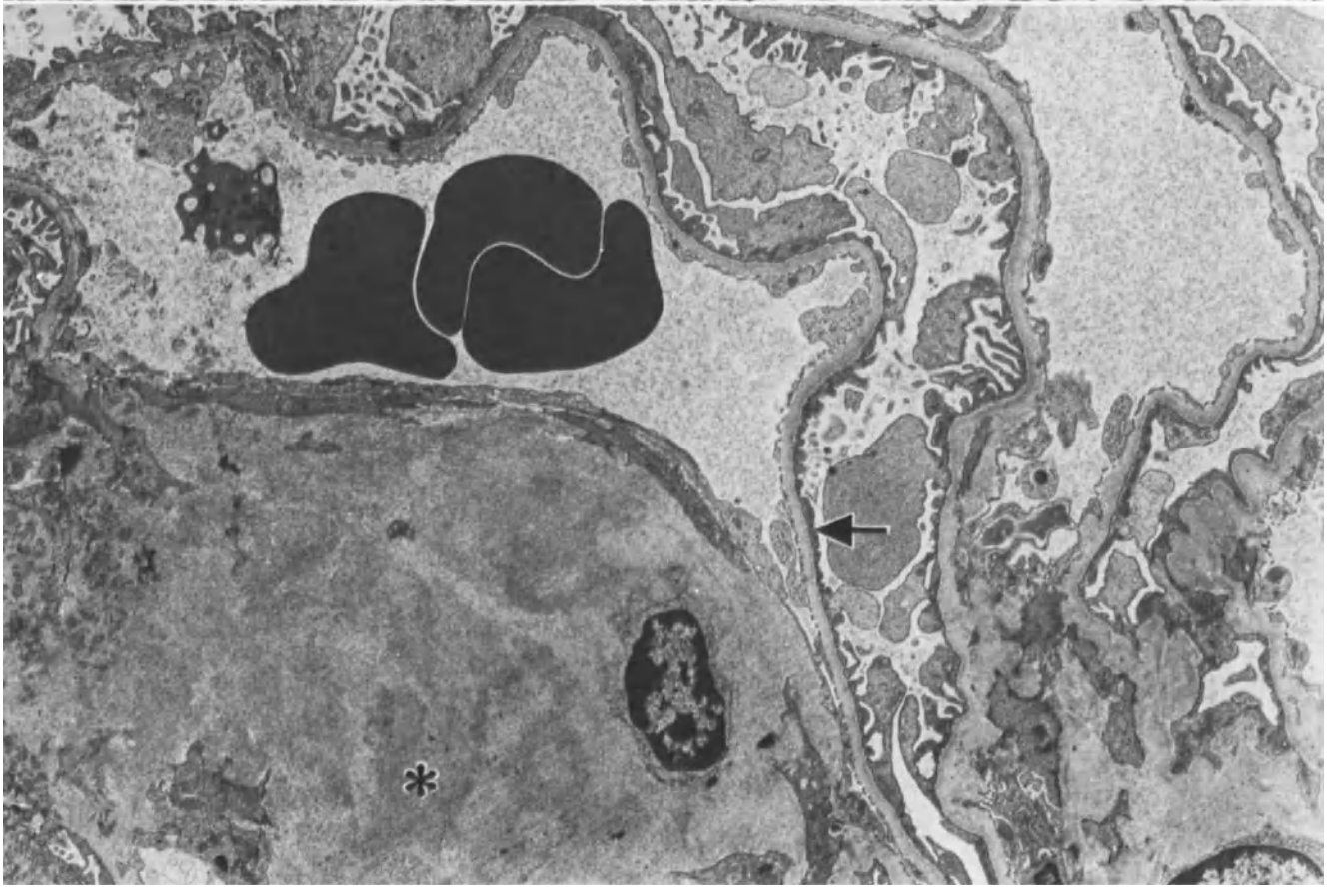

19.10

## Differential Diagnosis

Concerning differential diagnosis, attention to staining characteristics, chiefly with respect to the yellow staining of amyloid masses with the routine van Gieson stain, permits unequivacal diagnosis. Confusion between small amyloid deposits and fibrin or fibrinoid capillary loop thrombi in the early disease stage is possible, but it is recalled that both types of thrombi stain far more intensively red with HE and that fibrin thrombi are fibrillar. In cases of doubt, Congo red staining and thioflavin T fluorescence provide unequivocal proof. The lobular form of membranoproliferative GN (see p. 235) as well as nodular diabetic GS are easily differentiable from (PASM negative) amyloid by their strongly increased PASM stainable matrix.

## Complications

Secondary renal vein thrombosis (see p. 503) is an infrequent but typical complication which is said to result from polyuric dehydration [82, 1013].

## Prognosis

In the long run, the prognosis is not good. Cases of regression following elimination of the basic disease [643a, 785a, 976, 1694] are rare. One of our own patients with acquired amyloidosis due to osteomyelitis of the femur showed partial remission of clinical symptoms following amputation. Follow-up in 20 of our patients showed that 6 out of 20 lived 5 years and longer; 12 out of 20, however, died within a year after biopsy. In 7 out of 12 cases, death was due to uremia. The average survival time after appearance of the nephrotic syndrome is 3 years [1527]. Two transplants functioned for 5 and 12 months respectively without signs of recurrence of amyloidosis [296] as was the case in 5 out of 6 in another series in which 1 case of recurrence of amyloidosis was found 6 months after transplantation [785a].

## Pathogenesis

The pathogenesis of the disease still awaits satisfactory explanation. A classic antigen-antibody reaction is no longer thought to be involved. Current interest is mainly focused on the theory [1602] that amyloidosis results from a derangement of the humoral antibody-forming system. This is further substantiated by biochemical studies of amyloid fibrils in plasmocytoma [785a] which have shown them to consist of proteins closely related to the light chains of the immunoglobulins (AL, see p. 382) [660], and to be arranged in form of a $\beta$-pleated sheet ([1832]; see also 186, 295, 308a, 1756]). Thus, the amino acid sequence of amyloid fibrils in 2 cases was identical to that of the kappa Bence-Jones protein [566].

The occurrence of amyloidosis in plasmocytoma possibly depends on the relationship of the kappa/lamda chains in that a predominance of the lamda chains is reported to favor the development of amyloidosis [1267]. Amyloid obtained from cases with secondary amyloidosis and Mediterranean fever do not consist of light chains only but mainly of a protein of unknown cellular origin (A-protein) a precursor of which is found in the serum (SAA-protein) ([785a, 1832]; see also [420]). But it is not yet completely understood how the soluble precursors are transformed into amyloid fibrils. Cells with proteolytic activity, e.g., mesangial cells, podocytes (possibly) and endothelial cells (possibly) could play a significant role in the formation of the amyloid fibrils [186, 565, 767, 1503, 1715, 1832].

◁ **Fig. 19.8.** Same case as in Figure 19.5. Tubular foam cells in severe amyloidosis (→). Crescent formation (*) in severely afflicted glomerulus. Male, 62 years. Congo red (×280)

**Fig. 19.9.** Amyloid fibrils. Female, 29 years. EM (×113,000)

**Fig. 19.10.** Massive mesangial amyloid deposits (*). Slight edema of podocytes and foot process fusion (→). Female, 42 years. EM (×5200)

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**Fig. 19.11.** Amyloidosis of a glomerular capillary loop. Amyloid fibrils permeating the BM (→←) which appears thickened. Podocyte (*P*), endothelium (*E*). Female, 56 years. EM (×28,000)

**Fig. 19.12.** Glomerular BM in amyloidosis. Original lamina densa (*LD*) is severely narrowed and occasionally permeated by amyloid fibrils. There are massive deposits of amyloid fibrils in the lamina rara interna (*). Two subepithelial spike-like accumulations of amyloid fibrils are present (→). Same case as in Figure 19.9. Female, 29 years. EM (×29,000)

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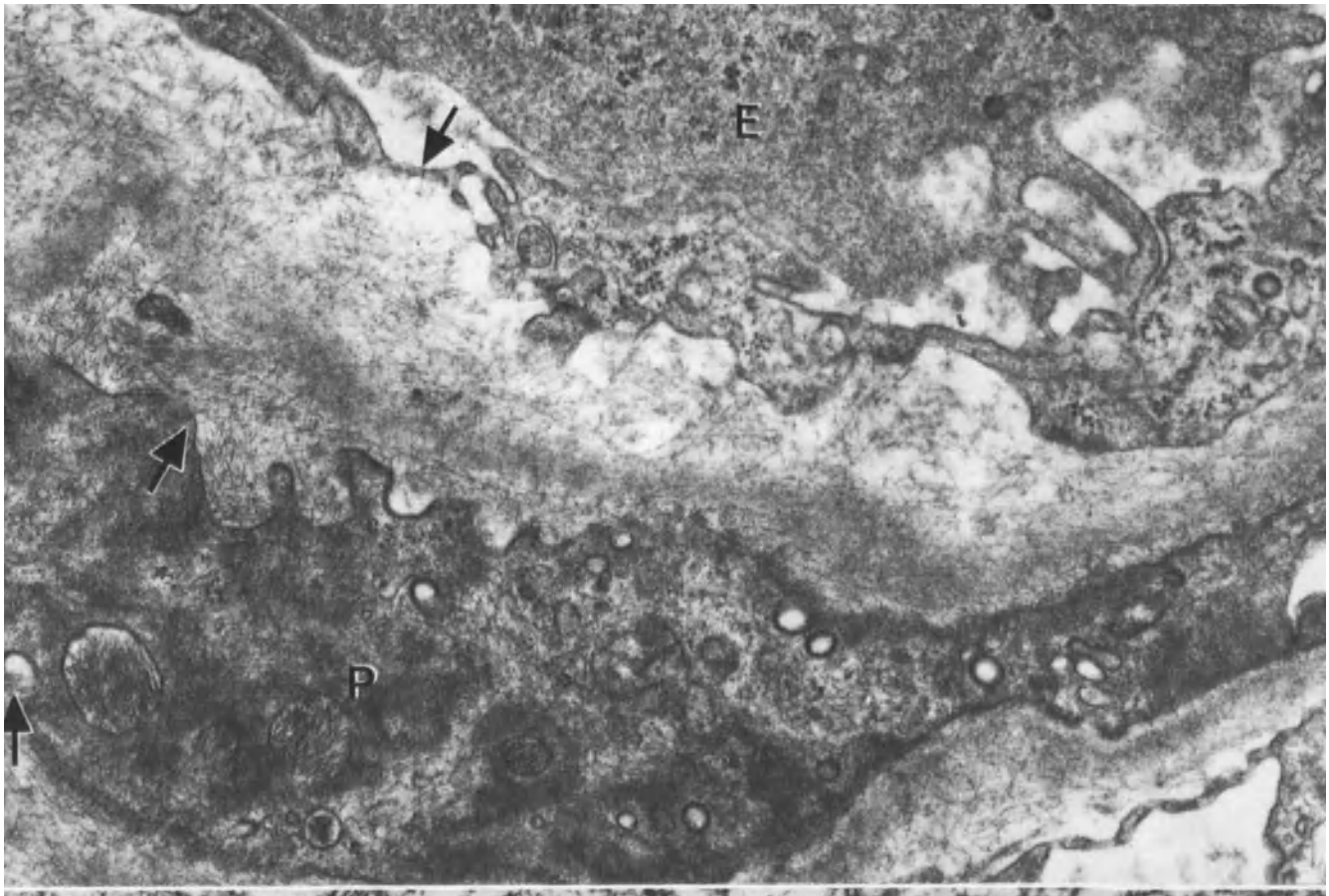
**Fig. 19.13.** Same case as in Figure 19.12. BM of a peripheral glomerular capillary loop permeated with amyloid fibrils with spike-like accumulation of fibrils (→) covered by severely hypertrophied podocytes. Lamina densa is still partially discernable. An amyloid mass (*) is invading the capillary loop and compresses an endothelial nucleus. Female, 29 years. EM (×7000)

**Fig. 19.14.** Massive amyloid deposits (*) in the media and intima of an arteriole. The same case as in Figure 19.5. Male, 62 years. EM (×4200)

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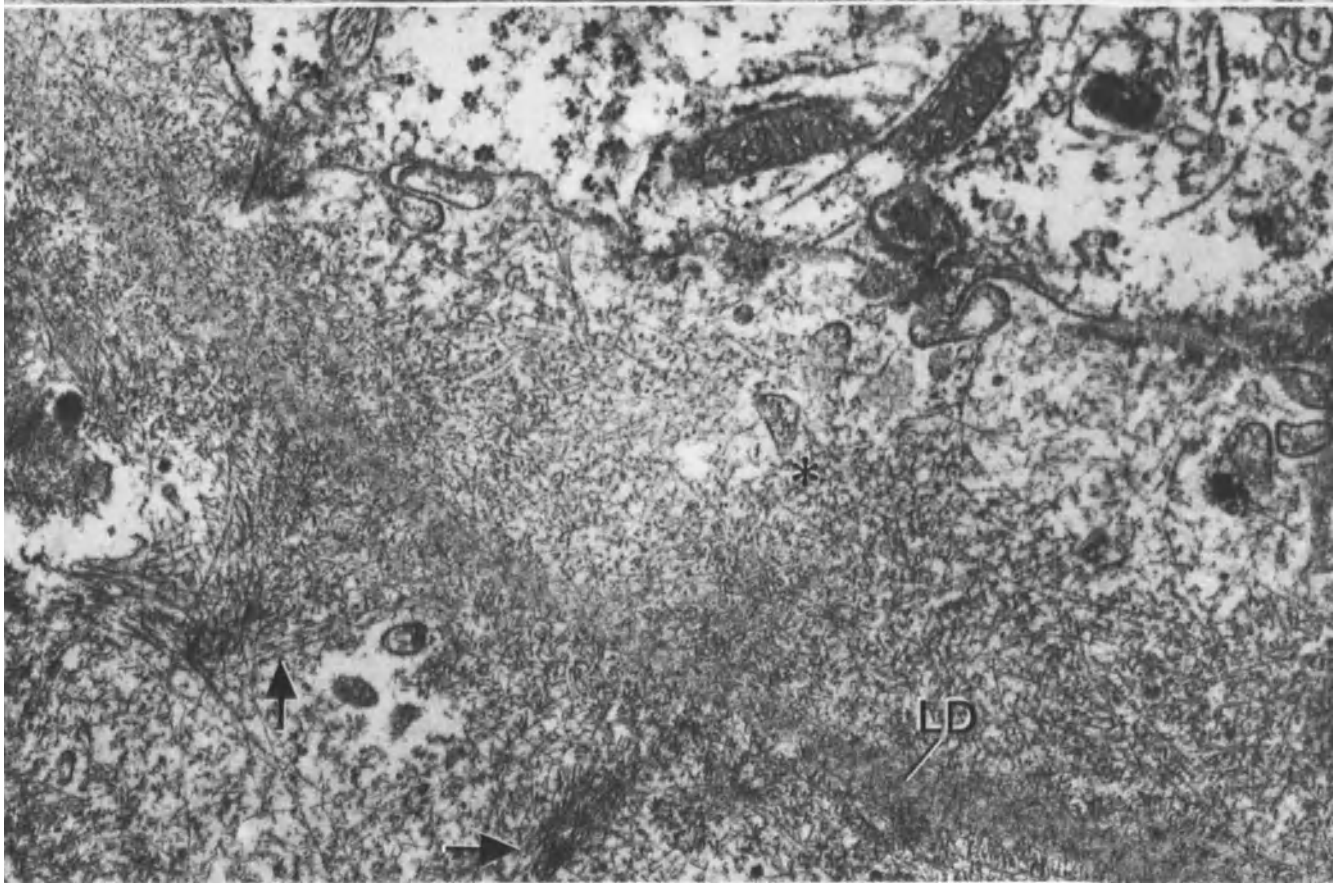


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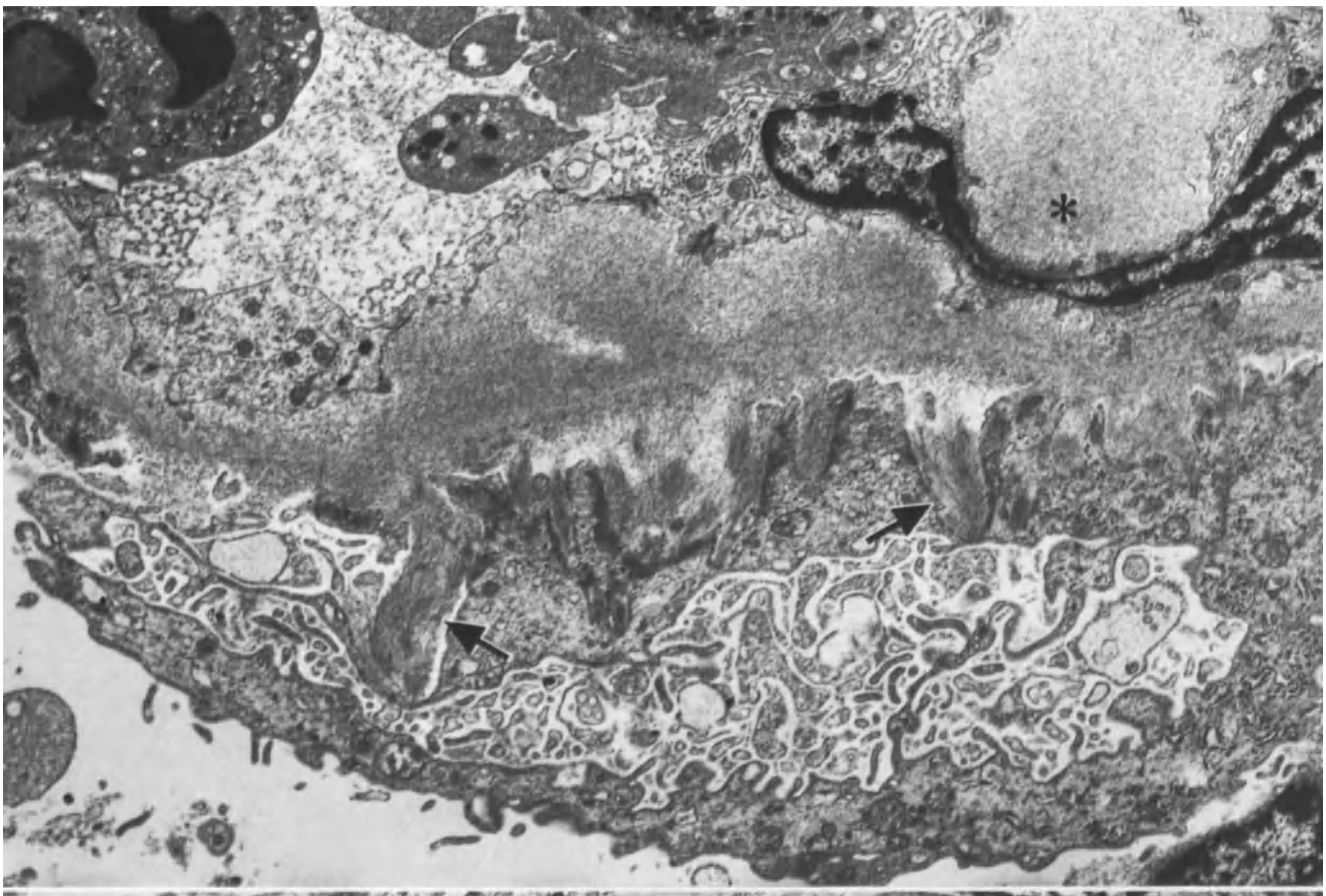

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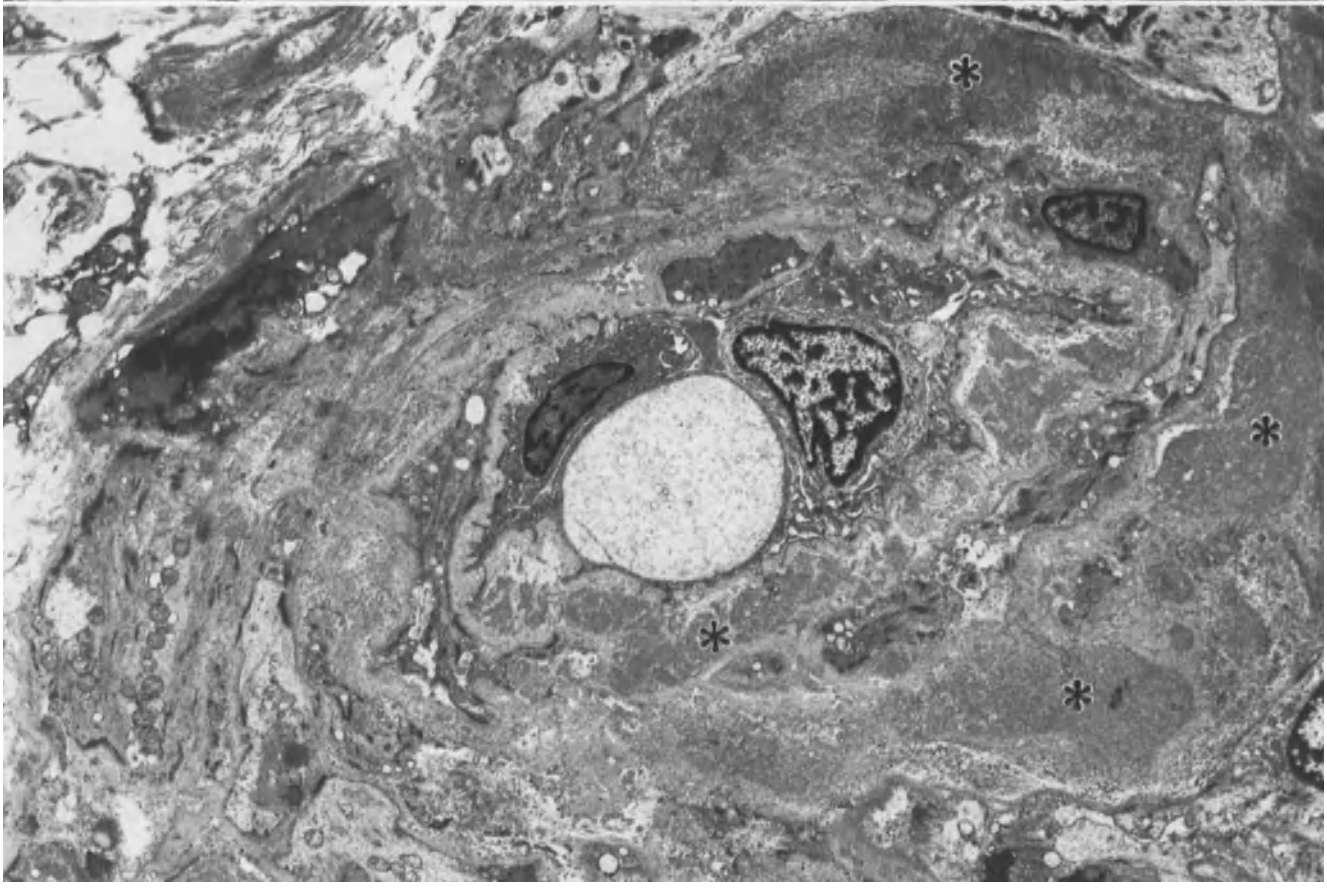

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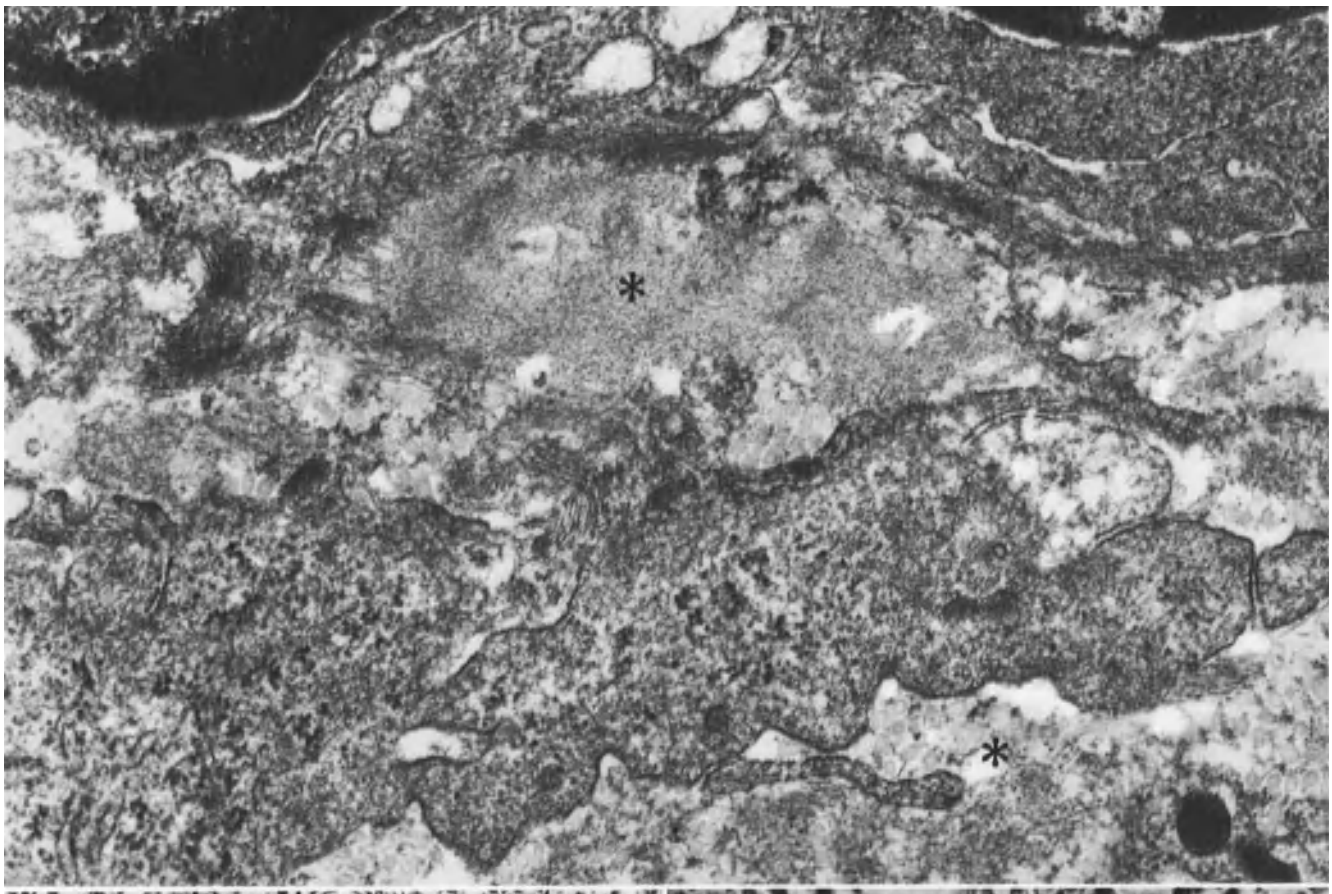

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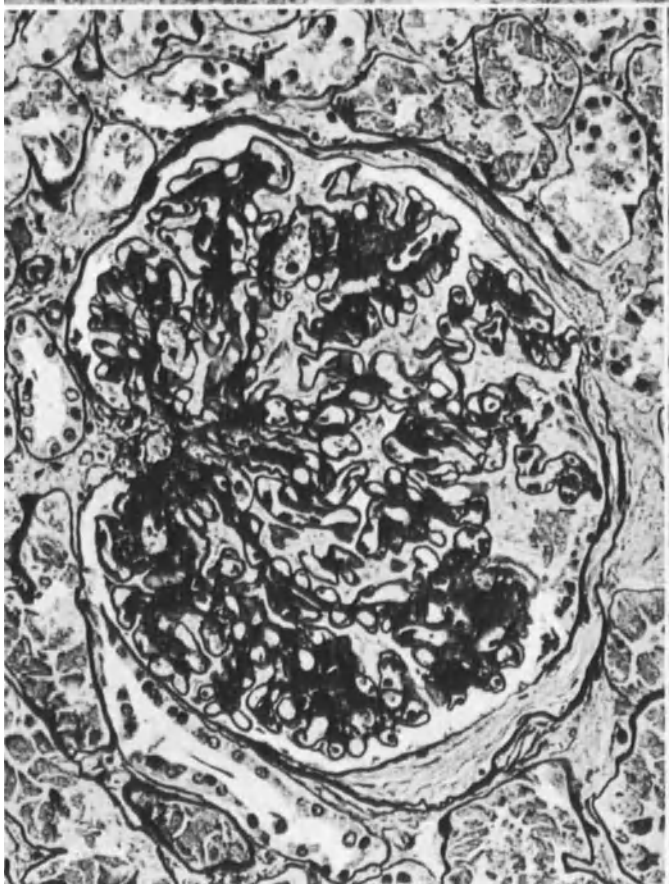

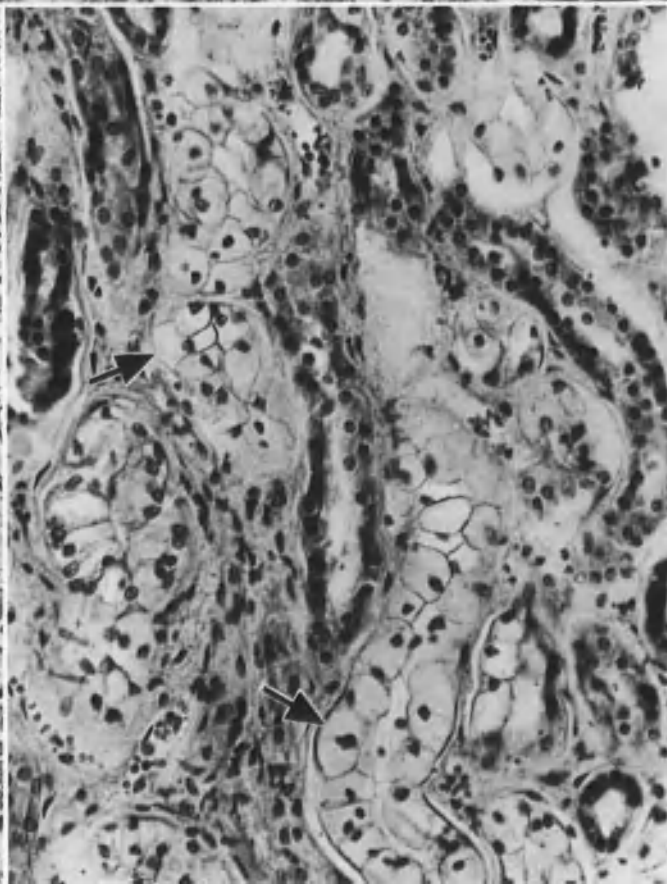

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### Etiology

Etiologically (Table 19.2), the most frequent cause of amyloidosis is chronic inflammation (>50% of our cases) which is less often demonstrable today than in the past. Typical chronic infections are pulmonary tuberculosis, rheumatoid arthritis, chronic osteomyelitis, infected bronchiectases, colon diverticulosis, Crohn's disease, syphilis (stage III) and Mediterranean fever (regionally one of the major etiologic factors: 28%: [1527, 1683]. The percentage of cases associated with rheumatoid arthritis varies [130, 546, 643a] considerably (17%: [1694]; 60% of autopsies and 10–14% of biopsies: [1158]; 14%: Z). It is not known whether these variations in frequency can be explained by the far more extensive use of corticosteroids in rheumatoid arthritis in USA. Amyloidosis complicates Bechterew's disease in 3.5% of cases [546]. Further important etiologic factors are malignancies: medullary plasmocytoma (5–10%: [1683]; 2–15%: [1624]; 7%: Z), Waldenström's disease (3 out of 16 cases: [1135]), as well as Hodgkin's disease (2 out of 49: Z), and carcinomas (12%: Z) among which renal cell carcinoma is said to be the most frequent [369]. Renal symptoms are not rarely the first sign of amyloidosis and thus of an occult basic disease which, accordingly, requires appropriate clinical clarification.
Despite all efforts, a basic disease cannot be demonstrated in one-quarter to one-third (30%: Z) of patients.

Table 19.2. Etiology of amyloid nephrosis in 69 of our own cases

| Basic disease | Frequency in biopsy material ($n=20$) | Frequency in autopsy material (several basic diseases possible) ($n=49$) |
|---|---|---|
| Unknown | 4 | 17 |
| rheumatoid arthritis | 4 | 6 |
| Osteomyelitis | 4 | 2 |
| Chronic pulmonary tuberculosis | 3 | 11 |
| Crohn's disease | 1 | – |
| Colon diverticulosis | 0 | 3 |
| Bronchiectasis | 0 | 5 |
| Mediterranean fever | 1 | – |
| Plasmocytoma | 1 | 4 |
| Carcinoma | 2 | 6 |
| Hodgkin's disease | 0 (2) | 2 (8) |

## Diabetic Glomerulosclerosis
[1484, 1791]

### Definition

Diabetic glomerulosclerosis (GS) is either an unspecific diffuse GS or a specific nodular GS (Kimmelstiel-Wilson).

### Incidence

The nodular form occurs in 5.6% of all autopsies and in 14.2% of those of diabetics [1791] (17–25.8%: [1624]). It has been reported in 34.5% of 764 needle biopsies obtained from diabetics [375] and in 12–25% in another series [276]. The diffuse form appeared in 44.4% [375] and 60% [276] respectively of needle biopsies from diabetics. Diabetic GS is rarely seen in children (2 out of 1368 cases: [624]).
It has been reported that with EM study, practically 100% of the needle biopsies from diabetics evidence damaged glomeruli [276]. It is not easy to give exact data on the frequency of diffuse diabetic GS since it is difficult to draw a line from mesangial changes attributable to age; and in a large percentage of cases reviewed, other renal lesions are also present which in turn can give rise to similar changes (Table 19.3). Data on the relative frequency of severe diffuse diabetic GS and the nodular form only make sense by considering diabetics not requiring drug treatment, those requiring drug therapy, and those dependent on insulin each separately. We have handled our material in this fashion (Ta-

◁ **Fig. 19.15.** Amyloid deposits (*) in renal interstitium. Same case as in Figure 19.5. Male, 62 years. EM (×36,000)

**Fig. 19.16.** Extensive unspecific diabetic glomerulosclerosis. Mesangium is enlarged by matrix increase only. Glomerular capillary loop BM appears delicate but capsular BM evidences incipient splitting and thickening. Male, 45 years. PAS (×500)

**Fig. 19.17.** Armanni-Ebstein cells, appearing similar to cells of a lilac pith (→), in straight parts of proximal tubules in diabetes mellitus. Autopsy specimen. HE (×350)

Table 19.3. Biopsy diagnosis and therapy in diabetes mellitus as related to therapy

| Therapy | Biopsy diagnosis | | | |
|---|---|---|---|---|
| | Diabetic glomerulosclerosis (diffuse and nodular) | Pyelonephritis | Glomerulonephritis | Others |
| Insulin ($n=18$) | 77.8% | — | 16.7% | 5.5% |
| Oral antidiabetics ($n=15$) | 13.3% | 20.0% | 26.7% | 40% |
| Latent diabetes treated with diet ($n=62$) | 6.4% | 29.0% | 48.3% | 16.3% |

Table 19.4. Clinical findings in diabetic glomerulosclerosis from 10 of our biopsied patients

1. Age at time of biopsy (in years)

| Age | Incidence |
|---|---|
| < 30 | 3 |
| 30–50 | 2 |
| > 50 | 5 |

2. Duration of diabetes mellitus at time of biopsy (average and range in years)
   20.3 (13–41)
3. Duration of nephropathy at time of biopsy (average and range in years)
   9.7 (1–34)
4. Anamnestically diabetic coma: 5 out of 10 patients
5. Proteinuria / Hypertension (mm Hg)

| g/day | Frequency | mm Hg | Frequency |
|---|---|---|---|
| > 3.5 | 5 out of 10 | ≧160/100 | 10 out of 10 |
| < 3.5 | 5 out of 10 | | |

6. Cause of death (several factors possible for each patient)

| Cause | Frequency |
|---|---|
| Uremia | 4 |
| Miliary tuberculosis | 2 |
| Gangrene (leg) | 2 |
| Acute pyelonephritis | 2 |
| Heart infarct | 2 |

ble 19.3) and have obtained an increase from 6.4% in patients treated with diet alone to 77.8% in those receiving insulin therapy.

Diabetic nephropathy has progressively increased since the advent of insulin therapy. Thus, from 1937 to 1943, it was demonstrated in 12.3% of young insulin-dependent diabetics and from 1950 to 1953 in 63% [1006a]. The lesion probably depends not only on the severity and long duration of the disease (13–41 years in our cases: Table 19.4) in insulin-treated diabetics but also on the quality of insulin adjustment. It is more frequent—even after a shorter duration of the disease—the less successfully the diabetes is brought unter control [817a]. This is also reflected in our material in which half of our patients experienced one or more episodes of diabetic coma due to inadequate insulin scheduling.

## Clinical Findings

Proteinuria is always present as evidenced by our findings (Table 19.4). Slight to moderately severe proteinuria is encountered in the diffuse form of the disease, while severe proteinuria is usually observed in the nodular form which is accompanied by the nephrotic syndrome in about 30% of the cases. With demonstrated BM thickening, the incidence of the nephrotic syndrome may be as high as 50% [1707]. Renal hypertension is present in almost 100% of young diabetics with nodular GS (Table 19.4) and in approximately 30% in older subjects [276, 832]. The severity of retinopathy usually parallels that of the renal changes.

## LM Findings

In diffuse diabetic GS, only two changes are noted in thin paraffin sections: (1) unspecific enlargement of the mesangium (Fig. 19.16) as determined morphometrically [816, 1624, 1705]; see also [1230, 1231] and (2) thickening of the BM, usually first demonstrable 2–5 years after disease onset (43 out of 80: [1214, 1707, 1708]).

Occasionally, a few isolated endothelial foam cells are observed; they are rarely observed in large numbers, and then in association with severe hyperlipemia [1061]. Glomerular capsular BM is unchanged, but ischemic glomerular loop injury is now and again encountered and is due to severe arteriolosclerosis.

In general, the tubules are not significantly changed. Hyaline (protein) droplets and casts are rarely present. In extremely rare cases, swollen cells, so-called Armanni-Ebstein cells reminiscent of lilac pith and optically almost empty and sharply delimited, can be found mainly in the straight parts of proximal tubules from the deepest cortical and outer medullary regions (Fig. 19.17). They are stuffed with glycogen granules as can be demonstrated by staining after tissue fixation in abolute alcohol.

According to findings we have obtained from autopsy material, these cells are found only in cases in which blood glucose levels exceeded 500 mg/100 ml.

In nodular GS, in addition to changes already described, there occurs a severe nodular transformation of the mesangium giving rise to another designation for the lesion, namely intercapillary glomerulosclerosis. The lively red nodules (in van Gieson stain) appear lamellated—especially with PAS and PASM stains (Figs. 19.18, 19.19). They push the glomerular capillary loops, much in the form of a string of beads, towards the glomerular periphery.

The nodules contain lipids and are rich in mucopolysaccharides. The loops are simultaneously constricted, such that peripheral aneurysms of loops (Figs. 19.20, 6.3) develop which, however, bear no relation to the well-known retinal aneurysms [832]. The number of cells of the nodules is pronouncedly increased in the early phase of the disease and decreased in the late phase.

A further typical but not pathognomonic change is the van Gieson yellow fibrinoid "loop cap" (Figs. 6.19, 19.21) which is also designated as hyaline or exudative change [276, 1159]. They always lie peripherally in the glomerulus and appear to be covered by podocytes with LM; with EM, their subendothelial position can clearly be demonstrated.

We have not been able to confirm the presence of epimembranous GN as has been diagnosed exclusively with LM in 9 out of 80 biopsies from diabetics [1707].

Van Gieson-yellow, clumpy, spindly distensions of capsular BM [832], also called "capsular drops" (Fig. 19.22; [716]), are highly characteristic for diabetic GS. They are ultimately collagenized. In very severe cases, small segmental crescents as well as synechiae may be present over occluded loop segments (compare: [429]).

In the advanced nodular form, the tubules are focally severely atrophic and often evidence numerous foam cells (secondary lipoid nephrosis) and considerable BM thickening. This thickening may be present in the absence of tubular atrophy and interstitial change, a condition apparently only occurring in diabetics. The interstitium is usually slightly widened and shows a scanty infiltration with lymphocytes.

Arteriolosclerosis is present in over 70% of the cases [375] (Fig. 19.22) and is especially pronounced in juvenile diabetes mellitus. It is important to note that the change is also observed on occasion in nonhypertensive diabetics [276, 491, 832]. Involvement of the vasa efferentia is typical for the nodular form [832]. The larger arteries are consistently arteriosclerotic and, in the most severe nephropathies, they demonstrate adaptive intimal fibrosis.

Our experience has shown that the diagnosis of diabetic contracted kidney is extremely difficult after long-lasting dialysis when no van Gieson-red glomerular nodules are present (Fig. 19.23).

**IF Findings**

The findings vary considerably. Mesangial deposits of immunoglobulins and complement are most frequently mentioned [1624]; spontaneous diabetic mice: [1711]. Complement and $\gamma$-globulin have been found in the fibrinoid loop caps and arterioles [375]. Isolated findings of subendothelial linear deposits of the same composition have been reported [525], [1624, 1711] and fibrinogen was mentioned once [355]. Most probably, however, IF findings arise from an insudative and not from an immunopathologic process [355].

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**Fig. 19.18.** Typical nodular diabetic glomerulosclerosis (Kimmelstiel-Wilson). Slightly layered (van Gieson red) spheres (*) are easily differentiable from the uniformly homogeneous appearing peripheral glomerular capillary loop caps (→). Peripheral loops are severely narrowed in the region of the spheres. Capsular thickening and synechiae are recognizable. Autopsy specimen. PAS (×250)

**Fig. 19.19.** Nodular diabetic glomerulosclerosis (Kimmelstiel-Wilson). Peripheral glomerular capillary loop BM is intact. It is readily seen that the lamellated nodules are lying in the mesangium which, in other places, shows unspecific glomerulosclerosis. There are again very abvious thickening and splitting of the capsular BM. Autopsy specimen. PASM (×625)

**Fig. 19.20.** Pronounced aneurysm-like distention of a few glomerular capillary loops in diabetic glomerlosclerosis. There is severe atrophy of the tubules, the BM is thickened. Male, 65 years. PASM (×500)

**Fig. 19.21.** Diabetic glomerulosclerosis (Kimmelstiel-Wilson) with massive so-called exudative lesion; capillary loop cap (*); hyaline nodule (→); arteriolosclerosis (⇨). Autopsy specimen. HE (×250)

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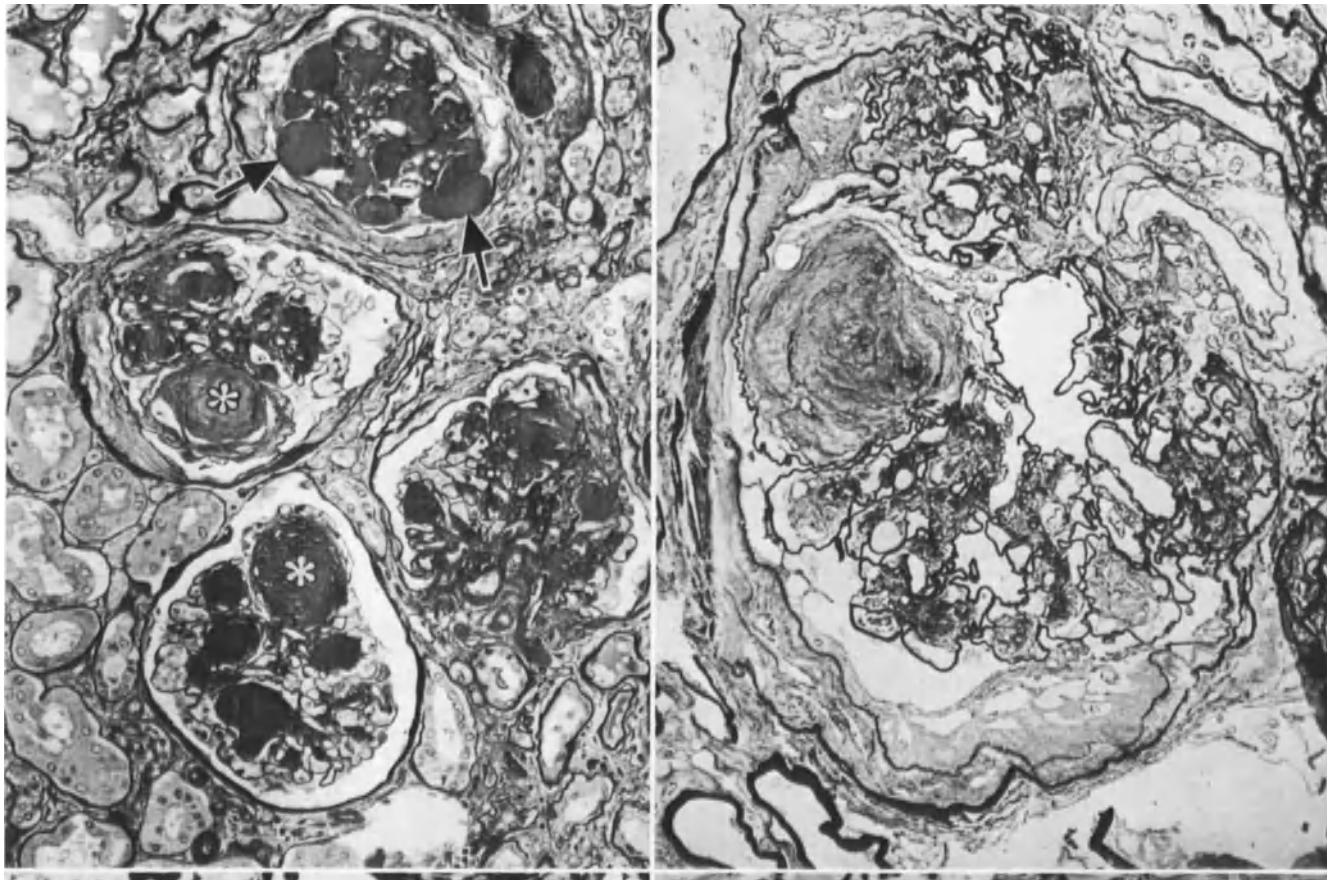
**Fig. 19.22.** Diabetic glomerulosclerosis. Note hyaline drop in capsular BM (⇨), and nuclear increase in glomerular tuft. Note severe arteriolosclerosis (→). HE (×540)

**Fig. 19.23.** Contracted kidney in diabetic glomerulosclerosis (Kimmelstiel-Wilson) after many years of hemodialysis. Glomeruli are completely obsolescent. There are very few hypertrophic cyst-like tubules filled with hyaline casts. Bilateral nephrectomy was performed (kidneys weighed 100 g and 60 g respectively). Female, 42 years. PAS (×32)

**Fig. 19.24.** Diabetic glomerulosclerosis (Kimmelstiel-Wilson). Compare severely thickened glomerular capillary loop BM with normal BM which is shown in the inset. Male, 46 years. EM (×4400) for both preparations



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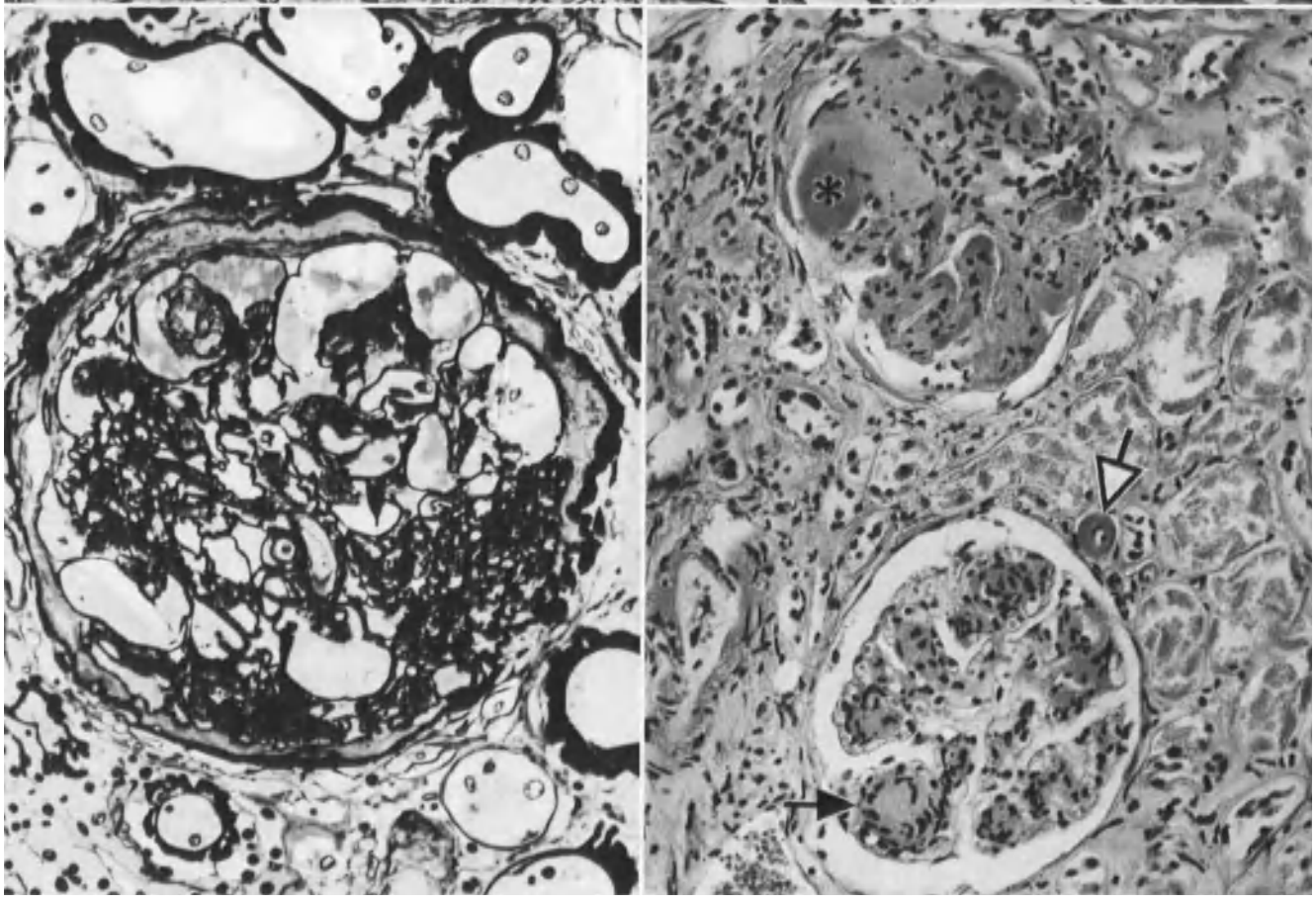

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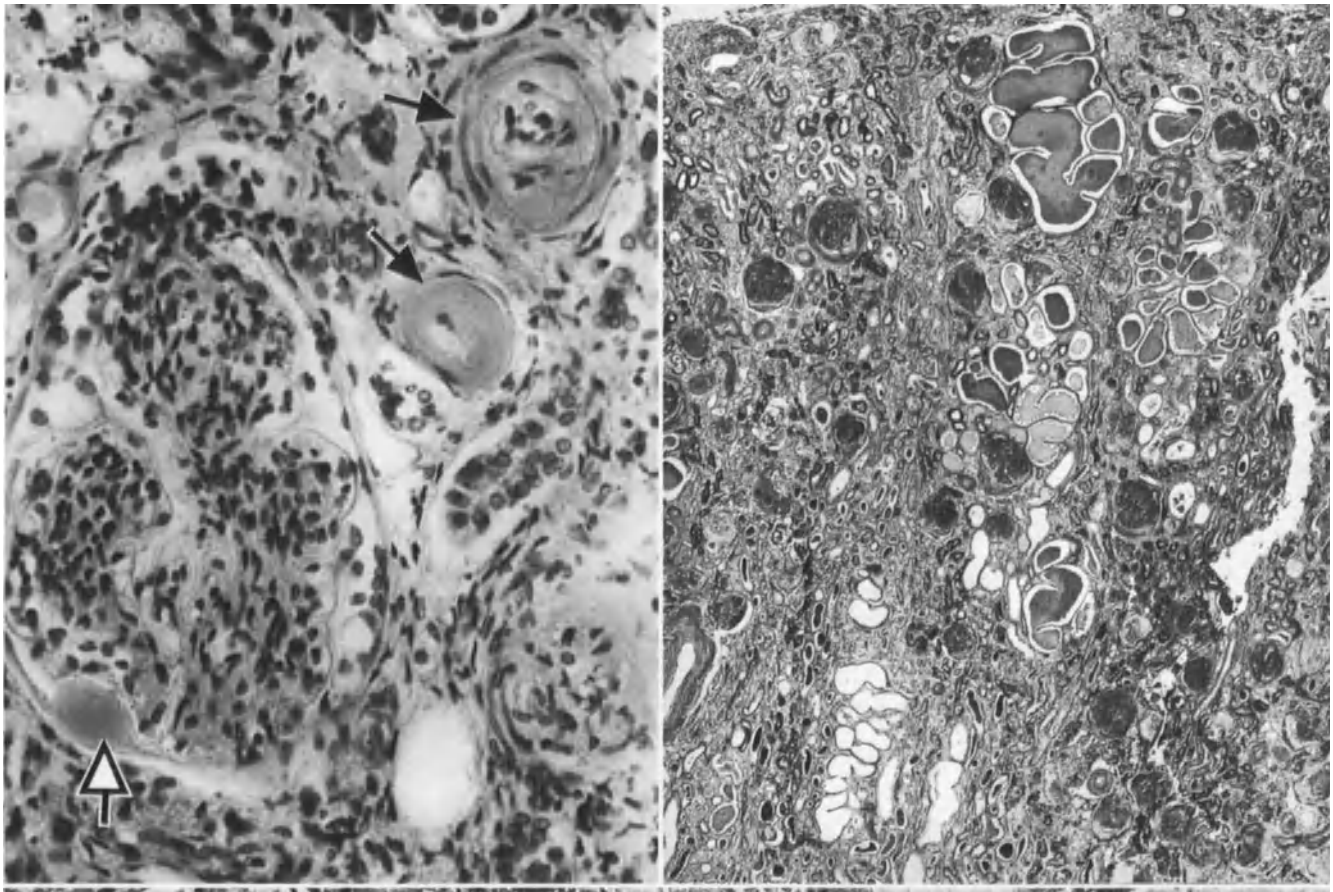

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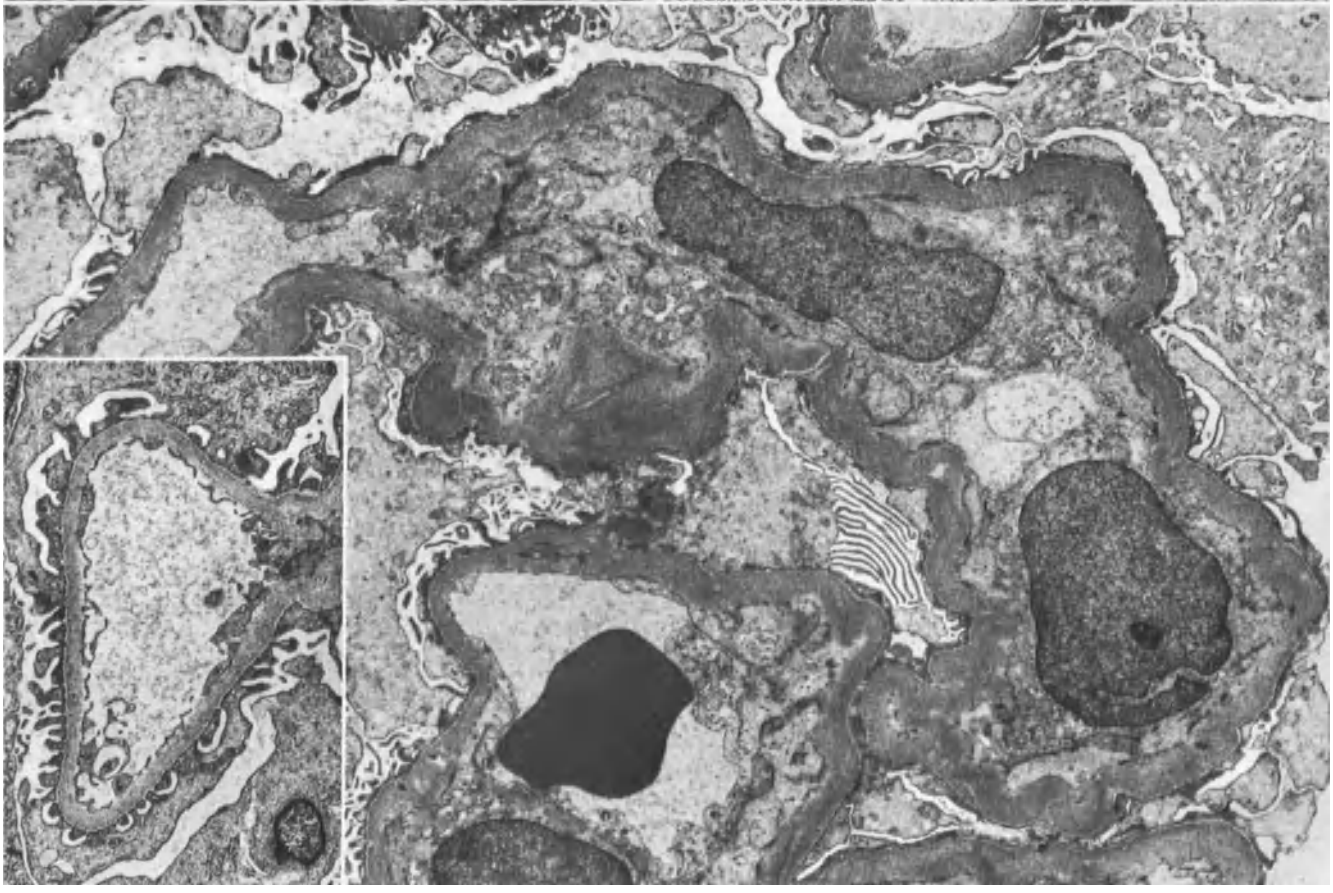

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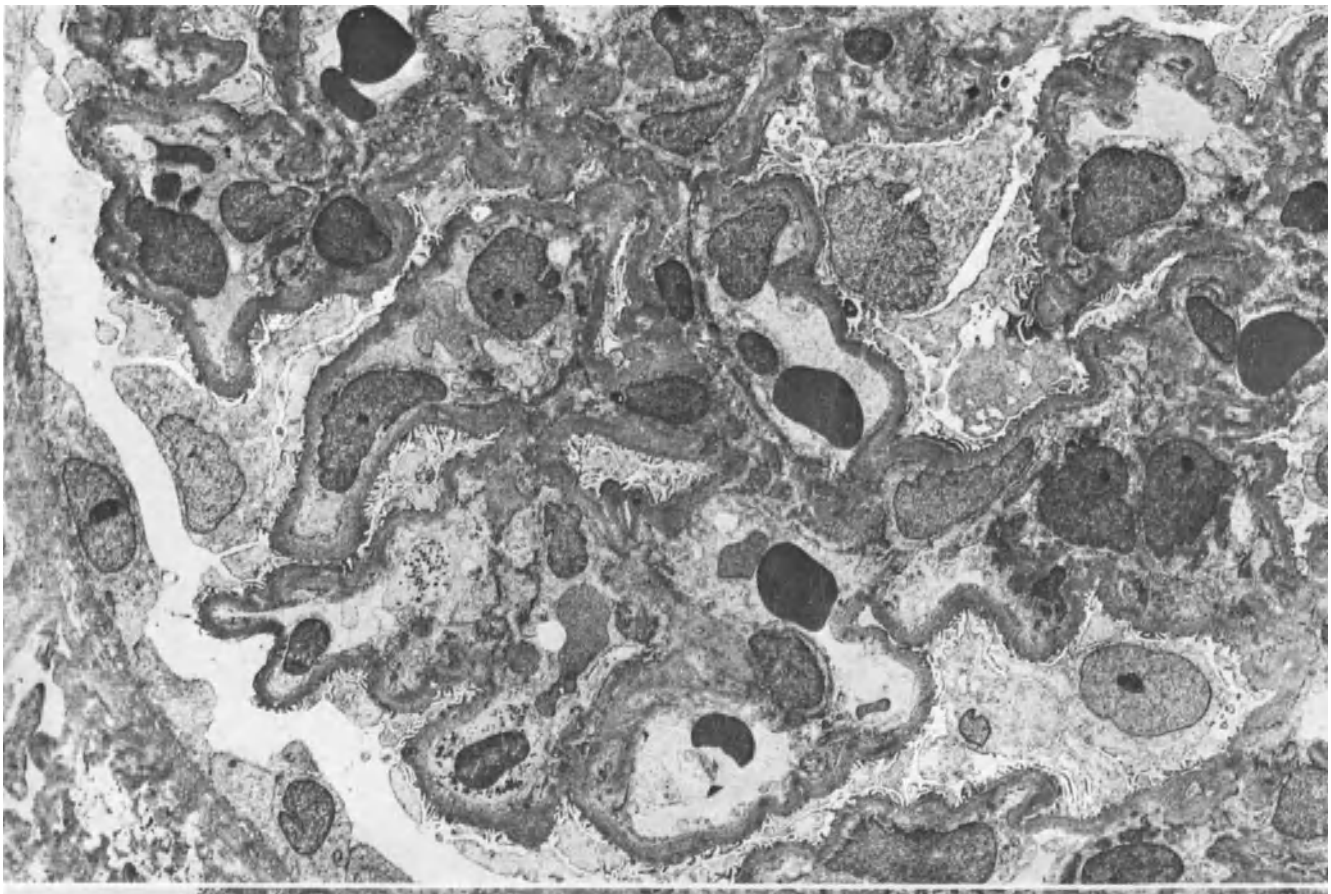

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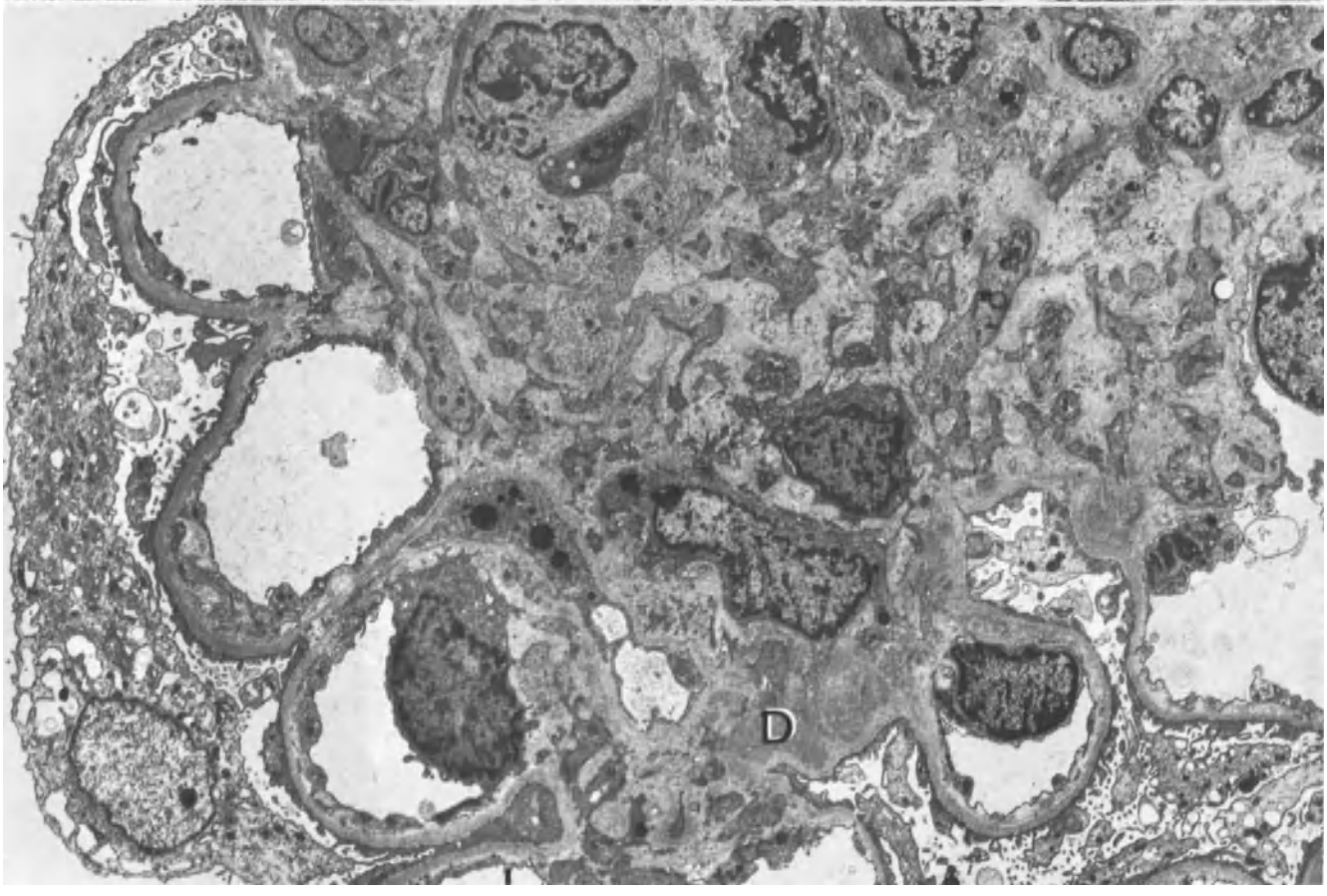


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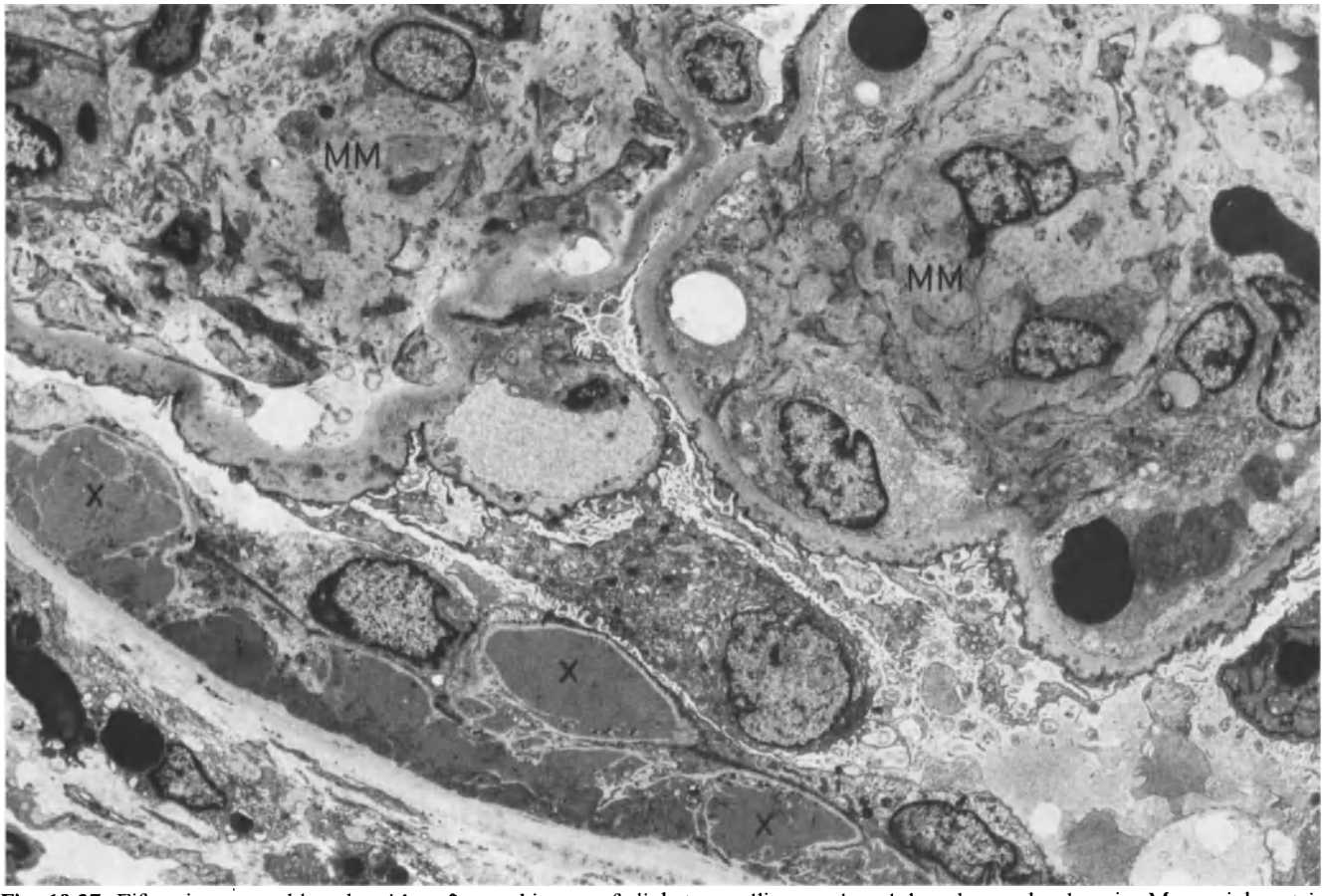



**Fig. 19.27.** Fifty-nine-year-old male with a 2-year history of diabetes mellitus and nodular glomerulosclerosis. Mesangial matrix (*MM*) shows severe nodular increase without concomitant increase of cells. Peripheral BM is highly thickened. Podocytes are intensely activated. There are typical exudative lesions in the form of capsular drops (X)

## EM Findings

BM thickening of greater than 7000 Å with involvement of the lamina densa and lamina rara interna only is a very characteristic finding (Figs. 19.24, 19.25; [832, 1413]). The thickening is, however, inconstant, appears only after long duration of diabetes (2–5 years: [1214, 1707, 1708]) and bears no quantitative relationship to mesangial widening ([276, 832, 1229, 1231], contra: [491]). We have clearly observed BM thickening in one case of latent diabetes.

◁ **Fig. 19.25.** Same case as in Figure 19.24. Severe enlargement of mesangium due to matrix increase without significant nuclear increase. Note pronounced thickening of glomerular capillary loop BM. Podocytes are edematously swollen but rarely hypertrophied. Male, 46 years. EM (×1500)

**Fig. 19.26.** Nodular diabetic glomerulosclerosis (Kimmelstiel-Wilson). Massive mesangial enlargement with very coarse matrix bars, cells are not significantly increased. Osmiophilic deposits (*D*). Male, 46 years. EM (×1200)

Loop caps are found in 47% of cases with the nodular form with EM [716]. They represent subendothelial deposits containing 35–70 Å-sized granules [276, 1413]. Analogous—but smaller—deposits have been reported subepithelially and intramembranously [1413]. In diffuse as well as nodular glomerular sclerosis (which develops from the former), the mesangial matrix is considerably increased (Figs. 19.25, 19.26, 19.27a). Mesangial cell drops containing a fibrillar BM-like material as described in the rat [34] have not been observed by us in man. The "capsular drops" (Fig. 19.26a) lie on the inner aspect of the BM and are reportedly demonstrable under EM in 60% of all biopsies [716].

The tubules are often atrophic and dedifferentiated. The basal labyrinth disappears and the BM is strongly thickened and often lamellated [276]. Armanni-Ebstein cells, usually not present in biopsy tissue, are stuffed with glycogen which lies freely in the cytoplasm [377]. After glycogen removal from fixation, these cells appear empty (Fig. 19.28).

Except for a clear-cut thickening of the BM [1222], the arteries show no other deviations than those of typical arteriosclerosis [1413].

### Complications

A very frequent complication (ca. one-third of cases) is pyelonephritis (Table 19.3) often accompanied by papillary necrosis. The occurrence of complicating diffuse GN [564, 1707] (Table 19.3) is probably a random finding.

### Differential Diagnosis

The simultaneous presence of mesangial van Gieson-red nodules, loop caps, capsular drops, and arteriolosclerosis of the vas efferens is practically proof for the presence of diabetic GS. It is noted that extremely rarely, cases evidencing all the above-instanced findings are clinically completely negative with respect to manifest or latent diabetes [177]. We have also studied such atypical cases. These rare cases may be due to the almost unheard-of occurrence of nodular GS in plasmocytoma [1455] or in carbon disulfide poisoning [1640, 1225] of which we saw one case each.

Morphologic findings in diffuse diabetic GS are completely unspecific. In biopsies, the nodular form is occasionally not diagnosed since mesangial nodules are initially present in only a few glomeruli. Thus, in one case 6 months prior to autopsy which revealed the nodular form, we diagnosed the diffuse form in biopsy material. In an other similar case, the biopsy-to-autopsy interval was 6 years.

One cannot always rely on mesangial cell increase to differentiate nodular GS from lobular (membranoproliferative) GN since the mesangium may be very poor in cells in the late stage of lobular GN. EM demonstration of extensive BM doubling and the presence of considerable subendothelial and mesangial deposits speak for membranoproliferative (lobular) GN. In general, however, mesangial widening in membranoproliferative (lobular) and endotheliomesangial GN is considerably more cellular than in nodular GS. In these cases, the EM demonstration of a homogeneous global thickening of the peripheral BM – characteristic for diabetes mellitus – may be helpful.

### Prognosis

The prognosis for the nodular form in young patients is very bad; it is somewhat better in the older. We found death due to uremia in 6% and to hypertension in 65% of our autopsy cases (see also Table 19.4). The prognosis can be considerably improved by appropriate antihypertensive medication and proper management of the diabetes. A further decrease in mortality due to uremia has been brought about by dialysis and renal transplantation of which the latter is more favorable [1834]. As far as we know, there have been no reports of recurrence in transplants – 34 cases without recurrence, except for vascular lesions [1835], have been described [854]. Even after 5 years, there was no evidence of diabetic renal changes in one of our cases.

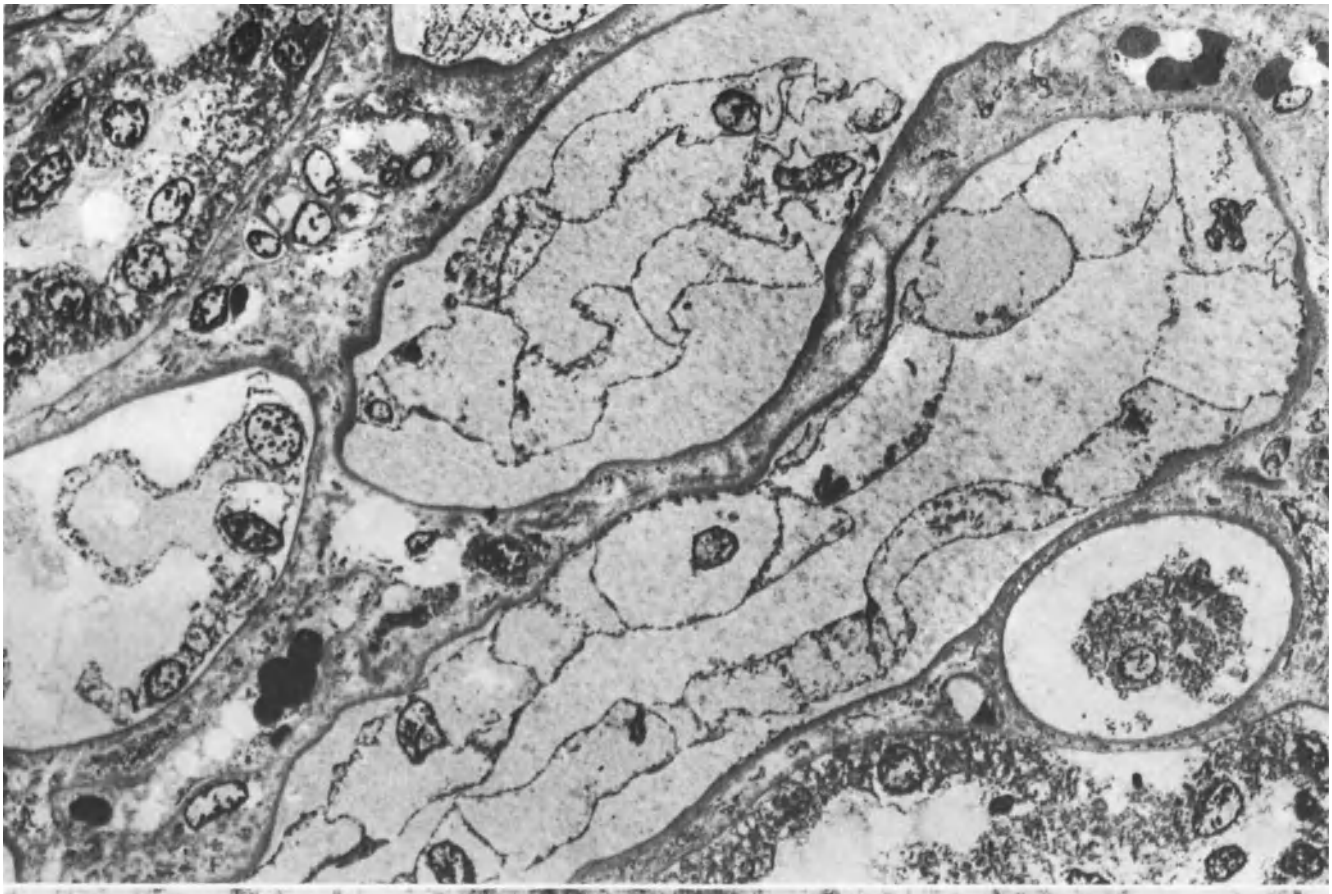
### Pathogenesis

The central pathogenetic role is thought to be played by an increase of structural carbohydrates (insulin deficiency) which leads to glomerular BM thickening and mesangial matrix increase [834]. It thus belongs within the framework of diabetic angiopathies [1231]. Structural carbohydrates (mucopolysaccharides, muco- and glycoproteins) provide the ground substance in which scleroproteins (collagen) are embedded [276]. The same disturbance is proposed for the very early appearence of tubular BM thickening. A genetic defect of the BM is unlikely. It is still not clear whether BM and mesangial changes are due to decreased turnover or increased production. Another concept associates the BM and matrix changes to an increased serum level of glycoproteins [1624]. Finally, it has been conjectured that the glomerular lesions are a reflexion of immunological injury caused by insulin AB [1704] perhaps in association with further injury from metabolic disturbances. This thesis appears improbable to us since the lesion also occurs in the absence of insulin therapy [1208, 1214] and is independent of the presence of insulin AB [1325].

The loop caps as well as the deposits demonstrable with IF and EM are probably the consequence of increased insudation of plasma components due to impaired endothelial permeability [1413].

**Fig. 19.28.** Armanni-Ebstein cells (poorly fixed) in diabetes mellitus. Male, 21 years. HE (×978) ▷

**Fig. 19.29.** Experimental hepatic glomerulosclerosis caused by carbon tetrachloride administration in the rat. Isolated, fine-granular, relatively loosely organized subendothelial and intramembranous (*) osmiophilic deposits. EM (×46,000)



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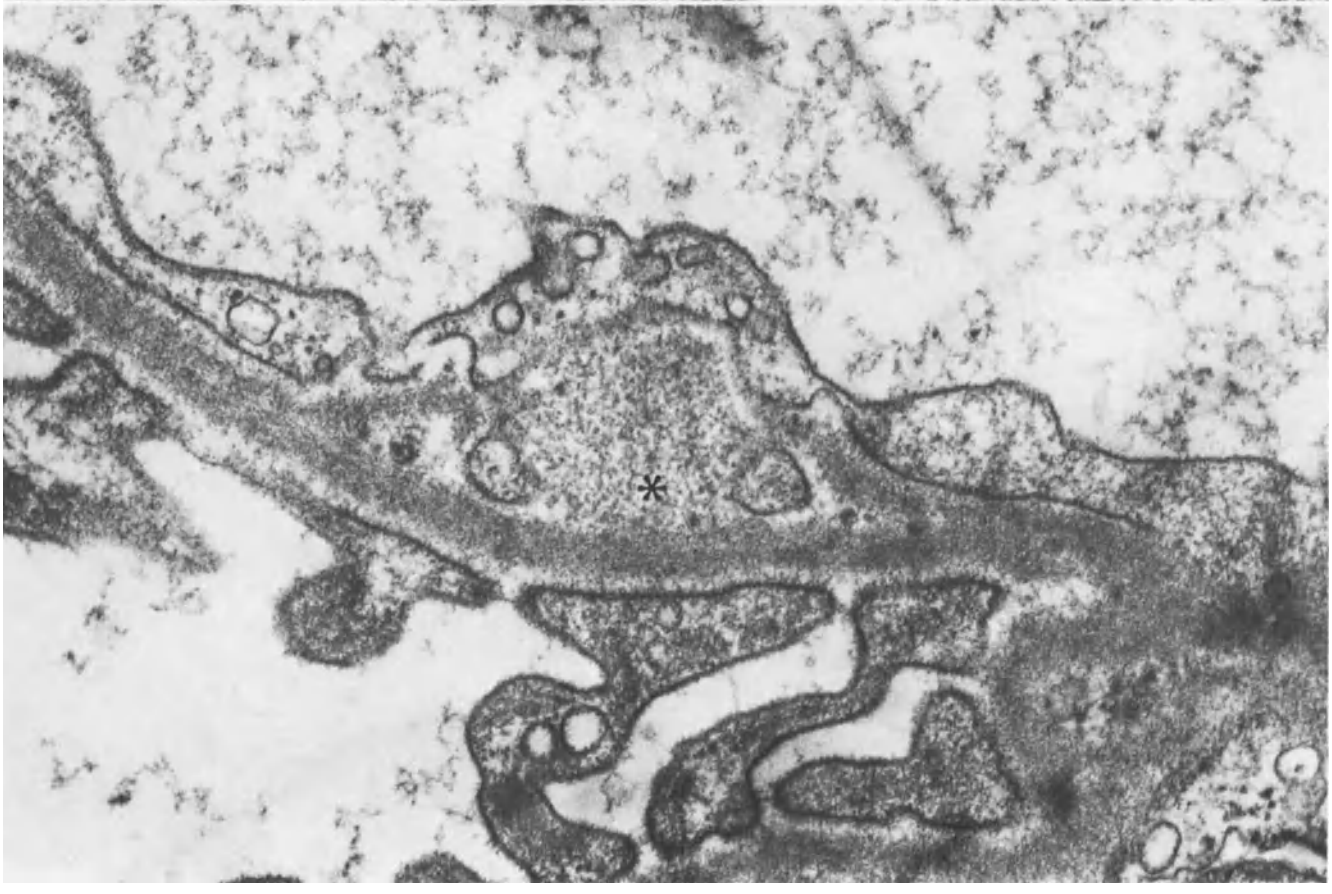



19.29

## Hepatic Glomerulosclerosis
[490, 1409, 1410]

### Definition

Hepatic glomerulosclerosis (HG) is defined as the non inflammatory glomerular lesion occurring in association with liver diseases of various etiology. HG must not be confused with or considered equivalent to the so-called hepatorenal syndrome [1238a] or GN.

### Incidence

HG, usually mild, can be found with LM in 6.5% of severe liver cirrhosis [1624]. Evaluation of this series is rendered difficult by the concomitant presence of diabetes mellitus in 27% of the cases. HG is the rarest renal lesion—as noted in biopsy material—occurring with liver disease (0.29% of biopsies: Z; Table 19.5).
Another investigator [1409] found 8 severe and 44 mild cases of HG in 85 patients suffering from liver cirrhosis. In children, the lesion has been reported as being more frequent [1201].

### Clinical Findings

Clinically, HG, in common with cholemic nephrosis, is (with exception of a minimal proteinuria) usually insignificant. In severe cases, pronounced proteinuria, slight hematuria, granular casts and decreased urine sodium may be observed [1240]. Glomerular filtration is reduced, and plasma renin level increased in some cases of chronic liver disease [440, 1452].
Acute renal insufficiency (so-called hepatorenal syndrome) occasionally occurring in (decompensated) liver cirrhosis, inflammatory bile duct lesions and, more rarely, following hemihepatectomy, is in no way related to HG but is probably attributable uniquely to circulatory factors [440, 1240, 1452]. Needle biopsy in such cases reveals the finding of shock kidney.

Table 19.5. Diagnosis from renal biopsies in 77 patients with bioptically and clinically verified liver diseases

| Biopsy diagnosis | Incidence (%) |
|---|---|
| GN | 50.7 |
| Pyelonephritis | 20.8 |
| HG | 7.7 |
| Others | 11.7 |
| ± Normal | 9.1 |

### LM Findings

Some glomeruli are normal in size and some are enlarged (especially in alcoholic liver cirrhosis) due to overload [1706]. In mild cases, the mesangium is widened in about 10% of the glomeruli, and in severe forms in over 40% [269, 1624], in which either no morphometrically demonstrable mesangial cell increase is present [1624, 1706] or, if so, of slight character (Fig. 19.30; [1624]).
Peripheral glomerular BM shows slight, partial thickening in severe cases only. When jaundice is present, greenish bilirubin-containing casts (HE stain) are present in the tubules. The epithelial cells of the convoluted parts of the proximal tubules may contain bile droplets. The interstitium and vessels are generally unchanged. The JGA may be enlarged in some cases.

### IF Findings

The currently available literature is scanty and does not permit definitive conclusions. Gamma globulin, in granular or linear arrangement, has been reported to be present along the peripheral glomerular BM [1410]. There have been no reports of positive findings for complement or fibrin(-ogen).

### EM Findings

The morphologic differentiation of different degrees of severity of the lesion is the key for the understanding of its evolution [1410]. In acute liver disease, loose, amorphic deposits are initially formed subendothelially along the peripheral BM (Fig. 19.29). Occasionally, intensely osmiophilic particles (35–100 Å large)—some of which are reminiscent of ferritin [1410, 490]—are present. They can sometimes be demonstrated intramembranously. Dark particles, with a diameter of about 1000 Å, can be found subendothelially but chiefly mesangially. At this stage, osmiophilic deposits may also be demonstrated in small amounts in the mesangium.
The second stage of the disease is mainly characterized by a considerable increase of the mesangial matrix and by the merging of the amorphic mesangial deposits with it.
The third stage is marked by changes of peripheral BM which shows irregular, usually focal thickenings of 3000–9000 Å [490]. The subepithelial side of the BM is irregular and evidences focal invaginations which are filled in with evaginations of podocytes.
Splitting of the lamina densa is observed only in severe cases [490]. The podocytes are considerably hypertrophied, and sometimes focal fusion of foot processes or their destruction is observed, so that peripheral BM is denuded of a podocytic cover [1410]. Large lamellated bodies, with a diameter of 3000–8000 Å, are occasionally found within the mesangial matrix.

### Differential Diagnosis

With LM, the changes are unspecific and cannot be differentiated from diffuse diabetic GS. This is of importance in view of the frequent combination of liver cirrhosis and diabetes mellitus.
With EM, the full picture of HG with its various deposits and particles, which is said to be very characteristic, will probably scarcely give rise to confusion regarding other glomerulopathies. Nevertheless, HG must be carefully distinguished from membranoproliferative and epimembranous GN, both of which may arise as a sequel to viral hepatitis (see p. 250).

### Pathogenesis

Despite much experimental and clinical study, the pathogenesis of HG has eluded clarification. Causative factors most frequently mentioned include dysproteinemia [1624], immunologic mechanisms (experimental findings: [990, 1113]) and ischemia [1624]. Among the factors considered, most investigators in the field tend to regard renal ischemia as the most important pathogenetic mechanism as evidenced by decreased glomerular filtration and plasma flow, increased plasma renin levels and evident ischemia as demonstrated by the xenon wash-out technique [440, 826, 1240, 1452, 1492].
The possible pathogenetic significance of a functional disturbance is illustrated in an interesting observation from our material on the course of the disease. The patient, a 33-year-old female, suffered from biopsy-proven primary biliary cirrhosis for 11 years. In the urine, a few erythrocytes, leukocytes, granular casts, and protein traces could be demonstrated during periods of jaundice. During these episodes, glomerular filtration decreased to a $C_{cr}$ of 40 ml/min, whereas during remissions, glomerular filtration was a $C_{cr}$ of 85/ml/min. Following transplantation of kidneys with HG, glomerular changes can disappear [878], a finding which speaks for a primary functional disturbance. Despite these arguments in favor of renal ischemia, the exact mechanism is still to be elucidated.

## Glomerulopathy of Pregnancy (GP)
[20, 1273, 1484, 1494]

### Definition

Glomerulopathy of pregnancy is herein operatively defined as noninflammatory glomerular changes occurring in pregnancy associated with the EPH syndrome (edema, proteinuria and hypertension). Pyelonephritis frequently observed during pregnancy, idiopathic postpartal renal failure (see p. 499) as well as lesions present prior to pregnancy, do not belong to GP.

***Synonym:*** Glomeruloendotheliosis [1541, 1501].

### Incidence

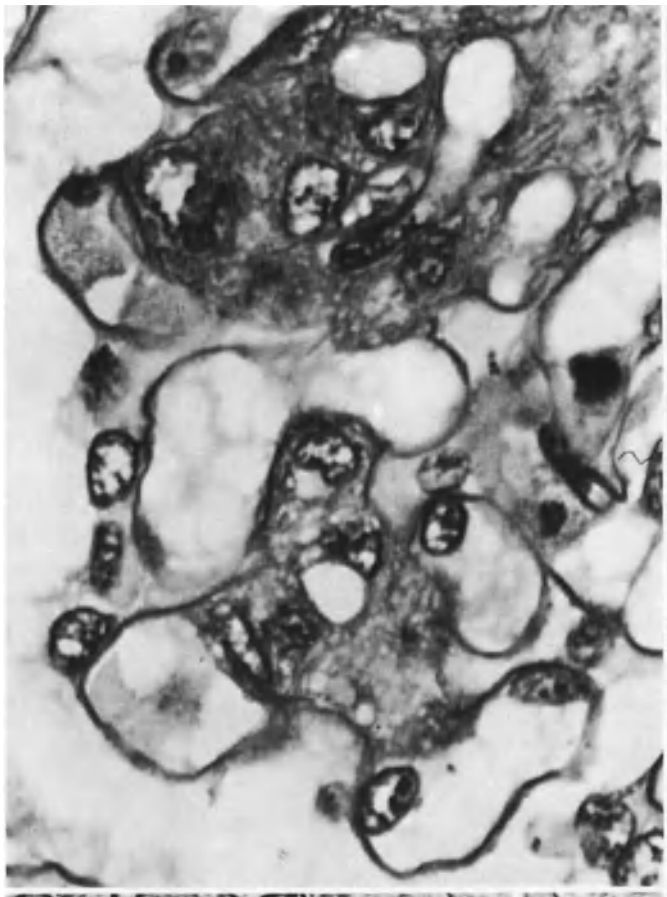
Morphologically, the incidence of GP is not known but its functional counterpart, the EPH syndrome, is encountered in 6–7% of all pregnancies [20]. Nevertheless, in one biopsy series encompassing 100 EPH patients, the full picture of GP was present in 45 of the cases [1603].

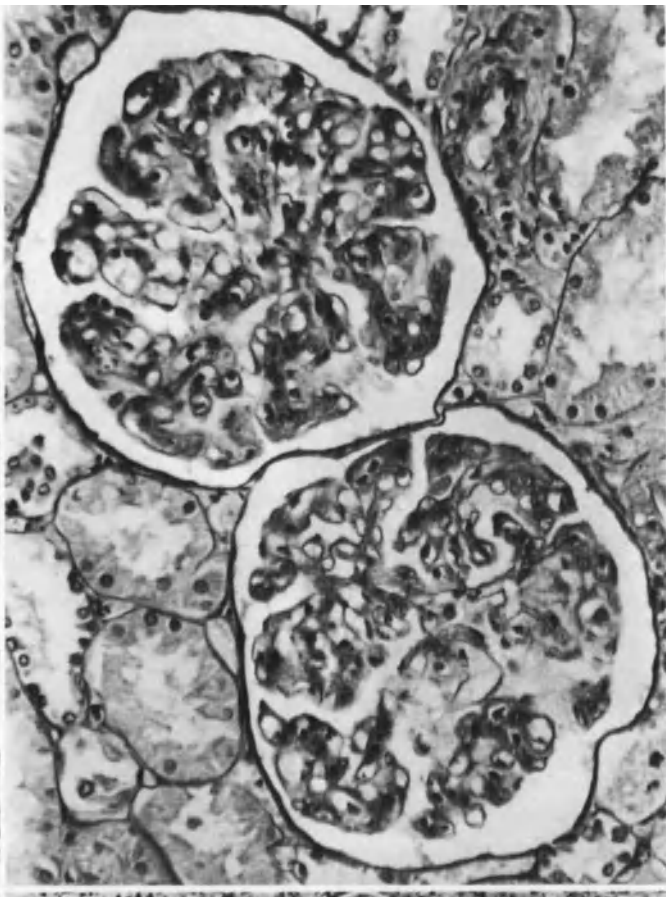
### Clinical Findings

Three degrees of severity are recognized [1340]: (1) simple gestosis (uncomplicated by symptoms of the central nervous system) with edema and/or proteinuria and/or hypertension, (2) pre-eclampsia with headache, dizziness, nausea, occular symptoms, and vomiting, (along with EPH), and (3) eclampsia with unconsciousness and/or cramps (15% cerebral hemorrhage [1060]) in addition to the above-mentioned symptoms).
It is very questionable as to whether or not significant histologically recognizable renal changes are already present in simple gestosis. Findings from renal needle biopsy do not permit differentiation between pre-eclampsia and eclampsia [478].
Additionally, primary GP is differentiated clinically from secondary GP, i.e., GP instigated and concomitantly caused by pre-existing renal disease which was found in 17% of cases [1603]. Biopsy is often performed in an attempt to determine pre-existing renal disease. In our material, the ratio between secondary and primary (EPH) gestoses was 4:1 (Table 19.6).

Table 19.6. Renal biopsy diagnosis in 53 patients with clinical history of pre-eclampsia and eclampsia after a mean latency period of 230 weeks (range 2–850 weeks)

| | Renal diagnosis | No. of patients | % |
|---|---|---|---|
| Possibly secondary gestosis (81.1%) | Glomerulonephritis | 27 | 51.0 |
| | Chronic pyelonephritis | 11 | 20.7 |
| | Hypertensive vasculopathy (arteriolosclerosis) | 5 | 9.4 |
| Possibly primary gestosis (18.9%) | Status after eclampsia | 5 | 18.9 |
| | ± normal | 5 | |
| | normal | | |





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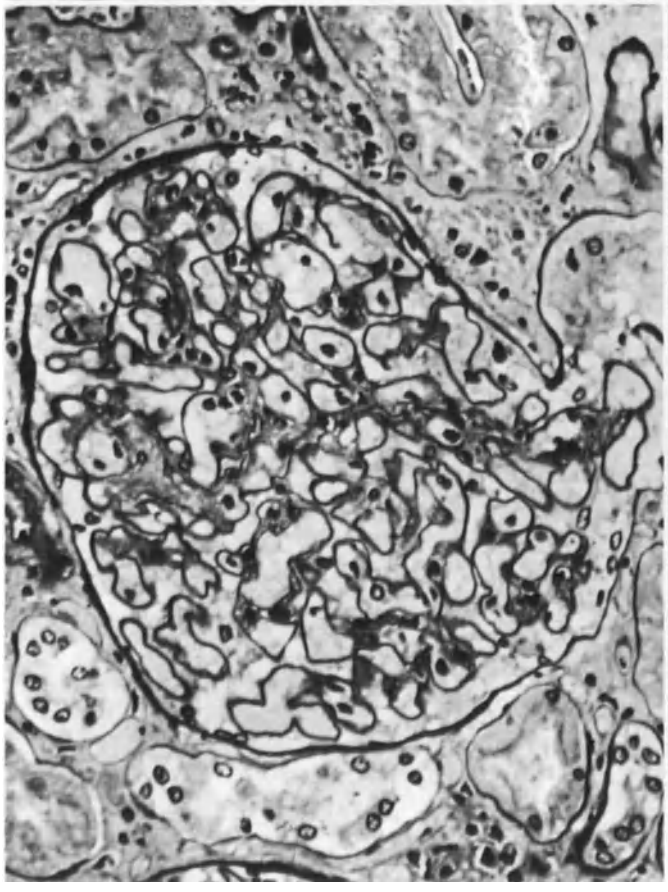

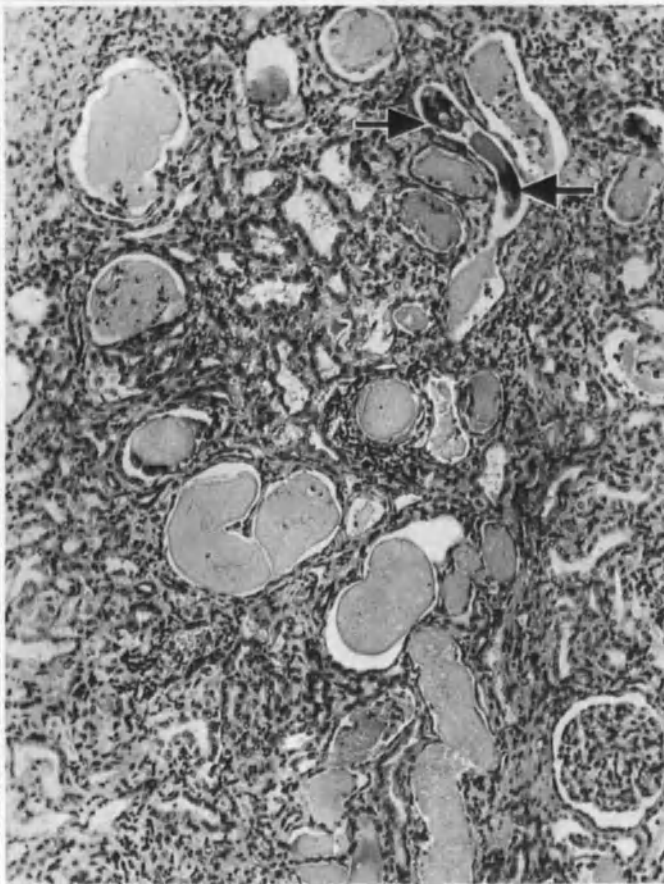

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19.33

### LM Findings

Even cursory study of a slide from the early stage reveals the striking lack of blood in the noncollapsed and frankly enlarged glomeruli (Fig. 19.31). The loop wall, as seen in HE, is thickened. The BM (PAS/PASM stain), however, is delicate. The capillary loop lumen appears to be occluded or narrowed by the endothelium, although the cellular elements are, in general, not increased. In a very few instances, there occurs slight widening of the matrix and increase of mesangial nuclei [1273, 1614].

Endothelial cells are markedly swollen, hence the designation "endotheliosis" for GP. The severity of swelling has been reported to parallel the severity of clinical symptoms [1068]. It is thought that the cellular swelling is due to the phagocytosis of fibrin [1690].

Occasionally, intraglomerular foam cells and aneurysms of capillary loops are encountered [1494].

The number of granulated juxtaglomerular cells is often obviously increased [20, 1279, 1509]. We have not been able to confirm reported atrophy of the macula densa [20].

The maximum of renal changes is observed a few days postpartum [478]. Capillary loop thrombi, given such importance in earlier studies [1614], belong, as such, not to GP but to conditions with intravasal coagulation. Ischemic glomerular changes in the sense of glomerular collapse as occurs in pre-existing hypertensive vasculopathy [1273] are not obligatory.

Tubules and interstitium are generally unchanged. Intertubular capillaries may undergo thrombosis in pronounced intravasal coagulation and possibly give rise to tubulonecrosis and findings of acute, nondestructive interstitial nephritis. Casts are present in about 25% of our cases and partly contain chromoprotein. The vessels themselves are usually unchanged. It has been reported that secondary collagen formation in vessels may occur from fibrin insudation [842]. A pronounced contraction of the vas afferens [20] could not be confirmed in our cases.

### IF Findings

The few findings available from IF study are unspecific. It is not at all surprising—in view of the frequent occurrence of intravasal coagulation in the EPH syndrome—that fibrin is present [478, 1263, 1273, 1509]. The finding is certainly more frequent than observed with LM, it is not, however, obligatory (contra: [1060]). Complement and immunoglobulins were not always found [1273]. According to other investigators [1263] C3 was present in glomeruli in all severe cases and consistently present in the vas afferens and efferens.

### EM Findings

Intense cellular swelling, especially of endothelial cells, is immediately apparent (endothelial edema: [1079]). Cells identified with LM as foam cells are, with EM, apparently endothelial elements [454]. Mitosis in endothelial cells was noted once [764].

The BM, with exception of a few focal thickenings of the lamina rara interna, is unchanged. We ascribe these thickenings to anoxia, but other investigators feel that they are due to deposits of fibrin [842]. Subendothelial osmiophilic deposits are found rather frequently [1273, 1484] and are said to be quickly reversible [1484]. A few of these deposits sometimes contain material suggestive of fibrin fibrils [1614].

In massive intravasal coagulation, thrombi are present in the capillary loop lumen. These thrombi are surrounded by proliferating endothelial and mesangial cells [454].

Podocytes are considerably activated and evidence microvilli formation [1273] without accompanying foot process fusion. The mesangial matrix is slightly widened and shows a slight increase in cellularity [20, 1263, 1614]; contra: morphometrically [1494].

Mesangial cellular swelling is basically caused by edema and is reversible [275]—often first after 2 years [1031]. Protein droplets and, rarely, fibrin fibers are demonstrable in both endothelial and mesangial cells [1275].

◁ **Fig. 19.30.** Hepatic glomerulosclerosis associated with liver cirrhosis in a 1.5-year-old boy. Peripheral glomerular BM is delicate. There is intense fibrillar enlargement (matrix bars) of the mesangium. PAS (× 1000)

**Fig. 19.31.** Typical glomerular changes in nephropathy of pregnancy. Glomerular capillary loops appear narrowed and their walls thickened but they do not evidence hypercellularity. Autopsy specimen. PAS (× 345)

**Fig. 19.32.** Glomerulosclerosis associated with medullary plasmocytoma. Mesangium is slightly segmentally enlarged due to matrix increase. Concomitant cell increase is not present. BM of glomerular capillary loops and capsules is delicate. Male, 64 years. Semi-thin section. PASM (× 550)

**Fig. 19.33.** Massive hyaline casts in tubules which are partly distended and evidence atrophic epithelium in a case of medullary plasmocytoma. Tubular giant cells as reaction to the casts (→). Autopsy specimen. HE (× 80)

A peculiar, often-reported finding is that of mesangial interposition which is possibly simulated, however, by cellular swelling [1273] or by protusions of mesangial cells [20, 764]. This finding has been reported to persist for months [1273] or even for years [764].
Collagen formation within obsolescent loops indicates previous intravasal coagulation [842].

### Differential Diagnosis

With the exception of unspecific toxic glomerulonephrosis in infants and children, we know of no other lesion besides GP which demonstrates such severe swelling of endothelial cells.
The main task of the pathologist is the demonstration or exclusion of pre-existing renal disease (secondary GP) and especially of chronic pyelonephritis (Table 19.6). Pre-existing GN (Table 19.6; 7 out of 100: [1603]; 21 out of 169: [764]) and arteriolosclerosis, etc., are further well known causes of secondary GP. In cases of difficulty in delineation of GP from GN, the predominance of fibrin(-ogen)—without or with only rather scanty accompanying immunoglobulin deposit—speaks in favor of GP.
GP does not occur as a consequence of acute fatty liver degeneration in pregnancy complicated by uremia. In such cases, uremia is thought to be purely due to intravasal coagulation [110].

### Prognosis

The prognosis as such is good, although some of the changes may persist for quite some time (see above). Extensive fibrin deposits may lead to an inflammatory reaction (cf. p. 287). As a rule, irreversible injury is not to be expected.
A small percentage of patients develop chronic hypertension, which is possibly a consequence of hypertensive vascular injury arising in the course of GP [1273]. It is noted in this connection, however, that the presence of or disposition to hypertension prior to GP may not have been adequately considered. Nevertheless, the decisive element for prognosis is the behavior of the blood pressure [1158].
Cases with endothelial swelling and BM thickening lasting for years, as well as with synechia, have been described [478]. These cases, however, arouse suspicion of the presence of independent GN or severe intravascular coagulation. A report detailing normalization of renal function of only 10 out of 15 cases [944] strongly implies secondary GP.

### Complications

Pyelonephritis appears to occur frequently after GP, although the relationship between GP and urinary tract infection is controversial. Thus, it is not clear whether repeated urinary tract infections dispose to GP, or whether a chronic nephropathy (i.e., pyelonephritis) is the cause of repeated urinary tract infections on the one hand and GP on the other. It is not known whether or not GP alone can cause hypertension (the hypertension or disposition to hypertension was most probably present before GP in most cases). Pre-existing GN (45 cases) is clearly worsened by GP; lupus GN is the least affected (12 out of 14: [453]). In one of our cases of epimembranous GN, complete remission of clinical symptoms occurred during pregnancy.
In 3 of our own 10 patients with possible primary gestosis who were biopsied 5–13 months after birth, blood pressure was normalized and remained so during a 6–12 year follow-up period. Hypertension is still present in 7 out of 10 patients 14–15 years subsequent to GP. Familial hypertensive stigmata were demonstrated in 3 of the patients. In 2 patients (2 and 4 years respectively postpartum) a renal artery stenosis, or nephroptosis of the nonbiopsied kidney was operated on unsuccessfully.

### Pathogenesis

The most attractive hypothesis for GP is that of release of pressor substances from the ischemic uterus with subsequent sodium retention, hypertension and cellular edema [1273]. It is agreed that vasospasm is decisively involved in the process [1494] as it is in triggering intravasal coagulation [1060]. Increased activation of pressor amines has also been proposed as a causative factor. Electrolyte and water retention have been ascribed to increased aldosterone production [1509].
Intravasal coagulation, assumedly caused by release of thromboplastin from the placental attachment area, is currently viewed by many investigators as the chief and integrating factor in the pathogenesis of GP [842, 1060, 1690, 1691]. The glomerular changes assumedly arise by insudation of plasma elements especially of fibrin(-ogen)—into the capillary loop wall (see also [1158, 1690]).
Finally, immunological processes have been proposed as causative in that a fetus, showing intolerance to maternal tissue, transfers antibodies against maternal HLA antigens to the mother [1263].

## Kidney in Plasmocytoma

[60, 379, 510, 1116, 1624, 1454a, 1454b]; for rare paraproteinemias see also [60]

### Definition

Glomerular, interstitial and tubular changes typically associated with multiple medullary plasmocytoma (multiple myeloma, Kahler's disease).

### Incidence

Plasmocytoma GS was found in severe and mild form in 7 out of 30 autopsy cases each [1624]. The full picture of renal changes in plasmocytoma with impacted casts has been reported in two-third [1012], one-third [1457] and 11 out of 92 [747] cases. The overall incidence in our biopsies was 0.38%. We have the impression that the lesion has become less frequent due to improved therapy.

### Clinical Findings

Proteinuria, chiefly of prerenal origin and often severe, is present in 77% of the cases [1012, 1791]. If it is absent, no significant GS, interstitial or tubular changes are present. A nephrotic syndrome is very rare [379, 510] (2 out of 8 cases: Z). Acute circulatory failure is frequently a terminal event [1457].
Pyelonephritic symptoms are not infrequent. Occassionally, a secondary De Toni-Debré-Fanconi syndrome is observed which is thought to arise as a consequence of excessive protein overload of tubules with immunoglobulins and their fragments (possibly tubular toxicity) [1683]. Oliguria and anuria with rapidly progressive renal failure were much more frequent previously as they are today due to better therapeutical control of extracellular fluid volume (see also [1454b]).
Hypertension was present in 13% of our autopsy cases [1791] and was found in 1 out of 8 of our biopsied patients; it does not appear to be more frequent than in control series.
Individual serum globulins corresponding to the plasmocytoma type are considerably increased as is serum sedimentation rate. The latter may be nearly normal when there is a predominance of light chains. Bence Jones's protein is nearly always present in urine (8 out of 8 cases: Z).

### LM Findings

GS occurring with plasmocytoma has no specific characteristics (Fig. 19.32). In the presence of severe disease, the morphometrically demonstrable mesangial widening (without significant cell increase) [1624] leads to a typical, finger-like enlargement of the mesangium. Very rarely, nodular transformation of the mesangium may occur and it cannot be differentiated from the nodular GS of Kimmelstiel-Wilson (one case of our own; see also [1455]; in IgE gammopathy: [232]).
Interstitial fibrosis in 65% (71% [1454a]) with focal lympho-plasmocytic infiltrates in 82% of cases [1012] occurs almost exclusively in the corticomedullary region. Accordingly, it is frequently missing in needle biopsies which usually contain only cortical tissue.
The typical picture of the kidney at autopsy in plasmocytoma is characterized by massive casts which are often fragmented transversely, they are sometimes surrounded by granulation tissue rich in foreign-body giant cells (Fig. 19.33; 45% of a biopsy series: [1012]; 39%: [1454a]).
A usually moderately pronounced accumulation of hyaline (protein) droplets in the proximal tubules is present in all cases with severe proteinuria but only in 30% of all cases [1454a], whereas hyaline droplets in podocytes are comparatively rare (7%: [1454a]). In about one-third of autopsy cases, neither GS nor interstitial tubular changes are present [1457]. Tumor cell infiltrates are rarely observed (10% of cases: [1454a]).

### IF Findings

Glomerular findings may be completely negative [948] or, in a few cases, positive in granular form: 7 out of 14: IgG; and 2 out of 14: IgA [1667].
Casts have been shown to be positive for IgG, fibrin and albumin [948]. $\kappa$-light-chains have been demonstrated in glomerular capillary loops subendothelially and in tubular BM deposits as in vascular walls and the interstitium [37]. In one of our own cases of an IgG plasmocytoma with lambda-chain paraproteinemia, IF revealed a severe, diffuse global granular deposition of C3 in the mesangium without IgG or lambda chains in the glomeruli. But the latter were positive in tubular casts and tubular protein droplets (compare: [948]). There is good agreement between the type of urinary paraproteins (kappa, lambda) and IF findings [948].

### EM Findings

The BM may be focally thickened up to 12,500 Å [1, 1207, 1360]. In the thickened foci, either abnormal osmiophilic areas [379] or massive osmiophilic subendothelial deposits [1360, 1667] are demonstrable in a few instances. The subendothelial deposits contain up to 500 Å-large granules [1]. Now and again subepithelial deposits are present [510].
With the exception of widening caused by an increase in matrix and the presence of a few foam cells [1360], the mesangium evidences no particularities. Long-spacing mesangial collagen has been demonstrated in the presence of nodular mesangial transformation [1455].
Podocytes are usually hypertrophic in the presence of proteinuria and, rarely, show a slight fusion of the foot processes [1207] or protein droplets [1454a].
The presence of a few microcrystals has been described in endothelium [1667], podocytes [1454a], tubular cells [379] (6% tubular crystals: [1454a]) as well as in tubular lumens [1454a]; for animal experimentation [518].
The glomerular capsule is usually unchanged, but the connective tissue component may be thickened in very

severe GS with capillary loop obsolescence. With the exception of the unspecific signs of protein storage, the tubules remain unaffected. Osmiophilic deposits in tubular BM were described [37].

### Complications

The chief complications consist of pyelonephritis, usually acute with impacted casts (30%: [1012], severe in 8%: [1457]) and of secondary amyloidosis (2–15%: [1624]; 8%: [1454a]; 1 out of 84 autopsies and 1 out of 8 biopsies: Z).
Amyloidosis possibly begins in the proximal tubules where lysosomes transform resorbed light chains into amyloid fibrils [784]. Amyloidosis of old age does not appear to be increased [961].
A further complication of the basic disease is the frequent but slight metastatic nephrocalcinosis associated with massive bone destruction (46%: [1454a; 1683, 1791]). In 5 out of 84 autopsy cases we found nephrolithiasis.
A formerly more frequent complication was that of acute renal failure due to intravenous pyelography [1255a] or resulting from circulatory collapse and/or massive cast formation and consecutive tubular obstruction in association with generalized dehydration [1207].

### Differential Diagnosis

The glomerular findings are unspecific (see p. 382). On the other hand, the tubulo-interstitial change with foreign body giant cell granulomas and massive occurrence of strongly stained hyaline casts are apparently pathognomonic. This change is absent in Waldenström's disease as well as in other paraproteinemia [747, 1135], but it has been reported in two cases of malignant lymphoma [227a].

### Prognosis

Prognosis in plasmocytoma patients depends less on the severity of plasmocytoma kidney, if not complicated by amyloidosis or pyelonephritis, than on acute renal failure which is present morphologically in 60% of autopsy cases [1454b]. Improved therapeutic control of extracellular body water volume reduced uremia as a cause of death—formerly reported in one-third of cases [1791]—in recent years (1971–1973) to only 12% [1454b].

### Pathogenesis

Unspecific GS as well as the complex of impacted casts are the consequence of the paraproteinemia. Glomerular subendothelial deposits are viewed as pure insudation of pathologic globulins and lipoproteins [1360] without participation of any immunologic process.

## Glomerulosclerosis in Waldenström's Disease [60, 1038, 1457, 1780, 1791]

***Synonyms:*** Macroglobulinemia, IgM-gammopathy [1667].

### Clinical Findings

In general, this rare disease occurs in and after the sixth decade of life [1038]. Proteinuria occurs late in the disease and is reported in 20–30% of the cases [41]. Other investigators have reported renal symptoms in 30–60% of the cases [1457]. Bence Jones's protein is rarely demonstrable in the urine (3 out of 41: [1228a]). Macrohematuria and acute renal failure are also infrequent [41]. Chronic renal insufficiency is reported in variable frequency (5 out of 16: [1135]; 3 out of 10: [1457]; 8 out of 8: [1789]).
Serum findings are characterized by a marked increase of IgM globulins occasionally accompanied by monoclonal cryoglobulinemia [201] and now and again by a hyperviscosity syndrome [1038]. Pathologically increased lymphoid cellular elements are demonstrable in bone marrow and in other tissue.

### LM, IF, and EM Findings

The essential finding is that of unspecific GS. A few isolated PAS-positive loop protein thrombi as well as partly massive PAS-positive, osmiophilic subendothelial deposits (12 out of 17 [40; 1135, 1141, 1667]) can be present as result of plasma hyperviscosity and/or cryoglobulinemia.
If the deposits are massive, they are accompanied by endothelial mesangial proliferation (contra: [1141]). With IF, they are shown to often contain IgM [1135, 1141]. Also with IF, similar deposits can be found in benign monoclonal gammopathy as well as in essential cryoglobulinemia [1667] (see p. 169).
There is one report of an unusual finding of giant cells in the capsular space [40].These cells are otherwise found in significant numbers in Goodpasture's syndrome (Table 8.1, p. 337).
The blood vessels are unchanged. Interstitial and tubular changes are similar to those encountered in plasmocytoma without, to be sure, the granulomas observed in plasmocytoma. At autopsy, the morphologic substrate of acute renal failure may be observed as well.

### Complications, Pathogenesis

Secondary amyloidosis is frequent: 3 out of 16 [1135]; 3 out of 17 [1667].
Pathogenetically, the observations made for plasmocytoma are valid for Waldenström's disease. It appears that immunologic processes are not involved.

# 20. Inflammatory Interstitial Renal Lesions

[687a, 1333a, 1791]

### Nosology

Nondestructive, usually abacterial interstitial nephritis (IN), i.e., interstitial nephritis in the narrower sense, is to be differentiated from destructive, bacterial IN, which is better designated as pyelonephritis. In the larger framework, specific granulomatous lesions may be classified under pyelonephritis.

## Acute, Nondestructive Interstitial Nephritis (IN)

[1793, 1780b]

### Definition

This entity (IN) is characterized by lympho-plasmohistiocytic interstitial inflammation without direct parenchymal injury from inflammatory processes. The primary form is a distinct disease. The secondary form ("accompanying nephritis") is associated with other distinct renal lesions where it usually occurs focally with perivascular predominance.

### Incidence

Apart from corresponding transplant changes which will not be discussed here (see p. 569), we have found severe acute IN in 431 out of 25,000 autopsies (biopsies: 1.2%) and chronic IN in 63 out of 25,000 autopsies (biopsies: 0.48%). The above figures are based on consideration of only essential and diffuse findings. It follows from these data that acute IN rarely becomes chronic. We found no difference in disease distribution with relation to sex or age.

### Clinical Findings

The symptomatology of acute IN is often completely determined by the symptoms of the underlying disease (see p. 408). A listing of clinical symptoms encountered in our material—in which the symptomatology of mainly shock-free cases is apparent [1780b]—is detailed in Table 20.1. The clinical picture is often completely dominated by oligo- and anuria which may occur from one instant to the other and which we have observed associated with 73 out of 431 autopsy cases and with 18 out of 22 biopsies (see also [185]). Oliguria or anuria are also frequently the initial symptoms of the disease (13 out of 21: Z; Table 20.1). They can however be missing in so-called nonoliguric renal failure as especially encountered in cases due to nephrotoxic antibiotics which only become apparent by progressive increase in serum creatinin or in polyuric renal failure which we observed in 4 out of 21 cases. Tubular acidosis is nowadays very rare; it was formerly found after use of tetracycline whose date of use had expired.

Skin rash, especially in cases of allergic etiology, may initially be present [687a, 1215]. We have observed transitory hypertension in 7 out of 22 biopsies.

Urinary findings are ambiguous. Microhematuria, leukocyturia and usually mild proteinuria are relatively frequent. Leukocytic casts, erythrocytic casts, bacteruria, as well as massive proteinuria are rare, but this wide spectrum of urinary findings may be misleading in regard to the underlying disease. Thus, in more than half the cases, pyelonephritis, glomerulonephritis or other renal lesions were clinically diagnosed (see Table 20.1).

### LM Findings

The interstitium at the corticomedullary region—and less so in the cortex—is diffusely edematous (connective tissue stain!), widened, and often infiltrated with coalescing foci of lymphocytes, plasma cells, and histiocytes (Figs. 20.1, 20.2) and a few eosinophilic leukocytes which may be very frequent in cases of drug allergy. These infiltrates are especially evident perivascularly (Fig. 20.3). Tubulolymphatic and tubulovenous shunts are filled with small PAS-positive casts (see p. 134).

The epithelium of the proximal convoluted tubule is frankly flattened, even in the absence of clinical shock [171]. The cortex shows a considerable decrease in the filling of interstitial capillaries with blood but the glomerular capillary loops are, surprisingly, rarely collapsed. In autopsy material, the papillary capillaries are dilated and

Table 20.1. Clinical findings in acute interstitial nephritis from 22 of our own biopsy cases

| 1. Symptoms at disease onset[a] | Frequency[b] | |
|---|---|---|
| Oliguria/anuria | 13/21 | |
| Polyuria | 4/21 | |
| Fever | 7/21 | |
| Hematuria | 5/21 | |
| Renal pain | 3/21 | |
| 2. Oliguria/anuria during the disease course | 18/22 | |
| 3. Clinical findings at the time of biopsy[a] | Frequency | |
| Shock | 4/22 | |
| Microhematuria | 14/22 | |
| Leukocyturia | 14/22 | |
| Proteinuria (0.5–12 g/day) | 9/19 | |
| Bacteriuria | 5/19 | |
| Erythrocytic casts | 3/19 | |
| Leukocytic casts | 2/19 | |
| Blood pressure $\geqq$160/100 mm Hg | 7/22 | |
| 4. Etiology | Frequency | |
| Uncharacteristic "influenza-like" prior disease | 7/22 | |
| No definite prior disease determined | 2/22 | |
| Infections | 5/22 | |
| Q-fever | | 1/22 |
| Streptococcal tonsillitis | | 2/22 |
| Rubella | | 1/22 |
| Acute pulmonary tuberculosis | | 1/22 |
| Poisoning | 3/22 | |
| $CCl_4$ | | 1/22 |
| Wood alcohol | | 1/22 |
| Formic acid | | 1/22 |
| Hemorrhage | 2/22 | |
| Possible causes | 3/22 | |
| Novalgin® allergy | | 1/22 |
| Tetracycline allergy | | 1/22 |
| Postmyocardial infarction syndrome | | 1/22 |

[a] Several possibilities.
[b] No. of cases in which finding was present/stated.

they frequently contain myelogenous cells, e.g., myelocytes, megacaryocytes, etc. (Fig. 20.4; [1319]; see also p. 490).
We speak of serous IN when there is quantitative predominance of edema (Fig. 20.4) and of cellular IN when cellular infiltrates predominate.

***Acute eosinophilic nondestructive IN*** is very rare (3 out of 25,000 autopsies: [1791]). It is extremely rich in eosinophilic leukocytes. We encountered it once each in ascaridiasis, drug allergy and Duhring's herpetiform dermatitis.

**IF Findings**

Of our own cases, 6 of 10 yielded positive findings. In one of these cases there were diffuse ultralinear deposits of slight intensity for IgG which were accompanied by granular deposits peripherally and mesangially of IgM, IgA and C3 with focal-segmental distribution. In the other 5 cases, we found C3 only or IgM and C3 with mesangial and peripheral, focal-segmental distribution. In 3 of the 10 cases, the interstitium stained diffusely for immunoglobulins and fibrin(-ogen). Linear deposits in the tubular BM of IgG or other Ig were not present in our material. They were described in drug-induced cases with antitubular BM antibodies [176a, 1086a].

**EM Findings**

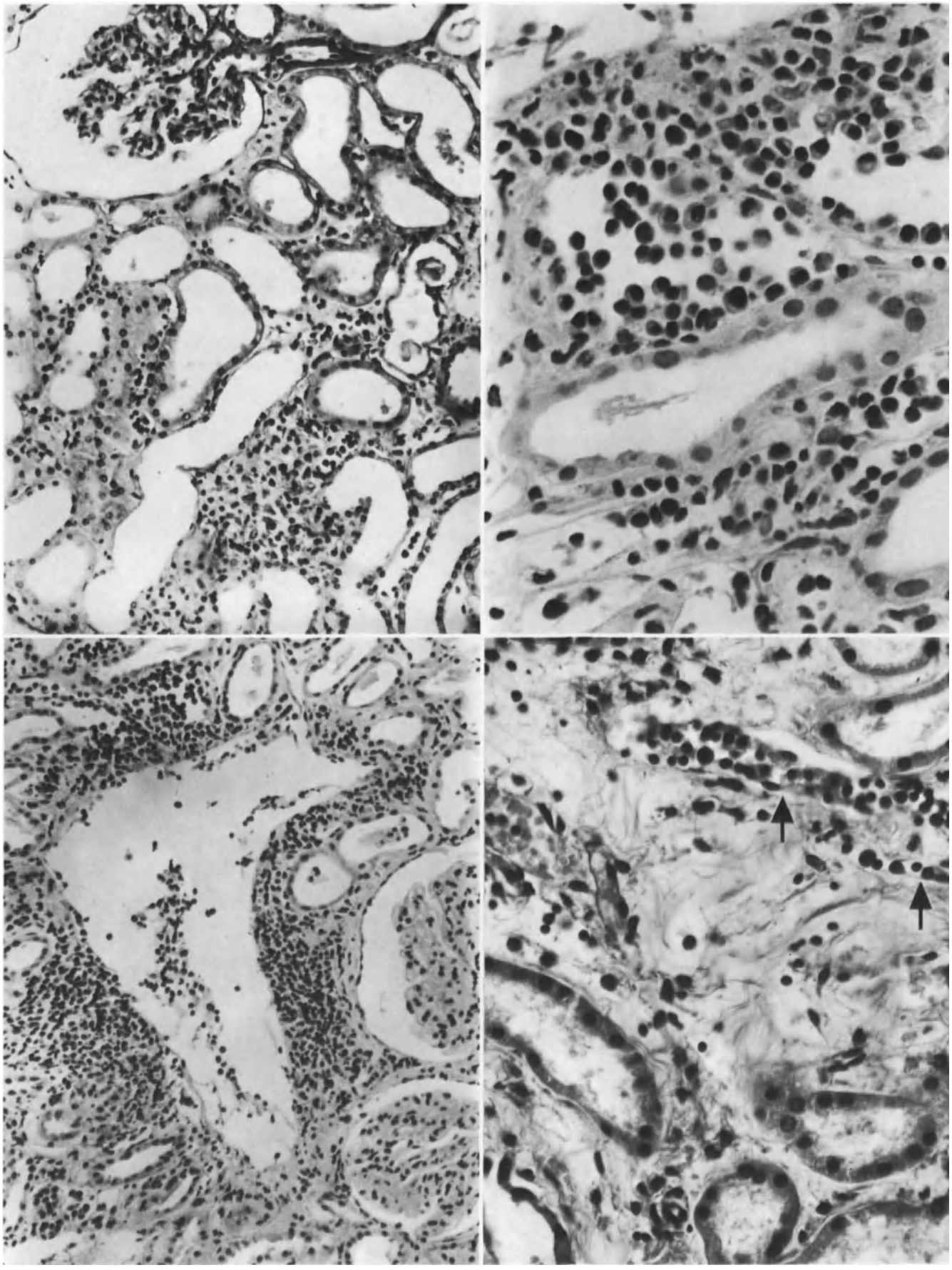
No characteristic glomerular lesions are present (see Figs. 6.9, 6.21, 6.34, 6.57, 6.64, 6.80, 6.88). In a few cases, the peripheral glomerular BM is focally somewhat thickened—especially the lamina rara interna.
Podocytes are edematous and their nuclei swollen. Occassionally, lipid and protein droplets are found in the podocytes. A slight, patchy fusion of foot processes is infrequently observed.

**Fig. 20.1.** Acute interstitial nephritis following exanthema from ▷ arsenic ingestion. Edema and lympho-plasmocytic infiltrates are present in the interstitium. There are tubular dilatation and atrophy of the epithelium (as seen in so-called shock kidney). Glomeruli are unchanged. Female, 53 years. Autopsy specimen. HE (×220)

**Fig.20.2.** Acute interstitial nephritis. Angina was present 3 weeks prior to biopsy and anuria for 2 weeks. Interstitial infiltrate present consists predominantly of plasma cells and lymphocytes. Male, 18 years. Giemsa (×720)

**Fig. 20.3.** Same case as in Figure 20.2. Perivenous accumulation of interstitial infiltrates. Male, 18 years. HE (×120)

**Fig. 20.4.** Predominantly acute serous interstitial nephritis 10 days after burn injury. Intertubular vessels are filled with immature white blood cells (→). Male, 38 years. HE (×680)



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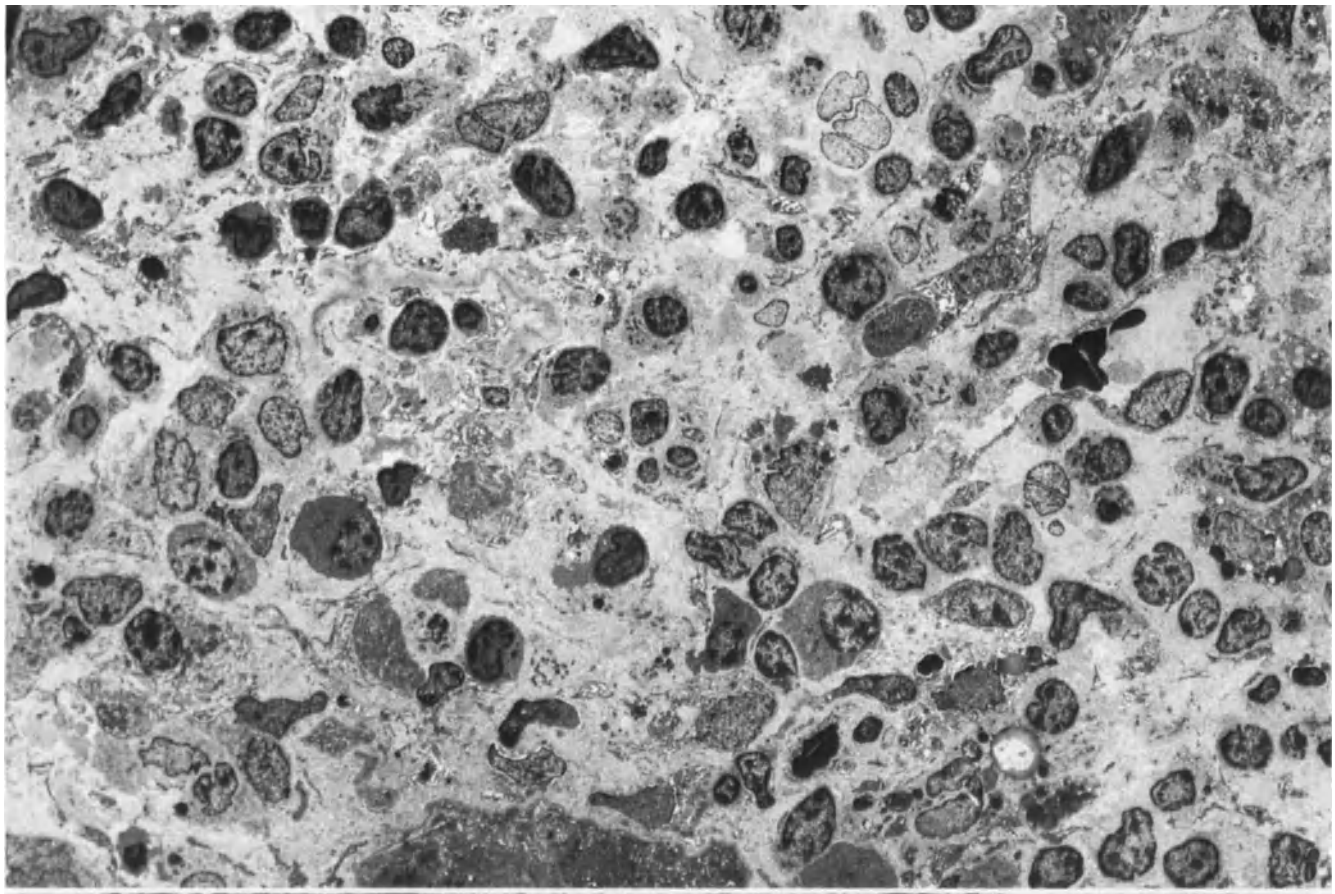

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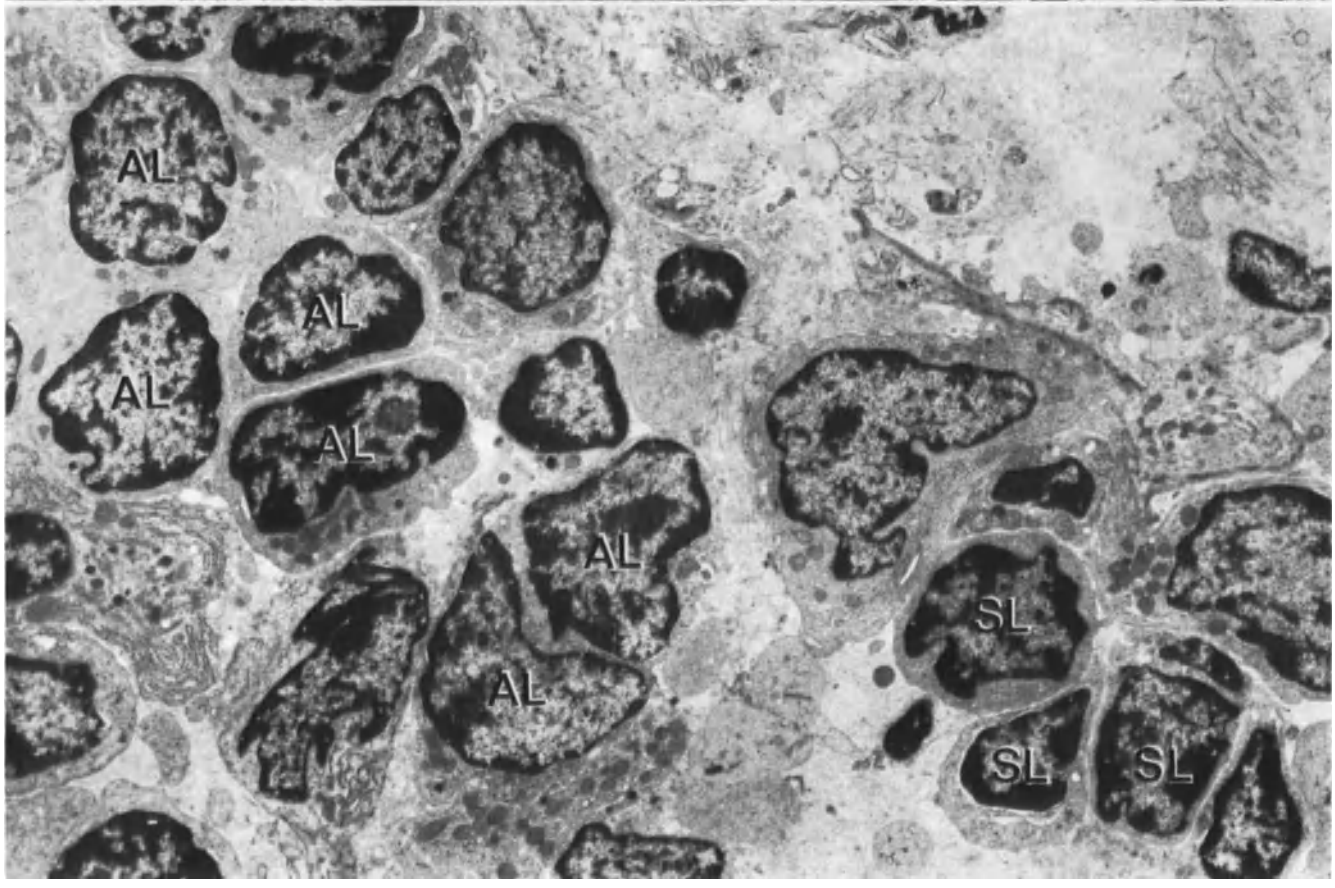


20.6

Endothelium and mesangium do not demonstrate any significant changes. A low power view of the interstitium permits easy identification of the infiltrates (Fig. 20.5). Exact differentiation of the various cell types requires higher magnification however (Fig. 20.6). The predominant cells of the early phase are activated lymphocytes and immunoblasts. Plasma cells are not found till the seventh day of the disease, and in increasing numbers thereafter. Histiocytes and small lymphocytes are also present (Fig. 9.2); eosinophilic leukocytes are generally absent or very scanty but may be present in large numbers in cases of allergy (see above). With EM, passage of lymphocytes and, occasionally, of plasmoblasts through the vessel walls (Fig. 20.7) is often observed. Also frequently recognizable are activated lymphocytes lying between the endothelium and BM of the intertubular vessels (Fig. 20.8). The interstitium itself is variably edematous (Fig. 20.5) and often contains cellular detritus (Fig. 20.9), a finding which is indicative of severe destruction of interstitial cells. Occasionally, fibrin can be demonstrated in the interstitium (Fig. 20.10).

We have found chromoprotein casts (hemoglobin/myoglobin: [1786]) in the collecting ducts in about one-third of our autopsy cases (Fig. 20.11). This finding is more rarely demonstrable in proximal tubules and Henle's loops (structures more readily accessible to needle biopsy). Its demonstration is significant since it indicates possible hemolysis from transfusion, etc. or myolysis lysis from electrical injury, toxicosis or acute polymyositis. Isolated intratubular oxalate crystals of 4–20 µm are present in almost every case (for secondary oxalosis see p. 462). The blood vessels are unchanged.

For differential diagnosis, see p. 415.

## Chronic Interstitial Nephritis

For the incidence of chronic IN, see p. 407.

### Clinical Findings

The clinical course is markedly insidious and is characterized by headache, anemia, tiredness, bone pain and spontaneous fractures (ribs, pubis, etc.). There occurs a grey-brown skin discoloration in cases of phenacetin addiction (38 out of 65: [1791]) which is, however, by no means either obligatory or pathognomonic. Urinary findings are insignificant except for frequent polyuria – a consequence of insufficiency of urine concentration – as well as for metabolic acidosis. Proteinuria of less than 1 g/day, and slight leukocytosis without accompanying leukocyturia are observed. Loss of urine concentration and metabolic acidosis are often of high degree in comparison to renal excretory insufficiency.

Hematuria is indicative of papillary necrosis or accompanying tumors of the urinary tract. Papillary necrosis is pronouncedly frequent – especially in analgesic addiction – but not obligatory. Sequester elimination under renal colic may be the first symptom. Finally, hypertension may develop (48 out of 63: Z). The course is slow but progressively uremic.

◁ **Fig. 20.5.** Typical cell composition in acute interstitial nephritis with anuria of unknown cause. Plasma cells, histiocytes and mostly activated lymphocytes are present in approximately the same numbers in the frankly edematous stroma. Female, 59 years. (× 1780)

**Fig. 20.6.** Infiltrate in acute interstitial nephritis in rubella with concomitant anuria. Activated (large) lymphocytes (*AL*), non-activated (small) lymphocytes (*SL*). Rubella antigen could be identified with IF in glomerular BM and mesangium, tubular epithelial cells and a few interstitial cells. Male, 18 years. EM (× 8300)

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**Fig. 20.7.** Plasmoblast (*PS*) seen penetrating through a vascular wall in acute interstitial nephritis following tetracycline therapy for sinusitis. Endothelial cell (*E*), basement membrane (*BM*) of a blood vessel, capillary lumen (*CL*). Male, 29 years. EM (× 12,100)

**Fig. 20.8.** Same case as Figure 20.7 showing an intertubular vessel in acute interstitial nephritis. Two activated lymphocytes (*AL*) between the endothelium and vascular BM. Capillary lumen (*CL*), endothelium (*E*), basement membrane (*BM*). Male, 29 years. EM (× 6300)

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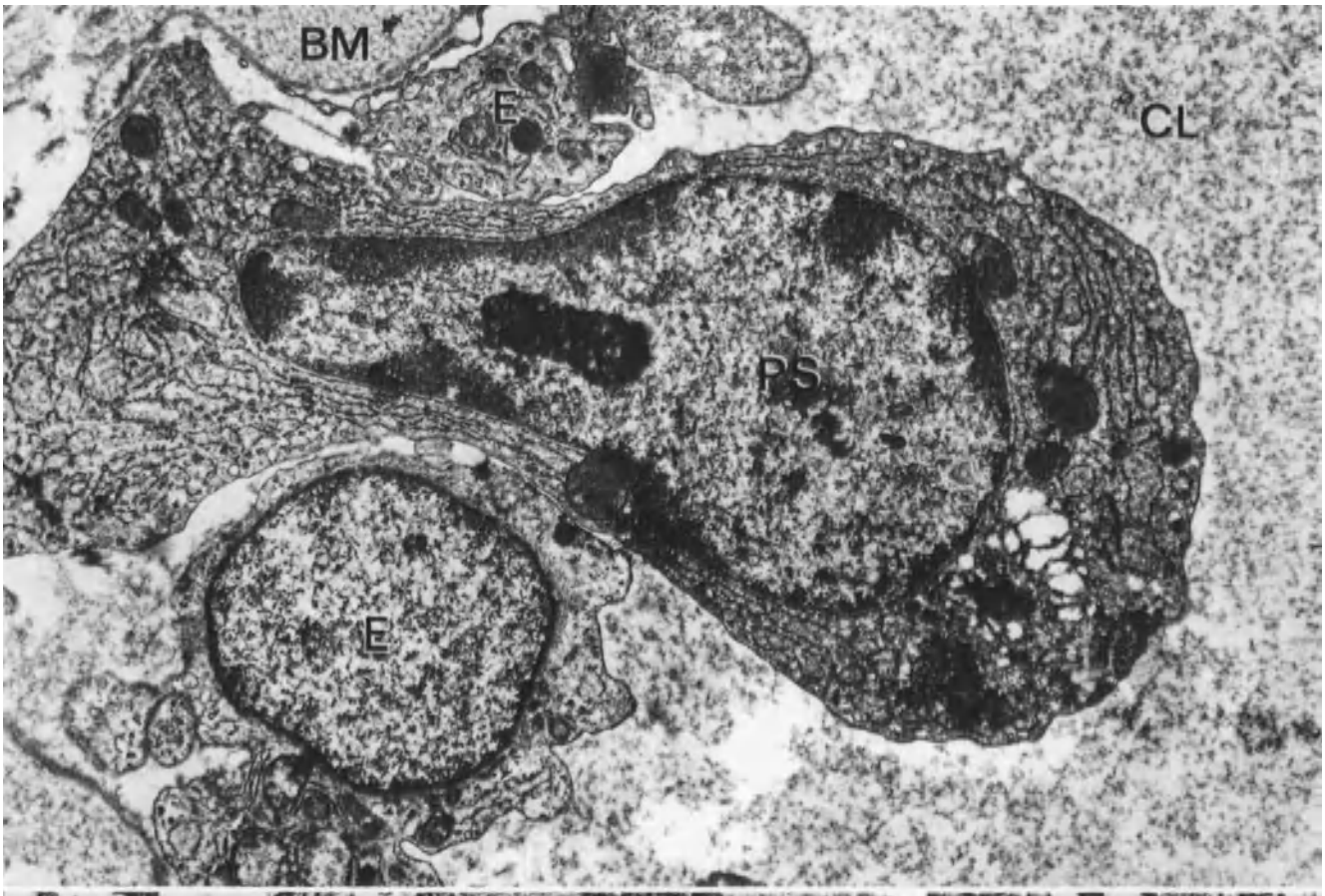
**Fig. 20.9.** Extensive cellular detritus in the edematous interstitium in acute interstitial nephritis in conjunction with anuria at the time of biopsy. Male, 60 years. EM (× 14,900)

**Fig. 20.10.** Same case as in Figure 20.9. Acute interstitial nephritis showing extensive fibrin deposition (→) in the interstitium. Male, 60 years. EM (× 6100)

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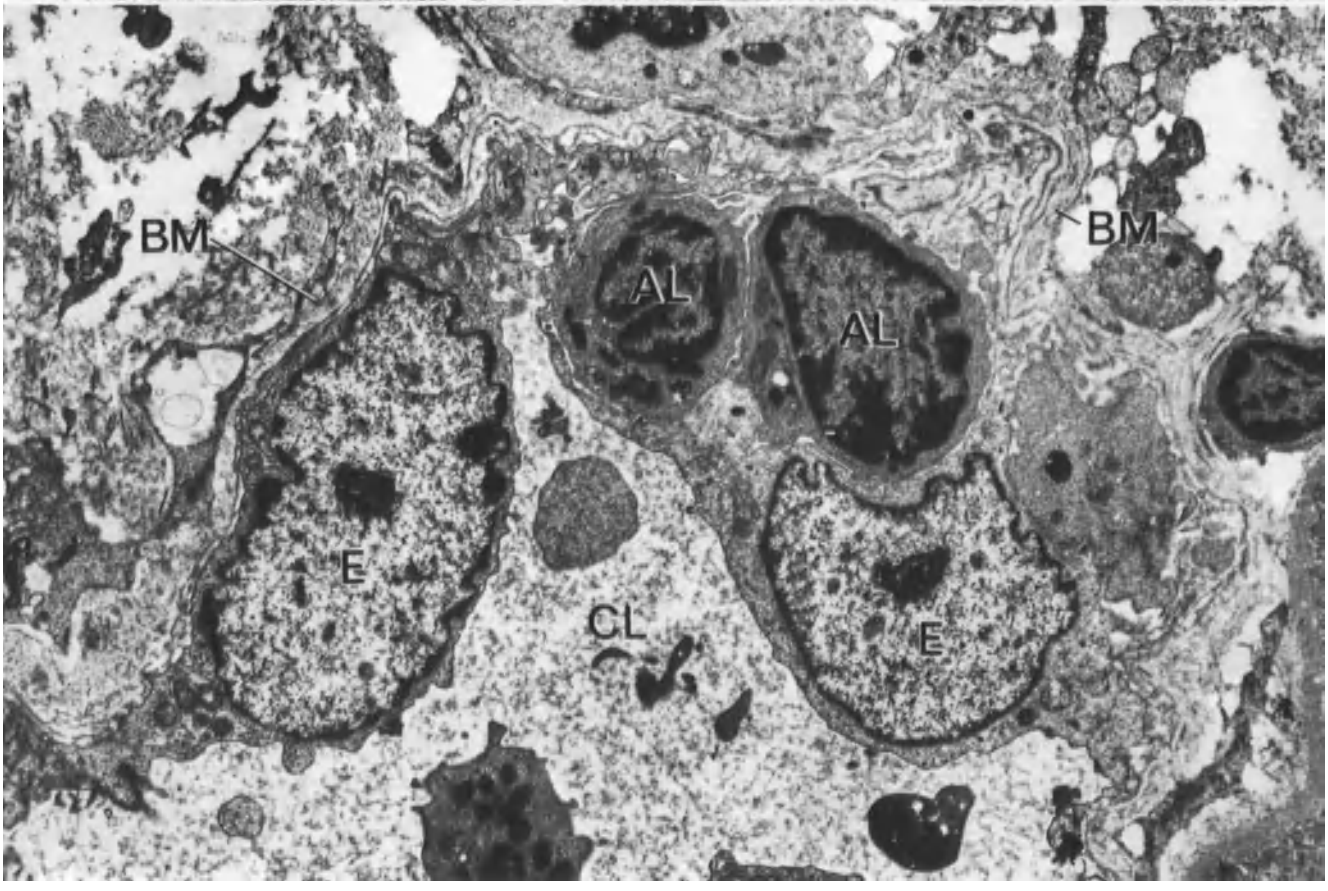


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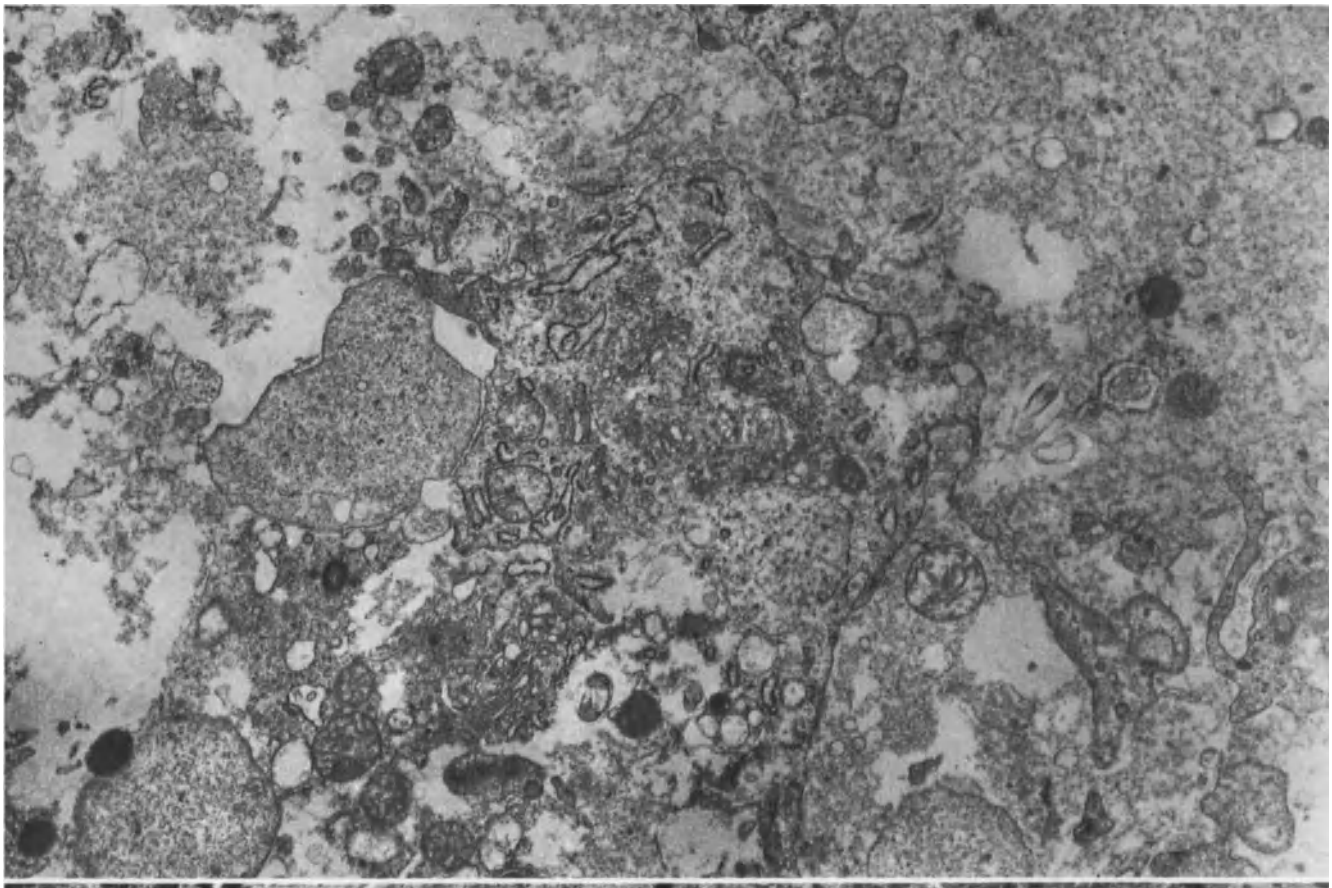

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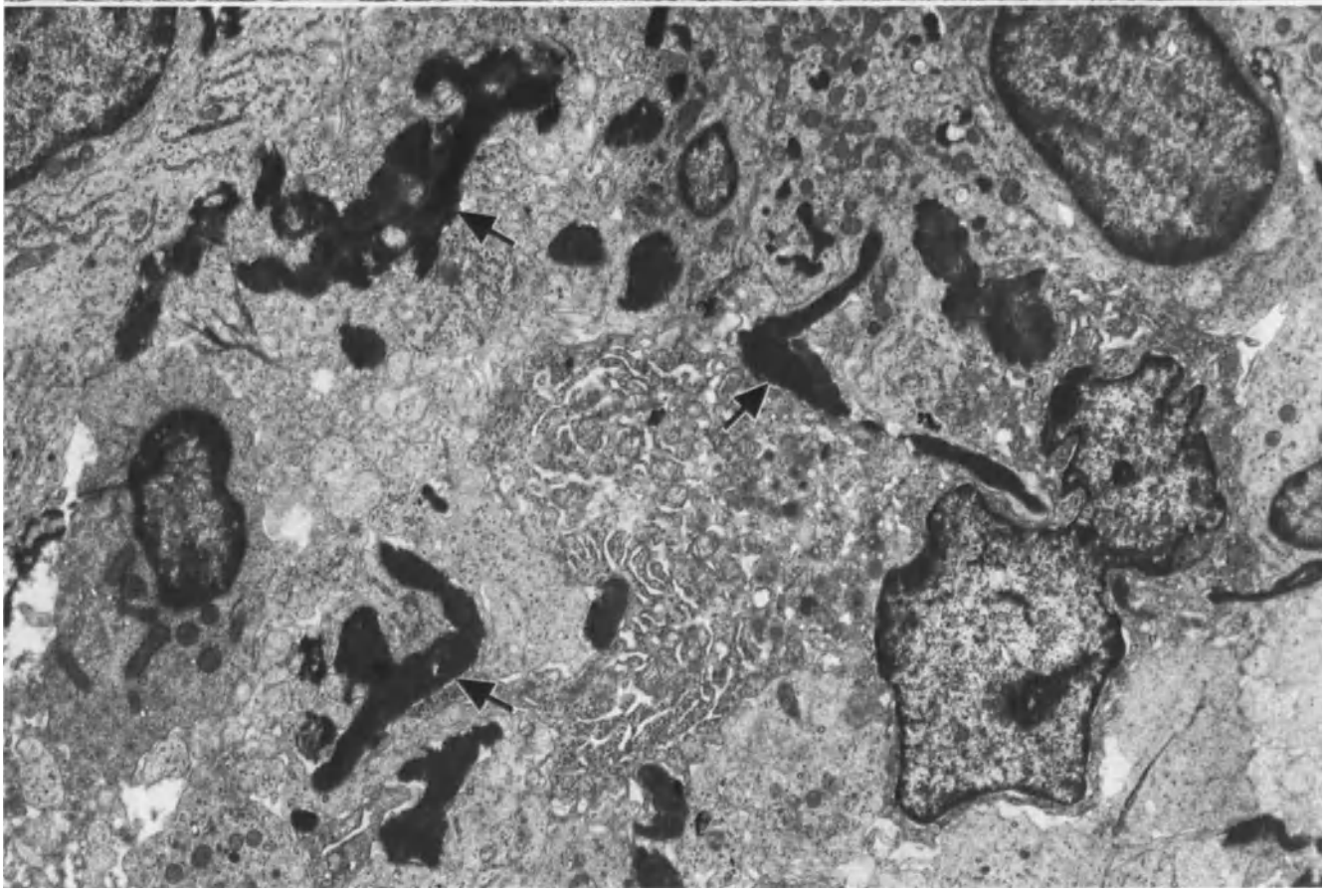

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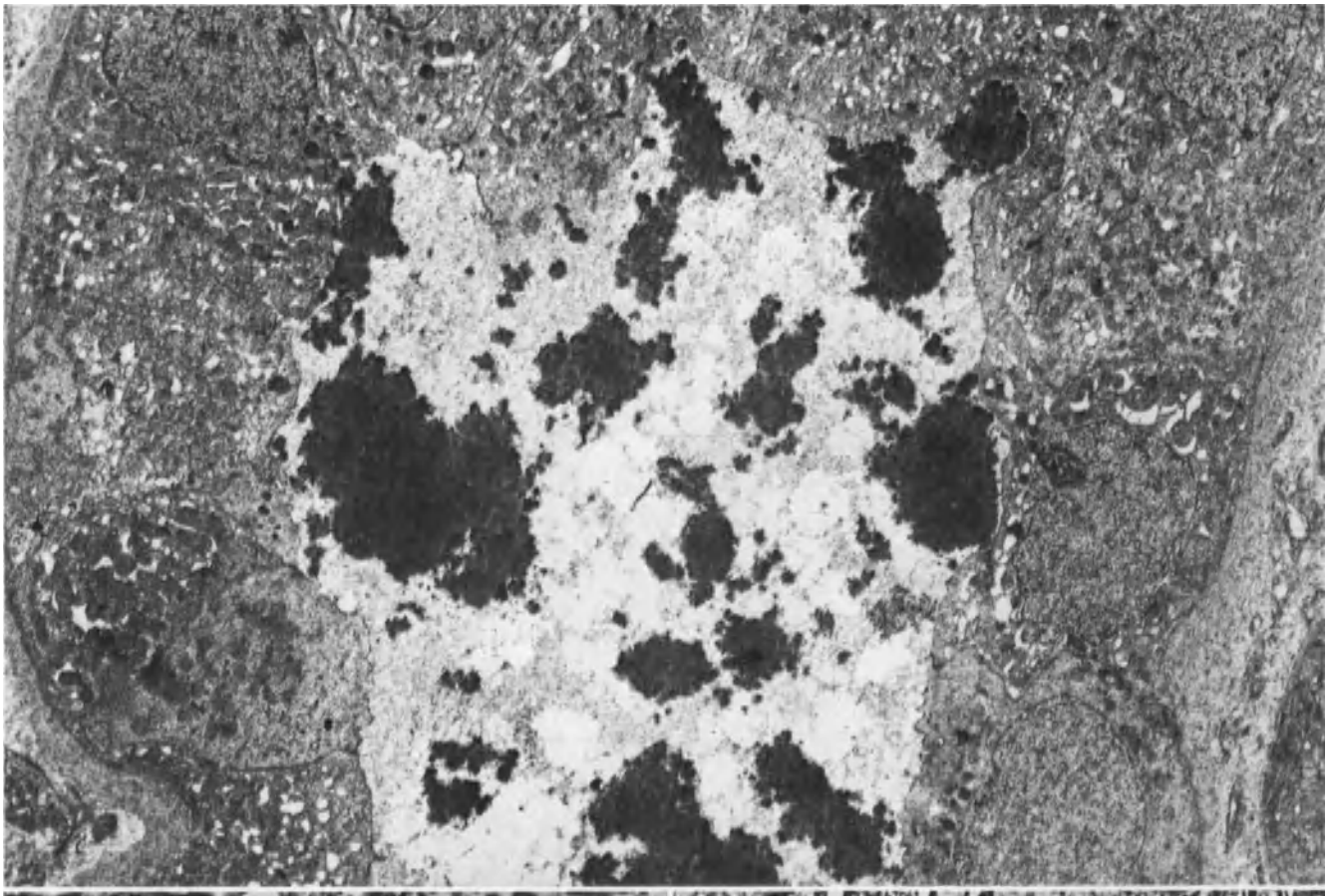

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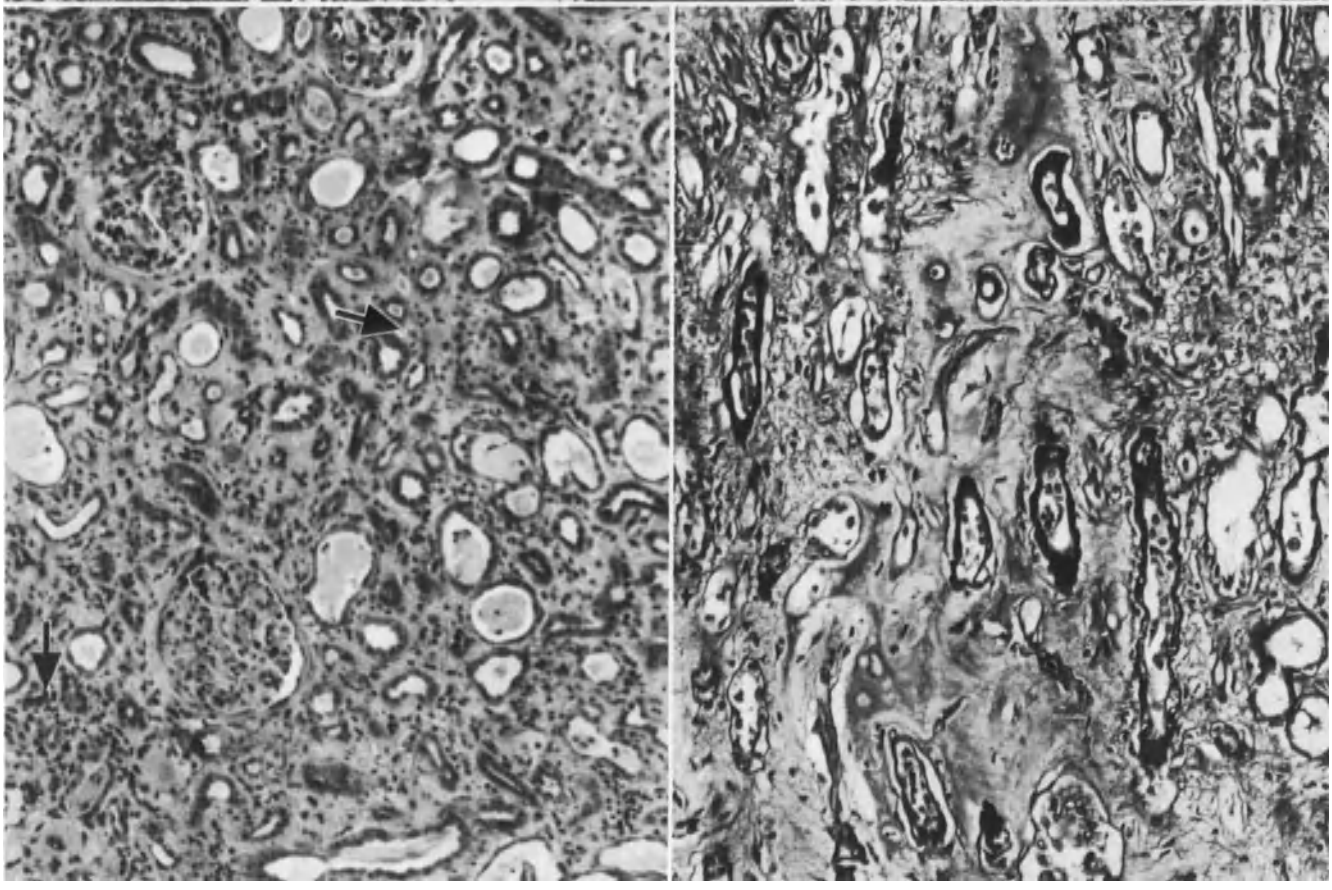

20.12
20.13

### LM Findings

LM study (Fig. 5.14) reveals sclerosis of connective tissue—which is widened and increased—instead of edema (Fig. 20.12) in acute interstitial nondestructive nephritis. This condition is especially pronounced in the medulla (Fig. 20.13). The interstitium demonstrates scattered lympho-plasmo-histiocytic infiltrates (Fig. 20.14). No scar tissue replacement of destroyed parenchyma is present as is clearly illustrated by PASM stain (Fig. 20.15). Late in the course of the disease, glomeruli show collapse (Fig. 6.111). The glomerular capsule is considerably thickened by connective tissue. The capsular epithelium remains intact for a considerable period.

The tubules are frankly atrophic and often demonstrate dedifferentiated clear cells with a thickened BM rich in lipids—as demonstrated by the sudan stain—a finding especially pronounced in the papilla in cases of phenacetin addiction. A few calcium oxalate crystals in the tubular lumen are often found. In cases of phenacetin addiction, the epithelium of the proximal convoluted tubules is said to contain a finely granular brown pigment (lipofuscin) more frequently than in other cases, a finding which we have not been able to confirm (see p. 440). The vessels exhibit slight and exclusively secondary changes (adaptive intimal fibrosis, hypertensive vasculopathy). In careful examination of autopsy material, papillary necroses of various age can be found in 90% of the cases regardless of etiology.

◁ **Fig. 20.11.** Clumps of chromoprotein (hemoglobin) are present in the lumen of Henle's loops in acute interstitial nephritis. Anuria at the time of biopsy. Male, 41 years. EM (×3900)

**Fig. 20.12.** Chronic interstitial, nondestructive nephritis in severe phenacetin addiction. Tubules are not destroyed but highly atrophic. Epithelium of the proximal tubules is flattened. Interstitium is diffusely broadened and sclerosed and evidences very scanty infiltrates (→). Glomeruli are unchanged. Male, 60 years. HE (×110)

**Fig. 20.13.** Same case as in Figure 20.12 showing typical sclerosis in the renal medulla in chronic interstitial nephritis. There is striking homogeneous broadening of the interstitium without cell increase. Infiltrates have almost completely disappeared. Tubules are atrophic and exhibit thickened BM. Male, 60 years. PAS (×200)

### EM Findings

Among the interstitial infiltrates, small and sometimes activated lymphocytes predominate and are accompanied by moderately numerous phagocytes and, rarely, by fibroblasts. It is also clearly recognizable that the individual collagen fibers (fibril bundles) are pronouncedly coarse (Fig. 20.16) and that tubular atrophy and BM thickening are also very marked (Fig. 20.17). Tubular atrophy can lead to extensive cellular dedifferentiation (Fig. 20.18).

### Differential Diagnosis

Of initial importance is exclusion of IN accompanying a primarily noninterstitial renal disease. Acute IN may be present in diffuse and segmental-focal accentuated GN as well as in the periphery of acute infarcts. In chronic IN, among other entities, GN, primary oxalosis and periarteritis nodosa, must be taken into consideration.

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**Fig. 20.14.** Chronic interstitial nephritis showing the corticomedullary zone in a case of severe phenacetin addiction. Scanty, almost purely lymphocytic interstitial infiltrates (→) in the diffusely broadened and sclerosed stroma. Female, 68 years. HE (×160)

**Fig. 20.15.** Same case of chronic, nondestructive interstitial nephritis presented in Figure 20.12. Interstitium is broadened. Tubular BM is thickened but nowhere eroded. Male, 60 years. PASM (×230)

**Fig. 20.16.** Composition of the infiltrate encountered in chronic, nondestructive interstitial nephritis of unknown cause. Infiltrate in the coarsely sclerosed stroma consists predominantly of small and middle-sized lymphocytes between which are isolated phagocytes (*PH*). Female, 42 years. EM (×3260)

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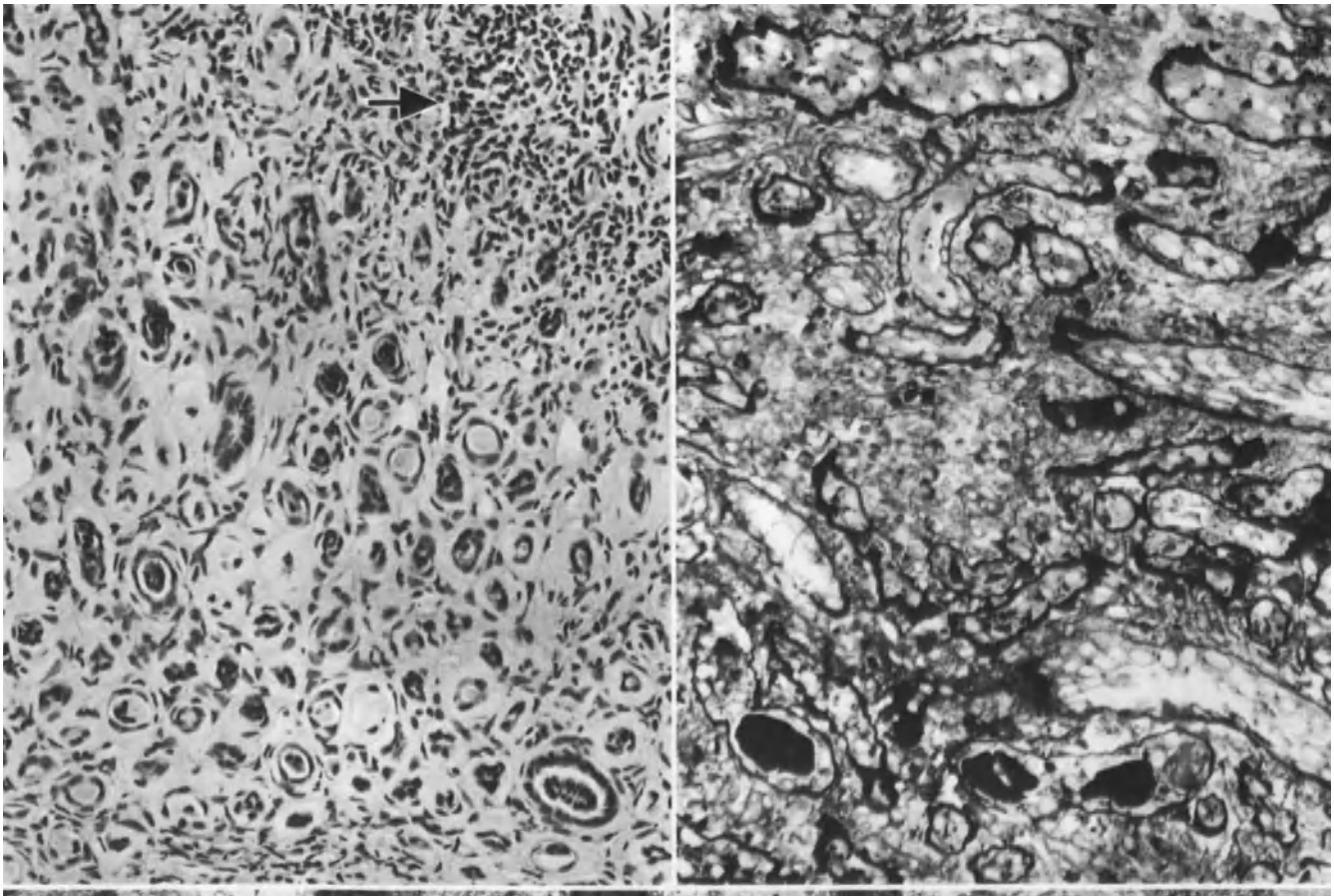
**Fig. 20.17.** Same case of chronic nondestructive interstitial nephritis as in Figure 20.16. There is severe tubular atrophy in the corticomedullary zone. Tubular BM is thickened (→). Coarse fibers and a few scattered infiltrates are present in the interstitium. Female, 42 years. EM (×1500)

**Fig. 20.18.** Same case of chronic, nondestructive interstitial nephritis as in Figure 20.16. A proximal tubule (*1*) and possibly a distal tubule (*2*) with signs of considerable dedifferentiation are seen. Female, 42 years. EM (×8500)



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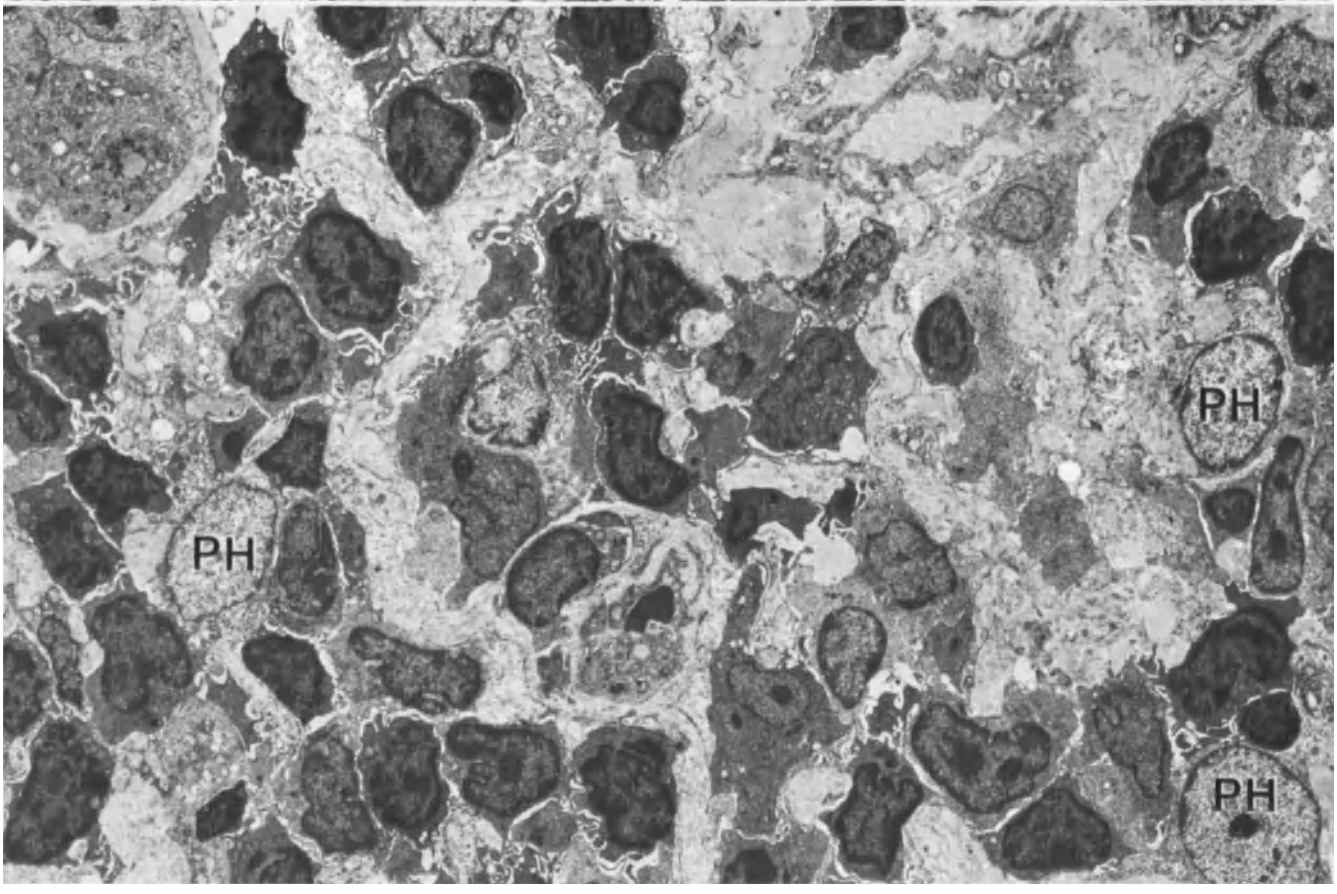


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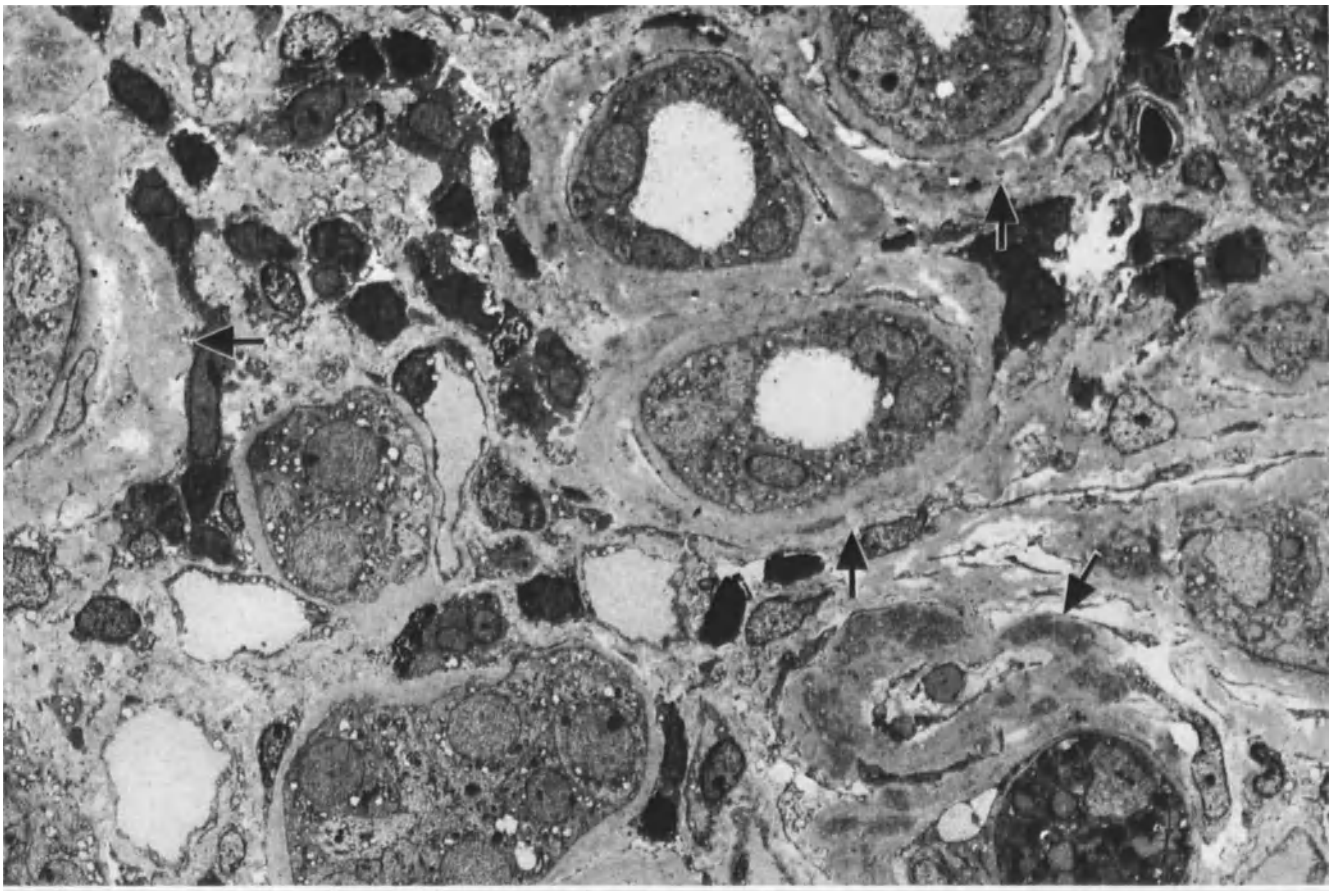

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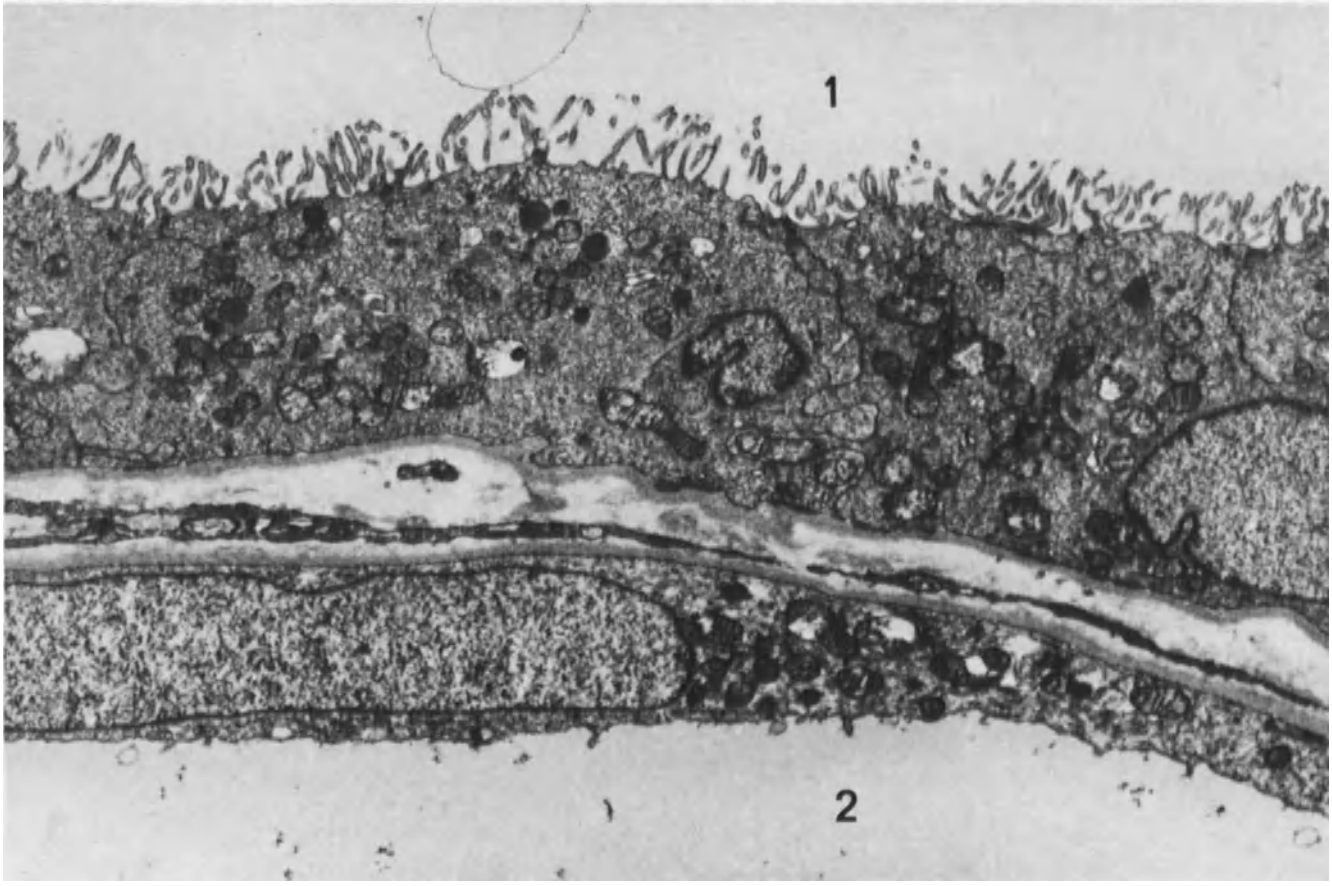


20.18

Small, circumscribed lymphocytic infiltrates in the immediate vicinity of obsolescent glomeruli and atrophic tubuli are found quite frequently in otherwise normal biopsy and autopsy tissue. The cause for such foci cannot usually be determined (possibly microemboli, possibly focal nephritis, possibly pyelonephritis or resorptive inflammatory reaction). If accompanying IN is excluded, differentiation from destructive interstitial nephritis (pyelonephritis) is important: pyelonephritis is radially arranged and not as diffusely, a finding which may not be apparent in needle biopsy. The presence of numerous neutrophilic leukocytes and the erosion of tubules, glomeruli and vessels is categorically indicative of pyelonephritis in the acute phase. In the chronic phase, foci of erosion have been replaced by scar tissue. In biopsies with a combination of pyelonephritis and nondestructive IN, it is usually impossible to determine which of the two lesions arose first.

## Prognosis

The prognosis for acute IN is good if the time for appropriate dialysis is not missed. Usually, renal function normalizes completely within months or up to a year or even longer [23,500] (for children: [1841]). In our material, 13 out of 14 cases had completely normal renal function after an average follow-up time of 3.3 years (0.5–12 years). In one case presenting with a contralateral contracted kidney, there was no worsening of renal function following recovery from acute IN. We observed remnant hypertension in one case only. On the other hand, frequent secondary urinary tract infections following IN in 59 out of 70 cases—in which 15 out of 59 lead to chronic pyelonephritis—have been reported [516].

If the causative noxious factors persist [1084, 1791] or recurrences occur [162, 1780b] or if serve injury to the tubular BM is present [458], chronic, progressive IN can develop.

In chronic interstitial nephritis, prognosis is bad. However, sufficient numbers of bioptically controlled cases are still lacking for confirmation of this assessment.

## Etiology and Pathogenesis

Current concepts relating to the genesis *of acute IN* take into consideration three factors occurring independently or in combination: shock, immunologic reactions and infection. The common end result of the three factors is destruction of body proteins e.g. hemolysis, myolysis, which may be enhanced by administered exogenous substances [1793].

In our own autopsy material, we observed pyemia without pyemic renal foci and shock each in one-third of our cases. In 198 out of 431 autopsy cases, chromoprotein casts were present in the tubules, a finding indicative of hemolysis or myolysis [1786, 1791]. These were attributable to transfusion reactions, traumatic causes of hemolysis or myolysis such as polytrauma, electric accidents, burns [1786], to inherent disease processes such as polymyositis [880] and hemolytic anemia [787] and to heroin and alcohol poisoning [868a].

In shock kidney, in which acute IN is usually present from the third day on [1791, 1792], myelogenous cells in the vasa recta (see p. 490) are one of the typical findings. It is not known whether shock leads to IN via tubular ischemia alone or whether other factors are involved (see p. 419). Toxic processes can arouse the same response, e.g., anaesthesia with methoxyflurane [274] or halothane [320a], in which calcium oxalate crystal formation may be partially responsible for the epithelial injury (see also [57]).

Today, immunoreactions to drugs [687a], e.g., to penicillin, methicillin, gentamicin ([73, 176a, 1765a, 1843, 1844], even with granuloma formation [1032a]), phenindion [1068, 1215], ampicillin [1398, 1418], dilanthin, hydantoin [1158], furosemid [983] as well as hemolysis from rifampicin therapy [1114] are receiving more and more attention [185]. In some of the cases, the drug behaves as a hapten, and has, together with gamma globulin, been demonstrated as being attached to tubular BM [73]. The slight secondary damage to tubules is thought to be due rather to chemical mediators than to the direct destructive action of the inflammatory cells [353a]. In a case of acute IN subsequent to streptococcal angina, properdin and C3 were demonstrated in the glomeruli—possibly representing alternative pathway activation of complement due to penicillin and/or streptococcal antigen [1686].

The fact that acute IN was found rather more frequently in the pre-antibiotic era [1780b] than today suggests to us that a certain overestimation of the role of drugs is present in the current literature.

In most cases, however, the question regarding etiology and pathogenesis of acute IN remains by and large unanswered. The significance of infections such as mononucleosis [1757a], brucellosis and leptospirosis is difficult to assess retrospectively (one case of subacute IN following smallpox vaccination (Fig. 20.19) was made available to us by Prof. Uehlinger, University of Zurich).

In general, the cause of *chronic IN* remains obscure. Experimentally, it has been produced in the rat by N-3,5-dichlorophenylsuccinimide [1586] and we have observed it in a case of nocturnal hemoglobinuria (Marchiafava-Micheli disease) of many years duration (see also [1084]). It has also been reported after heat stroke [826] and after many years of drug poisoning [687a]. Usually, a prior acute stage is not observed. It appears possible, however, that acute IN—in rare cases—does not heal but procedes on to chronic IN [1780b, 1791]. Some of

our cases developed after years of analgesic (phenacetin) addiction, a finding by no means specific for phenacetin abuse (see p. 440). Today, it is generally accepted that the chronic IN associated with phenacetin addiction arises in connection with primary papillary necrosis [233, 570, 837, 1846]. Nevertheless, it must be borne in mind that unequivocal cases of chronic IN due to phenacetin addiction without papillary necrosis do occur (5 out of 63 autopsies: Z). The relationship between papillary scarification or necrosis and chronic IN is illustrated by the occasional observation of circumscript, chronic IN occurring proximally over a noninfected renal cyst with concomitant medullary compression.

The cause of endemic chronic IN in Finland is unknown [900]. Balkan nephritis appears to be rather a bland-coursing pyelonephritis than a nondestructive IN (see p. 440). The reported case of a 6-year-old boy with familial chronic IN and antitubular BM antibody must be regarded as unique [129].

Polyuria, acidosis, and loss of concentration ability are explained as being due to anoxia of the distal tubules arising from compression of interstitial capillaries by edema, sclerosis, and tubular BM thickening and to the increased diffusion distance between capillaries and tubular epithelium. Transient, early hypertension in acute IN can be a consequence of hyperhydration or of decreased renal blood flow [1781]. Late hypertension appears to occur only if there is severe reduction of glomerular blood flow arising from intertubular sclerosis.

## Pathogenesis of Acute Reversible Renal Failure

As formulated previously, many primary diseases may give rise to acute renal insufficiency to which the reader is referred (shock kidney, p. 490; toxic tubulonephrosis, p. 487; acute IN, p. 408). For literature see [187, 274, 502, 1156, 1786, 1791].

With reference to the clinical course, two phases may be recognized in acute reversible renal failure; an initial phase usually characterized by oligo-anuria and a second phase characterized by persisting oligo-anuria (up to several weeks) or more often by polyuria.

A common terminal pathogenetic pathway of the multiplicity of etiologic factors is recognizable in relation to the first oligo-anuric phase: the tubules are injured by ischemia and/or by toxic products. This injury is reflected functionally by insufficient resorption—chiefly of sodium—in the proximal tubules and in the ascending limb of Henle's loop. This means that an increased amount of sodium is reaching the macula densa which, as shown in animal experimentation, leads to occlusion of the proximal tubules by cellular swelling due to contraction of the vas afferens subsequent to activation of the renin-angiotensin system [171, 1616a]. Although this mechanism explains the initiation of acute renal failure, it is not known with certainty whether it suffices to explain its maintenance [1616a]. In addition, it has been shown that animals can be protected against acute renal failure by diuresis in spite of elevated intrarenal renin concentrations [1604a].

In addition to decreased blood supply, increased tubular permeability and tubular obstruction from casts are repeatedly proposed as causes for oligo-anuria. The pathophysiologic significance of increased tubular permeability has not, as yet, been clarified. Some experimental models indicate that increased tubular permeability is not a relevant pathogenetic factor for oligo-anuria [1209, 1605].

On the contrary, in some experimental models of acute renal failure, obstruction does appear to be of pathogenetic significance since intratubular pressure in the proximal tubules increases and the lumens of the proximal convoluted tubules widen. The pressure increase may be caused by epithelial swelling, especially in the straight segments of the proximal tubules which are most sensitive to ischemia. Further factors may include a change in the viscosity of the tubular content and precipitation of casts in the distal tubules or collecting ducts [726, 1598, 1625, 1627].

Morphometric examinations on human biopsies have, however, revealed no evidence in favor of an increase in intratubular pressure since the inner tubular diameter of the proximal convoluted tubules remains unchanged [761, 167]. Accordingly, the regularly observed casts in acute renal failure in humans are not the cause but a consequence of oligo-anuria. Acute IN is first observed 3 days after clinical onset of acute renal failure. Accordingly, in the acute phase, IN does not play a decisive role in triggering oligo-anuria [1453, 1780b, 1786]. In summarizing, it may be said that the pathogenesis of the initial phase of acute renal failure—in experimental animals and probably also in man—is determined by different factors (vasomotor changes, back-flow of urine, tubular obstruction and probably others [1202a]). A combination of these factors results in variation between the clinical response of individual patients as well as that between different animal models.

In the second phase of acute renal failure (persisting oligo-anuria or polyuria), acute nondestructive IN—either in the form of the intertubular serous type or the perivascular cellular type—regularly occurs [1780b, 1786]. The maximal inflammatory response is located at the corticomedullary region and, accordingly, may be absent in biopsy tissue. Kidney enlargement is especially pronounced at the time of the maximal inflammatory reaction (days 4–9). The enlargement is independent of the phase of acute renal failure present at the time of death, i.e., oliguric or polyuric [167, 1786]. The functional significance of IN is evidenced by the presence of transient hypertension [1786] and of elevated serum

renin and angiotensin values attendant on kidney enlargement [874, 1198, 1250]. These findings support the fact that glomerular filtration rate is consistently depressed. As noted previously, it is thought that widening of the interstitium in acute IN leads to compression of the intertubular capillaries and to an increase in the diffusion distance between capillaries and tubules. These changes would explain the persistent ischemic injury of tubular epithelium and, accordingly, the polyuria appearing upon resumption of filtration [171, 1604].

## Weil's Jaundice. The Kidney in Leptospirosis Ictero-Hemorrhagica Infection
[199, 1800]

### Definition

Renal changes associated with leptospira ictero-hemorrhagica infection.

### Incidence

Weil's jaundice is a rare disease occurring in significant numbers in endemic regions only [199]. Most patients are males who have been bitten by rats or who have had contact with rat excrement. Analogous changes in seven individuals working with pigs (*Leptospira pomona*) are reported in the literature [68].

### Clinical Findings

Onset with high fever, headache, vomiting, diarrhea, as well as muscle pain in the calf, back, and abdomen are characteristic for Weil's disease. Later, jaundice and renal symptoms with proteinuria, hematuria, and casts become manifest. Rarely, oligo-anuria, purpura or exanthema develop. Since the agglutination titer may remain negative until the ninth day after clinical disease onset, the diagnosis may be suspected from the combination of the following symptoms: jaundice, hypofibrinogenemia, thrombocytopenia, normal Quick test, and only slightly raised transaminases. Liver biopsy assures the definitive diagnosis. Death may occur in anuria, but the renal changes usually appear to be less significant than the severe cardiovascular collapse [1438, 1514].

### LM and EM Findings

Acute IN of the serous type is clearly dominating. The findings reach their maximum on days 7–8 and are still clearly discernable on day 17 (Fig. 20.20).

**Fig. 20.19.** Subacute, nondestructive interstitial nephritis in a ▷ 9-month-old girl who was immunized against smallpox 7 weeks prior to biopsy. Newly formed interstitial connective tissue is loosely organized and evidences mild lympho-plasmocytic infiltrates which are especially pronounced at the corticomedullary junction. There is no destruction of tubules whatsoever. (By courtesy of Prof. Uehlinger, Zürich). PAS (×150)

**Fig. 20.20.** Acute interstitial (predominately serous) nephritis in Weil's jaundice (*Leptospira ictero-hemorrhagica*) as seen on the seventeenth day of the disease. Only slight damage to the tubular epithelium—which is flattened—is seen. Slight interstitial infiltrates in the edematously widened interstitium are present. Clinically polyuria, slight proteinuria and increased serum creatinine values were noticed. Male, 51 years. HE (×320)

**Fig. 20.21.** Same case as in Figure 20.20. 17 days after disease onset. Edema and an interstitial infiltrate, consisting chiefly of phagocytes, activated lymphocytes and a few fibroblasts, are clearly evident. Slight vacuolar degeneration of proximal tubule (→). Male, 51 years. EM (×2700)

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**Fig. 20.22.** Same case as in Figure 20.20. 3 weeks after disease onset. There is now severe tubular injury with necrobiosis (*N*) and cell debris in the lumen (→). Remaining tubular cells are dedifferentiated. Male, 51 years. EM (×2800)

**Fig. 20.23.** Same case in Figure 20.22. 3 weeks after disease onset. A distal tubule is filled with cell debris and vital, dedifferentiated cells. Male, 51 years. EM (×2000)

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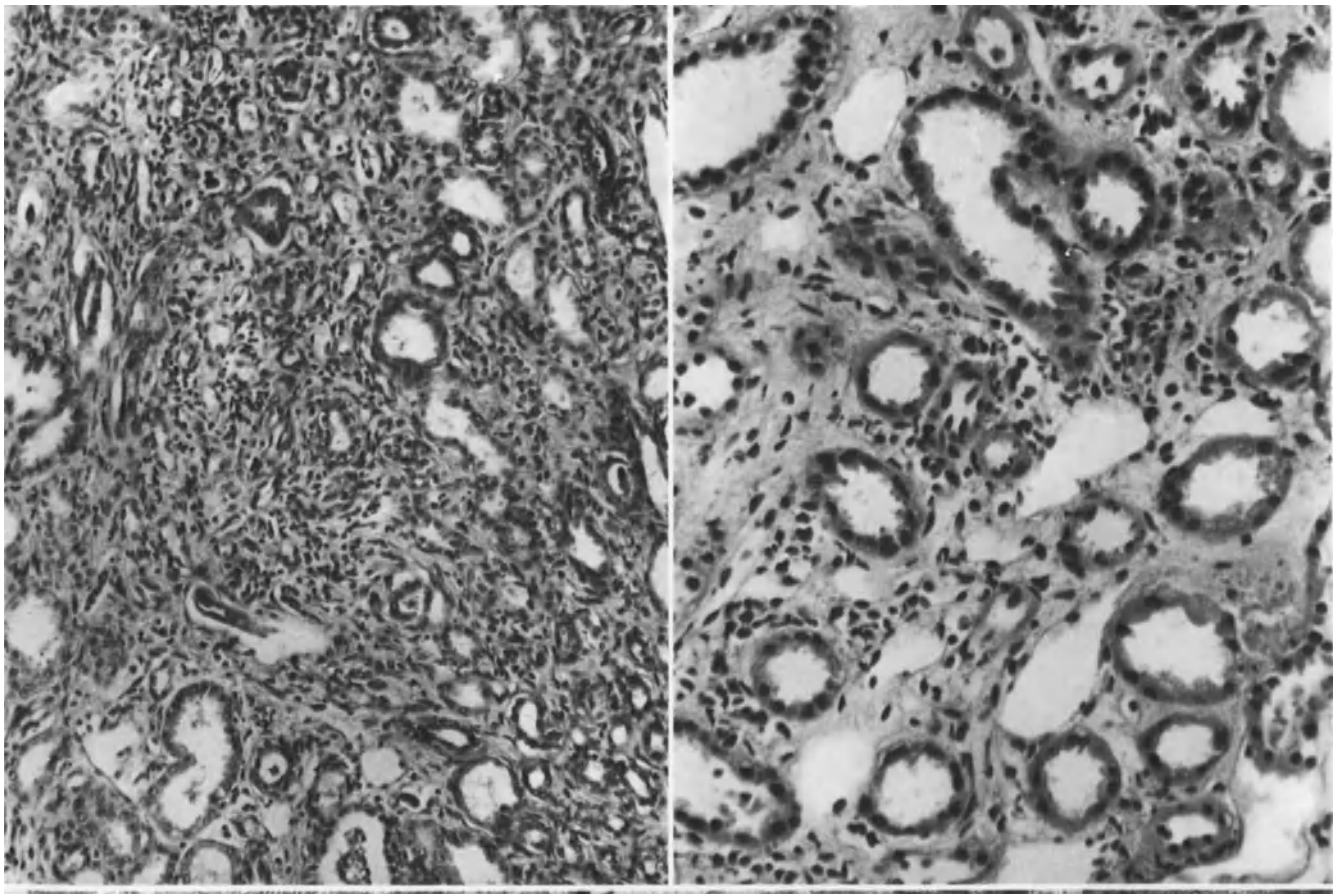
**Fig. 20.24.** Same case as in Figure 20.22 after 3 weeks of Weil's jaundice showing loosening and thickening of lamina rara interna which includes cytoplasmic elements. Podocyte foot processes (*FP*); endothelial processes (*E*). Male, 51 years. EM (×43,700)

**Fig. 20.25.** Same case as in Figure 20.22. 4.5 months after Weil's jaundice showing glomerular residual damage with slight irregularity and thickening of the lamina rara interna as well as slight swelling and protein droplet storage of the endothelium. Clinically normal urinary findings and creatinine clearance. Male, 51 years. EM (×7700)

**Fig. 20.26.** Same case as in Figure 20.22. 4.5 months after disease onset. Minimal interstitial fibrosis is present. Male, 51 years. EM (×3700)

**Fig. 20.27.** Severe, acute nonobstructive pyelonephritis. Masses of polymorphonuclear leukocytes in the edematous interstitium are assembled around the tubules. Five-month-old transplant. Male, 47 years. PAS (×1207)



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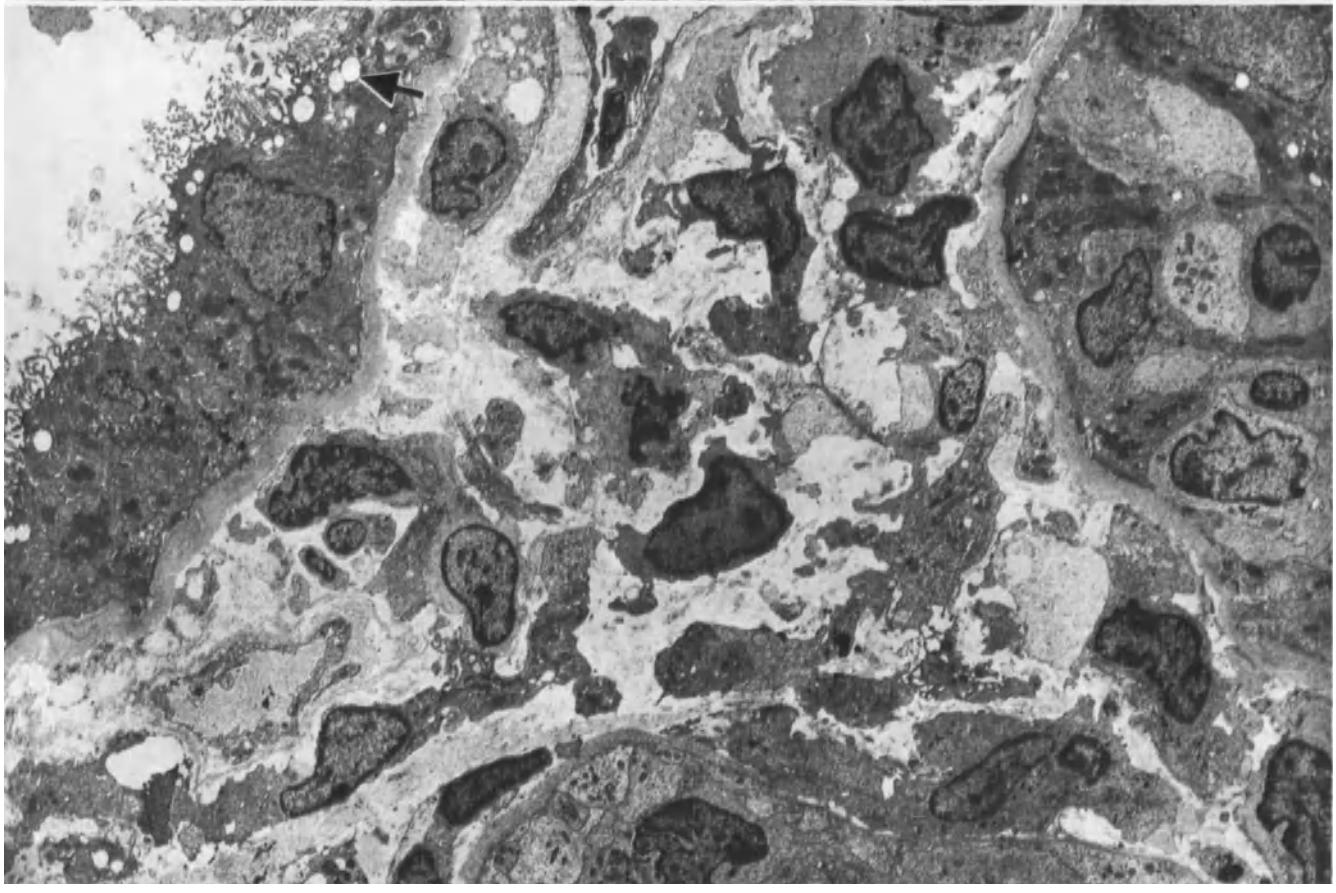

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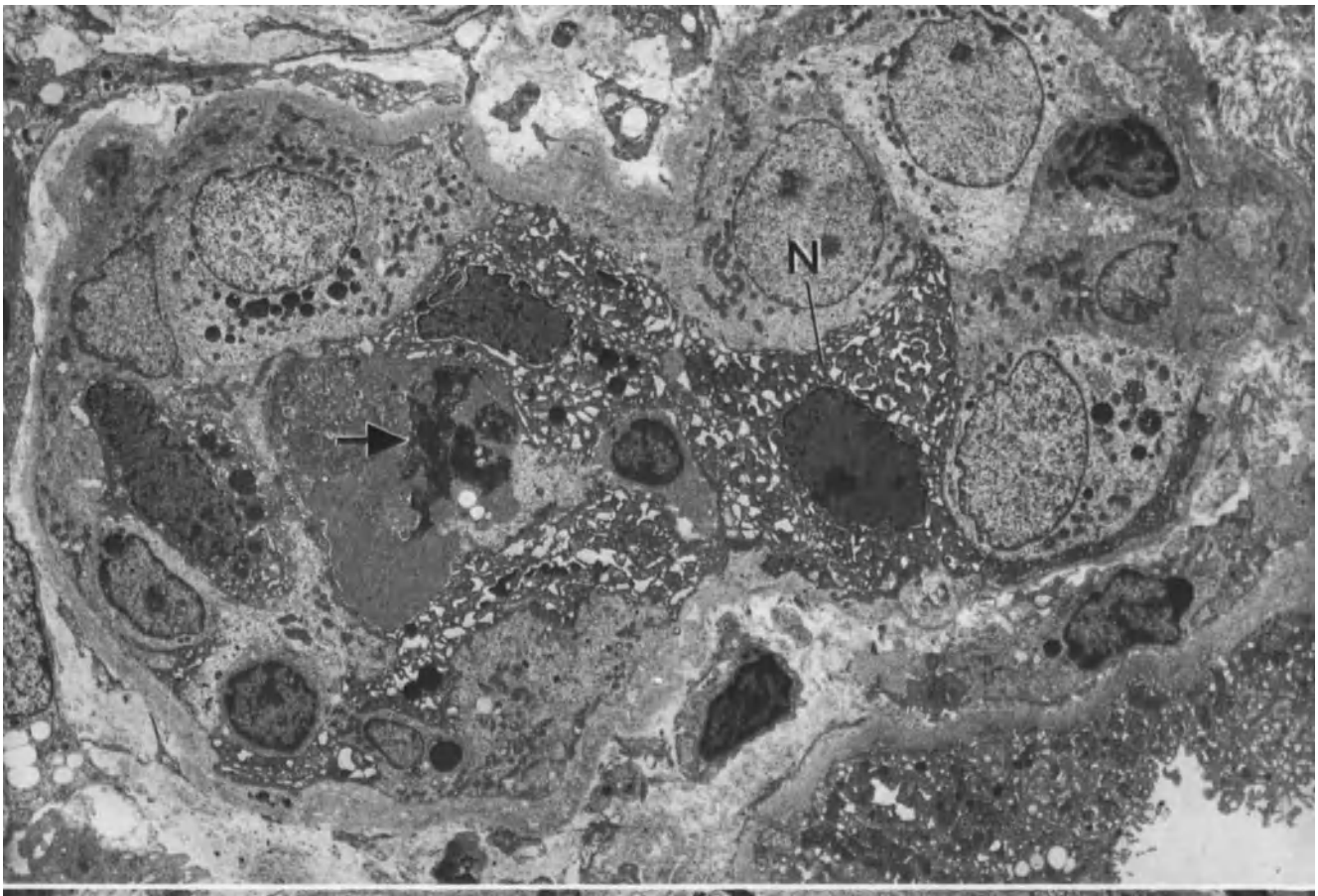


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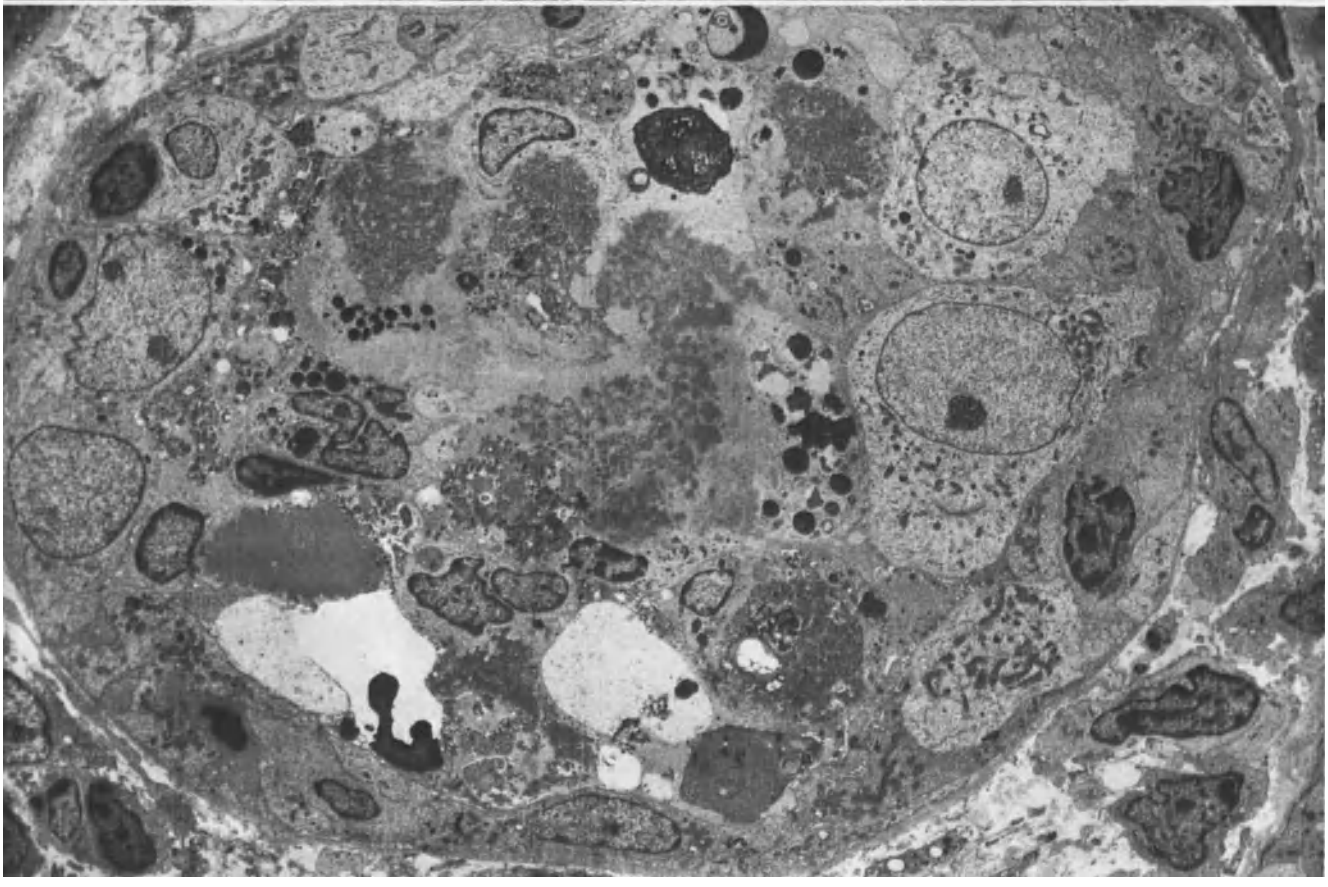

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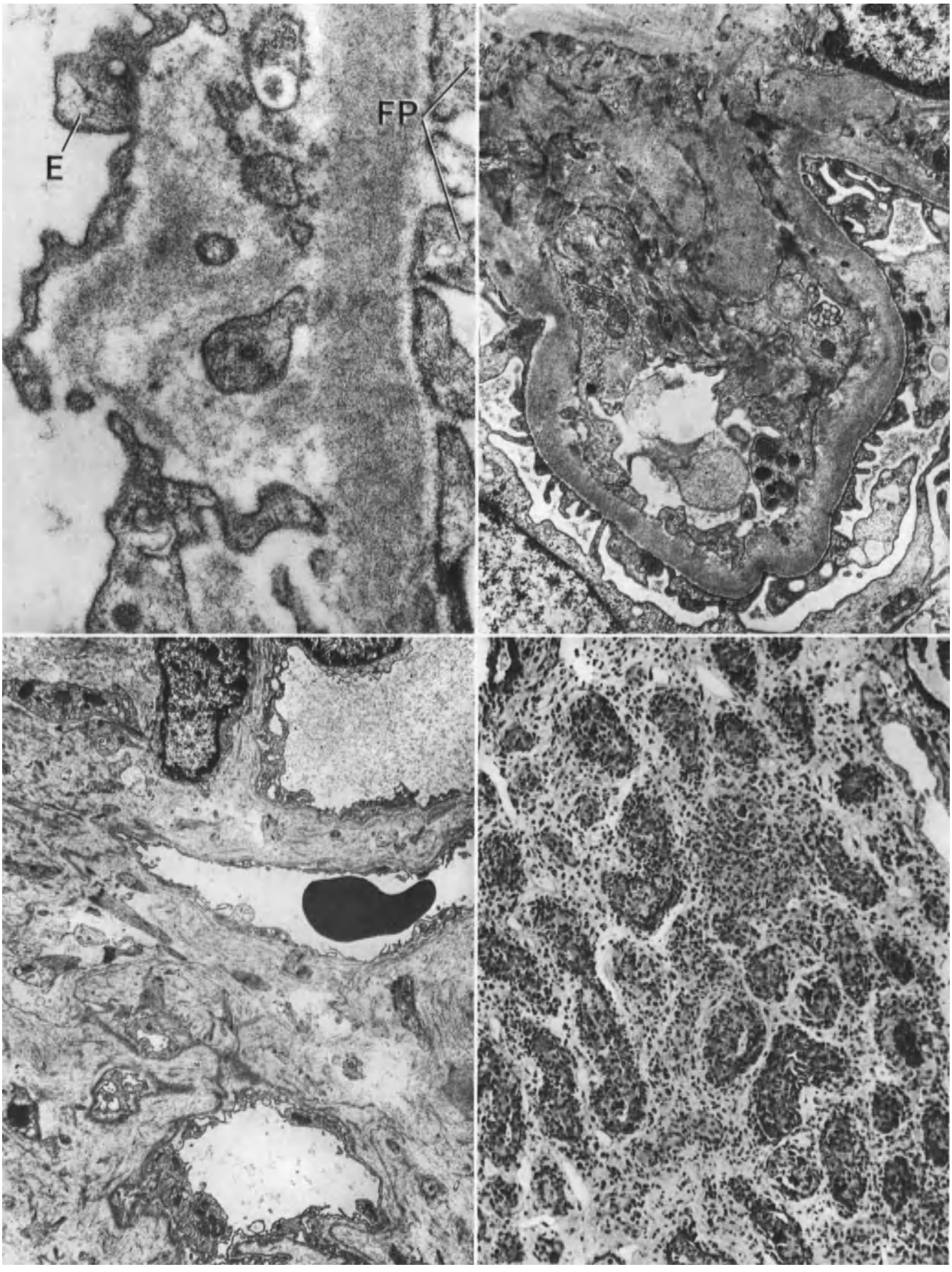


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20.27

The infiltrate consists of small and activated lymphocytes, immunoblasts, histiocytes as well as a few plasma cells which can be observed up to day 10 (Fig. 20.21). Tubular injuries are disproportionately severe (Figs. 20.22, 20.23). In one of our own cases—and with EM only—we observed, from day 17 onwards pronounced, very fine-granular thickening of the lamina rara interna of the capillary loops (Fig. 20.24) as well as degenerative and reparative changes of loop and intertubular capillary endothelium (see also [68]). As is well known, endothelial cells are the most important target for leptospirae.

The BM change can probably be explained as a consequence of disturbed permeability arising from endothelial injury; it can be demonstrated as long as 4.5 months after complete endothelial regeneration (Fig. 20.25; [1800]). In our case, the interstitium was only slightly fibrosed (Fig. 20.26) and the tubular changes were completely restituted. In one report [68], frank interstitial fibrosis was still present 6 months after infection with L. pomona.

## Pyelonephritis (Destructive Interstitial Nephritis) [138, 569, 1781]

### Definition

Pyelonephritis (PN) is a disease characterized in the acute phase by polymorphonuclear leukocytic inflammation and in the chronic phase by the replacement of destroyed parenchymal elements by scar tissue. Both phases are primarily interstitial and the causative agents are almost always bacteria.

### Nosology

Nosologically, acute and chronic as well as relapsing forms can be recognized and pathogenetically, obstructive and nonobstructive forms distinguished.

### Incidence

In our autopsy material, 8.6% of all cases showed moderate to severe pyelonephritic changes of which 2.1% were acute. In our biopsy material 19.3% of all cases demonstrated PN (Table 20.2).

We confirmed 75% of clinically diagnosed PN in needle and open biopsies (between: 4 out of 13–73 out of 78 cases [195]). Other investigators have reported 60% PN in the presence of normal creatinine clearance and 100% PN in cases with decreased clearance values in needle biopsies [208].

Table 20.2. Pyelonephritis in our biopsy material (n = 400 = 19.3% of all biopsies reviewed)

| Form of PN | Incidence in % |
|---|---|
| Acute pyelonephritis | 15 |
| Small pyelonephritic scars | 20.5 |
| Chronic pyelonephritis without acute attack | 44.5 |
| Chronic pyelonephritis with acute attack | 9.5 |
| Chronic PN with overload glomerulitis | 4.5 |
| Special forms | 6.0 |

In our autopsy material, the occurrence of PN is about the same for males and females but distribution according to age and cause is different. Nonobstructive PN is more frequent in females (female: male = 105:62) where it occurs at a younger age than in males [1791]. In autopsy material, obstructive cases are, of course, predominant in association with prostate hyperplasia and cancer of the bladder, uterus, prostate, colon, and ureter. In our biopsy material of 245 PN cases, 115 were obstructive and 130 were nonobstructive. In the latter group, phenacetin addiction was present in 44 out of 130. The sex ratio of all biopsy cases was female: male = 1.3:1; the mean age was 41.4 years (in contrast: GN 29.4 years).

In early childhood, acute PN is a frequent disease and is predominantly found in girls [555, 1791]. The majority of these show anatomical or functional abnormalities of the urinary tract-especially reflux.

We have found PN contracted kidneys in 1.4% of all autopsies, bilateral in 34% and unilateral in 66% (accounting for one third of all unilateral contracted kidneys in our material).

### Clinical Findings

The classic picture of acute PN is characterized by fever, flank pain, pyuria, dysuria, and pollakisuria. But acute PN may also be asymptomatic if only small segments of the kidney are involved. In our cases (Table 20.3), only one-fifth of the patients evidenced classic acute PN whereas the others showed minor clinical symptoms so that about 20% were discovered accidentally.

Acute oligo-anuria is, in nonobstructive cases, rarely observed. Chronic PN—without acute episodes—often remains asymptomatic for years (18% of all cases had no urinary findings at the time of biopsy) or lumbar pain, dysuria, and subfebrile temperatures may be present. Proteinuria is very frequently absent or slight ($\sim$1 g/day), nephrotic syndrome occurs only exceptionally [691a].

During infection-free intervals, urinary findings often exhibit slight leukocyturia, granular casts, and microhematuria, whereas acute relapses are manifested by bacteriuria, massive leukocyturia and leukocytic casts (Table 20.2). Insidiously developing uremia with anemia, acidosis, polyuria and, frequently, hypertension, occur later [138, 702, 1781, 1791]. After an average of 3–5 years' duration of illness, 65% of the patients are hypertensive (50% of all cases: Z; Table 20.3) as compared to 15% in a control group of the same age [115].
Bacteriuria of over 100,000 bacteria/ml is only found in acute infection and indicates the need for antibiotic therapy. Repeating episodes of urinary tract infections in the past history are suspicious of chronic PN but neither necessary for nor proof of its presence.
Signs of papillary necrosis (14.5% of our PN autopsy cases) are colic with elimination of sequesters, hematuria and the typical pyelogram findings. Contracted kidneys as well as large scars are demonstrable by pyelography [701, 702] as are scars with secondary widening and distortion of calyces (hydrokalikosis: [1404]).

Table 20.3. Nonobstructive pyelonephritis in our biopsies. (No data on possible vesicouretral reflux)[a]

| Parameter | | Without phenacetin addiction (n=53) | With phenacetin addiction (n=36) |
|---|---|---|---|
| Age distribution years | <20 | 3.8 [9.4%] | – |
| –at biopsy | <30 | 15.0 [28.3%] | 2.8% [8.3%] |
| –[at disease onset | <40 | 18.9 [26.3%] | 13.8% [36.0%] |
| | <50 | 20.7 [16.9%] | 50.0% [24.9%] |
| | <60 | 28.2 [13.2%] | 22.2 (22.2%] |
| | >60 | 13.2 [5.6%] | 11.1 [8.3%] |
| Latency between disease onset and biopsy: average in weeks (range) | | 340 (1–1959) | 280 (4–1850) |
| Sex distribution ♂:♀ | | 1.2:1 | 1.1:25 |
| Symptoms at disease onset (in%) | | n=50 | n=30 |
| –Dysuria/Pollakisuria | | 6 | 13.3 |
| –Pyuria | | 16 | 26.6 |
| –Macrohematuria | | 8 | 13.3 |
| –Microhematuria | | 8 | 13.3 |
| –Proteinuria | | 26 | 13.3 |
| –Edema | | 12 | 6.6 |
| –Oliguria/anuria | | 4 | 6.6 |
| –Hypertension | | 30 | 20.0 |
| –Fever | | 22 | 20.0 |
| –Flank pain | | 38 | 56.6 |
| Disease course until biopsy (in% of cases) | | n=47 | n=28 |
| Less than 3 months duration | | 19.1 | 10.7 |
| Stationary | | 19.1 | 7.1 |
| Progressive without attacks | | 23.3 | 32.1 |
| Progressive with attacks | | 12.7 | 28.6 |
| In attacks | | 4.2 | 7.1 |
| Average No. of attacks (range) | | 4 (3–5) | 3.7 (2–9) |
| Chance discovery | | 21.3 | 14.3 |
| Clinical findings at time of biopsy (in% of cases) | | n=53 | n=36 |
| No urinary findings | | 18.8 | 16.6 |
| Hematuria | | 37.6 | 30.5 |
| Leukocyturia | | 35.7 | 55.4 |
| Bacteriuria | | 9.4 | 16.6 |
| Proteinuria | | 30.1 | 22.2 |
| Leukocytic casts | | 3.8 | 0 |
| Granular casts | | 43.3 | 21.9 |
| Hypertension | | 41.4 | 60.9 |
| S-urea/S-creatinine ↗ | | 50.8 | 60.9 |
| S-urea/S-creatinine ↗↗ | | 33.8 | 30.1 |
| Accompanying predisposing disease (%) | | 16.9 | 16.6 |
| –Diabetes mellitus (n) | | 4 | 3 |
| –Gout (n) | | 2 | 1 |
| –Laxative addiction (n) | | 0 | 2 |
| –Chronic liver disease (n) | | 5 | 3 |
| Follow-up (≧1 year) in % of cases | | n=44 | n=30 |
| Patients died | | 50 | 70 |
| –Death in uremia | | 47.7 | 70 |
| Complete remission | | 15.9 | 3.3 |
| Clinical improvement | | 6.8 | 6.6 |
| Clinically unchanged | | 15.9 | 13.3 |
| Survival rate (%) [335a] from biopsy onwards | | | |
| – 5years | | 52.5 | 43 |
| –10 years | | 40.7 | 31 |

[a] See for Definitions etc. Table 14.3, p. 193.

In children, especially girls, remissions are frequent (41%), 27% of the cases, however, are asymptomatic and in 51% of relapses, the bacterial flora was different from that observed during the first attack [555]. It was possible to demonstrate bacteria in two-thirds of the cases in a series of needle biopsies [569].

## LM Findings

Typical for *acute PN* are leukocytic, often coalescing, destructive foci in the cortex and medulla (Figs. 20.27, 5.8) which later contain variable numbers of histiocytes and, after a few days, also a few lymphocytes and plasma cells. Tubules and vessels are eroded and destroyed by the inflammation as is best seen in PAS or PASM stains (Figs. 20.28, 20.29). Glomeruli are also destroyed centripetally (Fig. 20.30).

In other cases, embolic purulent glomerular foci with capillary loop and total glomerular destruction occur (Figs. 5.7, 20.31). In children, glomeruli may almost completely disappear (see p. 437). Bacteria can be demonstrated histologically only in the very acute phase.

*In chronic PN,* there occurs a mosaic of histologic changes which, especially in small needle biopsies, may prove difficult to interpret. Usually, the focal radiate character of the lesion can be recognized if needle biopsy does not accidentally contain scar tissue only (Figs. 20.32, 20.33). Preserved and severely changed nephrons are clearly demarcated from each other (Fig. 20.32).

The typical, chronic *PN scar* is characterized by the patchy destruction of renal structures (tubules, glomeruli and vessels) which are replaced by coarse-fibered scar tissue demonstrating a few lymphocytic infiltrates (Figs. 5.9, 20.33). Now and again—especially in children's chronic PN—lymph follicles can be observed in the interstitium (Figs. 9.10, 9.11, 9.13, 20.34). Fibrosis of interstitial tissue and tubular atrophy with BM thickening are present in the region surrounding the PN foci. Completely intact nephrons may be hypertrophic (Fig. 20.35) indicating the functional overload imposed by advanced renal destruction (i.e., contracted kidney). Thyroid-like foci (Fig. 20.35), i.e., groups of tubules with highly flattened epithelial cells and strongly PAS-positive colloid-like masses in the lumen (thickened urinary mucoid) are a typical consequence of extensive medullary scars with secondary tubular stasis. They are especially pronounced in early childhood PN (see below).

Glomeruli demonstrate at least four different changes:

1. In pure destruction following early childhood PN, only small stellate collections of PAS-positive BM and mesangial remnants—which are difficult to recognize—are present (Figs. 20.36, 20.37; see p. 437). In adults, total glomerular destruction is extremely rare; partial destruction with capillary loop obsolescence is somewhat more frequent.
2. The vast majority of the changed glomeruli demonstrate the well-known picture of collapse (Figs. 6.114, 20.38) with a wrinkled BM and a capsular space filled with exudate in which collagenous fibers subsequently develop. The cause of collapse formation is thought to be due to impairment of blood flow by destruction

**Fig. 20.28.** Acute pyelonephritis with destruction of tubular BM ▷ and epithelium by polymorphonuclear leukocytes. PAS (×500)

**Fig. 20.29.** Loosening and partial destruction of an arteriolar wall (*A*) following acute pyelonephritis. Small lymphocytes are predominant. Male, 36 years. PAS (×500)

**Fig. 20.30.** Same case as in Figure 20.27. Extension of acute pyelonephritis from interstitium to glomerulus. Male, 47 years. PAS (×375)

**Fig. 20.31.** Leukocytic destruction of a glomerulus in pyelonephritis arising from bacterial emboli (→). Numerous polymorphonuclear leukocytes fill the capsular space. Note periglomerular inflammation. HE (×500)

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**Fig. 20.32.** Chronic pyelonephritis. Subcapsular pyelonephritic focus (capsule: →) is sharply delimited from the intact renal parenchyma. Tubules in region of focus are completely destroyed and two glomeruli are obsolescent. A third evidences loop collapse. Female, 9 years. PAS (×150)

**Fig. 20.33.** Pyelonephritic cortical scar. Renal capsule (→). Scar is wedge-shaped and evidences scanty infiltrates and a rather coarse-fibered network. Tubules are completely destroyed in the region of the scar. BM is thickened in zone bordering the scar. Male, 79 years. PASM (×100)

**Fig. 20.34.** Lymph follicle formation with a germinal center (*GC*) in chronic pyelonephritis. There is a well preserved glomerulus side-by-side with a completely obsolescent one. Male, 3 years. PAS (×100)

**Fig. 20.35.** Pyelonephritic contracted kidney in phenacetin addiction. Note hypertrophic cystic widened tubules with severely flattened epithelium and hyaline casts representing a transition to a thyroid-like tubular change. Synechia in highly injured glomerulus is present. Male, 43 years. HE (×140)

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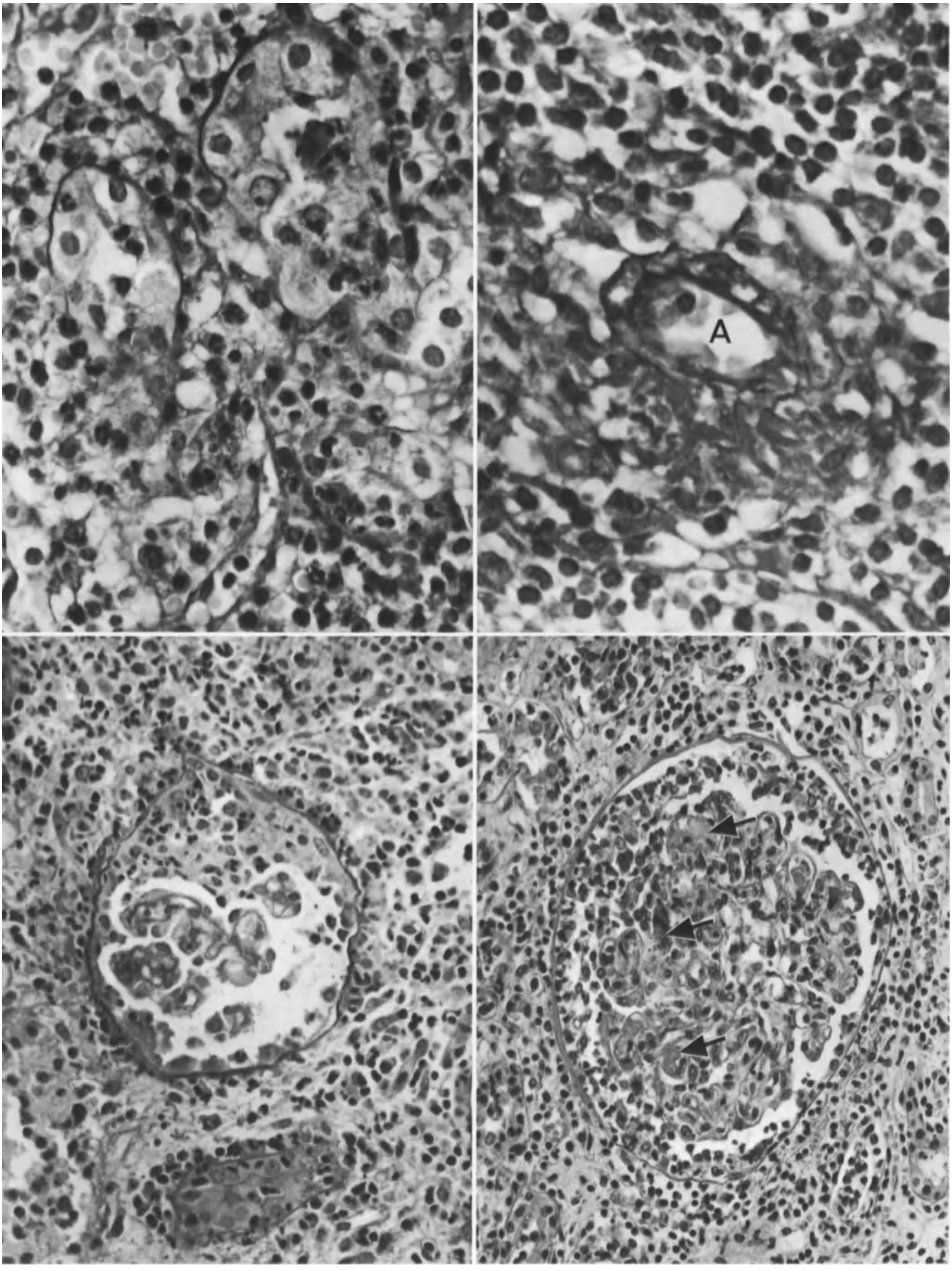
**Fig. 20.36.** Star-shaped glomerular spider-scar in early childhood pyelonephritis. Glomerulus is still relatively easily recognizable. PAS (×440)

**Fig. 20.37.** Extensive glomerular destruction in chronic pyelonephritis due to ureteral stone obstruction. Glomerular capillary loops are completely collapsed (→), and surrounded by an unclearly delimited exudate. Female, 2.75 years. PAS (×440)

**Fig. 20.38.** Chronic pyelonephritis. All glomeruli demonstrate collapse type and not pyelonephritic type of obsolescence. Tubules are almost completely destroyed. Female, 66 years. PAS (×160)

**Fig. 20.39.** Vascular changes in chronic pyelonephritis. Arteriolar and arterial adaptive intimal fibrosis (→). Female, 58 years. PAS (×180)

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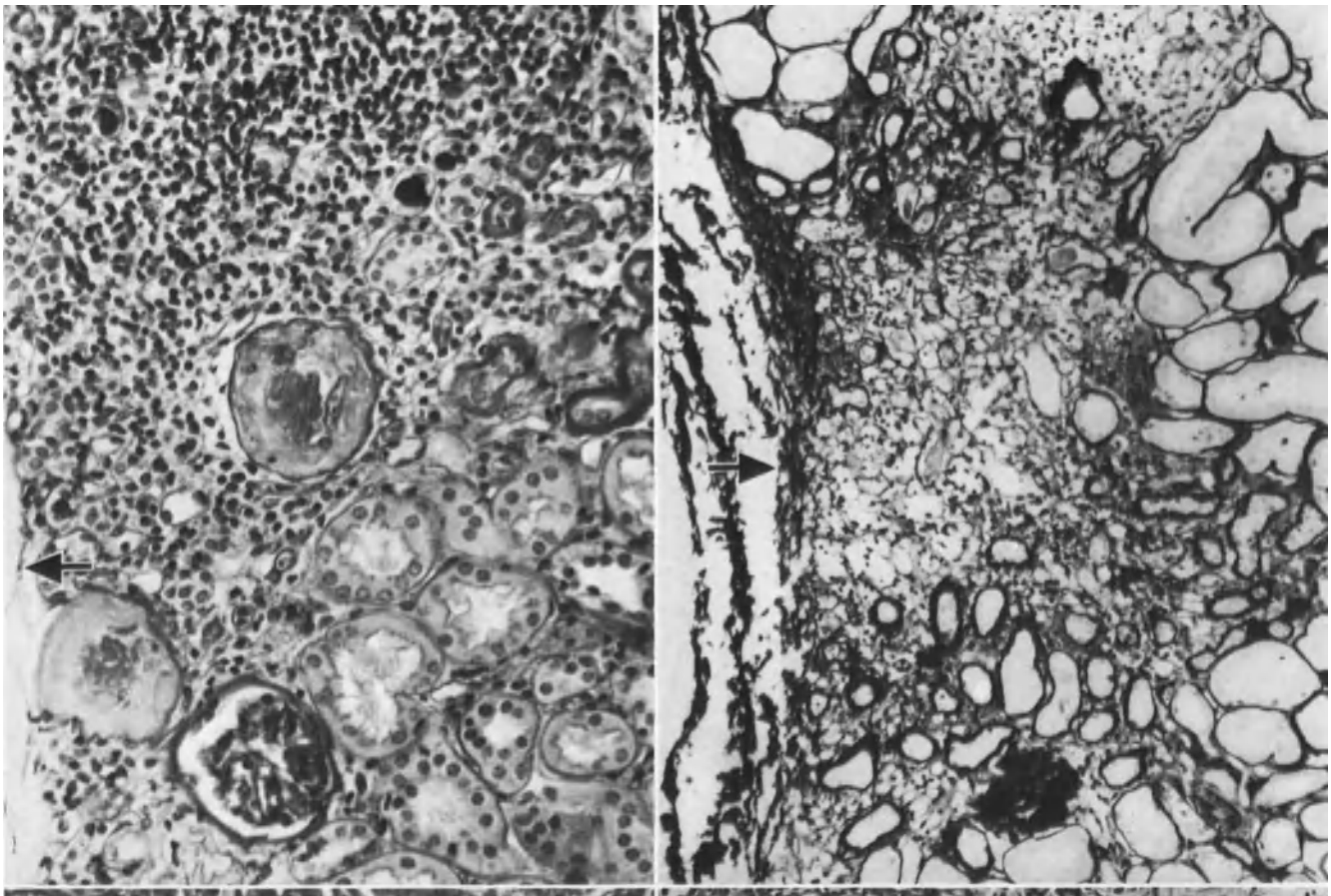

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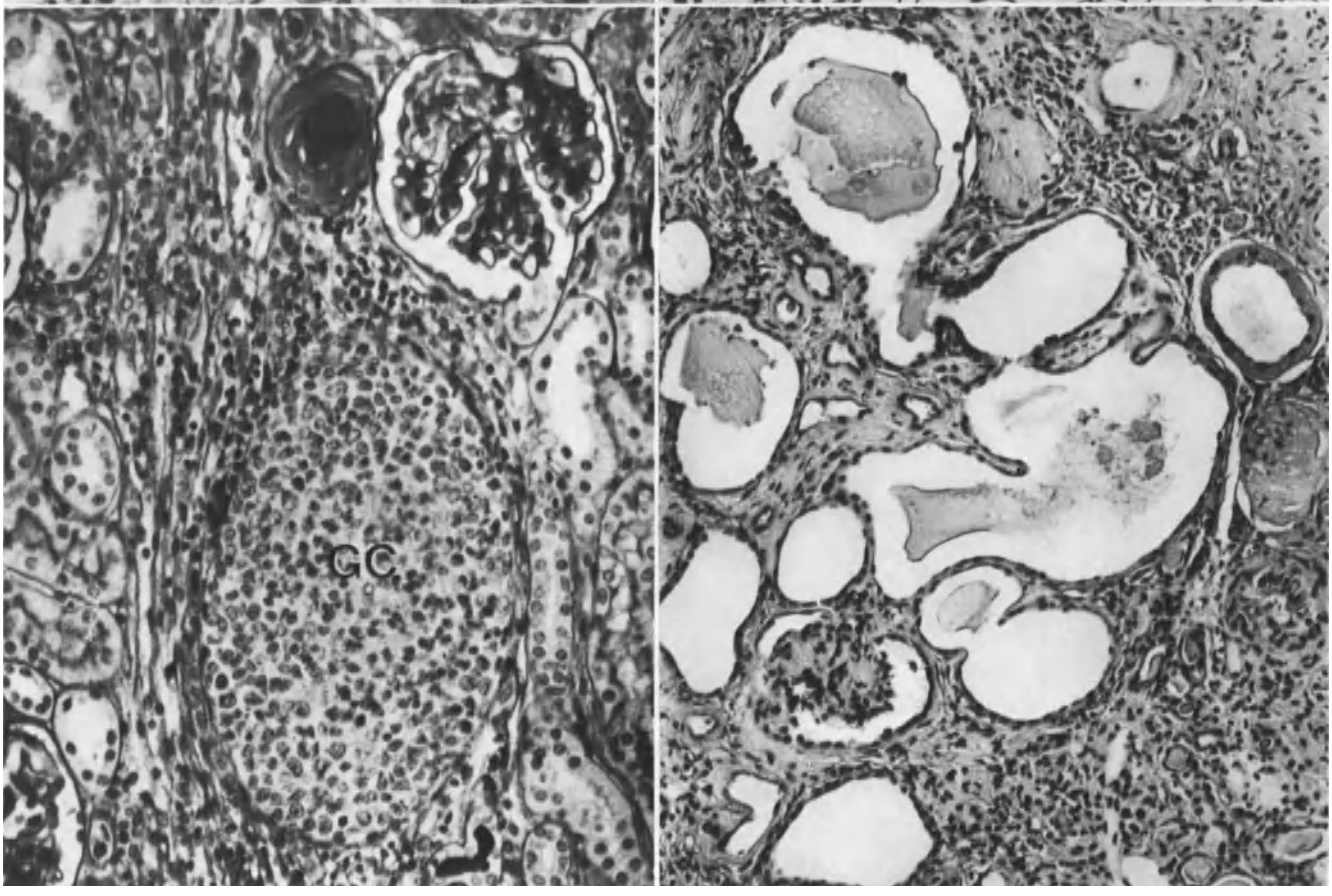


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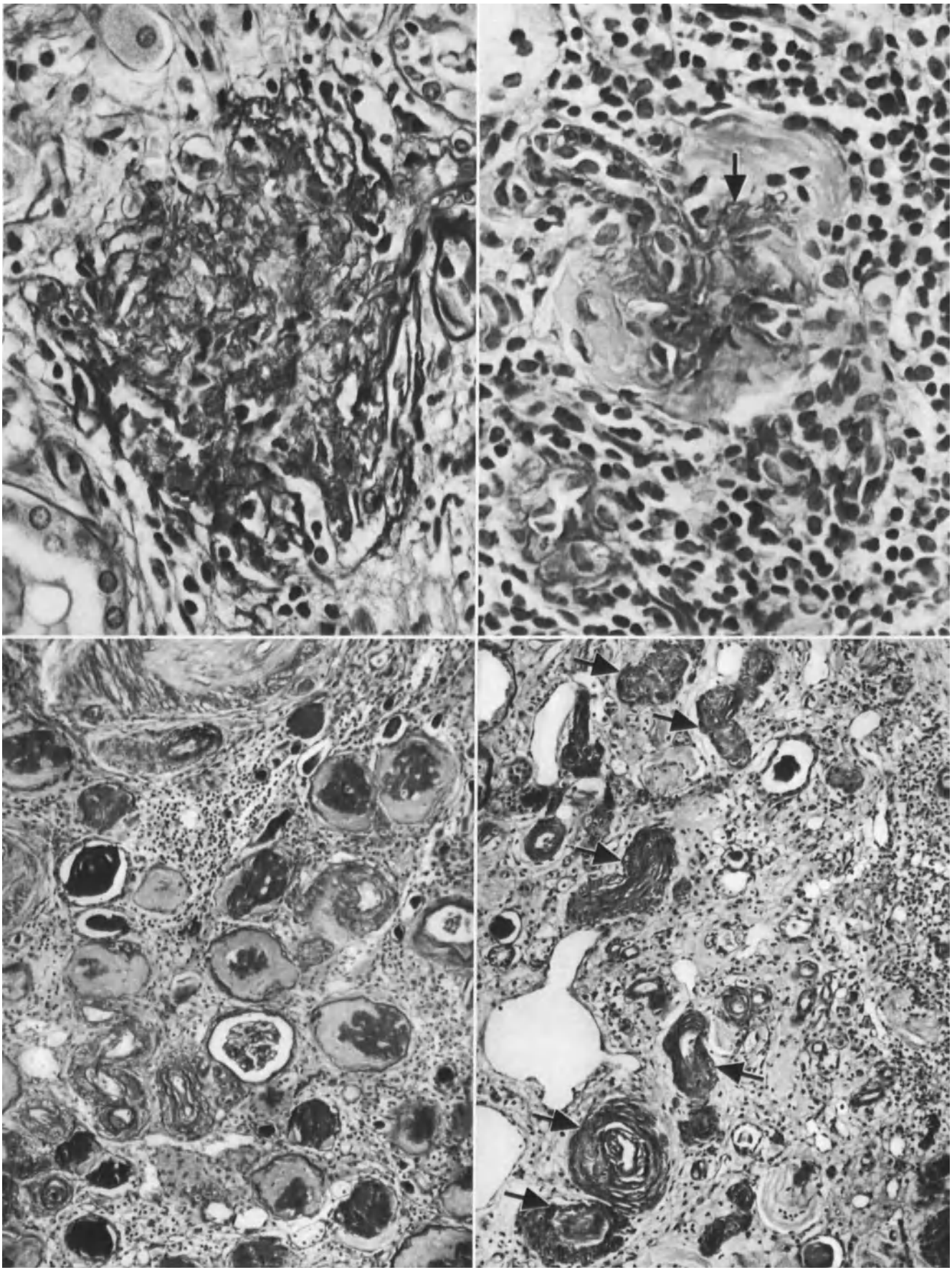

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and compression of the postglomerular interstitial capillary network by scars, and also possibly by destruction and scar transformation of the vasa afferentia and efferentia. Additionally, hypertensive vasculopathy may also be involved.
3. In severe hypertensive vasculopathy, corresponding glomerular changes may appear.
4. So-called overload glomerulitis (see p. 308) is a classic complication of severe PN contracted kidney.

The variety of vascular changes (Fig. 20.39) has already been illustrated by the discussion on glomeruli (Fig. 20.38). In contracted kidney—especially after long-term dialysis—extensive adaptive intimal fibrosis also occurs.
In relapse, changes of acute PN overlap those just described.
In addition to PN scar, an *active chronic* PN can also be recognized, indicating a progressive lesion. It is still controversial whether or not vital bacteria are present in the progressive form; we believe not. Needle biopsy from active chronic PN shows, in addition to the described changes, foci with very densly packed infiltrates strikingly rich in plasma cells and lymphocytes mixed with scattered neutrophilic leukocytes. The acute relapse must be differentiated from this form insofar as it consists of scar tissue besides foci of neutrophilic leukocytes.

## Special Forms of Pyelonephritis

***Xanthomatous PN*** is characterized by extensive foci of destruction bordered by lipid and, at times, PAS-positive material containing foam cells (Figs. 5.10, 20.40, 20.41) and giant cells. This form is mainly observed in infections with E. coli or staphylococci [32, 1791, 1781]. This lesion may sometimes be misinterpreted as tuberculosis.
Synonym: xanthogranulomatous PN

***Emphysematous PN*** is an acute PN with great numbers of large, oval lacunae (gas bubbles) in the tissue. Diabetes mellitus and gas-producing bacteria are usually present in this condition [1432].

***Hydrocalicosis*** is a special form of a PN scar in which cortical tissue is greatly narrowed and the associated calyx widened similarly as in hydronephrosis (Fig. 5.11; see p. 51 [1404]).

***Tuberculoid PN*** is a form we have observed following administration of cortisone in high doses as well as after thiazole medication [1780b].

***Large Cell PN (Malakoplakia),*** previously considered to be a special form of nondestructive IN [1780b], is now believed to be a form of PN. In this entity, very severe tubular destruction and strands and whorls of cells—strongly eosinophilic histiocytes (*van Hansemann* histiocytes)—are found (Figs. 20.42, 20.44). These cells evidence practically no sudanophilic substances. Lymphocytes, plasma cells, and a few, small leukocytic clusters are present. Many investigators suggest that large cell PN is the renal form of malakoplakia. However, Michaelis-Guttmann bodies, which are thought to be calcified giant phagolysosomes [971], are rarely present.
Another special feature of this form of PN is the extraordinarily severe tubular destruction which is assumed to be due to coliform bacteria [971, 1311]. The peculiar accumulation of phagocytes is attributed to digestive disturbances within their phagolysosomes resulting from deficient acidification. Drugs may also be involved in this process [1615].

## IF Findings

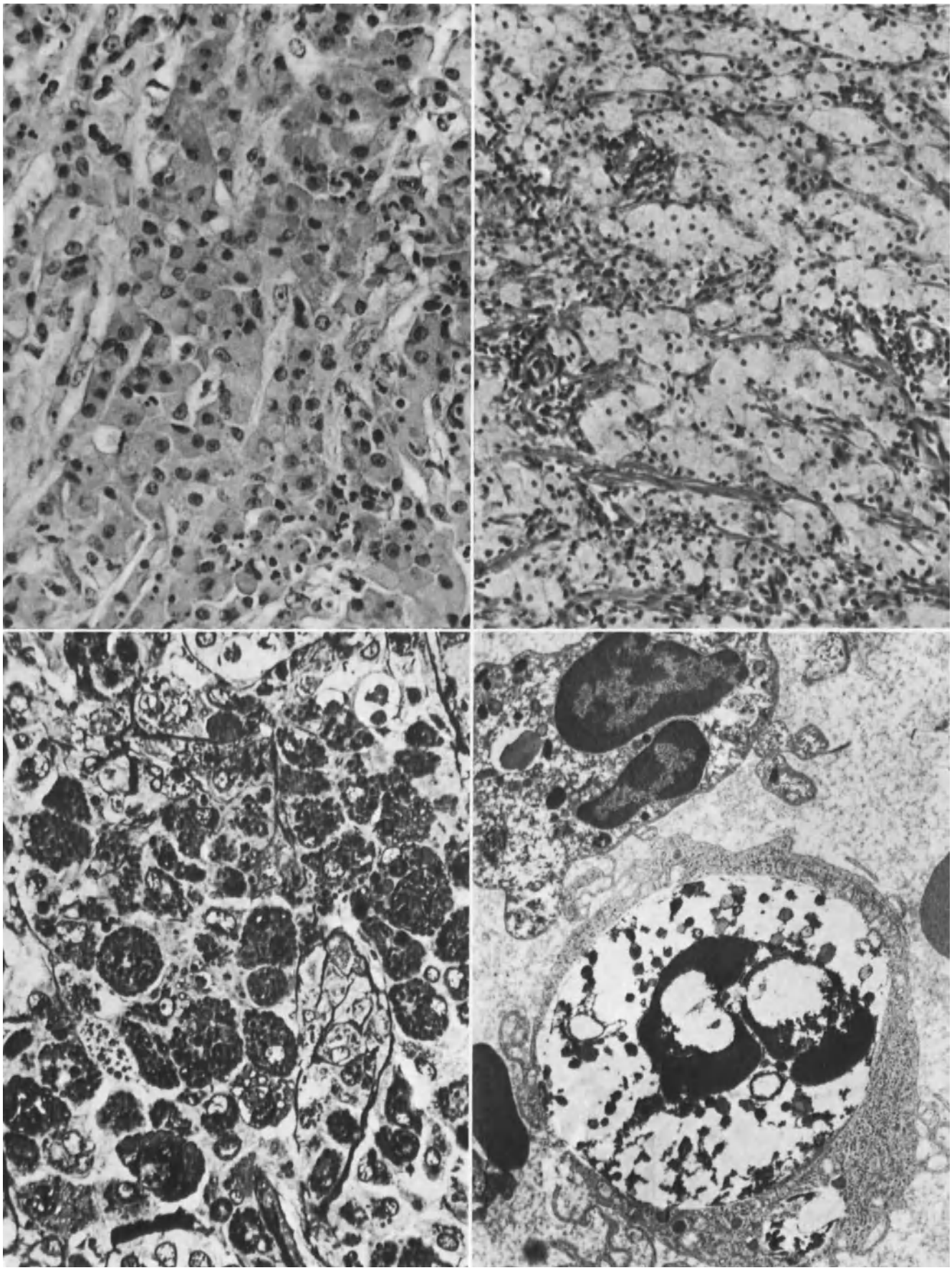
In 24 of our own cases (3 acute PN, 21 chronic PN) 15 demonstrated positive findings. IgM occurred alone in 5 cases, C3 alone in 2, and IgM and C3 together in 2 in a focal-segmental distribution pattern in the mesangium and/or peripherally. In the remaining 6 cases, a combination of IgM, C3 and IgA (IgA only peripherally) was found in 2 and a combination of IgG, IgM, IgA and C3 in 4 cases in which IgG and IgA occurred intraglomerularly, always segmentally, and purely peripherally, and in the kidney, focally or diffusely [51, 121, 865, 1010].
All investigators have emphasized the focal-segmental character of the immunoglobulin and complement deposition. In chronic PN, there have been various demonstrations of immunoglobulins, complement and bacterial AG in the interstitium, the tubular epithelium and the vessels [39, 319, 912]. In our own material, cell-bound immunoglobulins (IgG, IgM, IgA, IgE) were found in 5 cases, and fibrin was found free twice in the interstitium.

**Fig. 20.40.** Xanthomatous pyelonephritis in nephrolithiasis. Liver ▷ cell-like strands of phagocytes and a few polymorphonuclear leukocytes are seen. Female, 69 years. HE (×350)

**Fig. 20.41.** Same case as in Figure 20.40. Histiocytic foam cells are now clearly evident. HE (×170)

**Fig. 20.42.** So-called large cell pyelonephritis (possibly malakoplakia). Distended and often spherical phagocytes contain masses of argyrophilic granules but no sudanophilic material. Female, 69 years. PASM (×532)

**Fig. 20.43.** Same case as in Figure 20.44, demonstrating phagocytosis of a polymorphonuclear leukocyte. Male, 56 years. EM (×7300)



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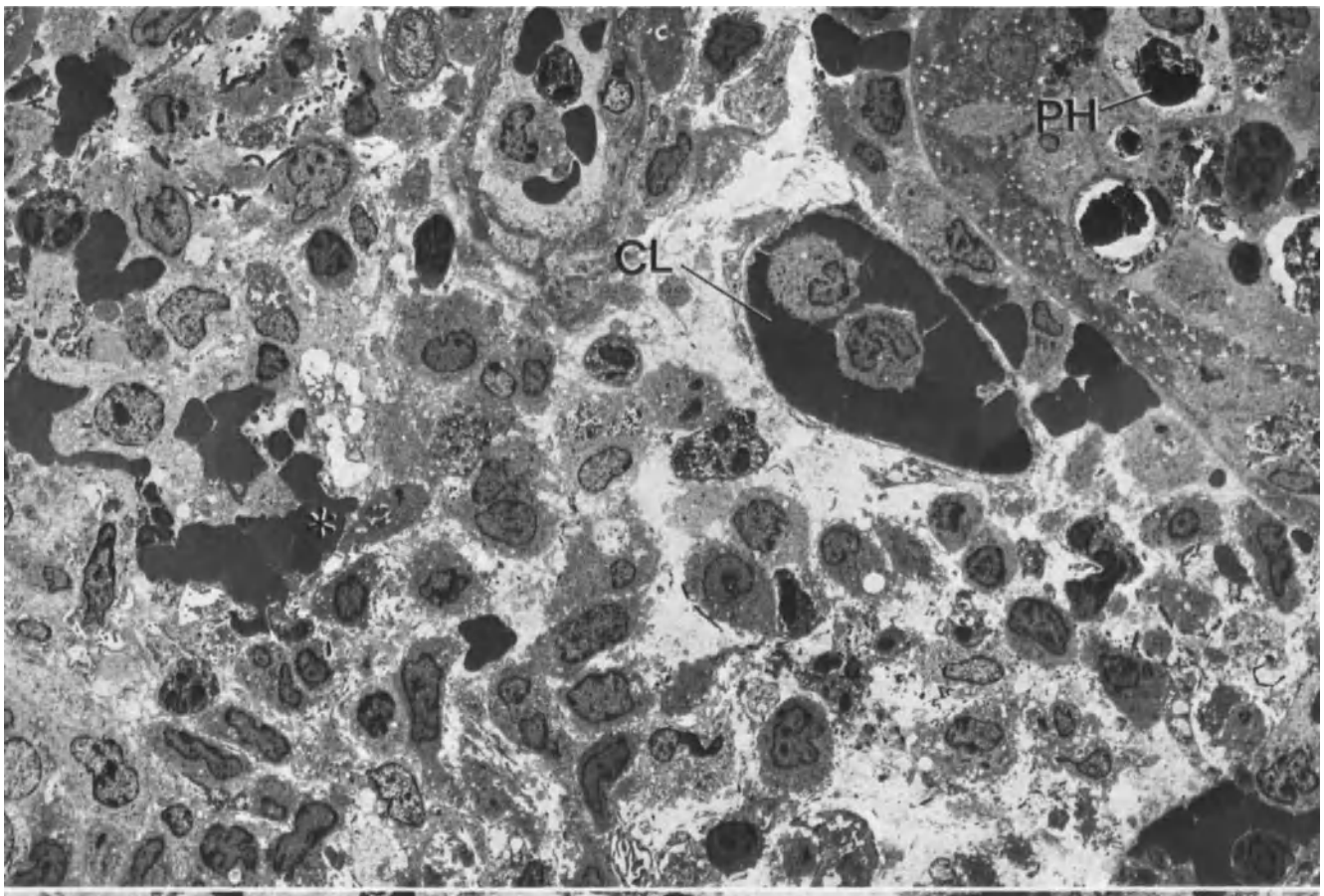


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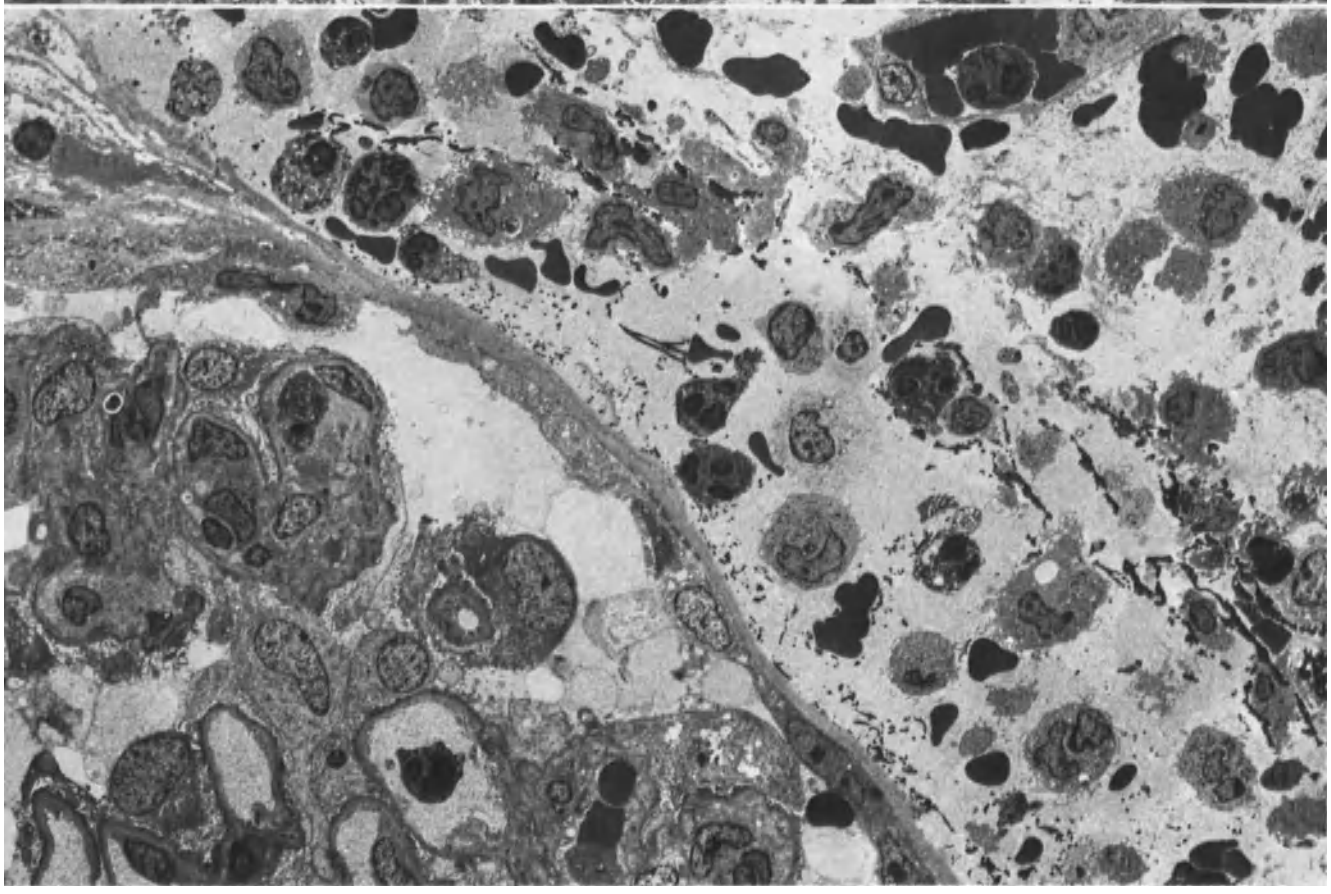

20.45

## EM Findings

In acute PN, the interstitium is dominated by extensive infiltrates of polymorphonuclear leukocytes and a few phagocytes as well as by severe stasis of intertubular capillaries which sometimes undergo rupture with attendant interstitial hemorrhage (Fig. 20.44). Tubules also contain polymorphonuclear leukocytes in addition to phagocytes (Fig. 20.44). The interstitial phagocytes contain a few ingested leukocytes (Fig. 20.43). A large number of leukocytes can be seen in the dilated periglomerular lymphatic spaces (Fig. 20.45).

In the region of the foci, the glomeruli often evidence a pronounced increase of polymorphonuclear leukocytes in the capillary loops (Figs. 20.45, 20.46). Endothelial cells and podocytes are either edematous or hypertrophic (Figs. 20.45, 20.46).

With chronic PN, there is a striking accumulation of periglomerular infiltrates as is present in the acute form (Fig. 20.47). Within infiltrates, the tubules and their membranes have completely disappeared. The infiltrates consist predominantly of small lymphocytes along with a moderate number of phagocytes (Fig. 20.47).

In the xanthomatous form (see p. 430) these phagocytes are especially numerous and contain many leukocytes and bacteria and are particularly rich in phagolysosomes [1294].

Segmental glomerular capillary loop collapse (for glomerular findings see Figs. 6.9, 6.22, 6.34, 6.57, 6.64, 6.80, 6.88) is present in about half of the cases and signs of segmental loop obsolescence in one-third of our cases (Fig. 20.48). Endothelial cells are, at times, edematous or hypertrophied and they form arcades frequently.

Glomerular BM is rarely completely unchanged; it demonstrates segmental thickening in about one-sixth and diffuse thickening in half of our cases. Thickening of the lamina rara interna is not infrequent. In about one-fourth of our cases, a few deposits can be identified within the BM. On the other hand, subendothelial deposits or deposits along the mesangial BM are rarely encountered. BM doubling occurs in a few cases accompanied by mesangial interposition in isolated loops. Podocytes are often edematous and microvilli are frequently formed on their surface.

Fusion of foot processes—occasionally extensive—is observed in about three-fourths of our cases. While the epithelium of Bowman's capsule rarely shows proliferation or synechiae (Fig. 20.49). The capsular BM is frequently considerably thickened and fragmented (Fig. 20.47) but rarely contains osmiophilic deposits.

◁ **Fig. 20.44.** Acute pyelonephritis. There is blood stasis in the intertubular capillaries (*CL*) which are occasionally ruptured resulting in interstitial hemorrhage (*). In the tubules, polymorphonuclear leukocytes and, sometimes, phagocytes (*PH*) can be identified. In the severely edematous intersitium, phagocytes are the predominant cell type in addition to somewhat scantily present polymorphonuclear leukocytes. No tubular destruction is recognizable. Male, 56 years. EM (× 1200)

**Fig. 20.45.** Same case as in Figure 20.44. Edematously enlarged periglomerular space is strikingly rich in infiltrates consisting of polymorphonuclear leukocytes as well as phagocytes, erythrocytes and some fibrin strands. There is slight activation of glomerular capillary loop endothelium and of podocytes as well as an increased number of polymorphonuclear leukocytes in the glomerular capillary loop lumens. Capsular space is almost empty; there is no destruction of capsular BM. Male, 56 years. EM (× 1300)

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**Fig. 20.46.** Same case as in Figure 20.44 showing leukocytosis of glomerular capillary loops and hypertrophy of the endothelium (*E*). Male, 56 years. EM (× 3300)

**Fig. 20.47.** Chronic pyelonephritis. Small and activated (large) lymphocytes as well as phagocytes represent the predominant cells. Splitting of glomerular capsular BM and connective tissue proliferation (→) are seen. Complete obsolescence of glomerular capillary loops (*G*) is present. Male, 77 years. EM (× 1400)

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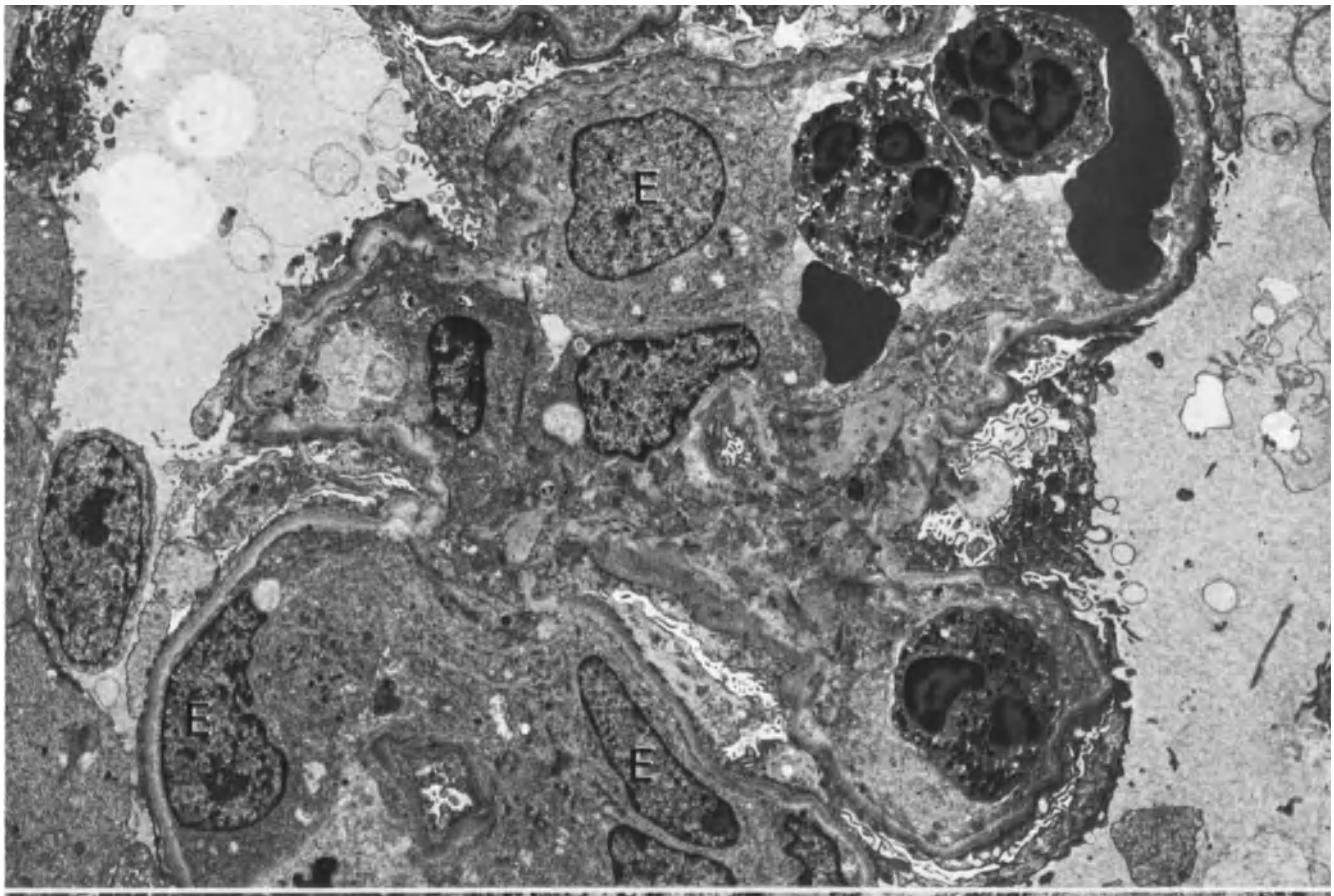
**Fig. 20.48.** Chronic pyelonephritis evidencing peripheral glomerular capillary loop collapse and incipient obsolescence. Male, 59 years. EM (× 7300)

**Fig. 20.49.** Crescent formation caused by proliferation of capsular epithelium in chronic pyelonephritis in a 3-year-old boy with myeloid leukemia. Most of the proliferated cells are from the capsular epithelium between which isolated, dark podocytes (*P*) can be identified. Outermost layer of the split and partially dissolved capsular BM (*CBM*); compressed glomerular capillary loops (*). EM (× 1700)

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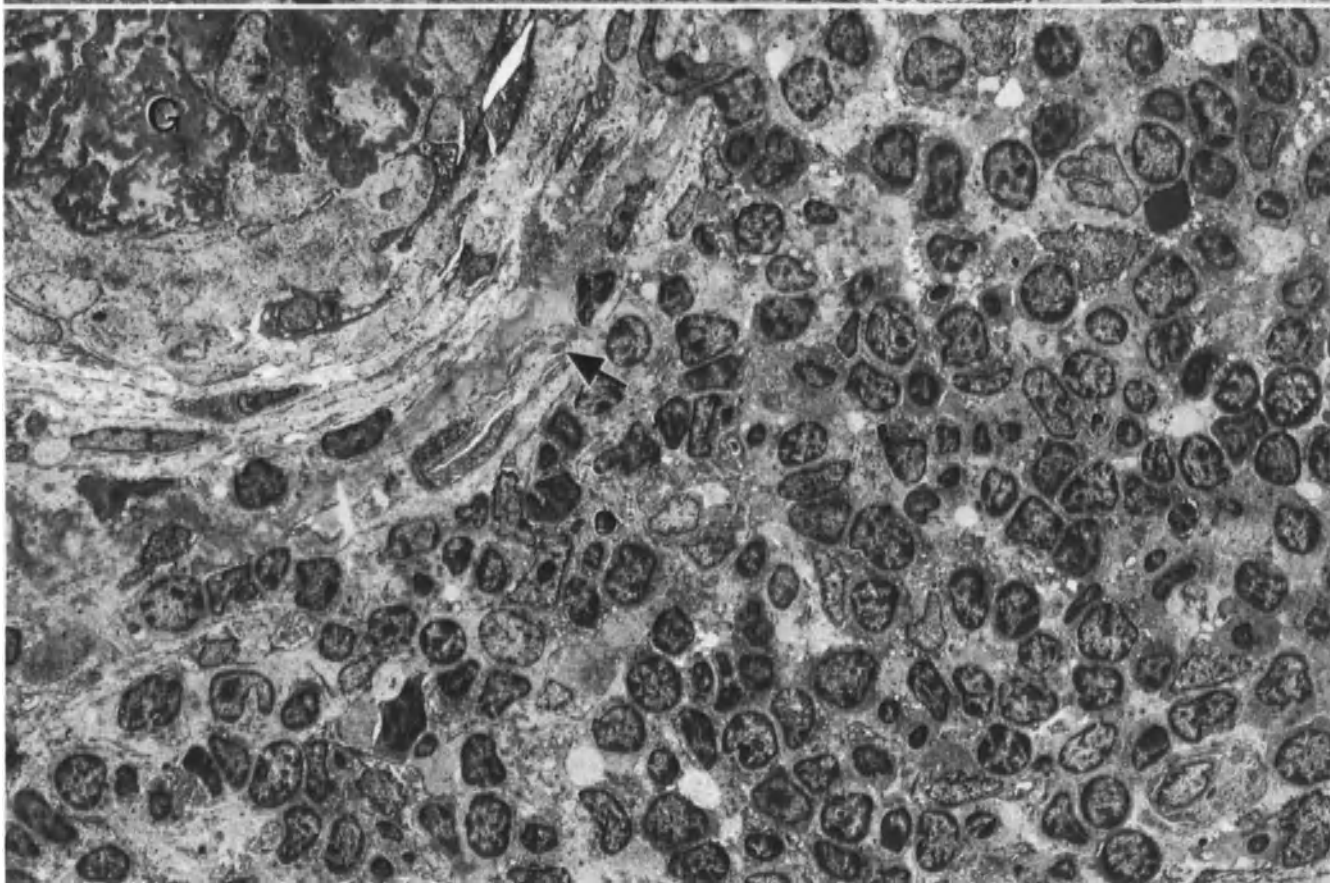


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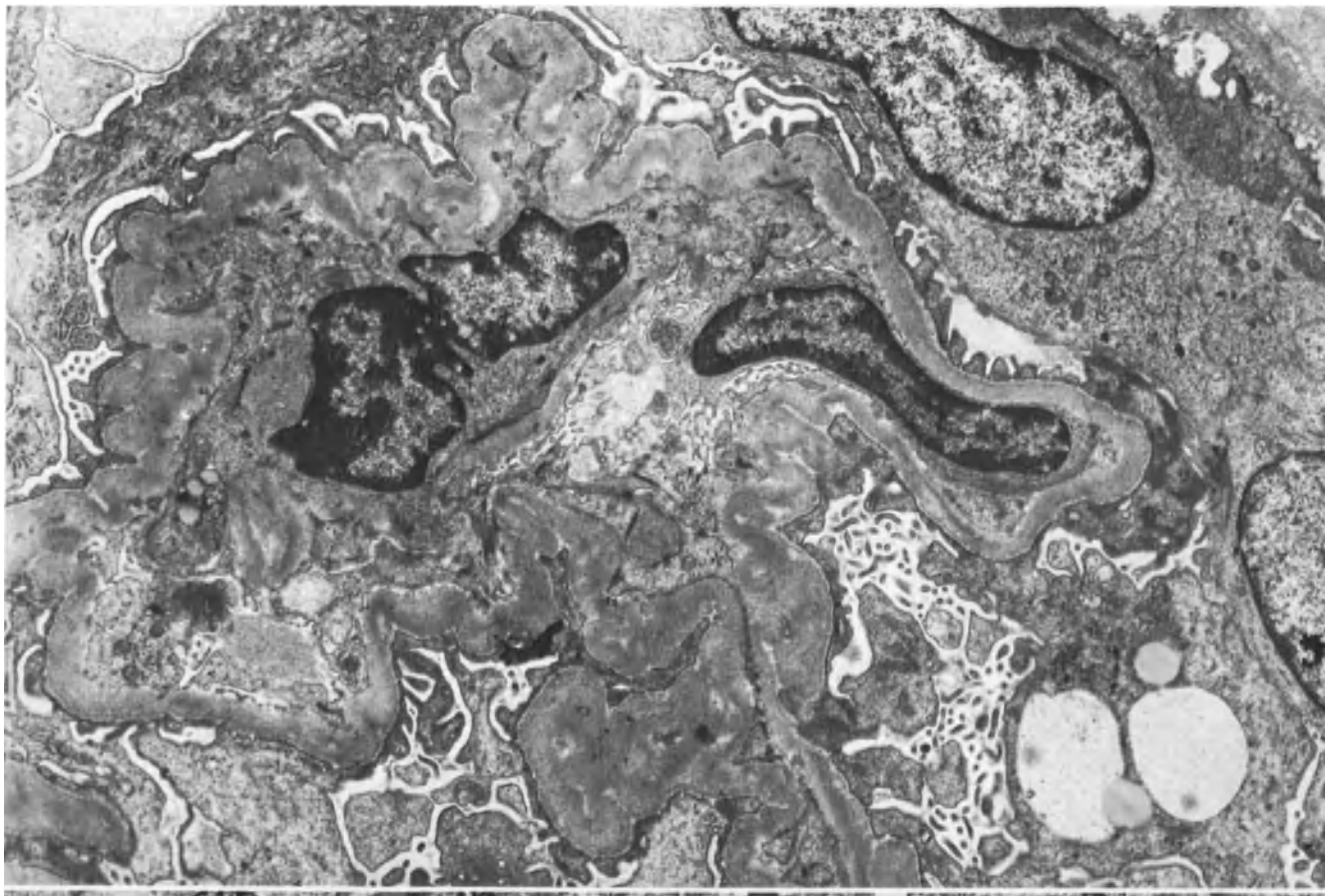

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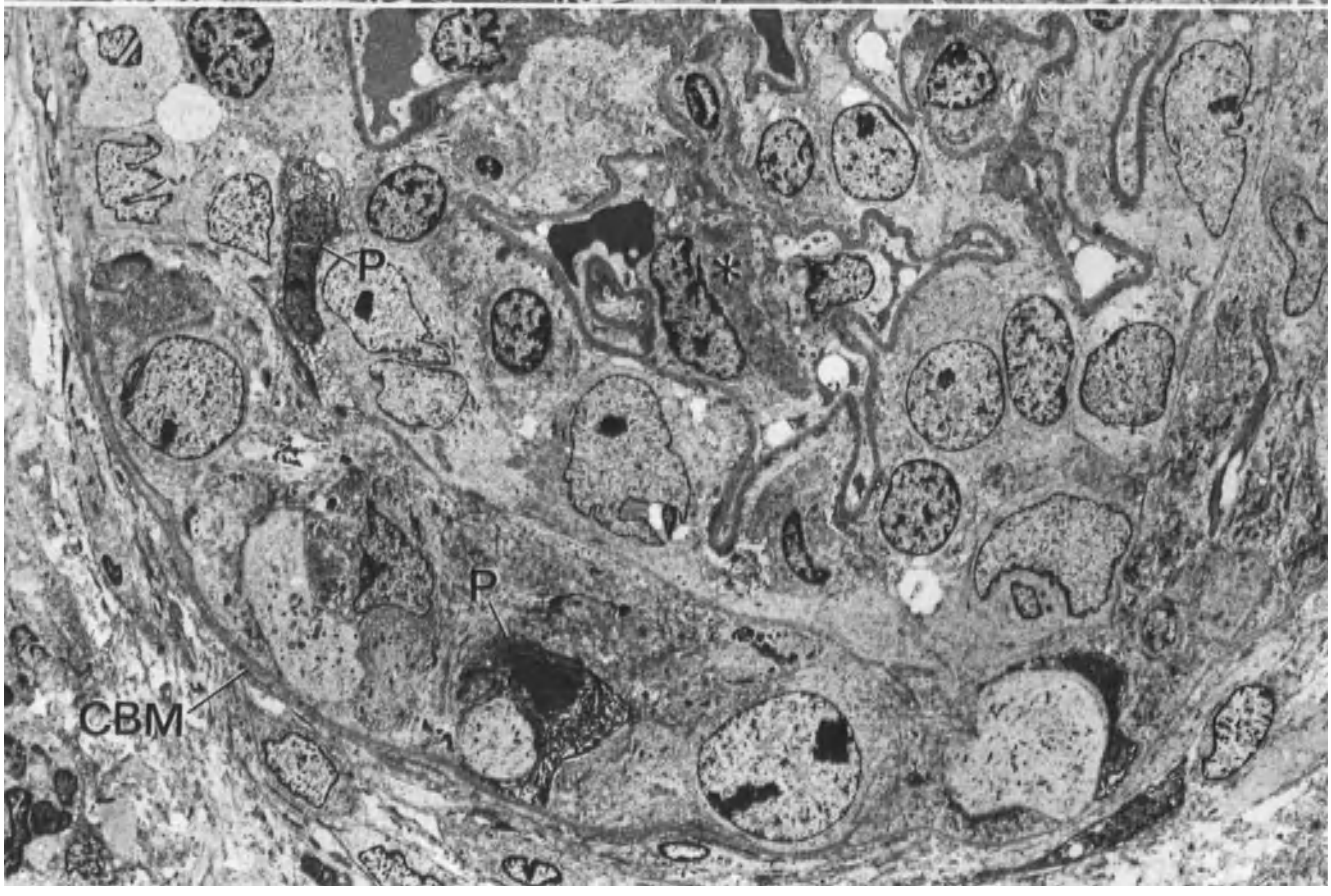



20.49

Tubules are severly atrophic and frequently dedifferentiated (Figs. 8.12, 8.14; see p. 124). Their BM is thickened and often fragmented (Figs. 8.10, 20.50) which may be viewed as a sequel of acute erosion.
Blood vessels show the same changes as observed with LM.

### Differential Diagnosis

In acute PN, no diagnostic problems are to be expected.
In this connection it is noted that there is no fundamental difference in findings between acute embolic purulent focal nephritis and acute PN, i.e., the PN can develop out of embolic, purulent focal nephritis evidencing highly virulent bacteria (see p. 282) or by ureteral ascension.
Differentiation from acute interstitial transplant rejection has never really caused problems since in transplants, large numbers of polymorphonuclear leukocytes and erosive destruction of tubules are both absent.
Chronic PN is differentiated from subinfarction (see p. 508) by the presence of the destructive tubular foci and inflammatory widening of the interstitium in the former. Tubular dedifferentiation and glomerular capillary loop collapse are present in both conditions. Chronic PN is differentiated from chronic IN and GN by its radial scars or focal spreading. Additionally, the changes in the more or less intact glomeruli characteristic for chronic GN are usually not subject to misinterpretation. Nevertheless, overload glomerulitis must be considered in the presence of obvious focal-segmental glomerular involvement (see p. 308). If the needle biopsy contains scar tissue, only two features will assure the diagnosis of chronic PN: (1) the destructive vascular, glomerular and tubular changes present, and (2) the occurrence of replacement scar tissue rich in fibroblasts instead of the interstitial sclerosis present in chronic IN. In advanced contracted kidney, however, differentiation between chronic PN, GN, and interstial nephritis may be impossible.

### Prognosis

Hypertensive vasculopathy is frequently encountered as are tubular adenomas in contracted kidneys. In very severely contracted kidney, overload glomerulitis is occassionally found (see p. 308). The vascular changes described can lead to small subinfarcts which considerably complicate interpretation.

### Complications

PN lesions can heal with scar formation and, except for hypertension—which is not obligatory—may not have any clinically significant sequelae. The greatest danger is relapse resulting, ultimately, in uremia. The course of PN, however, is unpredictable. Even in advanced renal insufficiency, renal function may become stationary for many years, but be followed by a rapid decline resulting in terminal uremia. Relapse of acute PN or exogenous factors such as phenacetin addiction are not, in all cases, responsible for changes in progression of the disease.
The reported follow-up results show that 13.6% of the patients died, 13.8% demonstrated persisting disease, 18.1% had remaining clinical damage, and that 54.4% were cured completely [138, 1099]. The prognosis in our material—chiefly comprising advanced stages of the disease—(Table 20.3) was bad, with 10-year survival rates for patients without phenacetin addiction of 40%, and for those with of 31%. Complete remission occurred only in 15.9% of patients without and in 3.3% of patients with phenacetin addiction.
If the first clinical attack occurs in children before the end of the second year of life, the mortality is 28% and if it occurs thereafter 14% [1568]. In infants with PN associated with vesico-ureteral or pyelo-renal reflux chronic PN often develops from acute PN (13 out of 17: [1355]; 22%: [555]).
Hypertension occurring with unilateral PN contracted kidney can sometimes be healed by surgery (3 out of 7: Z) or improved (4 out of 7: Z; [431]; see also p. 541.

### Pathogenesis

Acute PN may arise hematogenously or by direct (ascending) spreading of bacteria [1791]. Prior infection of the lower urinary tract is very frequent. The urethra appears to be an important reservoir for bacteria [324]. The greater incidence of acute PN in female infants wearing diapers is ascribed to the shortness of the urethra in the female.
Animal experimentation indicates that bacteria chiefly gain access to the bloodstream from the mucosa of the bladder, i.e., reach the kidney hematogenously. Urinary stasis is a powerful contributor to local infection and subsequent PN. In males, stasis is of significance in 58% of our patients (see Table 22.1) and in only 21% in females: 11% lithiasis; 6% cervix carcinoma; 3% urethral stricture; 1% bladder carcinoma. Further contributory factors which predispose for PN are hypercalcemia, hyperuricemia, diabetes mellitus, chronic hypokalemia, analgesic addiction, and hypercalciuria. In 70–75% of infantile PN, the infection is thought to arise from urinary stasis associated with vesico-uretral or pyelo-renal reflux [687a, 703]. Additionally malformations of the urinary tract play an important role in the development of PN in childhood [144].
We attribute the frequent development of collapse glomeruli and subinfarcts to the obsolescence of postglomerular intertubular vessels (see also [1068]).

### Etiology

In a large survey of the literature [138], the following bacteria and their incidence were found:

| Bacterium | Frequency (% of cases) |
|---|---|
| E. coli | 13.8–63.5 |
| Aerobacter aerogenes | 3.2–18.0 |
| Klebsiella | 0.2–11.0 |
| Proteus | 3.2–18.4 |
| Pseudomonas aeruginosa | 3.6–18.0 |
| Enterococci | 1.8–27.5 |
| Staphylococci | 3.2–46.0 |
| Others | 0 –15.7 |

Relapse is often caused by a bacterium different from the one producing the disease initially [555].
The possibility of PN arising from mycoplasms (800–5000 Å-large structures without cellular walls) has been proposed since these agents have been demonstrated in 10–17% of abacterial diseases of the urogenital tract [1406].
Cases of chronic, active PN with negative bacterial findings and the absence of urinary tract infection [39] point to the possibility of a nonbacterial etiology (12 out of 20 cases of active chronic, nonobstructive PN: [33, 687a]; see also Table 20.3). Nevertheless, the previously mentioned IF findings indicate prior bacterial infection with bacterial AG still present in renal parenchyma [39].

## Pyelonephritic Contracted Kidney of Early Childhood
[1791]

### Definition

Usually unilateral, partial or total contracted kidney with morphologic characteristics of chronic PN developing in early childhood.

***Synonyms:*** Segmental hypoplasia [626, 628]; Ask-Upmark-kidney [55].

### Incidence

In our autopsy material, we found 1.1‰ of such cases, chiefly in young women of all ages [362, 1791].

### Clinical Findings

In young patients, nephrectomy is usually done because of hypertension and/or because of intolerable flank pain engendered by PN attacks. In autopsy cases, we have noted the presence of hypertension in 21 out of 31 of the subjects (75% in females, 100% in males: [113]; 71.5% of all cases: [1391]; 57% of all cases: [1262, 1392]).
Patients subjected to the disease frequently show retarded growth at an early age [1392]. Arteriography combined with pyelography shows a total or partially contrast-free corticomedullary zone [1535]. Early childhood PN is, however, rarely elicited in the case history [1791].

### LM Findings

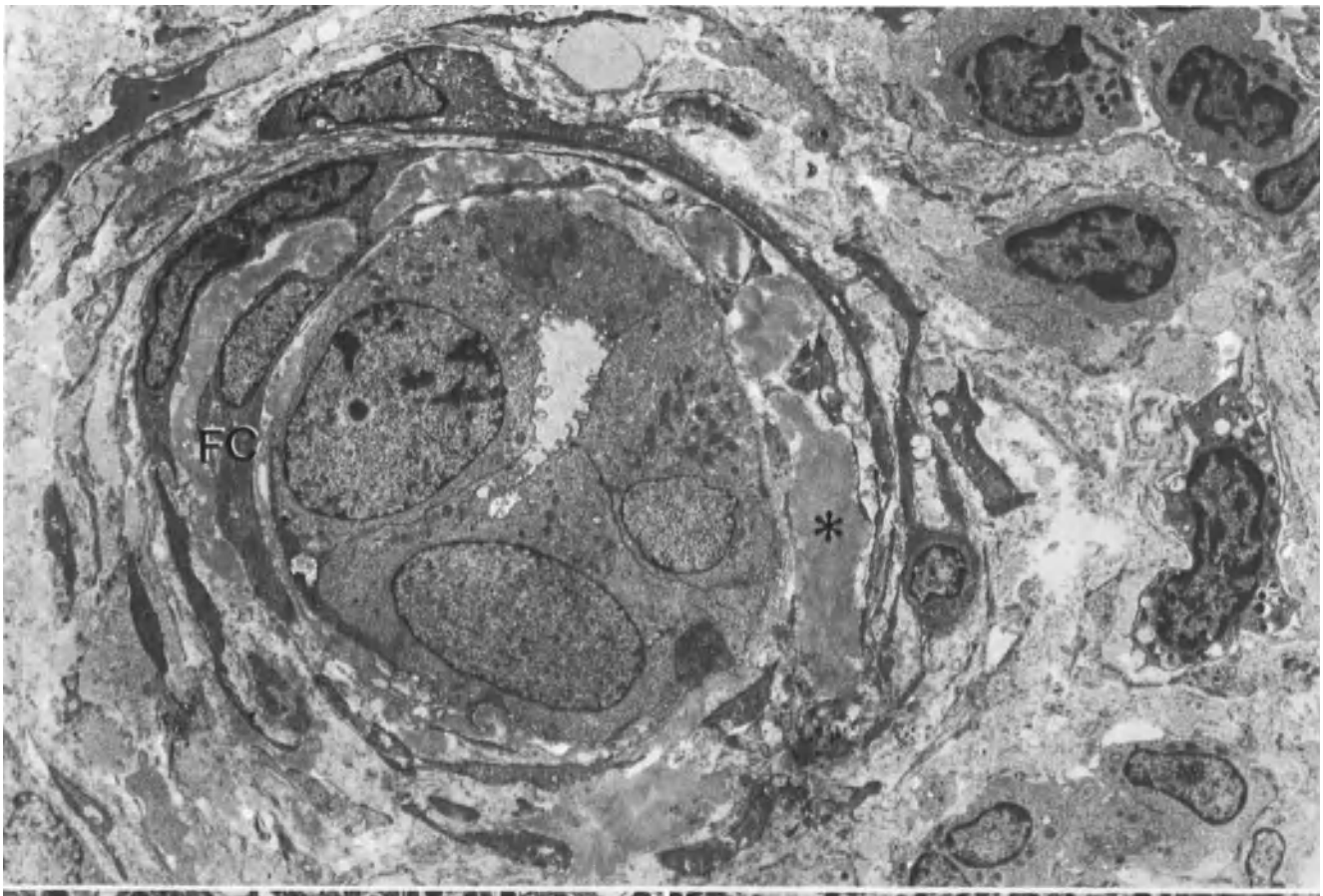
The changes may be sector-like (Fig. 5.11) and, as such, not unconditionally recognizable in needle biopsy. Histologically, chronic, almost always inactive (scar form) PN with the following special characteristics is seen:

1. Thyroid-like foci are markedly frequent and extensive (Figs. 5.11, 20.51)
2. At first glance, the number of glomeruli in scar foci appears to be considerably reduced. However, with higher magnification, rather numerous PAS-positive membrane stars (spider scars)—representing residues of destroyed glomeruli (Fig. 20.52)—can be recognized (Fig. 20.53). Complete glomerular destruction is far more frequent in acute PN of childhood than in later life.
   Completely obsolescent glomeruli are also recognizable as is noted by investigators favouring the segmental hypolasia theory [1392]. The JGA is occasionally considerably hypertrophied [1071].
3. Adaptive intimal fibrosis is usually exceedingly marked ("endarteritis sclero-elastica chronica" [626, 628, 1392], p. 151).

In remnant parenchyma, severe hypertrophy of intact renal elements (glomeruli, tubules) may be present in rare cases of severe, bilateral disease [1679].

### Prognosis

With the exception of complicating hypertension, the prognosis is good. This is illustrated by the frequent occurrence of early childhood contracted kidney in old and very old subjects coming to autopsy. The hypertension is often curable by partial or total nephrectomy (75%: [626, 628]; 2 out of 2: [1155]; 14 out of 14 cases: [1262]; see also [1791], and p. 541).

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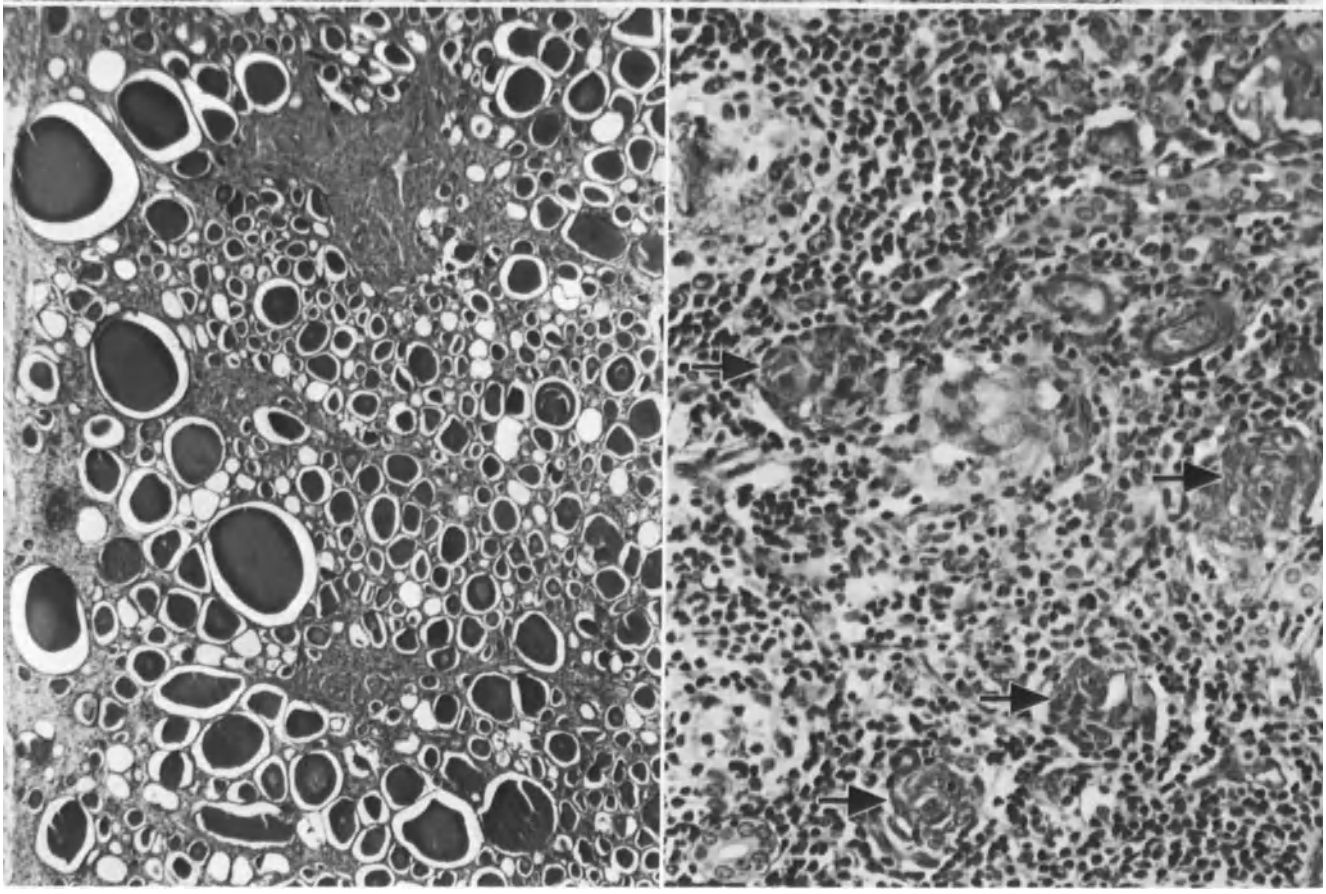

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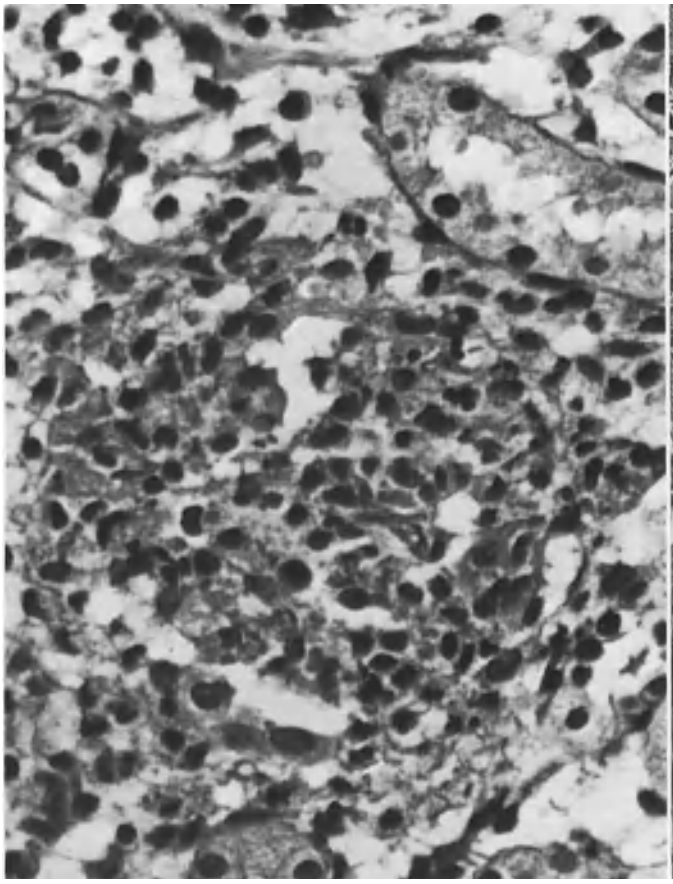


**Fig. 20.53.** Complete glomerular destruction in subacute pyelonephritis of early childhood associated with ureteral stenosis. Residues of the glomerular capillary loop BM are no longer recognizable. Male, 1.75 years. PAS ( × 420)

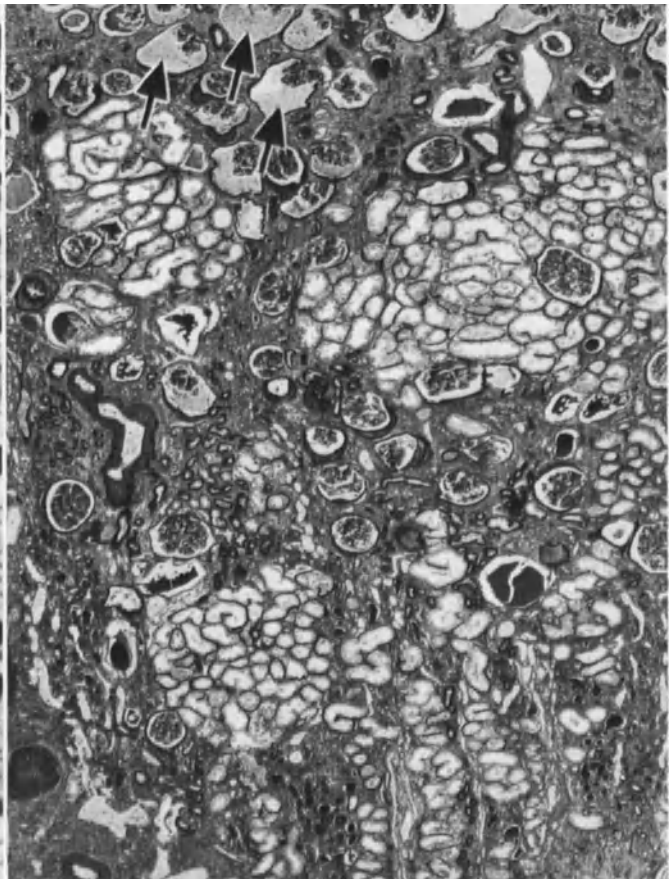


**Fig. 20.54.** Contracted kidney which weighed 70 g in a case of so-called Montaldo pyelonephritis. Only isolated nephrons with hypertrophied tubules are still preserved. Glomeruli are especially striking because of their severely widened capsular space (→). Male, 67 years. PAS ( × 29)

◁ **Fig. 20.50.** Tubular atrophy in pyelonephritic contracted kidney. Tubular BM is highly thickened (*), disintegrated into clumps, and permeated with fibrocytes (*FC*). Male, 52 years. EM ( × 3420)

**Fig. 20.51.** Thyroid-like focus in the renal cortex in chronic pyelonephritis associated with nephrolithiasis. Female, 61 years. PAS ( × 50)

**Fig. 20.52.** Active early childhood pyelonephritis associated with stenosis of the ureteral ostium and hydronephrosis with numerous glomerular residues still provided with vital cells (→). Tubules are almost completely destroyed and extensive inflammatory infiltrates are present in the widened interstitium. Male, 4 years. PAS ( × 210)

## Pathogenesis

In our opinion, this type of segmental or total contracted kidney is the consequence of PN (see also [24]). The extensive destruction of glomeruli with their occasional dissolution is typical for acute early childhood PN (see above; [1791]). Tubular changes are viewed as acquired malformations. It has been possible to produce them experimentally [8].

Other investigators consider the lesion to be segmental hypoplasia [113, 362, 626, 628, 923, 1071, 1155, 1262, 1392, 1535]. They support their view by pointing to the small number of well-recognizable glomeruli in the damaged zones. We reject this theory not only because of the special type of the glomerular destruction mentioned above, but also because of the usual absence of hypogenetic foci.

In only 2 out of 29 surgical specimens of early childhood PN contracted kidney were we able to demonstrate a few cartilagenous foci. As is known, early childhood

PN is especially prone to develop in partially malformed kidneys. A typical finding – which is relatively frequent – is ureter fissus or duplex (8 out of 41 cases: [1791]). In ureter duplex, that renal tissue is usually implicated which is associated with the heterotopic draining ureter. Extensive adaptive intimal fibrosis also points to scarification processes since it is absent in genuine hypoplastic and dysplastic kidneys; the same consideration is valid for thyroid-like foci. Finally, a further argument for our theory is that even proponents of the malformation theory have found vesico-ureteral reflux associated with early childhood PN, a well-known causative factor in the pathogenesis of PN in childhood as pointed out previously [923, 1392]. Infection of the urinary tract, which is not infrequently found in such patients, is considered by these investigators to be secondary [923, 1155].

## Montaldo's Pyelonephritis

This special form of PN, named after the first investigator [1130a] is characterized by the occurrence of small glomerular cysts located directly under the kidney capsule. The cysts are partially filled with proteinaceous fluid. The glomerular capillary loops are severely collapsed (Fig. 20.54). Since an analogous picture is very characteristic for the renal changes associated with chronic renal vein thrombosis (see p. 503), it is reasonable to assume that impairment of renal blood flow and maintenance of venous return by capsular veins are factors common to both lesions.

## Balkan Nephropathy
[540, 561, 562, 563]

### Definition

Balkan nephropathy may be defined as a renal lesion endemic in the Balkans associated with increased incidence of urothelial tumors (transitional epithelial tumors).

### Clinical Findings

The disease attacks young women much more frequently than men. It begins in early childhood and manifests itself by lumbar pain, intermittent hematuria, in rare cases by proteinuria, and by constant bacteriuria. Hypertension is rare. Nephrolithiasis is present in about one-third of the cases and anemia almost always.

### LM and EM Findings

The entity is usually described as blandly coursing chronic PN. After study of numerous cases, we also tend to this point of view. We have not been able to accept the notion [563] that the lesion represents a primary nondestructive nephritis with optional secondary PN.
With EM, unspecific changes have been observed [790, 791]. Only amorphic osmiophilic corpuscles (diameter: 0.1–0.5 μm) in tubular cytoplasm constitute a unique feature, but they elude explanation as is the case for 300–350 Å large virus-like particles [540, 39a].

### Pathogenesis and Etiology

In our opinion, pathogenesis and etiology of the nephropathy is not clear, although it is said to be due to PN acquired in childhood from ingestion of water contaminated with coli bacteria [563].
No evidence has been submitted indicating primary toxic tubular injury [1447] or causal significance of silicates [1008].
The association of the disease with urothelial tumors (48% of cases) arising secondarily remains completely unexplained [561, 905]. A similar situation is only known for phenacetin addiction (see p. 440) which, in Balkan nephropathy, can be excluded. In our opinion, factors other than simple coli infection must be involved, since otherwise, urothelial tumors should be found more frequently in PN caused by coli infections outside the Balkans. Recent findings of virus particles, possibly corona-virus, offer a better explanation [39a].

## Renal Changes in Phenacetin Addiction
[1094, 1184, 1259, 1606a, 1792]

Following recognition of the relationship between addiction to phenacetin and renal changes [1551, 1787] the only relevant finding was an increase of chronic IN with papillary necrosis. The much more frequent occurrence of pyelonephritis as a consequence of phenacetin abuse was realized later [1792].
Other drugs, such as aspirin have subsequently been implicated [534, 1366]. New evidence, however, appears to contradict this contention [989].
We do not believe that phenacetin causes specific renal lesions and information from case histories is often inadequate to allow reliable analysis of autopsy material. Clinico-epidemiologic surveys [395] including psychiatric institutions [830] show that 25% of phenacetin addicts in mental institutions and 70% of those undergoing outpatient or inpatient treatment in Swiss hospitals have

Table 20.4. Renal findings from biopsy material in phenacetin addiction ($n=95$)

| | Group I Total | Group II (amount < 10 kg) | Group III (amount > 10 kg) |
|---|---|---|---|
| Duration of addiction (mean ± SD) in years | – | 7.1 ± 3.4 | 20.6 ± 9.6 |
| Phenacetin amount in kg (mean ± SD)[a] | – | 3.9 ± 2.5 | 15.6 ± 5.3 |
| No. of patients (n) | 95[b] | 31 | 42 |
| Nephropathy (without relation to phenacetin, e.g. GN) | 25.3% | 32.2% | 14.2% |
| No. significant pathologic changes | 10.5% | 22.6% | 2.3% |
| Small PN scars | 12.6% | 22.6% | 7.1% |
| Chronic PN | 42.1% | 22.6% | 59.8% |
| PN contracted kidney | 6.3% | – | 11.9% |
| Chronic IN | 3.1% | – | 4.7% |

[a] Estimated form amount of phenacetin (g/day) × (duration of addiction in years).
[b] 22 patients included with incomplete information on duration and amount of phenacetin addiction.

clinically demonstrable renal lesions (131 out of 161: [395]).
Our findings based on renal biopsy are summarized in Table 20.4, demonstrating that the longer the duration of phenacetin addiction and the higher the total amount of phenacetin intake, the more severe the renal lesions (compare groups II and III).
Of patients with PCP, 20–30% are reported to suffer from a chronic renal lesion as a consequence of phenacetin abuse [130].
The incidence of renal pelvic carcinoma (occasional ureteral or bladder carcinoma) has been shown to be statistically significantly related to phenacetin addiction [112a, 938]. Therefore, patients with known phenacetin addiction should undergo regular urinary cytologic examination for detection of tumors of the urinary tract.

### LM Findings

There are no specific findings. Chronic IN or chronic PN may be present. Marked increase of papillary necrosis or merely increased widening of medullary and papillary connective tissue are striking [286, 534, 570], as of strong sudanophilia of the interstitial tissue and the thickened BM of papillary tubules and vessels [1624a].

### Prognosis

The prognosis depends on the type of renal lesion (for prognosis of chronic PN, see Table 20.3). Complete drug withdrawal appears to at least stabilize the disease or prevent its further progression [1192].

### Pathogenesis

The pathogenesis remains unclear and attempts at clarification by experimental study have been unrewarding [1626]. In part, tubular changes have been demonstrated [1259, 1366] which, however, were due to reduced food intake, i.e. tubular changes corresponded to those seen in starvation [1626].
Current views are focused on a primarily drug-induced papillary necrosis with secondary cortical atrophy and sclerosis [570, 1184, 1068, 1624a] and possible tertiary PN [233]. Papillary necrosis is attributed to the especially high concentration of the metabolite para-aminophenol in the papillae and the injury caused thereby to the vasa rectae [155].
Various investigators have produced papillary necrosis in rats by overfeeding them with phenacetin [845] but it must be noted that phenacetin metabolism is different in rodents than in man [59]. There are, however, many negative experimental findings [1626]. Additionally, unequivocal cases of phenacetin addiction with severe renal lesions and without papillary necrosis speak against the role of the drug in directly causing the lesion.
An allergic reaction to phenacetin or phenetidin [1304] has also been suggested. Accordingly, the increased frequency of PN is explained as a superimposed infection of a kidney previously injured by allergy. The increased incidence of renal pelvic tumors is explained as the direct action of the metabolites phenetidin and 2-hydroxyphenitidin sulfate.
It can only be said with certainty that chronic analgesic abuse—especially of phenacetin—injures the kidney in such a way that it becomes increasingly susceptible to infections, including tuberculosis [1791].

## Combination of Pyelonephritis and Glomerulonephritis

The combination of two acquired nephropathies is not rare and has been reported to occur in 10% of a series of autopsy cases [1779]. The combination of an acquired nephropathy with chronic pyelonephritis was present in 3% of a biopsy series [1271a] and in 5.2% of our own biopsy material.

Table 20.5. Combination of PN and GN in our biopsy material

| Morphologic diagnosis | | Leukocyturia, bacteriuria | Leukocytic casts | Radiologic PN findings | Morphologic PN |
|---|---|---|---|---|---|
| Total GN | n° | 718 | 670 | 554 | 805 |
| | %+ | 8.2 | 3.4 | 10.8[a] | 6.1 |
| Endotheliomesangial GN (including crescents < 50%) | n° | 178 | 161 | 138 | 209 |
| | %+ | 8.9 | 2.6 | 9.4 | 5.7 |
| Extracapillary accentuated GN (> 50% crescents) | n° | 24 ↑↑ | 20 ↑↑ | 10 | 33 |
| | %+ | 25 | 15 | 10 | 3 |
| Epimembranous GN | n° | 55 | 51 | 46 | 70 |
| | %+ | 1.8 | 2.0 | 8.7 | 8.6 |
| Membranoproliferative GN | n° | 33 | 29 | 20 | 42 |
| | %+ | 3.3 | 10.3 | 10 | 7.1 |
| Segmental-focal proliferative GN (including crescents < 50%) | n° | 125 ↑ | 107 | 91 ↑ | 129 |
| | %+ | 12.8 | 3.7 | 16.5 | 7.7 |
| Segmental-focal sclerosing GN | n° | 89 | 84 | 59 ↑↑ | 101 |
| | %+ | 12.4 | 1.2. | 22 | 10.0 |
| Glomerular minimal change | n° | 193 ↓↓ | 181 ↓↓ | 154 | 221 |
| | %+ | 3.6 | 0.5 | 8.5 | 4.1 |

Chi-square-Test: significantly more frequent (↗) more rare (↓) than in the sum of all other GN (see also Table 14.4).

(°) finding stated, (+) finding present in %

[a] n = 60.

10% : Nephrolithiasis
18.3%: Hydronephrosis
79.9%: Distortion of renal pelvis/calyces
18.3%: Obstruction of urinary tract.

Incidence of several findings in one case possible.
Consideration of radiological findings for both kidneys.

The diagnosis of combined renal lesions is especially difficult – if not impossible – in the advanced stages of disease due to overlapping of morphologic characteristics. This is especially valid for the diagnosis of chronic PN since, in the advanced stage, morphologic differentiation of overload glomerulitis accompanying PN with respect to primary GN with accompanying PN may prove to be well-nigh impossible (see p. 308).

The diagnosis of acute PN, on the other hand, rarely presents difficulties if it is recalled that a few tubular leukocytes and leukocytic casts also occur in GN and especially in the presence of capillary loop necrosis (see p. 218).

Data in the literature relating to the frequency of occurrence of the combination of GN with chronic PN show large variation (autopsy material 17%: [411]; 3.6%: [1779]; biopsy material 10.8%: [1183a]; clinical material 7.4%: [1606a]; bacteriuria in all GN: 21.6% [1183a]. In morphologically demonstrated combination of GN and chronic PN, bacteriuria was reported in 31% of the cases [1183a].

Among 805 of our GN biopsies (Table 20.5) certain or probable PN was present in 6.1%; clinical indication of PN – based on leukocyturia and bacteriuria – in 8.2% and based on leukocytic casts in 3.4%. There was no statistically significant correlation between the morphological incidence of PN and different GN forms.

Clinically, bacteriuria and leukocyturia were especially frequent in extracapillary accentuated GN and proliferative FGN, and radiologic indications for PN were found more frequently in proliferative and sclerosing FGN than in the total material.

The frequency of chronic PN with GN (6.1%) does not statistically differ from the frequency of chronic PN in large autopsy series (5.6%: [1304a]; 7.4%: [1791]). This is further emphasized by the fact that we were not able to discover a significant increase of PN in relation to clinical duration of GN (< 1 year, versus > 1 year). This leads us to the conclusion that an increased susceptibility of a GN kidney for (chronic) PN does not exist.

# 21. Kidney Tuberculosis and Rare Kidney Infections

[1791]

## Renal Tuberculosis

In renal biopsy procedures, tuberculosis is fortuitous finding.

### Nosology

We differentiate the following forms: miliary tuberculosis or miliary dissemination, productive-nodular tuberculosis, caseous-cavernous tuberculosis and, as the terminal form, the putty kidney.

### Miliary Tuberculosis

This form is characterized by numerous 1–2 mm-sized epitheloid-cell nodules with scanty Langhans giant cells surrounded by a narrow border of lymphocytes. Centrally, the nodules are usually necrotic (for differential diagnosis of giant cells see Table 8.1, p. 129).
Classically, the nodules are free of vessels, but since they arise hematogenously, remnants of vessels and glomeruli can often be demonstrated. In the very early phase, there is glomerular necrosis with incipient periglomerular granuloma formation (Fig. 21.1). If the miliary tubercles are productive and arranged in groups (Fig. 21.2), suspicion of perifocal extension of a cavernous renal tuberculosis, i.e., of organ disease without evidence of acute hematogenous dissemination, is aroused.

### Productive Nodular Renal Tuberculosis

This form is extremely rare. It consists of large, predominantly proliferative aggregates of granulomas.

### Cavernous Renal Tuberculosis

This form is relatively frequent. The lumen of the cavern is covered with caseous masses which often contain large numbers of tubercle bacilli as demonstrated by special stains. Peripheral to the cavern, there follows a zone of typical tubercular granulation tissue (see above) which is surrounded by a broad sclerosed and hyalinized scar wall. Small groups of miliary productive tubercles frequently disseminate lymphogenously into the surrounding area (Figs. 21.4, 5.12, see above).

### Putty Kidney

If the elimination of caseous masses is prevented by obstruction of the ureter, the necrotic masses are calcified and appear chalk-like (the putty kidney). Chronic PN develops almost regularly in the proximal renal tissue where thyroid-like foci are formed now and again (Fig. 5.11, see p. 50)! Patty kidney is occassionally associated with hypertension and can be cured surgically [1466].

## Brucellosis

Brucellosis (Bang's disease) must be considered above all in the presence of morphologic findings of exudative tuberculosis and, if doubt exists, appropriate clinical examinations should be undertaken [402, 818]. In brucellosis, giant cells are more bizarre than in tuberculosis, the boundaries of the granulomas are blurred, and the large numbers of plasma cells and leukocytes speak against tuberculosis.

## Echinococcus

Tuberculoid granulomas also occur around ecchinococcal cysts (Fig. 21.3, [363]) whose characteristic chitin membrane is easily overlooked in HE stain. In needle biopsy, they even may be absent. The nontubercular nature of the disease is usually indicated by the large number of eosinophilic leukocytes and plasma cells and—in late phases—by the presence of calcified chitin membranes [681].

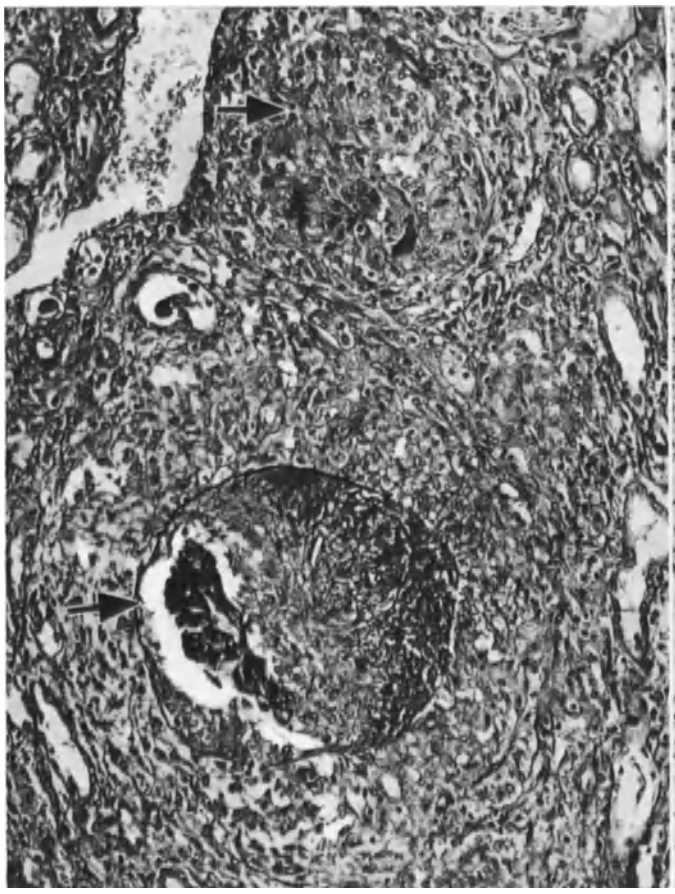


**Fig. 21.1.** Fresh glomerular foci in miliary tuberculosis. Glomeruli are completely destroyed (→) and surrounded by a crown of epitheloid cells. Male, 1.75 years. PAS (×200)

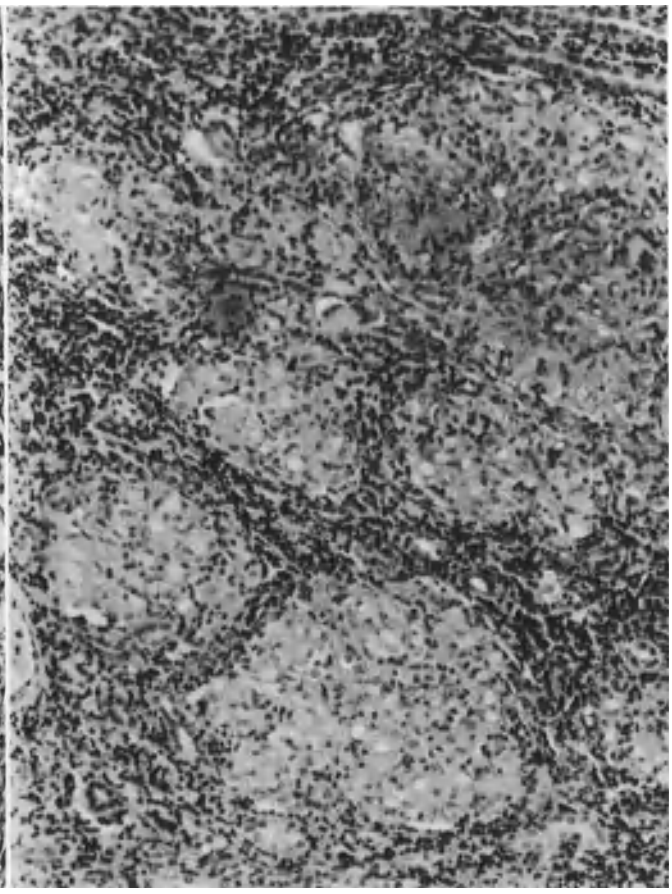


**Fig. 21.2.** Perifocal tubercular nodules (so-called "string of pearls" configuration) in cavitary renal tuberculosis. HE (×140)

## Sarcoidosis

Sometimes tuberculosis cannot be differentiated from sarcoidosis which causes renal complications in 6.8–28% of cases [736, 1791]. In 2% of the cases, renal insufficiency develops which, however, is reversible with steroid therapy [173]. Sarcoid granulomas are far more rare (1% in biopsies, 13.2% in autopsies: [292]) than nephrocalcinosis. Hypercalcemia is present in 8% of the cases and nephrolithiasis in 3.6% [873].

Suspicion of sarcoidosis is aroused by the presence of pure productive granulomas composed of giant and epitheloid cells with a lymphocytic border and a loose connective tissue envelope which extends slightly into the nodule.

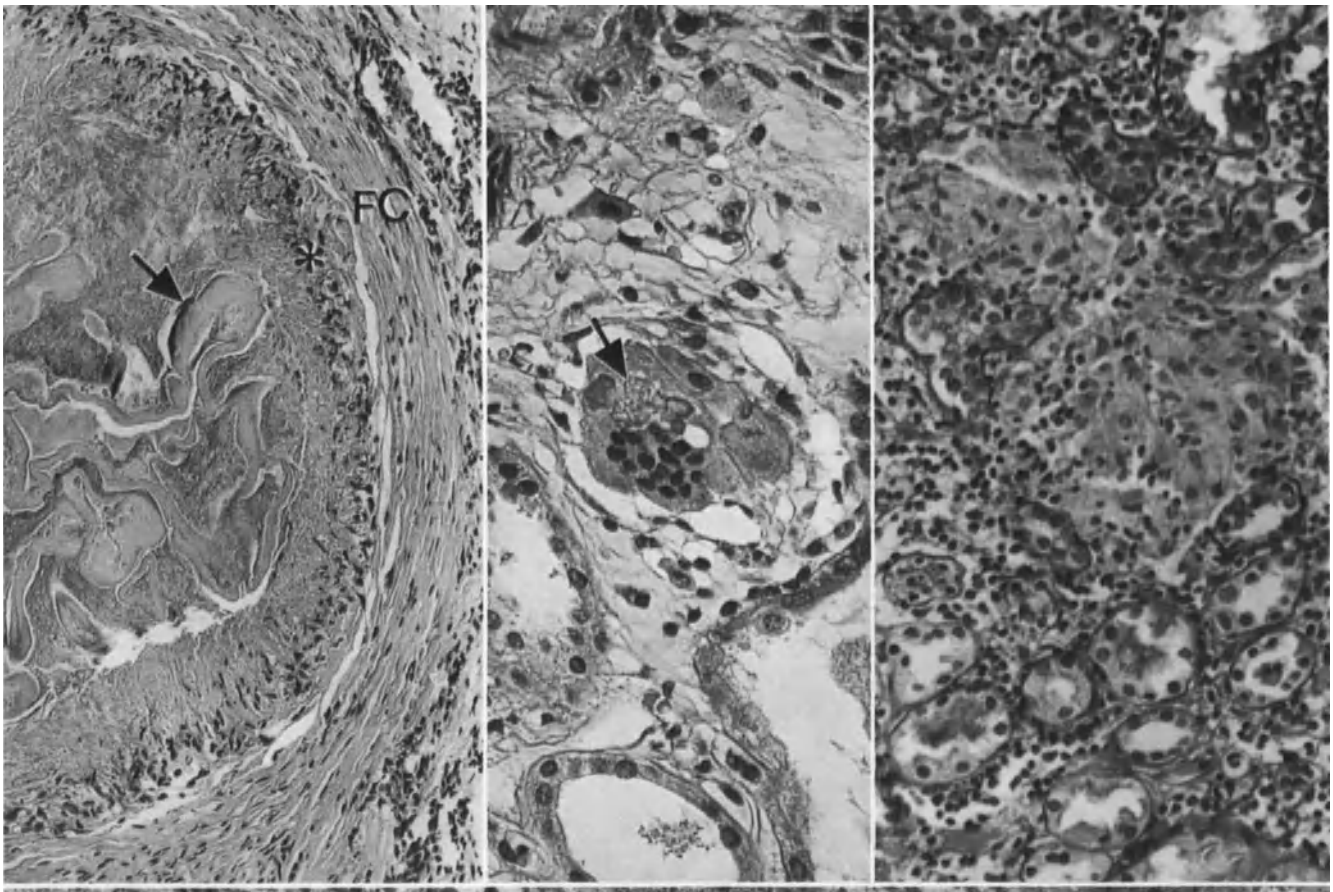
Schaumann and asteroid bodies (Fig. 21.4) are extremely rare in the giant cells and their presence is not, moreover, confirmatory. Isolated disseminated lymphogenous foci in cavernous renal tuberculosis can appear exactly like sarcoid granulomas, so that the diagnosis of sarcoidosis is dependent on the clinical picture, a negative tuberculin as well as a positive Kveim test.

**Fig. 21.3.** Echinococcal renal cyst showing folded chitin membranes (→). Entire lesion is surrounded by a fringe of epitheloid cells (*) which, in turn, is surrounded by fibrous tissue (*FC*). Male, 57 years. HE (×70) ▷

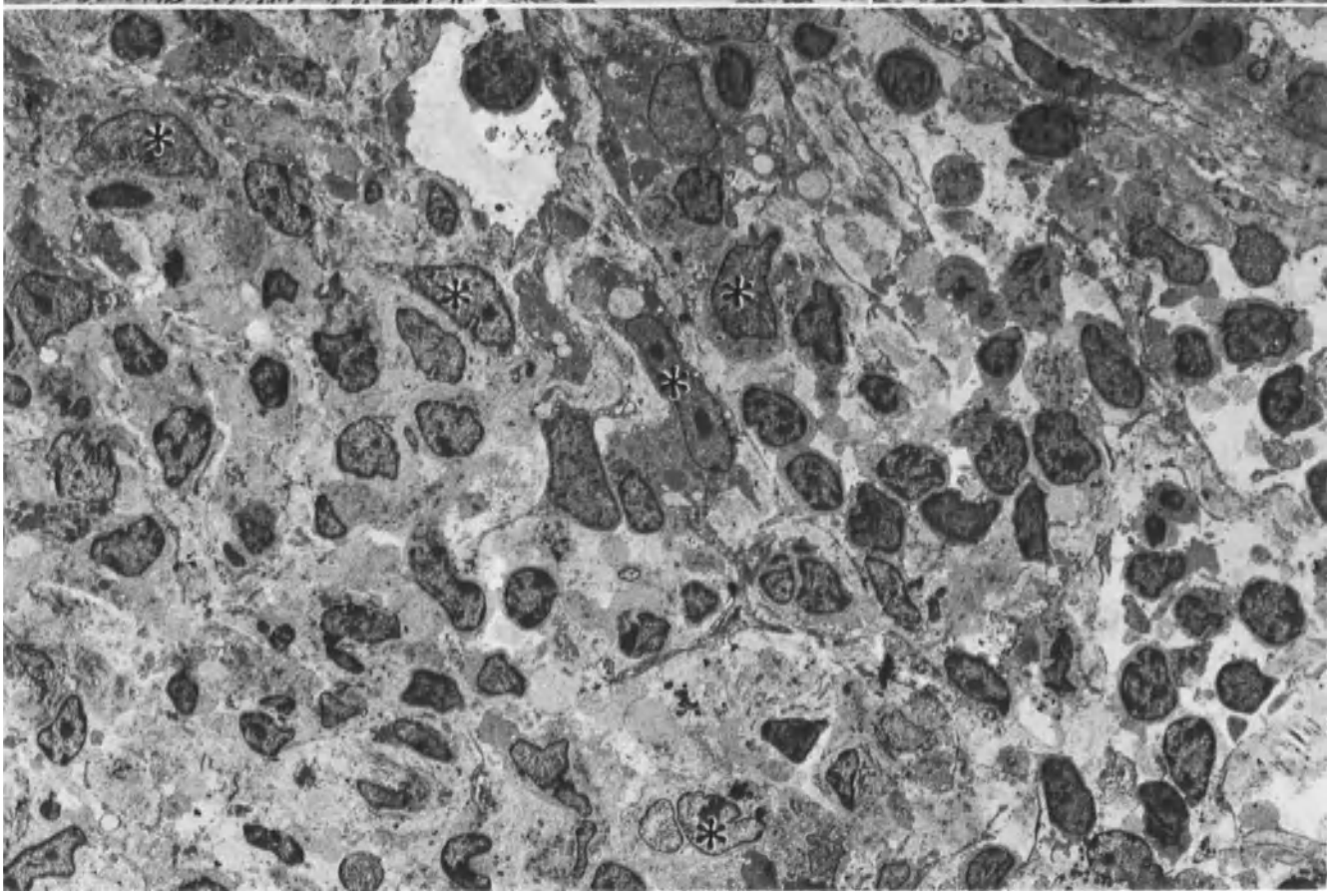
**Fig. 21.4.** Multinuclear giant cell with an asteroid body (→) as the only biopsy finding in sarcoidosis in addition to nondestructive interstitial nephritis. Female, 57 years. PAS (×260)

**Fig. 21.5.** Tuberculoid granuloma. Analogous granulomas were found in biopsies from the thyroid and a salivary gland. Clinically, no indication of sarcoidosis, tuberculosis or toxoplasmosis. Female, 56 years. PAS (×270)

**Fig. 21.6.** Tuberculoid granuloma in the renal cortex with clinical suspicion of toxoplasmosis which was not demonstrable under LM or EM. A few unambiguous epitheloid cells are present (*). Male, 30 years. EM (×1420)




21.3
21.4
21.5



21.6

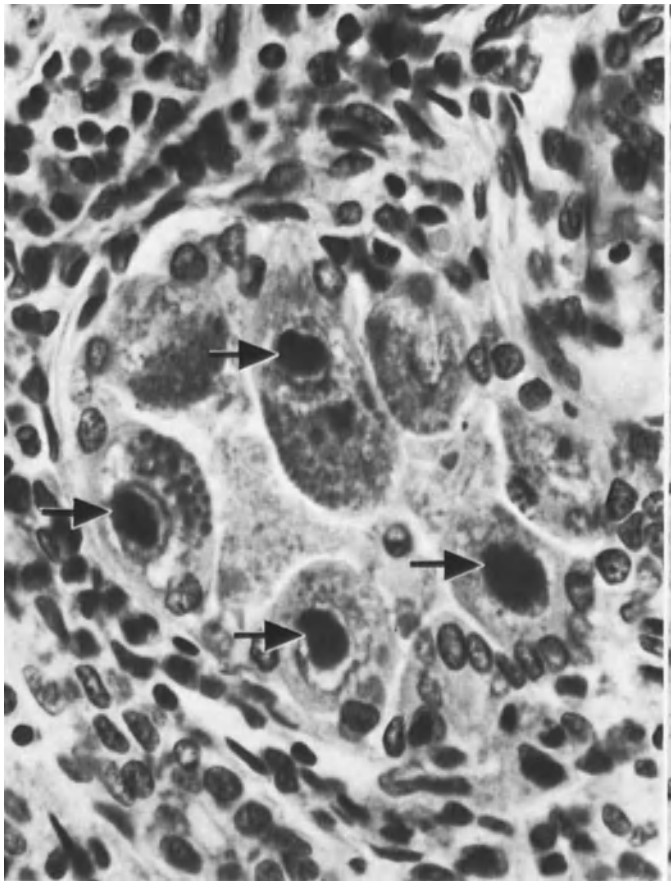


**Fig. 21.7.** Renal cytomegalovirus infection. Some tubular cells are greatly enlarged and evidence strikingly large intranuclear inclusion bodies (→) in addition to coarse cytoplasmic granules. There is a severe interstitial inflammatory reaction. HE (×600)

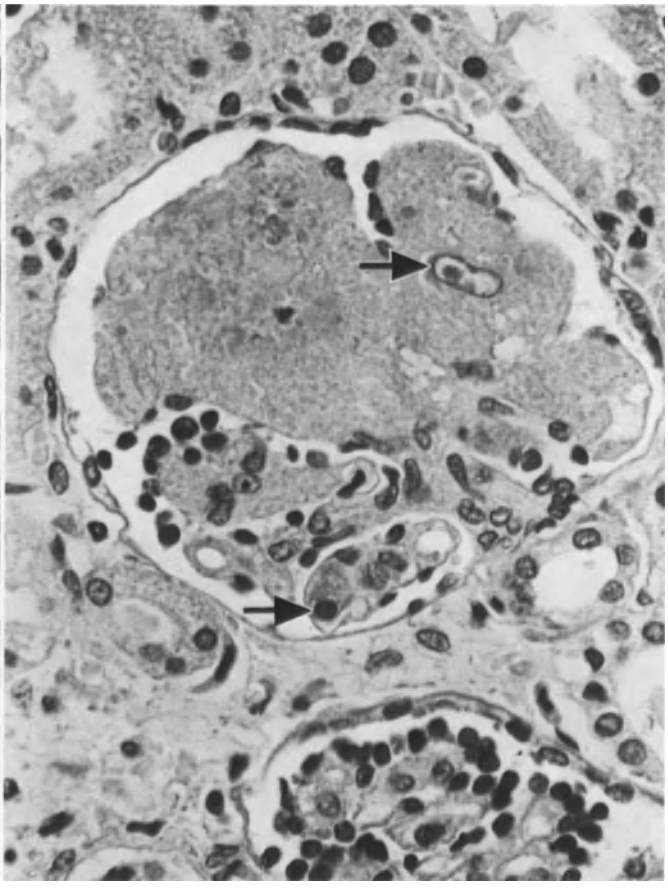


**Fig. 21.8.** Segmental-focal accentuated necrotizing GN in cytomegalovirus infection. Cytomegalic cells are present (→). The patient suffered from pure alymphocytosis. Female, 4.5 years. HE (×250)

There is an increased incidence of GN in sarcoidosis, which courses progressively, as noted in sequential biopsies; immunocomplexes are demonstrable with IF ([1045], see p. 217). This is explained by the fact that both sarcoidosis and diffuse GN represent immunoresponses to a disseminated unknown AG.

## Tuberculoid Granuloma of Uncertain Etiology

Occasionally (10 out of 2080 biopsy cases: Z) tuberculoid granulomas are encountered in needle biopsy, the etiology and pathogenesis of which defy explanation (Fig. 21.5). Two of our cases are of particular interest. In one case, we found toxoplasmosis as a possible basic disease (Fig. 21.6) but we could not demonstrate *toxoplasma* within the granulomas. There is an analogous case described in the literature [1485] with congenital toxoplasmosis and a nephrotic syndrome in which the antigen—together with IgM—was demonstrated in the glomeruli. A further case of ours was particularly intriguing: bioptically, tuberculoid granulomas could be demonstrated in lymph nodes, thyroid, parotid gland, and kidney. At autopsy 1 year later, neither granulomas nor disease residues were found. Clinically, both sarcoidosis and tuberculosis had been excluded as far as possible.

Once in a while, we have encountered tuberculoid granulomas in the region of a genuine cholesteatoma (squamous epithelial transformation of the urothelium) as well as at the edge of a cyst, demonstrating signs of prior bleeding and an inflammatory reaction to the blood and cholesterol masses.

Recently, attention has been drawn to tuberculoid granulomas accompanying interstitial nephritis due to adverse drug reactions (methicillin: [1032a]). Finally, the tuberculoid-appearing form of PN following diazol therapy or high doses of cortisone must be distinguished from tuberculous granulomas [1791]. It is also important to differentiate such granulomas from allergic granulomatous angitis (see p. 538). For xanthomatous PN, see p. 430.

## Actinomycosis

Actinomycosis is also reminiscent of tuberculous granulation tissue in which, however, the actinomycosis grains can scarcely be overlooked. In addition, there are numerous histiocytes (foam cells) and neutrophilic leukocytes.

## Aspergillosis

The hyphae can be clearly demonstrated with the PAS stain. On occassion, it is impossible to differentiate the granulation tissue in this disease from that of tuberculosis.

## Cytomegalovirus Infection
[391]

The increase in renal transplantation with attendant immunosuppression has resulted in a considerable increase of cytomegalovirus infection which previously was rarely encountered in the kidney. It is thought that immunosuppression activates latent virus infections.

In our 131 cases of needle and surgical biopsies, nephrectomy specimen, and autopsy material from renal transplantats, we were able to demonstrate cytomegalovirus histologically only once, even though the virus had been demonstrated in the urine of three patients.

Great care must be exercised in trying to demonstrate the virus-induced cell giants histologically (high magnification, control of suspicious cells with oil immersion) since usually only a very small number of cells is infected. The infected cells are enlarged and usually project into the tubular lumen. They contain up to 15 µm large acidophilic inclusion bodies in cytoplasm and nuclei (Fig. 21.7).

A perifocal lymphoplasmocytic infiltrate may be absent. The DNA virus can be demonstrated unequivocally in the kidney with EM [791, 796] and cytomegalovirus-infected cells can also be found in the urine with JF.

In a newborn with severe cytomegalovirus infection, we found segmental-focal necrotizing GN. Podocytes and endothelial cells had undergone extensive transformation into giant cells (Fig. 21.8).

# 22. Hydronephrosis and Nephrohydrosis

## Definitions

Hydronephrosis refers to a widening of the renal pelvis due to impairment of urinary flow in the urinary tract. Nephrohydrosis means tubular dilatation due to impairment of urinary flow.

## Incidence

We have found the conditions present in 4% of our autopsy material (see Table 22.1). There is no preference for laterality or sex.

## LM Findings

In nephrohydrosis (Fig. 22.1), all tubular segments may be dilated, while the tubular morphology in hydronephrosis—also without concomitant inflammation (pyelonephritis)—is not uniform. Nephrons, especially in the cortex, may be unchanged, collapsed or dilated. The latter are lined by an atrophic epithelium (Fig. 22.2).

The hydronephrotic "sac" kidney consists almost exclusively of these atrophic nephrons in addition to sclerotic connective tissue. The collecting ducts are already dilated in the early stages of impaired urinary flow (Fig. 22.3).

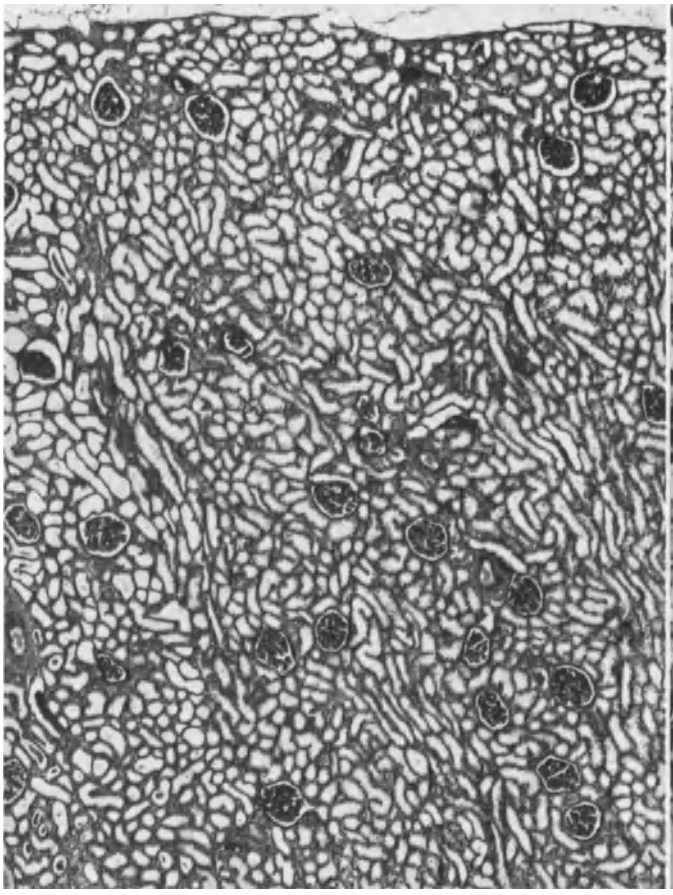
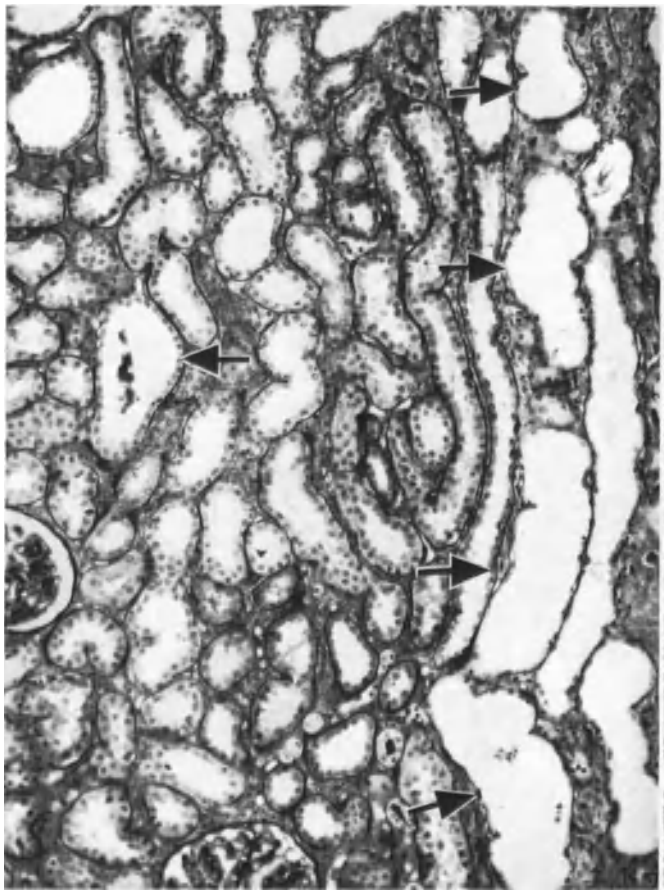
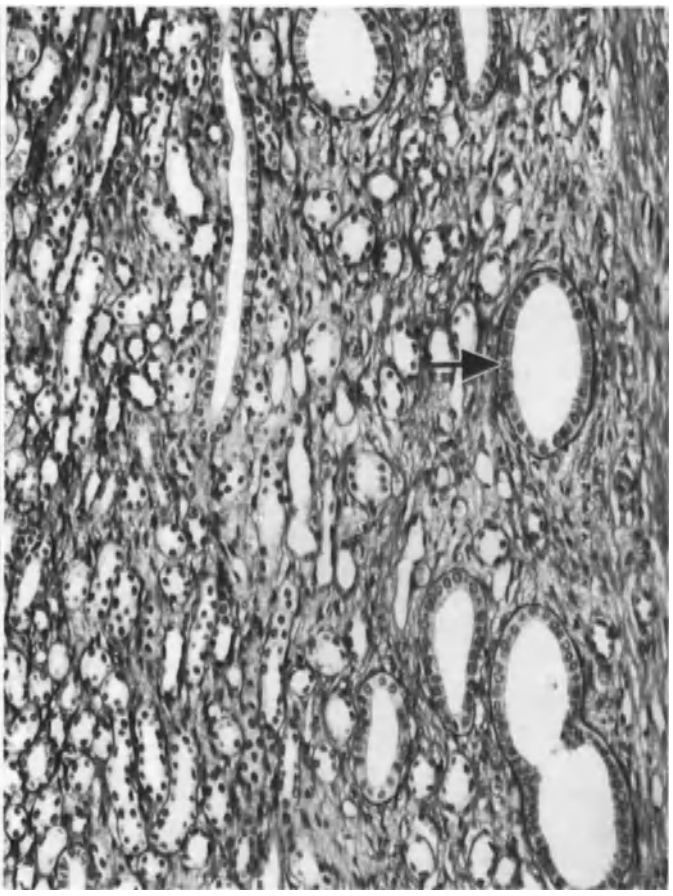


**Fig. 22.1.** Nephrohydrosis associated with compression of the ureter by an aberrant vessel. All the tubules are dilated. Female, 34 years. PAS (×30)

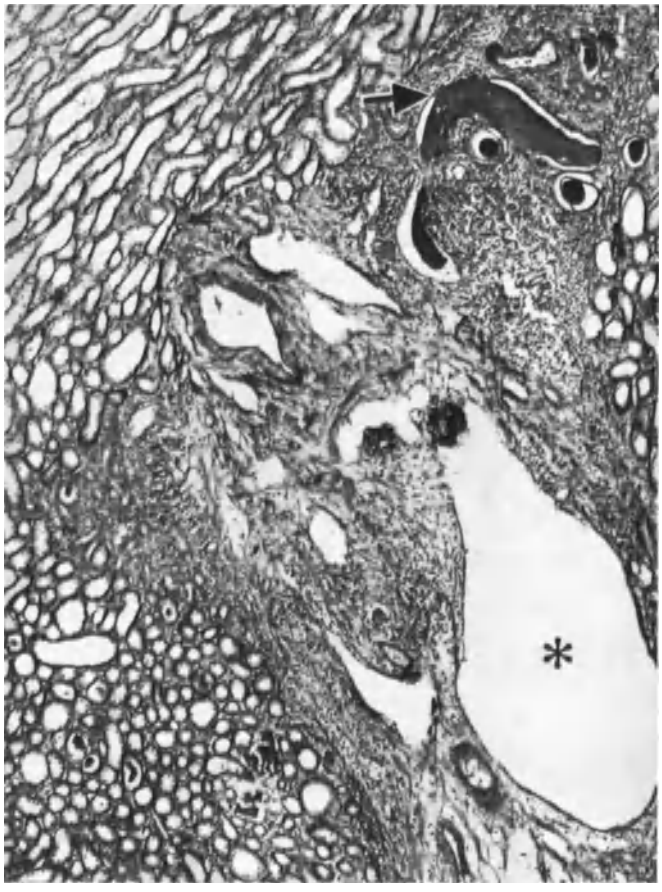
**Fig. 22.2.** Hydronephrosis associated with renal pelvic stone. Tubules show unequally distributed luminal dilatation. Female, 36 years. PAS (×170)



22.3



22.4




22.5

**Fig. 22.3.** Dilated collecting ducts (→) in hydronephrosis due to rectal carcinoma. Female, 72 years. PAS (× 140)

**Fig. 22.4.** Hydronephrosis. Collecting ducts are dilated and their nuclei are densely packed (→) as result of proliferation. Stroma is considerably increased and sclerosed. Female, 1 year. PAS (× 220)

**Fig. 22.5.** Lymph vessel dilatation, (*) and lymph vessel casts (→) in hydronephrosis due to scarring at the pyeloureteral junction. Male, 32 years. PAS (× 55)

Even in fairly advanced cases, glomeruli show no essential changes. Glomeruli undergo obsolescence in the terminal phase of the disease only.
The interstitium shows spotty sclerosis which, in severe parenchymal atrophy, becomes diffuse. The sclerosis is probably the consequence of edema which occurs in the acute phase of hydronephrosis.
The arteries do not demonstrate any characteristic changes. The veins are regularly dilated. The lymphatic vessels are also frequently dilated and lymphatic casts—surrounded by plasmo-lymphocytic infiltrates—are encountered now and again (Figs. 8.36, 8.37, 8.38, 8.39, 8.40, 22.5).
Dilated collecting ducts are especially prominent in the renal medulla and lined by an epithelium with normal internuclear distance. Accordingly, tubular cell proliferation must have occurred (Fig. 22.4). With increasing severity of hydronephrosis, at first atrophy of the papillae and medulla, and, lateron of the cortex, develops.
The histologic findings in animal experiments show the same characteristic morphologic variability [196, 704, 727, 1493].

## EM Findings

The epithelium of the dilated tubule is flattened. The proximal tubules evidence extensive loss of the brush border (Fig. 22.6). The basal labyrinth of proximal tubules (convoluted and straight parts) is sometimes absent. The cell organelles (mitochondria, lysosomes, microbodies, etc) show no special features. On the cell base of the proximal tubules, some finely fibrillar bundles within the cytoplasm are regularly encountered which, according to findings from animal experiments, probably correspond to actomyosin fibrils [378, 1374].
Tubular epithelial cells with cytologic signs of regeneration, i.e., large, irregular nuclei, numerous ribosomes but few other cytoplasmic organelles are also frequently observed (Fig. 22.7) (for findings in animal experiments see [378, 379]).

## Differential Diagnosis

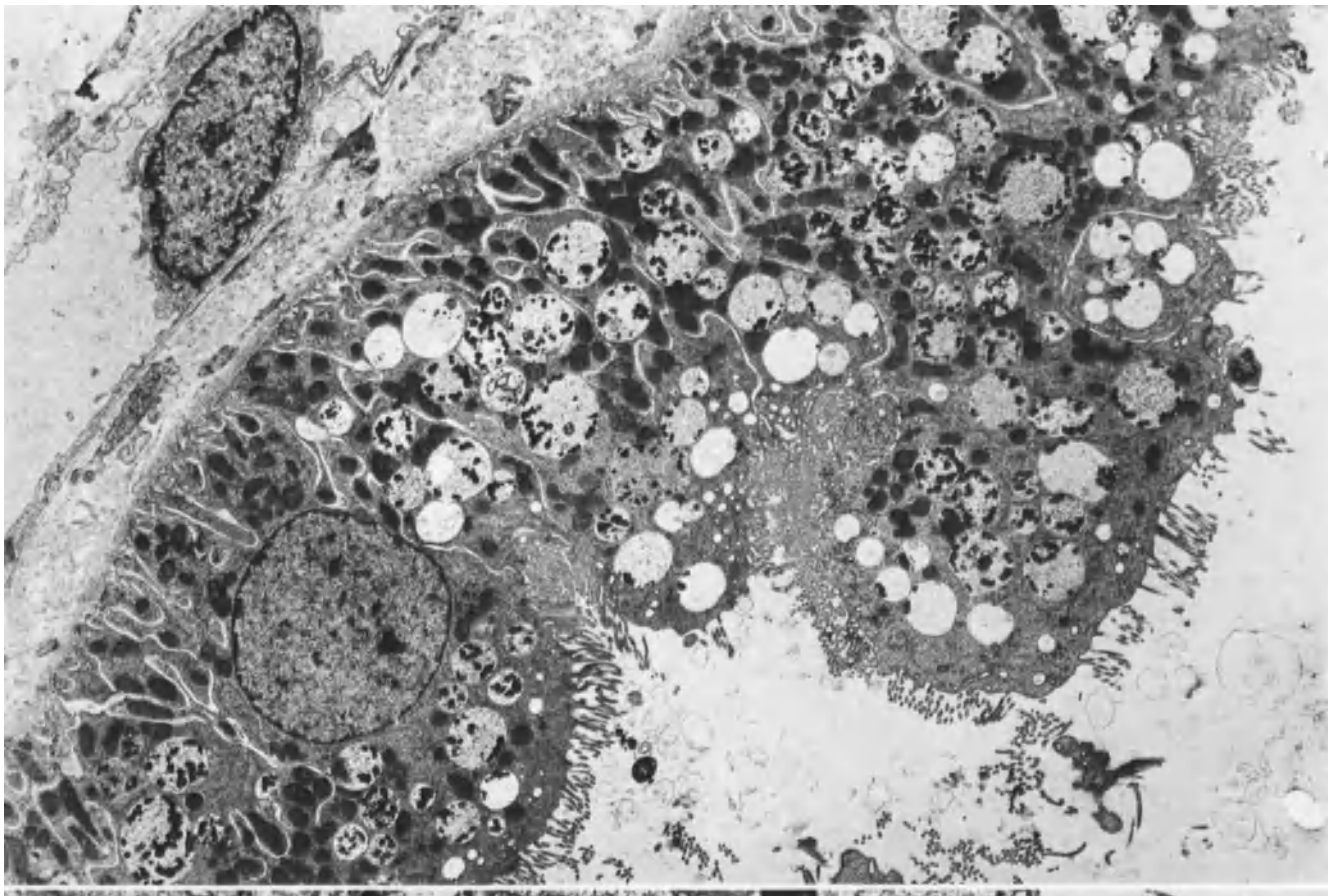
LM findings, which are variable, are not sufficiently characteristic to permit diagnosis from biopsy material (see [704]). If only the features of nephrohydrosis are present in needle biopsy, the possibility of a so-called shock kidney must also be considered. Differentiation between these two conditions on the basis of tubular morphology is not possible with either LM or EM, and especially not in the clinically important acute phase i.e. tubular dilatation, epithelial flattening and dedifferentiation are common to both conditions. Neither do glomerular, interstitial or vascular changes permit differentiation in the acute phase (interstitial edema is present in both conditions). The only possiblity of differentiation is the chance finding of lymphatic casts which, unfortunately, are nearly always absent in the acute phase.
Hydrocalicosis may prove difficult to differentiate from hydronephrosis. It can only be diagnosed with reliability in open surgical biopsies as only a very small part of the parenchyma—which exhibits extensive atrophy and secondary widening of the calyx lying underneath (Fig. 5.11) bordered by unchanged renal tissue—is affected.

## Prognosis

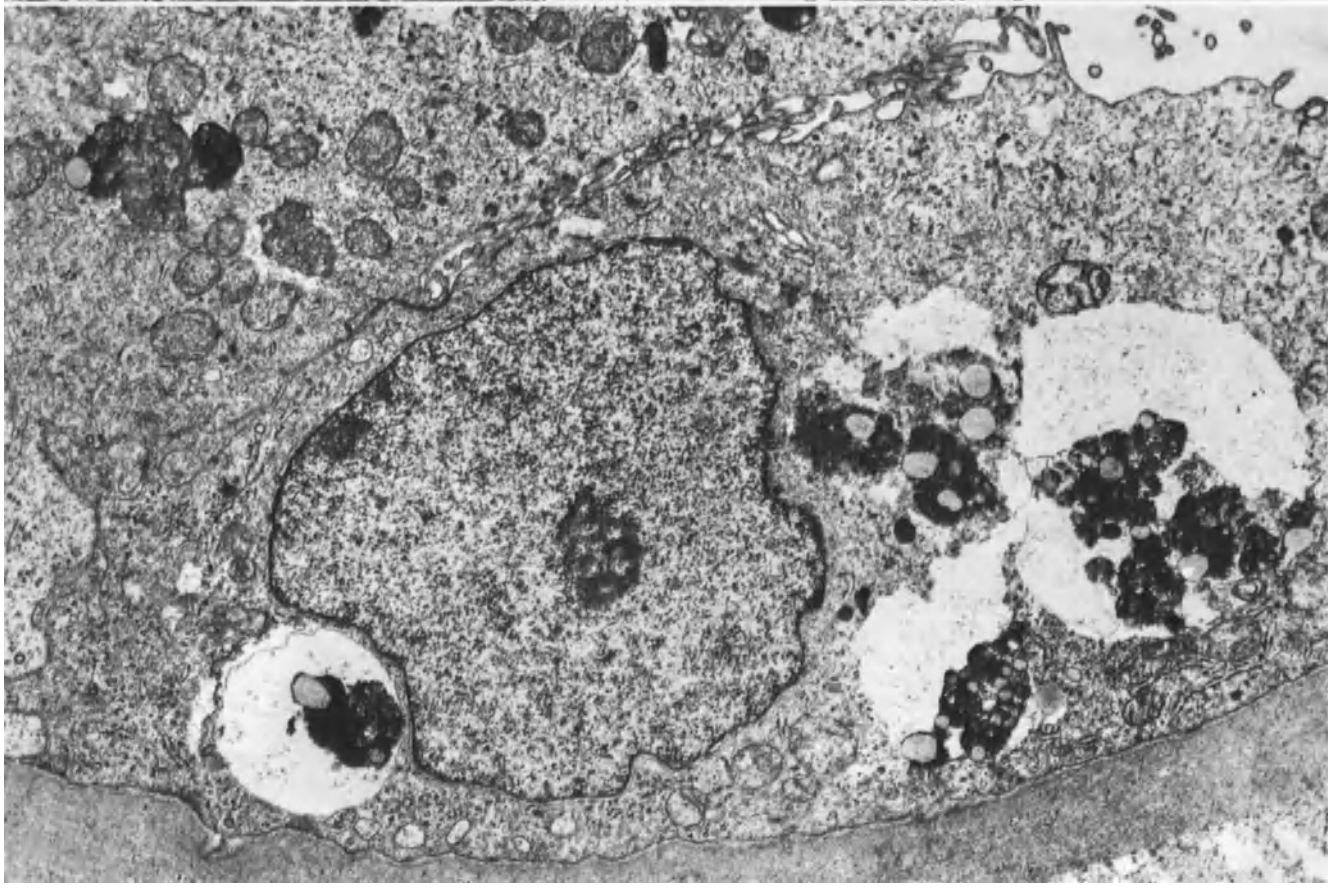
The prognosis depends by and large on the extent of interstitial fibrosis and architectural destruction. Total obstruction lasting up to 3 weeks may resolve with nearly complete recovery of renal function [143, 406]. Even after years of disease, functional improvement is still possible.
It has been shown experimentally that functional improvement is inversely proportional to the extent of irreversible parenchymal atrophy which itself is directly dependent on the duration of impaired urinary flow. The reversibly injured nephrons show progressive functional improvement following removal of the obstruction [725, 726].

**Fig. 22.6.** Proximal tubule as seen in acute urine retention due ▷ to renal pelvic stones. There is shortening and partial loss of brush border of proximal tubules which also show masses of lysosomes containing protein and lipid. Female, 36 years. EM (×3730)

**Fig. 22.7.** Regenerative tubular epithelium following acute urinary stasis. There are only a few organelles in the epithelial cell, the brush border of which is considerably reduced. Nucleus is lobulated and ribosomes are increased. Basal labyrinth is absent. Note numerous hetero-(phago-)lysosomes with chromoprotein (fortuitous finding). Male, 36 years. EM (×10,300)



22.6



22.7

Table 22.1. Frequency and etiology of hydronephrosis based on 27,570 autopsies with 1110 cases of hydronephrosis (4%) of which 136 (12%) with uremia

| Etiology | Total | | With uremia (n=136=100%) |
|---|---|---|---|
| | n | % | % |
| Malignant tumors of the urinary tract or others with obstruction of the ureter | 479 | 43.1 | 51.5 |
| Lithiasis | 180 | 16.2 | 18.4 |
| Myoglandular prostatic hyperplasia | 142 | 12.9 | 13.5 |
| Aberrant vessels with kinking of ureter | 53 | 4.8 | – |
| Malformations of urinary tract | 45 | 4.0 | 4.3 |
| Radiation injury | 39 | 3.5 | 1.2 |
| Ventil stenosis of ureter | 33 | 3.0 | – |
| Prolapse or fibro-leiomyoma of uterus | 27 | 2.4 | 1.8 |
| Cystic ureteritis | 11 | 1.0 | 0.6 |
| Miscellaneous (operation injury, parasites, etc.) | 11 | 1.0 | 3.0 |
| Unknown | 90 | 8.1 | – |
| Total | 1.110 | 100% | |

## Pathogenesis

Several pathogenetic factors are implicated in the parenchymal atrophy and limited functional capability. Experimentation has revealed a decrease of glomerular filtration pressure 24 h after occlusion of the ureter which is comparable to that occurring in increase of preglomerular resistance. In long-lasting occlusion, total renal blood flow decreases [759, 1165, 1178, 1587]. Histochemical and biochemical studies indicate that ischemia plays an essential role in parenchymal atrophy in that the parenchyma shows a decrease in oxydative metabolism [1436, 1628].

A further pathogenetic factor is the stretching of renal tissue which is a consequence of the progressive filling of the renal pelvis with urine. For this process, filtering glomeruli must still be present and the pressure in the renal pelvis must not exceed the filtration pressure of these nephrons [196].

Indirect confirmation of continuing filtration is resorption of urine from the renal pelvis in the presence of complete ureteral occlusion, as demonstrated experimentally.

## Etiology

The most frequent cause of hydronephrosis (Table 22.1) is stenosis of the urinary tract by tumors, lithiasis and prostatic hyperplasia (>70%) which also represent the major causes in cases with uremia (>80%). All other causes are considerably less frequent. The occlusion is generally incomplete [196, 1791].

A rare cause of hydronephrosis is inadvertent ureteral ligature during abdominal surgery, reported to occur in 2% of emergency gynecologic operations [143]. Since the exact time of uretral occlusion is known, the regenerative capacity of the kidney can be evaluated with exceptional reliability in such cases.

# 23. Enzymopathic and Metabolic Renal Diseases

In this chapter, all diseases will be discussed which are proven to be or are probably due to enzymopathies which involve the kidney primarily or secondarily.
From the nosologic standpoint, systemic enzymopathies and purely renal entities may be distinguished. Among the many diseases encompassed under the term enzymopathies, only those have been selected for discussion which are significant for renal biopsy and which lead to progressive renal injury. All other related diseases are synoptically summarized in Table 23.1.

## Fabry's Disease
[298, 395, 884, 1235, 1375]

### Definition

Renal lesions in Fabry's disease (ceramide storage disease).

***Synonym:*** Angiokeratoma corporis diffusum.

### Clinical Findings

Fabry's disease is a rare familial lesion, inherited via the x-chromosome, leading to renal death chiefly in men in their forties. Subcutaneously, numerous dark red to blackish nodules—already present in childhood—are found mainly between the knees and navel. These nodules correspond to phlebectases (angiokeratomas). Corneal opacity may be the initial symptom presenting in childhood [298]. Patients complain of pain in the hands and feet and of a reduction in sweating [298]. Isolated hematuria is occasionally encountered. Later—and especially in men—massive renal symptoms appear (edema, anemia, hypertension, azotemia).
The demonstration of the characteristic foam cells is possible in urine [395] as well as in biopsy material from the rectum, i.e., Meissner's plexus [395] and epithelial cells [66]; liver and spleen [1621], lungs [66] and from bone marrow [298].

### LM Findings

In the early phases of the disease, i.e., before the beginning of renal insufficiency, the histologic findings are highly characteristic. In addition to unspecific glomerulonephrosis, many cells are transformed into foam cells throughout the kidney, e.g., podocytes, parietal epithelium (Fig. 23.6), distal tubular epithelium and epithelium of Henle's loop, and also in the endothelium of glomeruli, intertubular capillaries and large vessels, in the smooth muscle cells of arteries [297] and in the interstitium [1235].
The stored material is slightly sudanophilic, birefringent, PAS-positive and luxol-fast-blue positive [395, 1004].
In the late phase of the disease, secondary reactive changes—analogous to Alport's disease, primary oxalosis, etc.—occur. They chiefly affect the glomeruli and lead to synechia formation (Fig. 23.7), segmental capillary loop and later to global glomerular obsolescence. The interstitium is severely widened and loosely infiltrated with lymphocytes which, in severe contracted kidney, may be completely absent (own observation, see also [217]).
We are not aware of any reports on IF findings.

### EM Findings

Foam cells are the only specific findings which—apart from localizations described with LM—are also found in the straight part of the proximal tubules and in the glomerular capsular space [1004]. They contain irregular, lamellated osmiophilic inclusions as well as irregular granules [1235] and fibrils with a periodicity of 50–60 Å [66, 395, 1004]. In general, these inclusions of ceramide trihexose are surrounded by a triple membrane.

### Differential Diagnosis

The clinical picture and histochemistry (in the case that part of the biopsy material was fixed in nonlipid-soluble fixatives) are highly characteristic, but allow only a conditional differentiation between the Fabry, Gaucher and Niemann-Pick diseases. Ultimate diagnosis should always be based on the biochemical demonstration of the enzyme deficiency.

Table 23.1. Enzymopathic renal disease

| Disease | Enzyme defect | Stored material/ pathologically increased serum metabolites | Renal findings | |
|---|---|---|---|---|
| | | | Clinical | Morphologic |
| Ochronosis alcaptonuria | Homogentisic acid oxidase deficiency | Homogentisic acid polymers Ochronosis pigment | Homogentisinuria Dark urine | Pigment deposition in convoluted and straight segments of proximal tubules; collecting ducts, interstitial cells, blackish-brown casts, accompanying IN [1236, 1791] |
| Homocystinuria | Deficiency in synthesis of cystathionine | Homocystinemia Hypermethioninemia | Homocystinuria | PN, frequent thrombo-embolic complications [252a] |
| Glycogenosis type I (hepatorenal glycogenosis) – van Gierke type | Glucose-6-phosphatase deficiency | Normal glycogen | Secondary Fanconi syndrome [906a] | Glycogen storage (Figs. 23.3, 23.4, 23.5) in glomeruli, proximal and distal tubules, vascular endothelium, smooth muscle [252, 906a] |
| Glycogenosis type II (generalized glycogenosis) – Pompe type | α-1,4 glucosidase deficiency | Normal glycogen | – | Lysosomal glycogen storage (Figs. 23.3, 23.4, 23.5) in proximal and distal tubules, glomeruli (endothelium, epithelium, mesangium) and in interstitium [209, 528, 692, 724] |
| Mucopolysaccharidosis types I–III | ? | Dermatan-heperan sulfate | Aminoaciduria [1446] | Podocytic foam cells, storage vacuoles with membrane-like content in distal tubules and collecting ducts [692, 864, 1322, 1684, 1755] |
| Gaucher's disease | Glucocerebrosidase deficiency | Glucocerebroside | – | Gaucher's cells in glomeruli, mesangial storage cells [198, 492, 692, 1369] |
| Metachromatic leukodystrophy | Sulphatase, β lactosidase | Sulfatides Gangliosides Sulphated mucopolysaccharides | – | Storage vacuoles with metachromatic contents in distal tubules and Henle's loops [692, 1322] |
| Niemann-Pick's disease | Sphingomyelinase deficiency | Sphingomyelin Cholesterol | Proteinuria [1780a] | Foam cells of glomerular endothelium, tubules, capillary endothelium, interstitial cells [329] |
| Wolman's disease | Acid esterase defciency (acid lipases) | Triglycerides Cholesterol (among others) | – | Glomerular endothelial foam cells, interstitial foam cells [692, 1303] |
| Plasma cholesterol deficiency | Lecithin, cholesterol-acyltransferase deficiency | Hyperlipemia Lecithinemia Glycerinemia | Proteinuria Erythrocyturia Uremia possible | Glomerular endothelial foam cells [557a] |
| Refsum's disease | Phytanic acid hydroxylase deficiency | Phytanic acid | Lipiduria [1334] Aminoaciduria [54a] | Chemically demonstrated [792] |

Table 23.1 (continued)

| Disease | Enzyme defect | Stored material/ pathologically increased serum metabolites | Renal findings | |
|---|---|---|---|---|
| | | | Clinical | Morphologic |
| Mucolipidosis type II (*I*-cell disease) | Decrease of acid hydrolases | Mucopolysaccharides | – | Podocytic foam cells, vacuolized interstitial fibroblasts [692, 1621] |
| Mucosulfatidosis | – | Mucopolysaccharides Sulfatides | – | Storage vacuoles in distal tubules and interstitital cells [692, 1322] |
| Fucosidosis | α-fucosidase deficiency | Fucose-containing lipids and glycoproteins | – | Podocytic foam cells occasionally with weakly PAS-positive contents [692, 405a] |
| $GM_1$-gangliosidosis types I and II | β-galactosidase deficiency | $GM_1$-ganglioside and asialo derivatives keratan-sulphate-similar mucopolysaccharides | Aminoaciduria glucosuria [1097] | Foam cell: podocyte (Figs. 23.1, 23.2) endothelium, mesangial cells, smooth muscle of the arterioles, proximal tubules [692, 1097] |
| $GM_2$-gangliosidosis type II (Sandhoff's disease) | Hexosaminidase deficiency | Trihexosylceramid $GM_2$-ganglioside Globoside (among others) | – | Storage vacuoles in tubules [692] |

### Prognosis

The prognosis is poor for men. Renal failure is the most frequent cause of death. In one of our cases, there was no relapse of disease 16.5 months following renal transplantation (see also [217]). In the literature [604, 1261], 4 out of 10 transplant cases are reported to be surviving without disease relapse and with great improvement of the overall disease. The primarily absent enzyme (see below) is said to reappear in the serum (see also [284a]), but this claim has been disputed [1605a].

### Pathogenesis

The glycolipid, ceramide (trihexoside- and digalactosyl ceramide), cannot be split from the trihexose because of congenital absence of ceramide trihexosidase [66, 1261]. The content of tri- and dihexoses is more than 10-fold greater in the diseased kidney than in the normal [1235]. Glomerular foam cells as well as arterial and arteriolar occlusion by foam cells gradually lead to glomerular collapse and progressive obsolescence.

## Cystinosis
[1444]

### Definition

Cystinosis is an inherited disease characterized by impairment of cystine metabolism with storage of cystine crystals in the RHS and kidney.

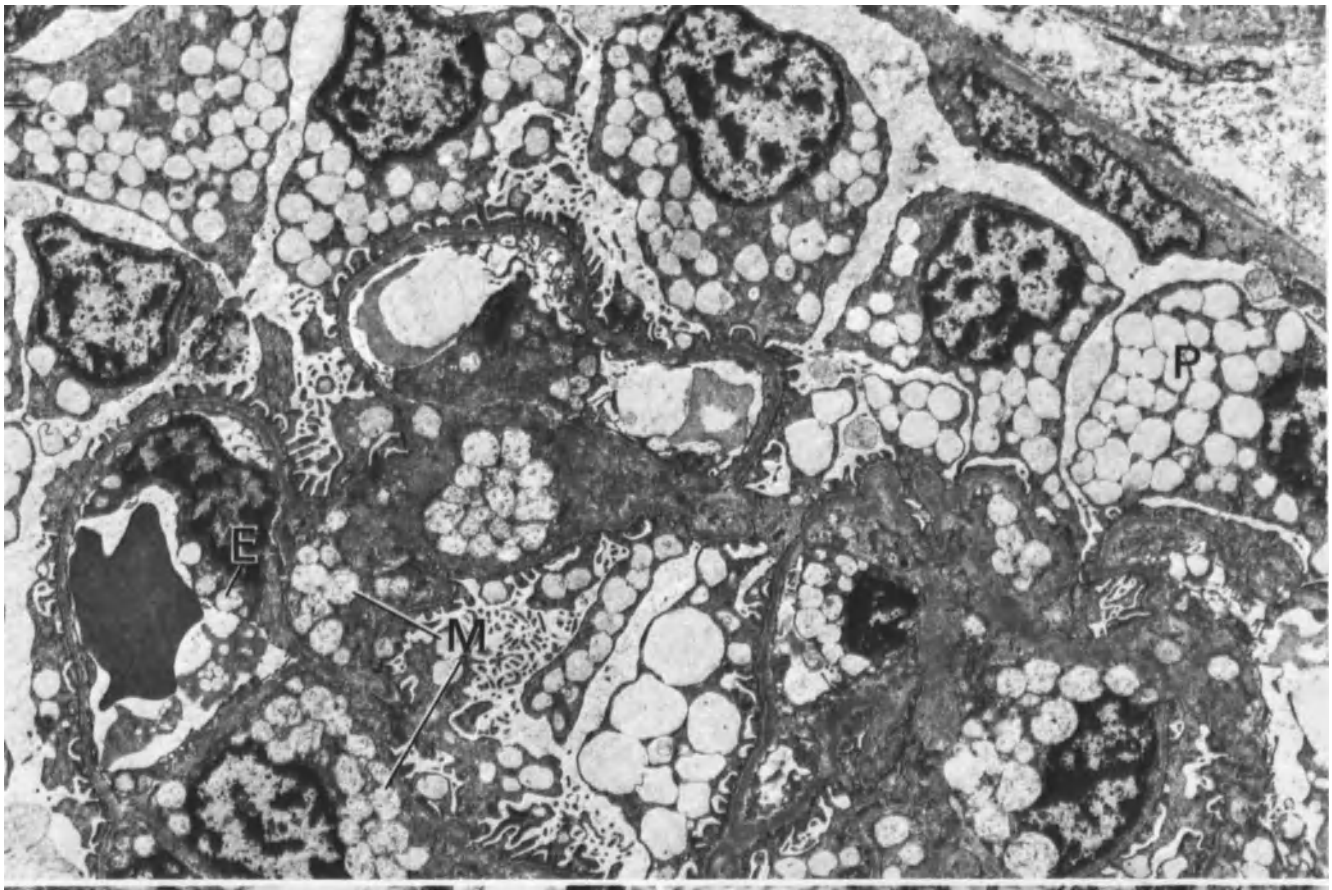
***Synonym:*** Lignac-de Toni-Fanconi-Debré syndrome.

### Clinical Findings

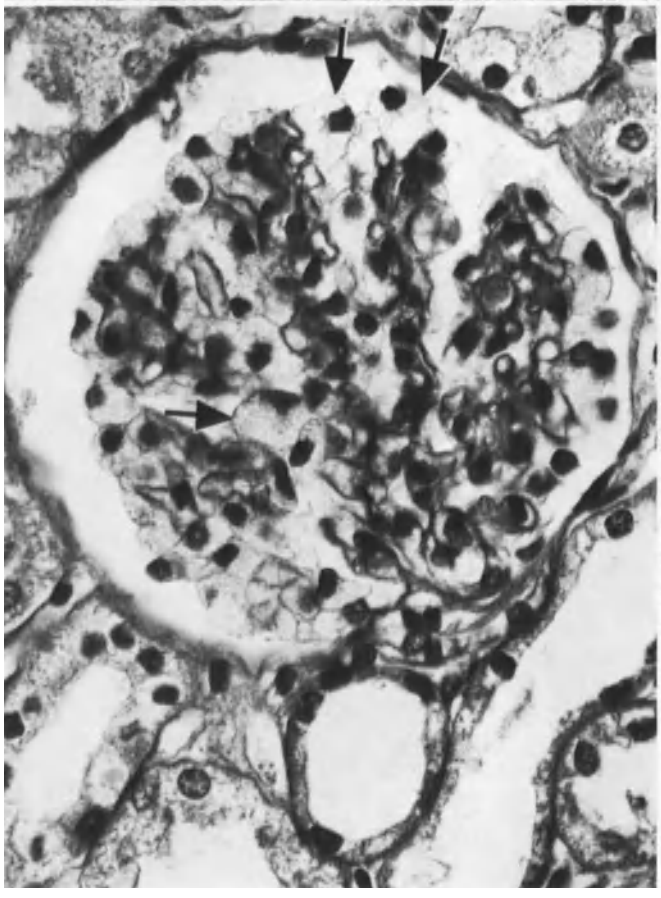
Cystinosis is a rare, recessively inherited disease whose severity varies from case to case. Three forms can be recognized on the basis of the cystine content of leukocytes [1444].

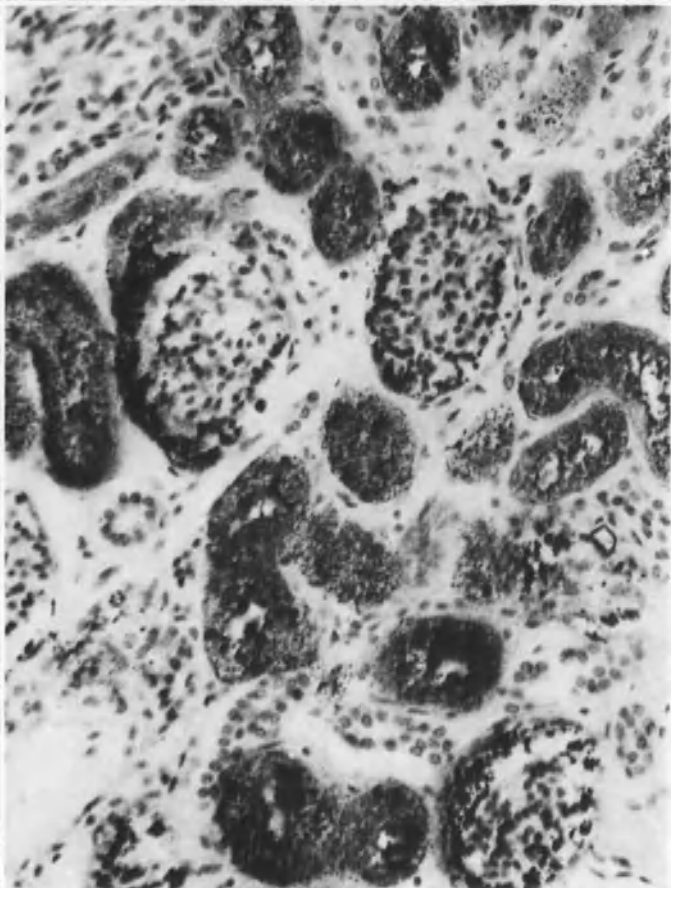
*1. Severe form:* The severe form leads to death in uremia within the first decade of life. The leukocytes contain 80–100 times more cystine than normal.

*2. Moderately severe form:* Patients survive up to the second and third decades of life. The cystine content of the leukocytes is 30–50 times greater than normal.




23.1






23.2
23.3

*3. Mild form:* This form is less frequent. There are no renal cystine crystals and the cystine content of leukocytes is only about 5–6 times greater than normal.

In severe cases, the Fanconi syndrome with aminoaciduria, phosphaturia, glucosuria and, usually, with impaired potassium and bicarbonate and rarely uric acid reabsorption, is generally already manifest in the first year of life. The first clinical symptoms are polyuria and polydipsia. Rickets accompanied by retarded growth, metabolic acidosis and photophobia are also present.

The clinical diagnosis in the severe form is easy since slit-lamp eye examination quickly identifies the reflecting crystalline deposits in the conjunctiva, iris and cornea. The right-angled or hexagonal cystine crystals are also demonstrable in biopsy material from bone marrow, gastrointestinal tract, lymph nodes and kidney. Since the cystine crystals are water soluble, tissue must be fixed in alcohol.

## LM and EM Findings

The pathology of cystine storage disease has received repeated and extensive attention ([61, 622a]; EM: [758, 968, 1384, 1459]; 16 original autopsy cases: [1791]).

In the early stages of the disease, the glomeruli – with the exception of a few but inconstantly present multinuclear podocytic giant cells and several strikingly small fetal glomeruli – are unchanged. The tubuli are normal (Figs. 23.8, 23.9). The interstitium is slightly fibrosed, somewhat loosened by edema and contains a few cystine crystals surrounded by lympho-histiocytic infiltrates.

With increasing severity of the disease, there occurs a slight thickening of the mesangium without cellular increase, as well as slight loop collapse in the glomeruli [758]. Finally, focal-segmental glomerular obsolescence, scattered segmental crescents over collapsed capillary loop segments, and completely obsolescent glomeruli develop (see also [662a]).

In later stages, tubular and interstitial changes tend to be more pronounced than those of the glomeruli. The tubules – especially the proximal and distal convolutes – are partially markedly widened and lined by a flattened epithelium. The tubular nuclei are sometimes strikingly polymorphic, and tubular multinuclear giant cells are frequently encountered. These swan neck-like changes of the proximal tubules (Fig. 23.8; [287]) are not to be interpreted as the cause but as the consequence of the renal changes; they occur with increasing frequency as the disease becomes more severe. Necroses and mitoses are rarely encountered in the dilated tubular sections (own observation; [758]). We have found vacuolization of tubular epithelium in contracted kidneys only. Such vacuolization is probably the consequence of the attendant hypokalemia. Atrophic tubules with thickened BM are also found [758].

◁ **Fig. 23.1.** GM-1 gangliosidosis. There are predominantly mesangial (*M*), and podocytic (*P*) and, less frequently, endothelial (*E*) foam cells. Male, 2 years. EM (×3100)

**Fig. 23.2.** GM-1 gangliosidosis. Numerous podocytic foam cells (→). Mesangium and capsule are unchanged. Male, 2 years. CAB (×730)

**Fig. 23.3.** Glycogenosis, Pompe type. Massive glycogen storage in tubular cells and capsular epithelium. Male, 3 years. Best's glycogen (×200)

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**Fig. 23.4.** Same case as in Figure 22.3, showing straight parts of proximal tubules in glycogen storage disease. Note the lilac pith-like cells. Male, 3 years. HE (1550)

**Fig. 23.5.** Contracted kidney in glycogenosis, type II. Female, 16 years. Van Gieson (×280) (published [1563])

**Fig. 23.6.** Contracted kidney in Fabry's disease. With the exception of capsular epithelium, glomerular cells are intensely swollen, and evidence extremely fine foaminess. Scanty lymphocytic interstitial infiltrates and obvious tubular atrophy are present. Male, 27 years. HE (×280)

**Fig. 23.7.** Same case as in Figure 23.6, showing extensive glomerular obsolescence. No Fabry cells are recognizable. PAS (×100)

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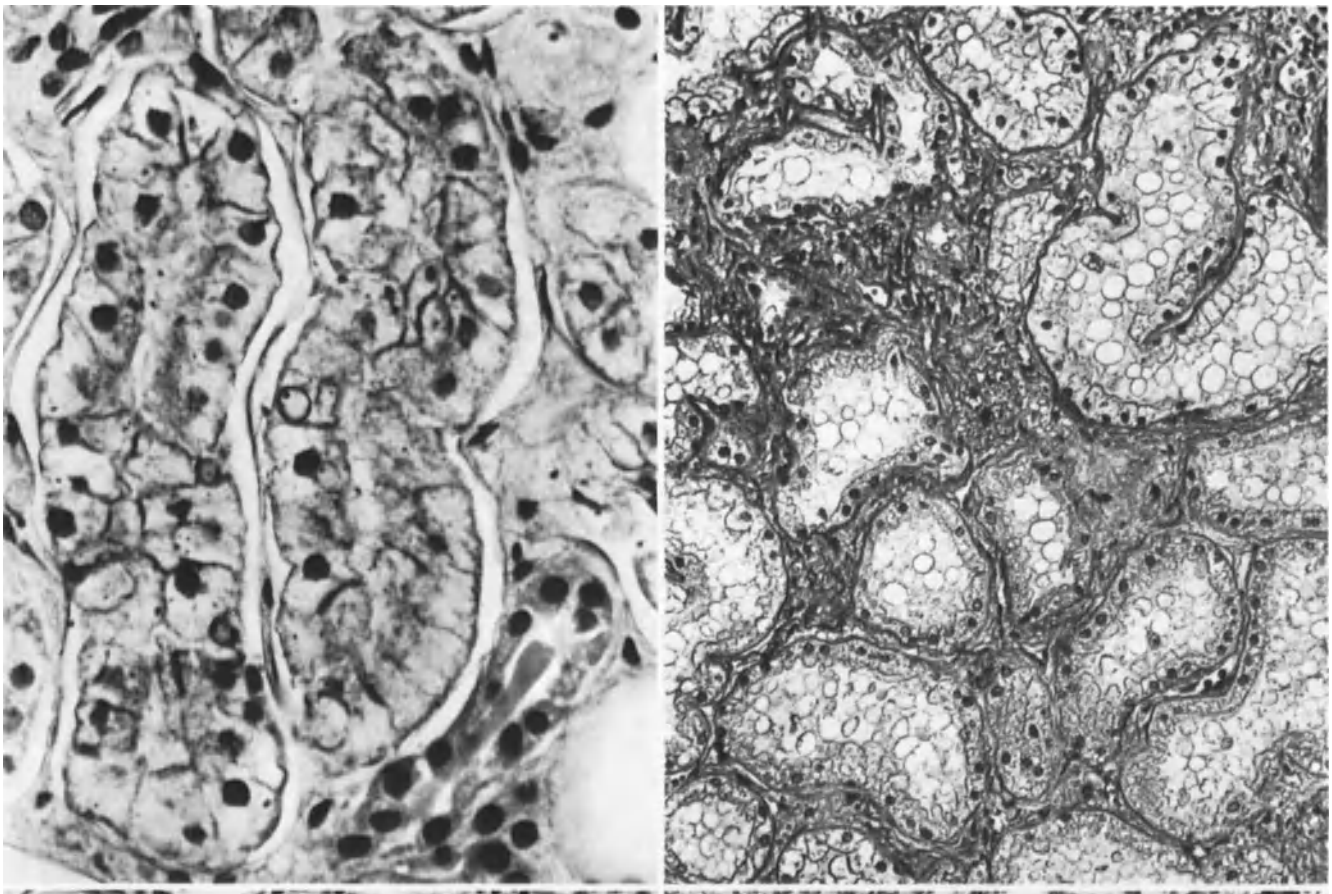
**Fig. 23.8.** So-called swan-neck-like proximal tubule in cystine storage disease. Note focal narrowing (→) of otherwise cystoid distended proximal tubule lined by flattened epithelium. Male, 27 years. HE (×250)

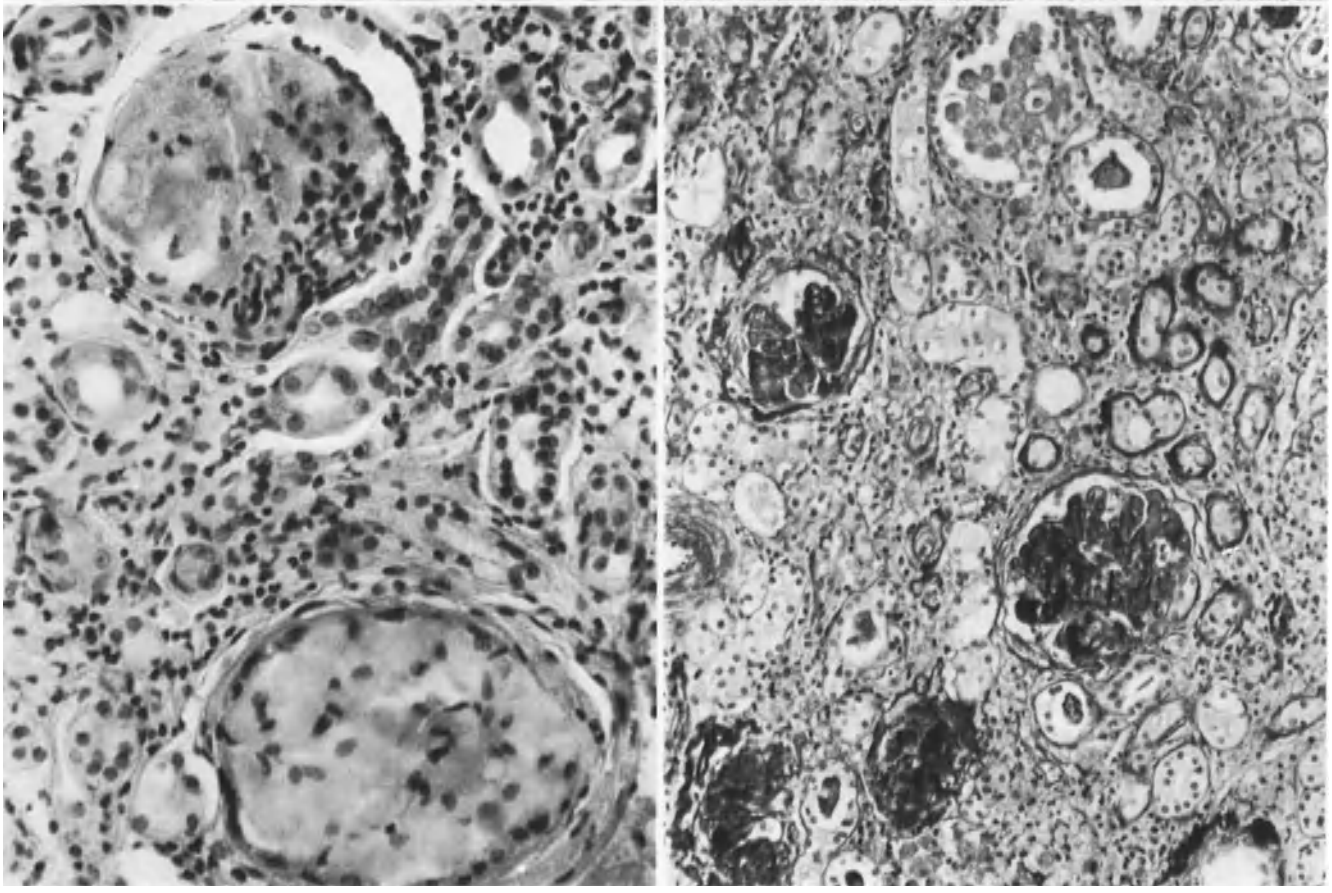
**Fig. 23.9.** Same case as in Figure 23.8, showing deposits of cystine crystals with partial birefringence in renal interstitium. Male, 27 years. HE (×800)

**Fig. 23.10.** Contracted kidney in primary oxalosis in 22-year-old son of the patient presented in Figure 23.12. Massive thickening of tubular BM without recognizable oxalate deposits. HE (×550)

**Fig. 23.11.** Extensive deposits of calcium oxalate crystals in renal medulla in primary oxalosis. Female, 5.5 years. HE (×100)



23.4
23.5



23.6
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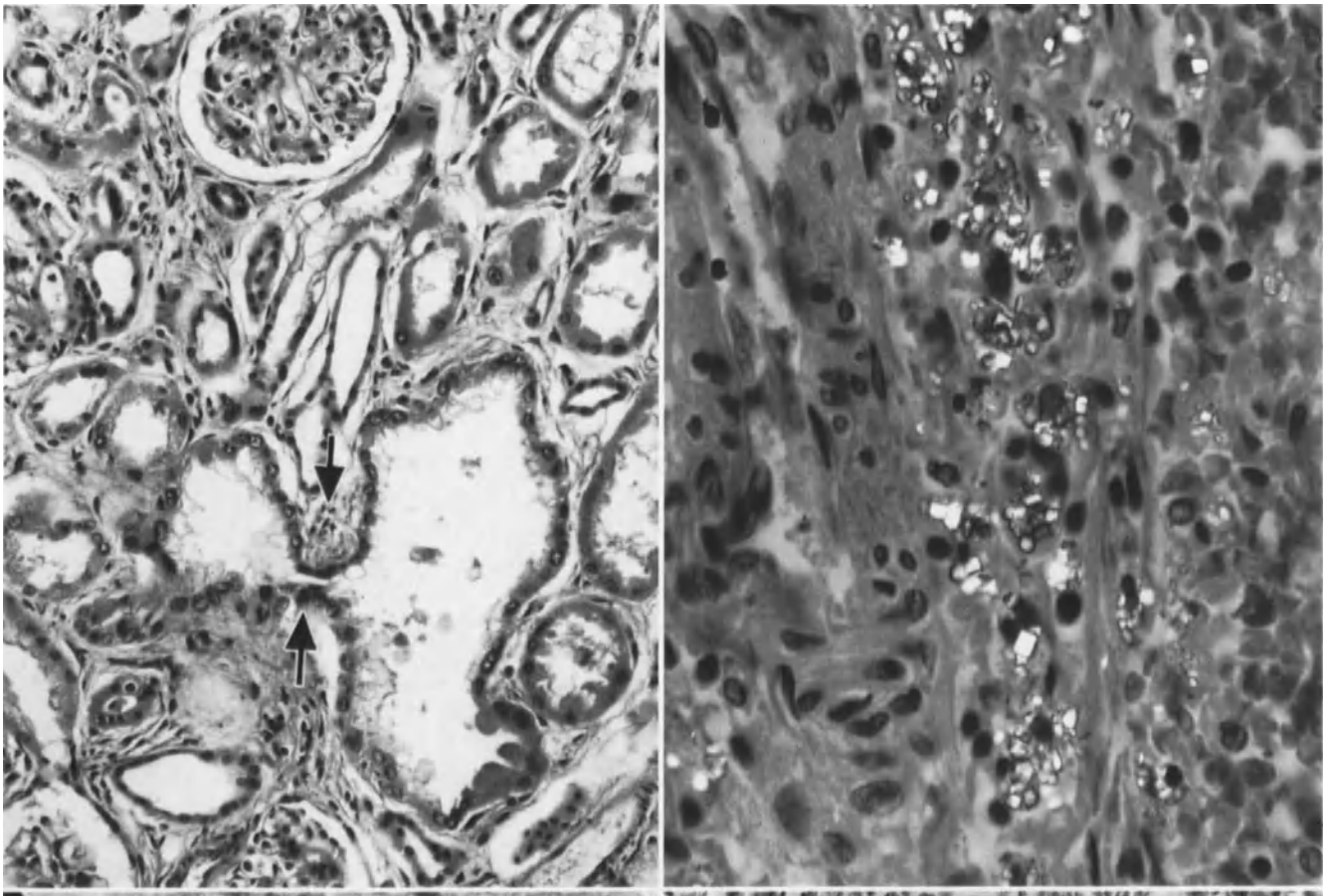
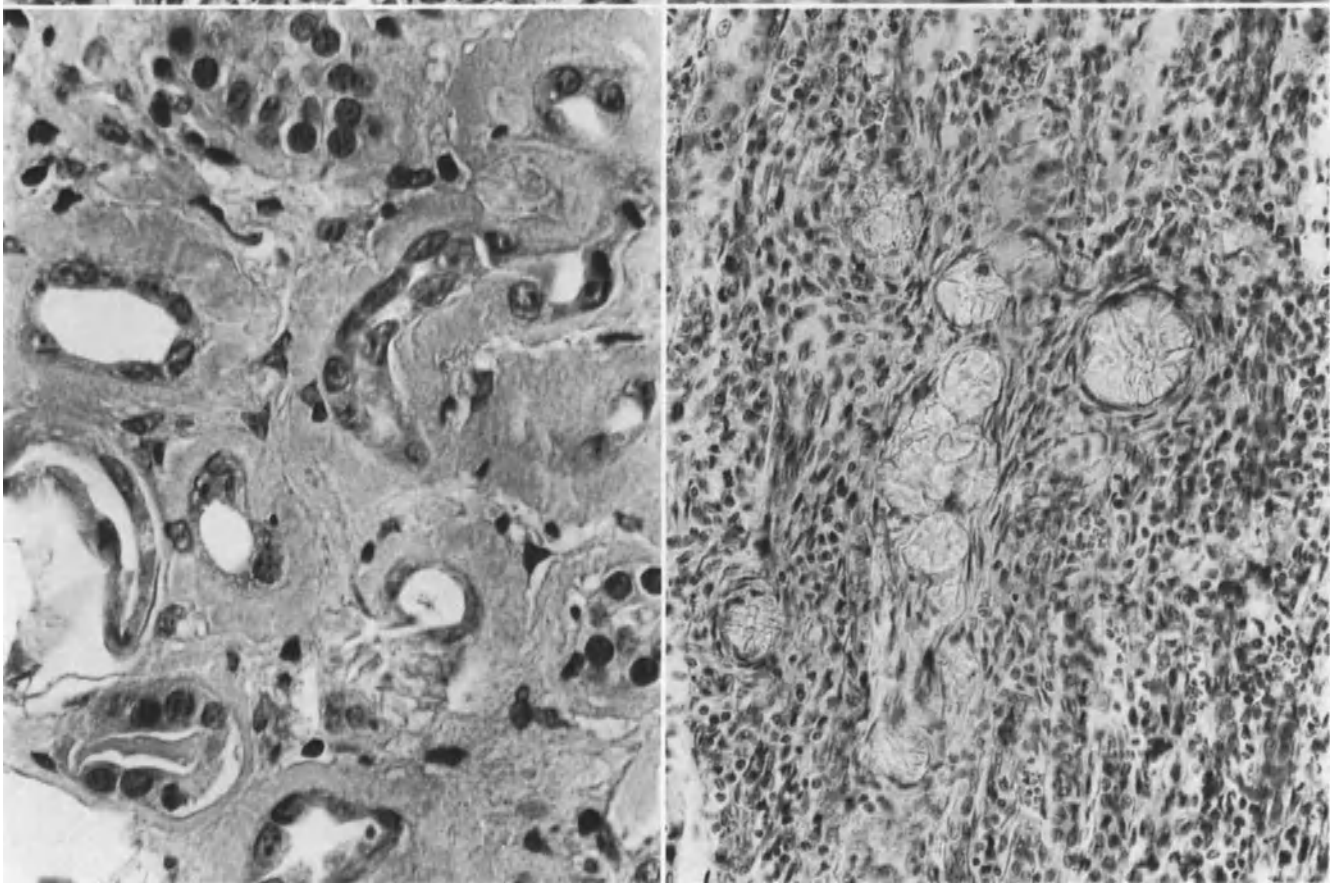


23.8
23.9



23.10
23.11

In the late stages of the disease, the picture is completely dominated by severe interstitial fibrosis which contains focal infiltrates of lymphocytes and histiocytes and, rarely, plasma cells. Additionally, groups of cystine crystals which, as shown in EM examination, lie in unidentifiable interstitial cells, are also found [758]. Cystine crystals in glomerular and tubular epithelial cells are very rarely present (own observation).

### Prognosis

The prognosis is hopeless in all forms of cystinosis which involve the kidney. Removal of cystine from the diet appears to promote the development of children. In renal transplants performed in patients with cystinosis (13 cases so far described), a few interstitial cystine deposits have been demonstrated [649, 930, 977, 1000].

### Pathogenesis

The pathogenesis of cystinosis is still unknown. EM study of various tissues indicates that the crystal formation takes place primarily in the lysosomes in the absence of any demonstrable lysosomal enzyme deficiency [1458]. Accordingly, attention is currently focused on a primary membrane disturbance or on a transmembranous transport impairment of cystine as a possible causes of the disease.
The pathogenesis of the renal symptoms (Fanconi's syndrome) has also eluded clarification. A cystine-caused inhibition of sulfhydryl-group containing enzymes as a result of an increase in cystoplasmic cystine concentration would offer a plausible mechanism [1444].

### Clinical Findings

***Primary Hyperoxaluria, Type I.*** We have encountered this form only rarely in our biopsy material (0.19% of 2080 biopsies). In 3 out of 4 cases, clinical diagnosis preceded bioptic confirmation. The incidence of type I is about the same in both sexes; it follows an autosomal-recessive inheritance pattern [1741]. Usually, the first unspecific renal symptoms appear in childhood and the patients generally die after a 10-year duration of the disease which occurs to 80% of the patients before the age of 20.
In addition to slight proteinuria, microhematuria is usually observed. Uremia can develop so very insidiously that patients first come to medical attention in terminal renal insufficiency. The disease rarely manifests itself with extrarenal symptoms such as total AV-block which we observed in one of our own cases [724a].
In about 50% of the patients, urolithiasis (calcium oxalate) occurring in youth points to the underlying disease. The disease rarely demonstrates a favorable course with renal symptoms first appearing after the age of 40.
In advanced renal changes, crystal deposition is recognizable radiologically by the presence of a fine, dense renal opacity [724a]. Hyperoxaluria may be the only sign of disease uncovered during examination of family members. At autopsy, calcium oxalate deposits in the form of crystals are found in numerous organs [1791, 724a].

***Type II.*** Only a few cases of this form are known [1741]. The mode of inheritance is also probably autosomal recessive.
The clinical picture is dominated by nephrolithiasis and microhematuria. Renal insufficiency apparently does not develop. We are not aware of any published morphologic data.

## Renal Oxalosis
[1337, 1741]

### Definition

Renal oxalosis is a disease characterized by the deposition of calcium oxalate crystals due to either a congenital enzyme deficiency or endo- or exogenous poisoning.

### Nosology

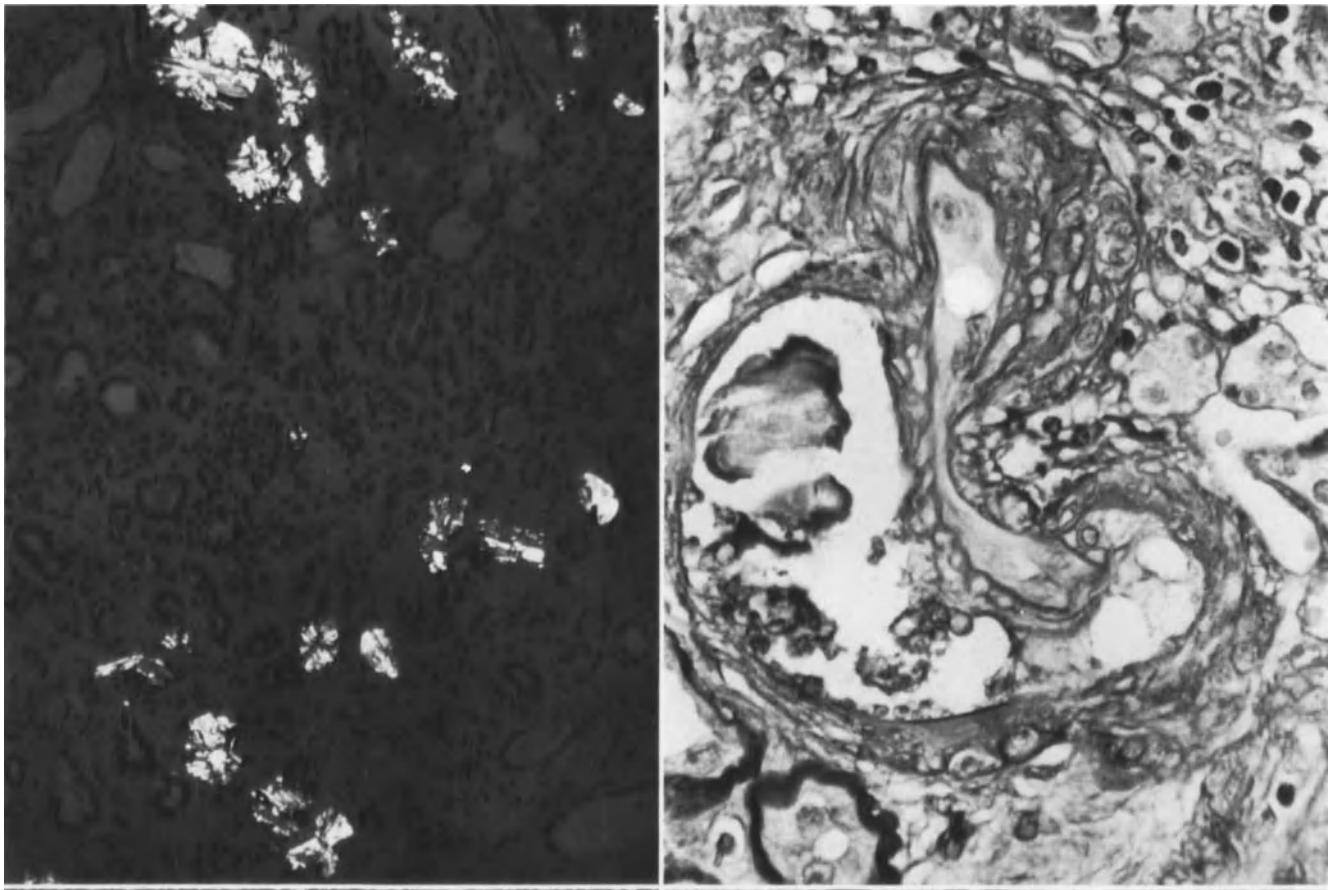
Primary hyperoxaluria (types I and II), and secondary hyperoxaluria in uremia (with severe acidosis), and in poisoning—among other causes—may be recognized.

**Fig. 23.12.** Oxalate crystals seen in birefringence (cf. Fig. 23.10). ▷ Female, 59years. HE (×100)

**Fig. 23.13.** Same case as in Figure 23.10, in which masses of calcium oxalate are seen in arterial wall in primary oxalosis. Male, 22 years. PAS (×400)

**Fig. 23.14.** Massive deposits of calcium oxalate crystals in the capsular space, in a glomerular mesangium and in tubules (*) in a 10-year-old boy with primary oxalosis. Stroma shows intense inflammatory infiltration, and tubules are more or less destroyed. HE (×350)

**Fig. 23.15.** Isolated calcium oxalate crystals in distal tubule. Patient presented with abscessing cholangitis, anuria, and severe acidosis. Female, 63 years. HE (×700)



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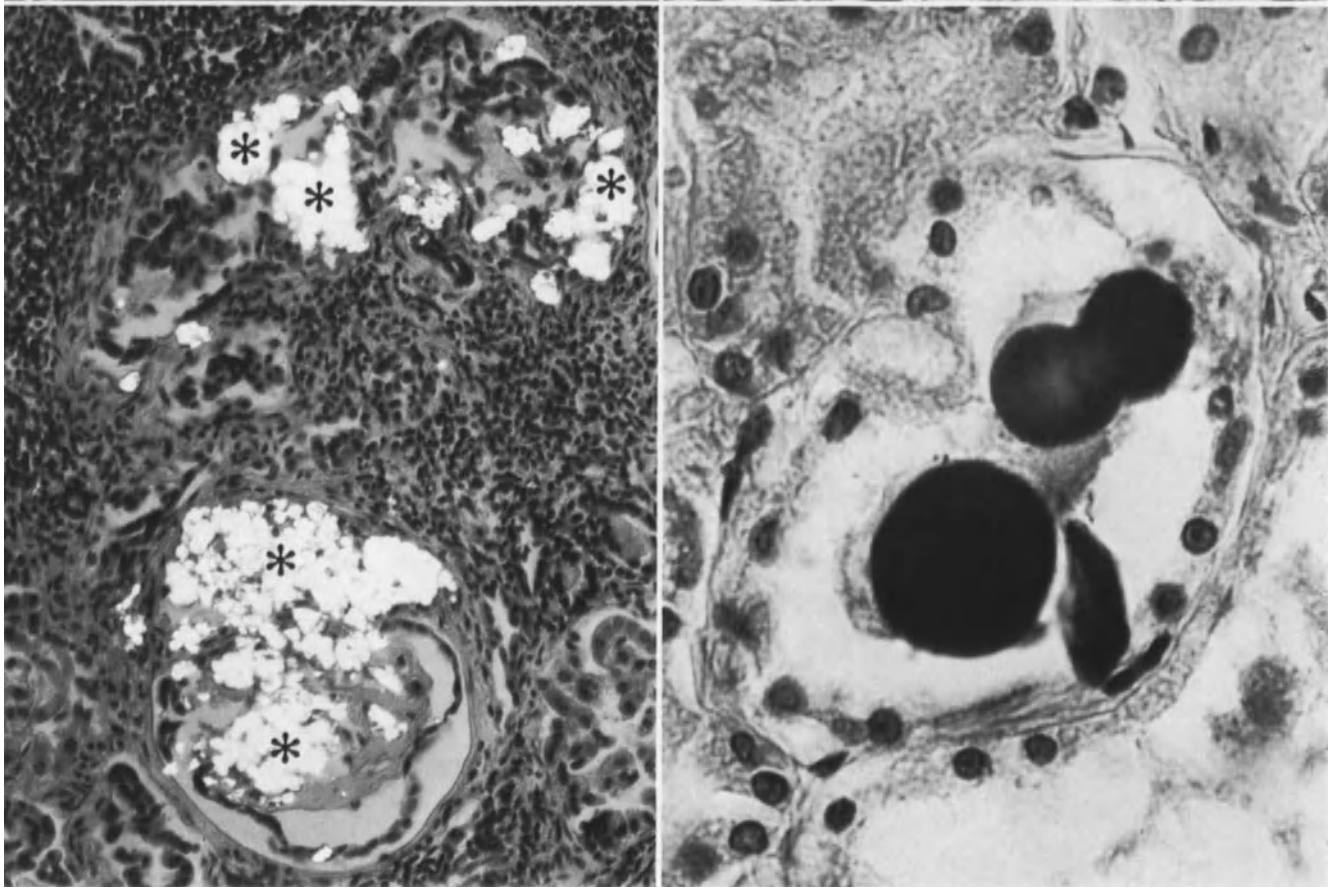


23.14
23.15

***Secondary Form.*** Isolated calcium oxalate crystals are found in about 70% of the autopsy cases with uremia. They are more numerous in the presence of acidosis (Fig. 23.15). There are a few reports of extrarenal crystal deposits [79]; however, we feel that the presence of a primary form in these cases has not been unequivocally excluded.

A very severe secondary oxalosis (125–500 crystals/cm$^2$) has been reported following methoxyflurane [57, 274] or halothane [320a] anesthesia. Following ingestion of ethylene glycol (antifreeze), severe oxalosis of the kidney and a coarse vacuolar epithelial change—chiefly of the proximal tubules—have been observed ([1769, 1791]; see p. 125). It appears that crystal deposition is less injurious to the kidney than are the ethylene glycol metabolites which lead to edema and decreased intrarenal blood flow [1247]. Renal changes and insufficiency improve with dialysis but irreversible damage is usually present [611]. Other causes of secondary oxalosis are pyridoxin deficiency and resection of small intestine [332a]. In the latter case, oxalic acid stone formation is the predominant symptom [332a].

### LM Findings

In the primary form (type I), the biopsy usually reveals severe collapse obsolescence of the glomeruli with severe focal tubular atrophy, striking thickening of tubular BM (Fig. 23.10) and marked increase of interstitial connective tissue infiltrated with lymphocytes (Fig. 23.11) and a few histiocytes. The deposited crystals may be overlooked in the PAS stain, but they are easily recognizable with the HE stain (Fig. 23.11). Their enormous number becomes apparent under polarized light due to their birefringence (Fig. 23.12).

The often slightly PAS-positive crystals are one-fifth to one-half the size of normal glomeruli. They are coarse and demonstrate dense, radial bands. They occur in interstitium and in tubules where they usually replace destroyed epithelial cells.

Relatively well-preserved epithelial cells contain a few very fine crystals demonstrable by their birefrigence [1769]. In glomeruli which are more or less intact, there occurs an unspecific glomerulosclerosis with mesangial thickening but without significant cellular increase. Glomeruli which are more severly changed show collapse as well as occasional massive crystal deposits in the capsular space (Fig. 23.14).

A few calcium oxalate crystals are found in the peripheral arteries present in the needle biopsy (Fig. 23.13). Additionally, marked adaptive intimal fibrosis may be observed in the region of the arcuate and interlobular arteries. In three-fourths of our hypertensive cases, there was no hypertensive vasculopathy. Moreover, arterioles in the neighborhood of crystal granulomas were inflammatorily split and fibrosed.

In secondary oxalosis, oval calcium oxalate crystals are present in straight parts of proximal tubules; they are not accompanied by an inflammatory reaction (Fig. 23.15).

### EM Findings

The glomerular BM is often clearly thickened and demonstrates small crystal deposits. Capsular epithelial cells are edematous (Fig. 23.16) as are podocytes which also exhibit degenerative changes. The mesangium is thickened and has an increased matrix (Fig. 23.16; experimental findings: [352, 522]). With scanning EM, the massive interstitial crystals appear as fine sheaf-like crystal aggregates [1143]. The much-thickened and multiply-split tubular BM is strikingly perforated [1337]. With careful preparation, fine groups of calcium oxalate crystals can be demonstrated in the perforations (Fig. 23.17) as well as large multilayered structures with light centers [1337]. On one occasion, we found numerous crystals in the myocytes of an artery (Fig. 23.18).

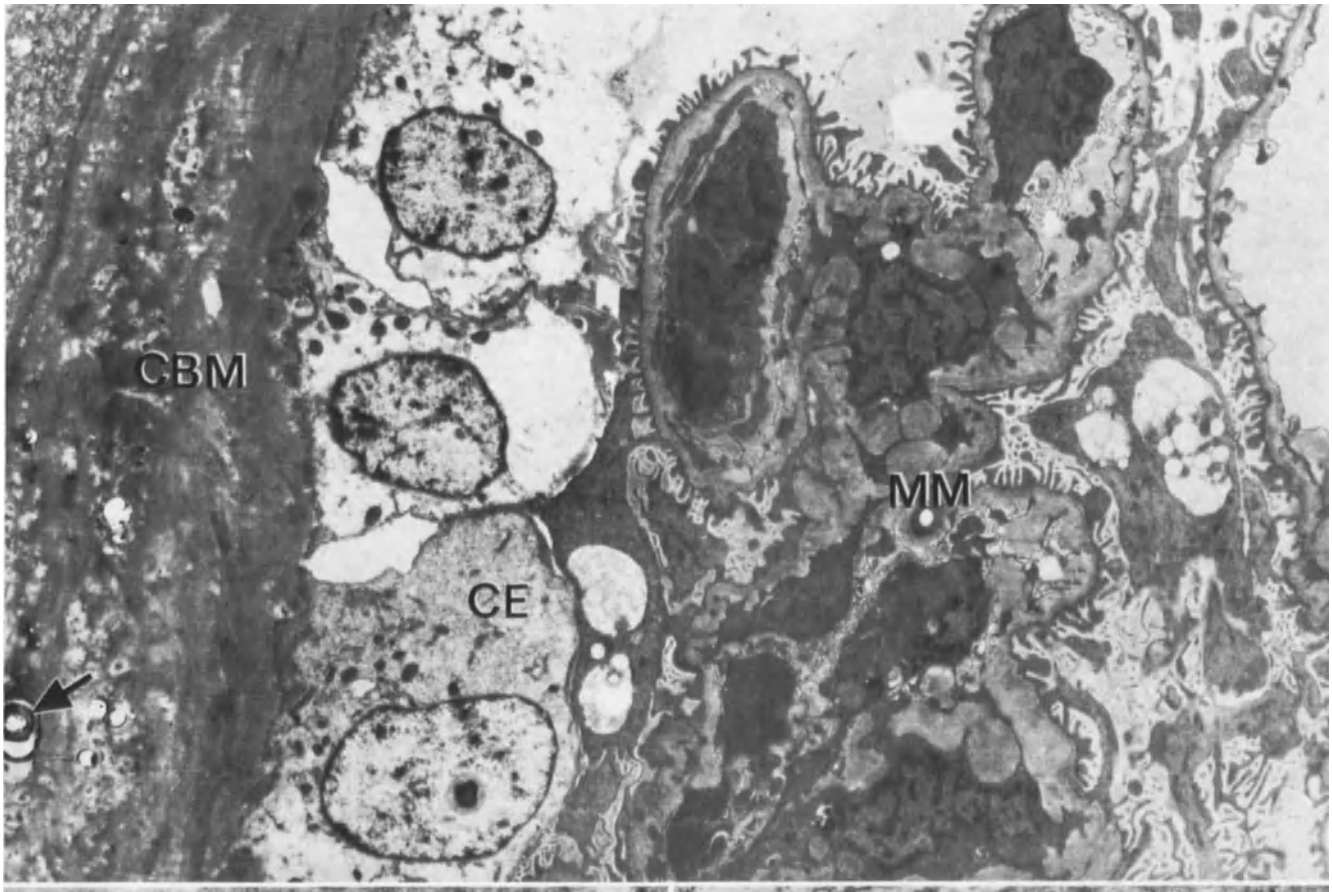
### Differential Diagnosis

Under polarized light, there are no diagnostic problems (see above for differentiation between primary and secondary forms). Urate crystals in gout are much finer, more sheaf-like, larger and, above all, water soluble.

**Fig. 23.16.** Same case as in Figure 23.10. Capsular BM (*CBM*) ▷ is highly thickened and split, and demonstrates a crystalline inclusion (→) and numerous lacunae indicating where crystals were torn out during tissue preparation. Highly swollen capsular epithelial cells (*CE*). Glomerular capillary loops are fairly well preserved. Mesangial matrix (*MM*) is increased. Male, 22 years. EM (×3600)

**Fig. 23.17.** Same case as in Figure 23.10, showing calcium oxalate crystals in tubular BM. Male, 22 years. EM (×24,000)

**Fig. 23.18.** Calcium oxalate deposits (→) seen in myocytes of a small renal artery. Female, 15 years. EM (×1500)

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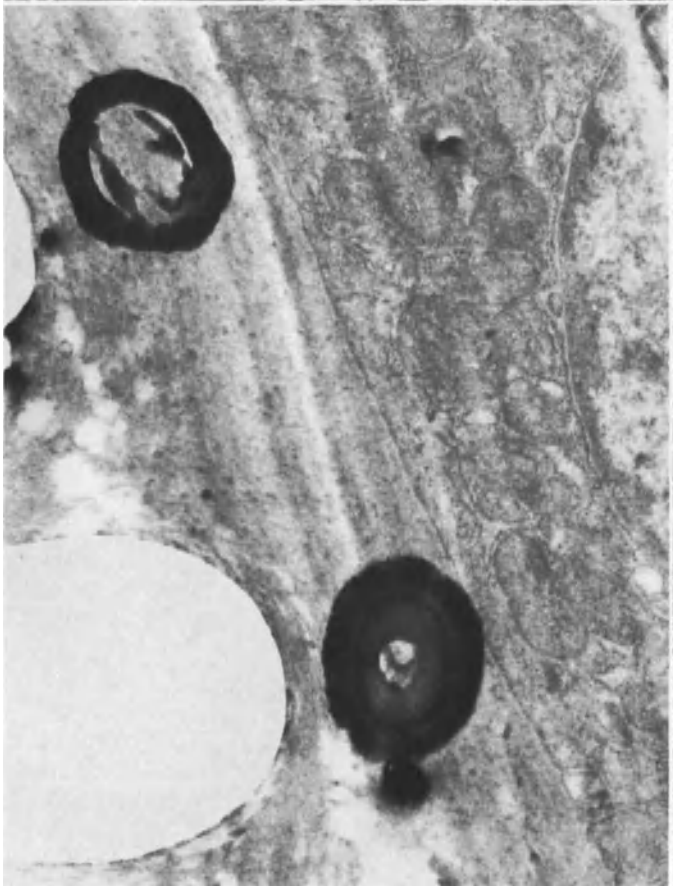

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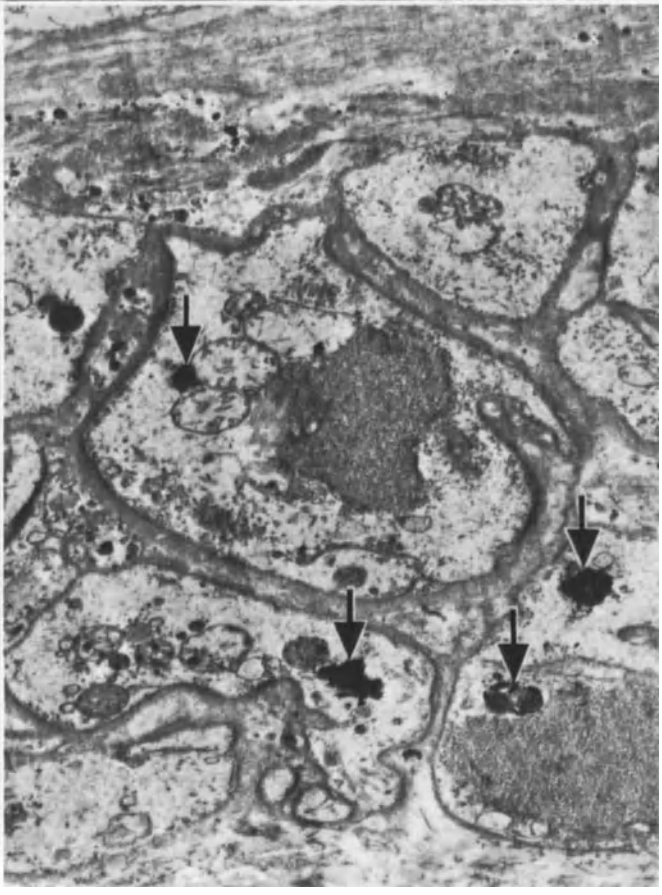


23.18

### Prognosis

In primary oxalosis (type I), prognosis is hopeless. Transplants show relapse (10 out of 10 [1420]). Accordingly, primary oxalosis (type I) is considered as a contraindication for renal transplantation [366, 481, 647].
Prognosis in secondary oxalosis depends on the causative factor.
Glycol lesions recover well with dialysis, but these patients, nevertheless, develop an interstitial fibrosis with chronic impairment of renal function [611].

### Pathogenesis

The primary form of oxalosis is due to an enzyme deficiency: type I is caused by a deficiency of alpha-ketoglutarate-glycoxylate carboligase [867] and the hyperoxaluric type II, by a deficiency of D-glycerate dehydrogenase [1741].
In type I, increased amounts of oxalic, glyoxylic and glycolic acid are excreted in the urine and in type II, oxalic and glyceric acid.
Crystal deposition (calcium oxalate monohydrate—whewellite) begins in the epithelium of the straight part of the proximal tubules by reabsorption [176, 1791] and by binding to mucopolysaccharides. The epithelium is displaced and destroyed by appositional crystal growth resulting in interstitial scarring. There finally occurs anoxia of tubular epithelium due to interstitial capillary obliteration in sclerotic regions.
Glomerular obsolescence is, we believe, chiefly the consequence of the severe pre- and postglomerular vascular changes recognizable in collapse glomeruli. Glomerulonephrosis hardly appears to play a role. We found glomerular crystals exclusively in glomeruli evidencing from a high degree of insufficient perfusion.
Pathogenesis in secondary oxalosis depends on the causative factors.

## Kidney in Gout
[1799, 1809]

### Definition

Renal changes in primary and secondary gout.

### Nosology

Primary gout is the classic, idiopathic form of the disease, and secondary gout is the term used to encompass all forms of the disease occurring in the presence of a basic disease entity such as renal insufficiency, leukemia and the Lesch-Nyhan syndrome.

Table 23.2. Renal biopsy findings in clinically diagnosed gout (n=18)

| Bioptic diagnosis | Incidence |
|---|---|
| Gouty kidney | 1 |
| Unspecific GS | 4 |
| Pyelonephritis | 5 |
| Glomerulonephritis | 8 |

### Incidence

Incidence of gout at autopsy varies considerably with region and life standard (60 out of 23 300 autopsies: Z). Since gouty tophi occur almost exclusively in the renal medulla, their presence in needle biopsy is almost incidental (1 out of 2080 biopsies: Z). The renal biopsy findings in patients suffering from gout are given in Table 23.2.

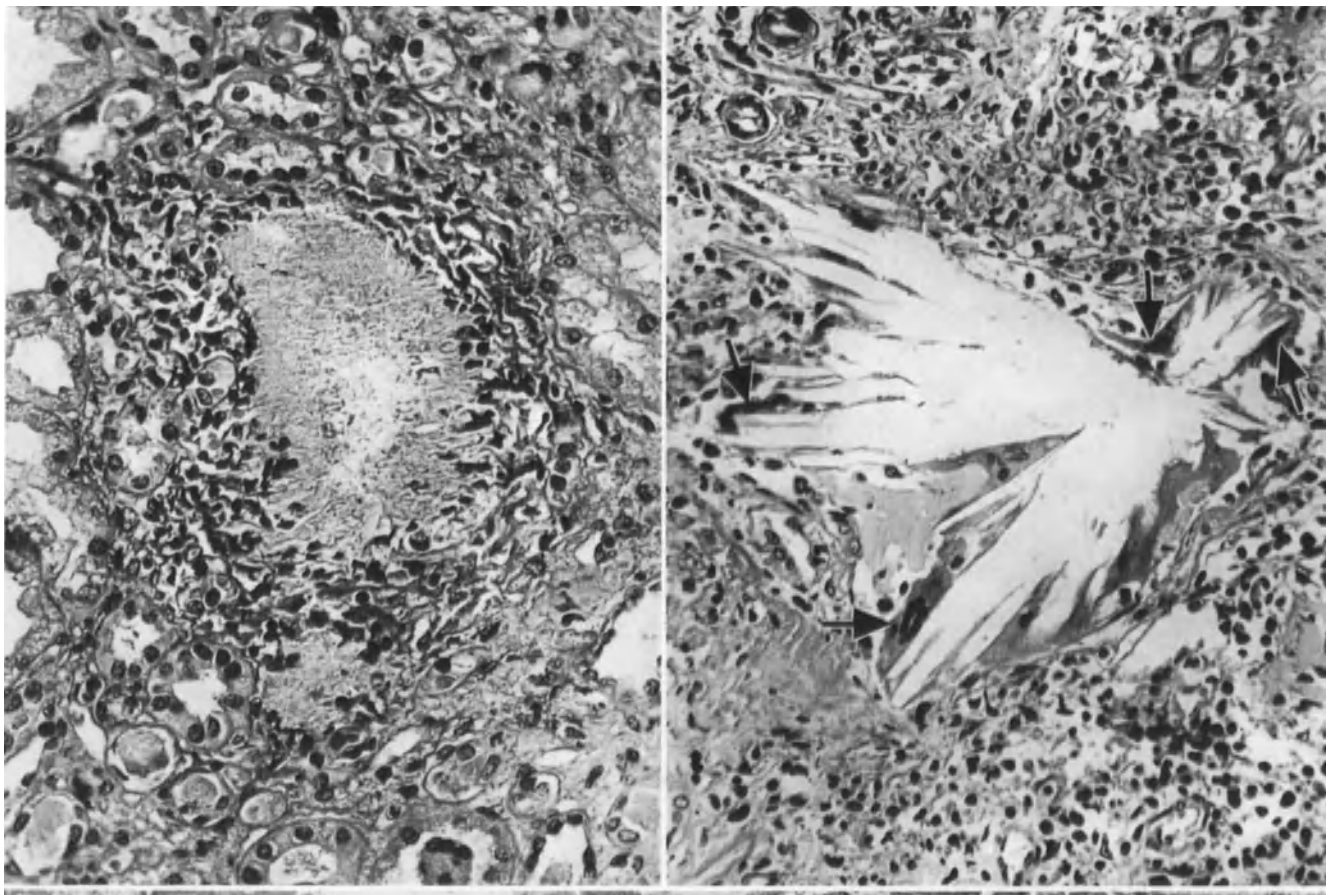
### Clinical Findings

Clinically, gout was unknown but later confirmed in our unique biopsy case and in 32 out of 60 autopsy cases with renal tophi. This is easily explained by the fact that acute attacks, joint involvement, and bursal tophi may be absent. Renal function is impaired in 10% of the patients [898]. Concomitant PN symptoms and hypertension are frequent (31 out of 60: Z). Nephrolithiasis occurs significantly more often than in control groups (13% of cases: [1799]; 28% of cases: [898]; 41% of cases: [1809]).
In the secondary form of gout, the symptomatology of the basic disease, e.g., leukemia, predominates. The Lesch-Nyhan syndrome [820] is characterized by developmental disturbances, athetosis, self-mutilation, and, terminally, by the consequences of renal gout.

**Fig. 23.19.** Small gout granuloma encountered fortuitously in a renal biopsy undertaken because of chronic pyelonephritis. Granuloma is seen surrounding amorphous sodium urate. Van Gieson (×120) ▷

**Fig. 23.20.** Typical gout tophus in kidney of a patient who succumbed from uremia due to chronic pyelonephritis. Sodium urate crystals have dissolved, and their remaining lacunae are surrounded by foreign body giant cells (→). There are numerous interstitial lymphocytes and phagocytes; sclerosis of surrounding connective tissue is present. Male, 64 years. HE (×120)

**Fig. 23.21.** Unspecific glomerulosclerosis associated with gout. Mesangial matrix is clearly increased without accompanying cell increase. Podocytes and endothelial cells are slightly swollen or hypertrophied; BM is unchanged. Note the two artificial punch nuclei (*). Female, 48 years. EM (×4100)



23.19
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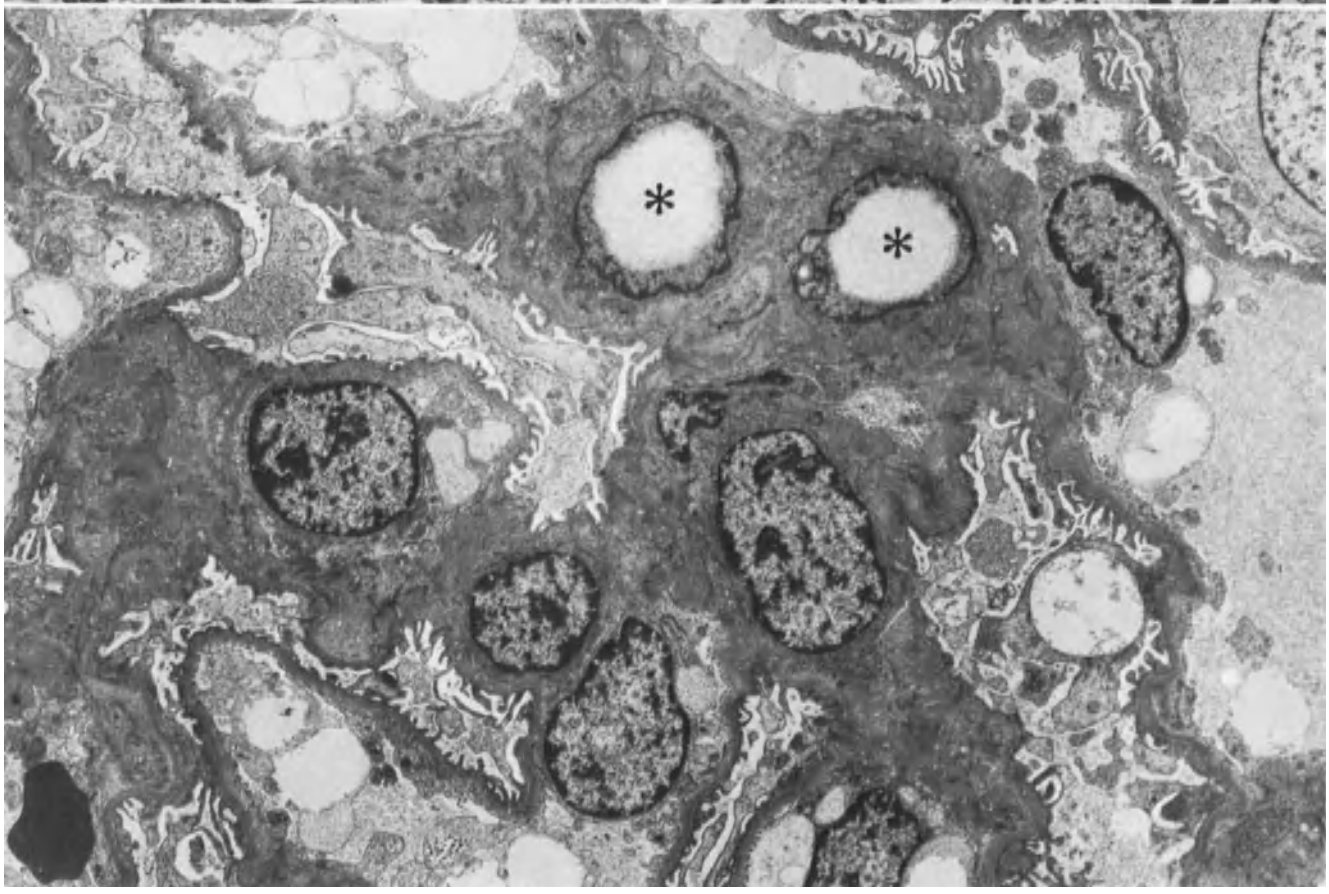



23.21

### LM and EM Findings

Of our autopsy gout cases, 23 out of 60 did not have gouty renal changes. Tophi (57% of autopsy cases: [1799]; 37% of autopsy cases: [581]) are pathognomonic for gout. They are only present exceptionally in cortical tissue, but usually in the medulla. They may demonstrate, in the beginning, a center of finely granular amorphic material (Fig. 23.19) or, in more advanced cases, aggregates of thin crystal-shaped lacunae (Fig. 23.20) since sodium urate is usually completely washed out in aqueous fixatives. Therefore, we recommend the Schultz stain (carmine methylene blue: [610]) on alcohol-fixed material in suspected cases. The lacunae arising from the dissolved crystals are surrounded by foreign body giant cells (Fig. 23.20) which, in turn, are surrounded peripherally by numerous histiocytes. These cells surround the amorphic urate masses in the form of a crown so that confusion with epithelial cells is possible. Unspecific granulation tissue follows in the periphery of the cellular wall which, around old tophi, is transformed into scar tissue.
Tubules are interrupted by fairly large granulomas. We encountered nephrohydrosis, however, in only 3 out of 60 cases. Cortical atrophy is always found proximal to large tophi. In 8 out of 60 autopsy cases and in 5 out of 18 biopsies, we found clear-cut evidence of unspecific glomerulosclerosis (Fig. 23.21; 57% [581]).
The mesangium is widened, there is no increase in cells, but an obvious increase of matrix (contra: [1243]). With LM, glomerular BM thickening is discernable which, with EM, is shown to be mainly due to a thickening of the lamina rara interna.
In 40% of our autopsy cases and 4 out of 18 biopsies (24%: [581]) chronic PN was present. This is five-fold the incidence of an age-matched control group [1799].
In secondary gout, e.g., leukemia, numerous tubular ammonium urate crystals without reaction of tubular and interstitial cells were our only finding (Fig. 23.24).

### Pathogenesis and Etiology

In primary gout, renal crystal formation primarily occurs either in the medullary interstitium, where sodium urate concentration is highest [1809, 1678, 799] or in the lumen and epithelial cells of the collecting ducts [435].
We have found an increased incidence of hypertension exclusively in cases with severe secondary PN. A direct triggering of hypertension by metabolic disturbances appears highly unlikely. We attribute the increased incidence of PN to impairment of tubular flow by interstitial tophi.
Symptomatic attacks of gout in the presence of polycythemia, treated myeloid leukemia, renal insufficiency etc. are not to be considered as primary metabolic disturbances. Acute renal insufficiency occurring in symptomatic hyperuricemia (uric acid serum concentration > 20 mg/100 ml) associated with malignant lymphoma and leukemia – which is more frequent after therapy – has been occassionally described [853]. The lesion appears to be caused by intratubular crystal formation and not by ureteral obstruction. There are no biopsy findings reported on this condition. The lesion is always reversible with appropriate therapy [853].
The Lesch-Nyhan syndrome is caused by a congenital enzyme deficiency of hypoxanthine-guanine-phosphoribosyl transferase [1475].

## Alport's Syndrome
[521, 757, 1422, 1496]

### Definition

Alport's syndrome is an inherited progressive renal disease usually associated with nerve deafness [18].

***Synonym:*** Hereditary nephritis, a term which also encompasses other diseases.

### Incidence

Exact data for the overall incidence are unknown. This familial disease is certainly rare, but more frequent than formerly believed. When pedigree studies are made in a given case (Fig. 23.22), it becomes evident that the disease is often overlooked clinically and misinterpreted at autopsy [521].
In our needle biopsy material, we have observed a total of 36 cases; 23 studied with LM and 13 with LM and EM (1.73% of all biopsies) from 19 families.
It must be noted, that since EM allows a definite diagnosis, frequency increased in our biopsy material from 1.2%, in biopsies investigated by LM only, to 4% in biopsies studied with EM.

### Clinical Findings

The disease follows on autosomal-dominant inheritance pattern and is more frequent in boys than girls. Sporadically occurring cases are rare. The majority of afflicted males die between the ages of 10 and 40 (Fig. 23.23) and women not rarely live to the age of 60. In a series of cases, 1 out of 7 women died postpartum [268]. In our own material encompassing information on 19 families, we encountered one postpartal death due to eclampsia (see also [521]).
The disease begins in childhood, usually with microhematuria (11 out of 36: Z) or macrohematuria (19 out

of 36: Z) and often in the wake of acute upper respiratory tract infection (11 out of 36: Z). Proteinuria and edema are more rarely present at disease onset (12 out of 36: Z). In women, the first sign of the disease may appear during pregnancy as proteinuria (6 out of 19 families: Z).

A nephrotic syndrome may appear lateron in the disease course (5 out of 15: [474]; 7 out of 10: [697]; 4 out of 36: Z). Renal insufficiency sets in with increasing duration of illness. Hypertension is rare (1 out of 36: Z).

Nerve deafness and eye symptoms occur in varying frequency in different families. In 19 families examined, nerve deafness were present in 9 and eye symptoms in 2—in one as fundus albipunctatus [1422]—and in the other as severe anterior lenticonus.

There are a few reports of hyperprolinemia [877, 1048, 1106], hyperhydroxyprolinuria [1106] and of hyperprolinuria [877].

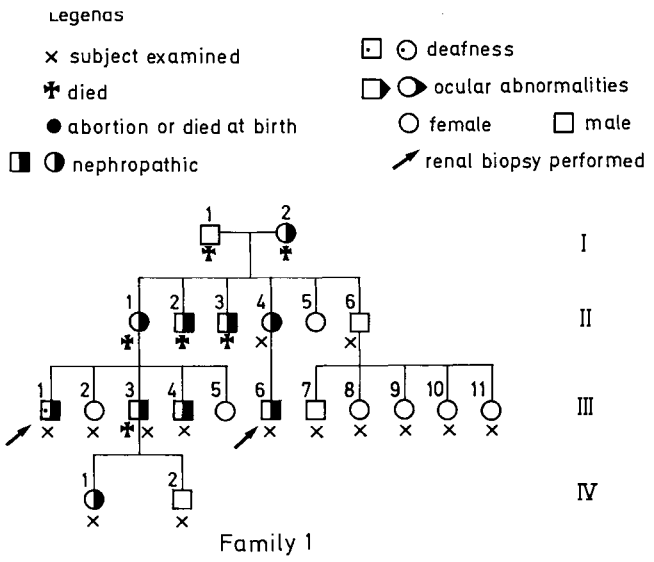



**Fig. 23.22.** Family pedigree in Alport's syndrome (published [521])

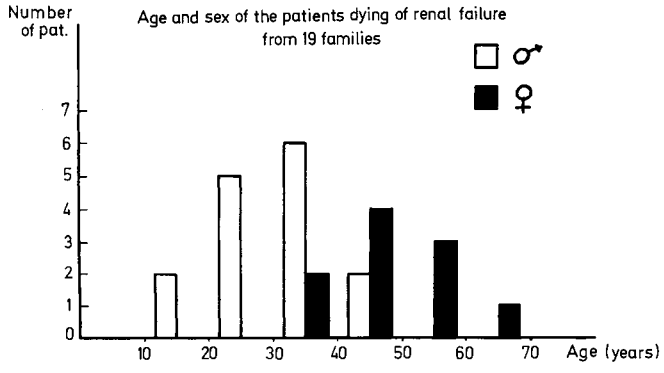



**Fig. 23.23.** Age and sex of patients dying of renal failure from 19 families with Alport's syndrome (published [521])

## LM Findings

The LM findings are unspecific. At autopsy, the disease was described diversely as GN, PN or nondestructive IN [77, 145, 264, 351, 586, 684, 894, 1325, 1422, 1791].

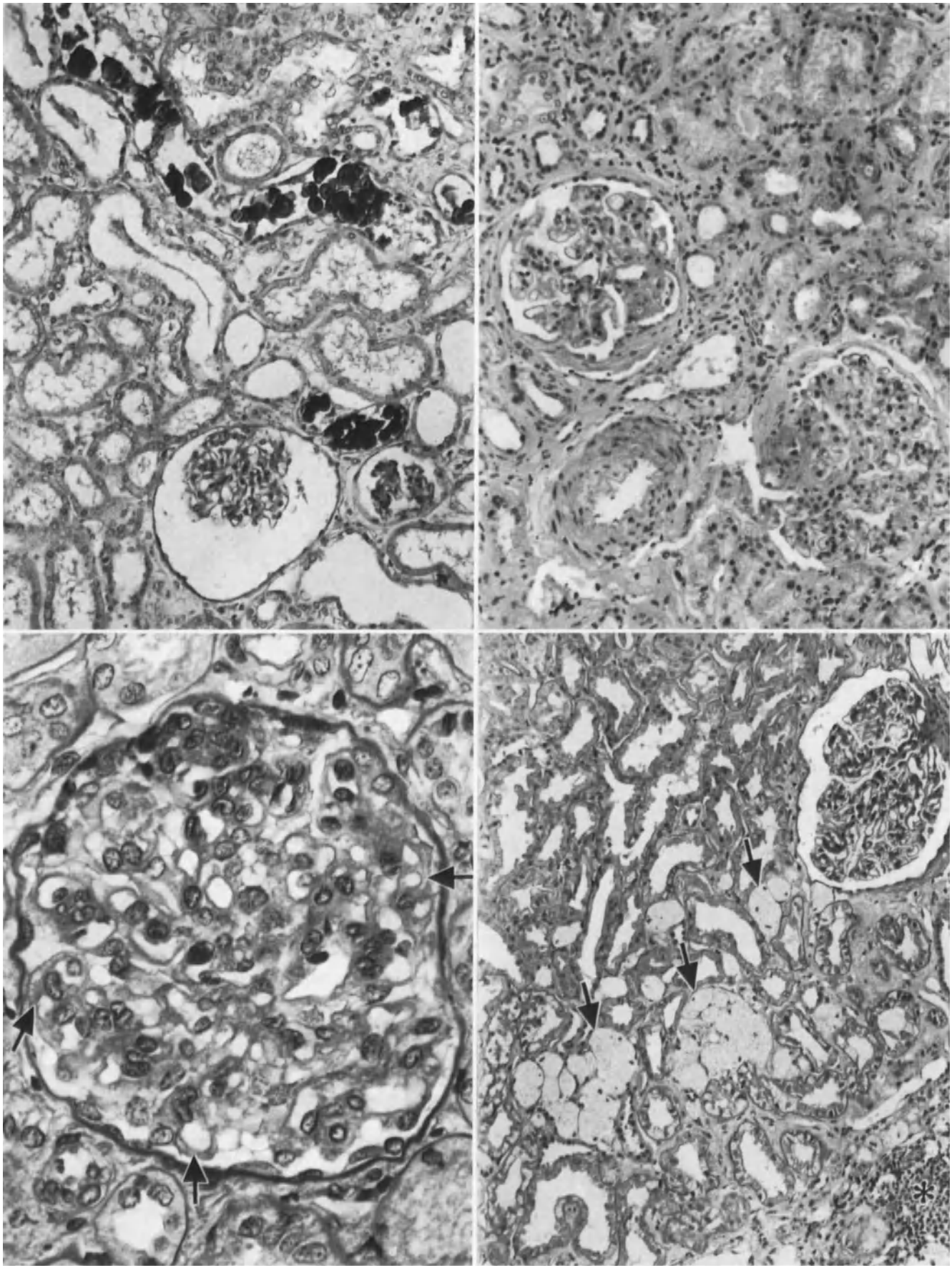
At autopsy, the glomeruli are extensively obsolescent and the interstitium is widened, fibrotic, and loosely infiltrated with lymphocytes. Massive occurrence of interstitial and tubular foam cells (Fig. 23.27) reported in 40% of a series of cases [521]—which we have also rarely found in glomeruli (see also [338, 145])—are viewed by us as characteristic of the disease. They are not, however, either obligatory or pathognomonic. They are usually of tubular epithelial and, occassionally, of histiocytic origin [1352, 1545]. The tubules are severely atrophic. We have never observed pyelonephritic destruction. The arteries are severely changed in the sense of adaptive intimal fibrosis. Some investigators [338] have also reported arterial foam cells which we have never observed.

A completely different picture may emerge upon examination of early cases without renal insufficiency or those before the stage of terminal renal insufficiency. In such cases, the glomeruli show minimal and axial mesangial matrix increase (Fig. 23.26) with or without segmental sclerosis (Fig. 23.25; [1545]). Glomerular BM is moderately or severely thickened in less than one fourth of the cases (8 out of 38: Z). The interstitium usually shows only scanty infiltrates of inflammatory cells. The vessels are unchanged. Interstitial foam cells are less frequent than those in the tubules (8 out of 36: Z; 5 out of 8: [1545]).

We have encountered fetal glomeruli, 30–120 μm large with cubic to prismatic podocytes and scarcely recognizable loop lumens (Fig. 6.1), in 10 out of 36 biopsies exclusively in patients under 10 years of age [36, 145, 915]. LM findings in 101 cases ([521] plus additional cases of our own) prior to terminal renal insufficiency are summarized in Table 23.3.

Table 23.3. LM findings in 101 cases of Alport's syndrome prior to terminal renal insufficiency ([521] plus additional own cases)

| Finding | Frequency (%) |
|---|---|
| Mesangial matrix increase | 84 |
| BM thickening | 80 |
| Mesangial cell increase | 67 |
| Interstitial fibrosis | 67 |
| Patchy tubular atrophy | 58 |
| Obsolescent glomeruli | 40 |
| Segmental glomerulosclerosis | 50 |
| Interstitial foam cells | 40 |
| Interstitial infiltrates | 40 |
| Synechiae | 35 |
| Segmental crescents | 35 |



23.24
23.25

23.26
23.27

### IF Findings

The findings are often negative (8 out of 19: Z; 38 out of 40: [814]; 4 out of 5: [697]). However, in 5 out of 19, we found IgM alone (Fig. 23.28), in 2 out of 19 in combination with C3 (see also [521]); in 4 out of 19 IgG was simultaneously present in focal-segmental distribution along the glomerular BM, and in one case IgA and in another fibrin was also demonstrable.
Other investigators have reported similar findings: IgG and complement in 2 out of 40 cases [814], complement alone in 1 out of 5 [697], complement in 5 out of 5; and in 1 out of 5 IgM and in 2 out of 5 cases fibrin [1546] were present.

### EM Findings

The characteristic EM findings [697, 1545] consist of a longitudinal splitting (lamellation) and of a fragmentation and reticulation of lamina densa (Figs. 6.24, 23.29, 23.30; 13 out of 13: Z) as well as thinning of BM (12 out of 13: Z). For glomerular findings see also Figs. 6.9, 6.21, 6.34, 6.57, 6.64, 6.80, 6.88.
In the youngest patients—who usually are the least afflicted—the glomerular changes are still focal and limited to a few capillary loops above which fusion of podocytic foot processes is observed. Later, more and more loops are afflicted and the BM is totally thickened with sharp but wave-like subepithelial demarcation (Fig. 23.29).

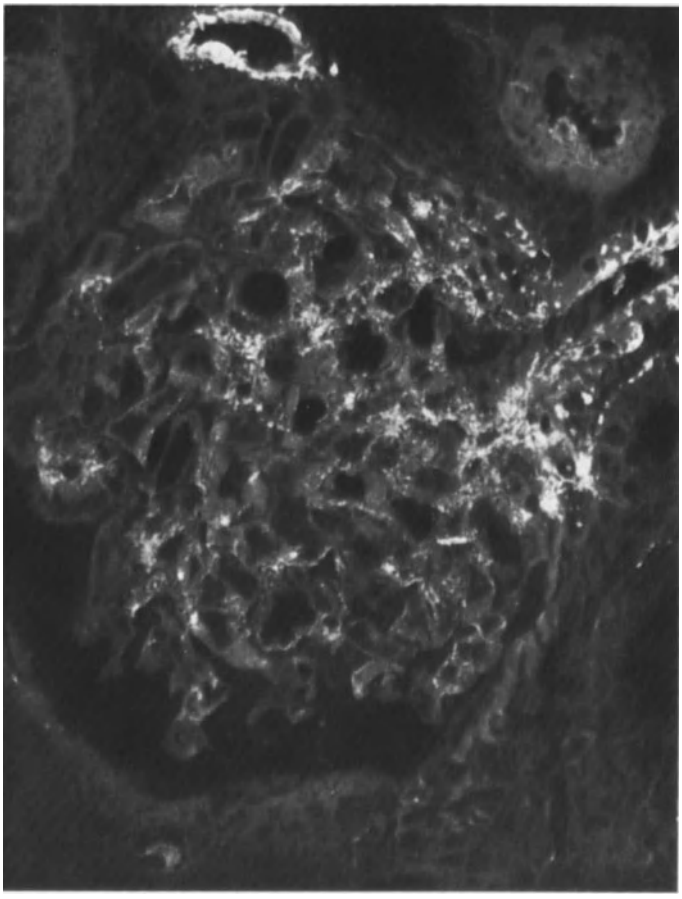


**Fig. 23.28.** Alport's syndrome with IgM deposits which are massive at vascular pole but only slight in the loop periphery and vas afferens. Male, 5 years. IF (× 500)

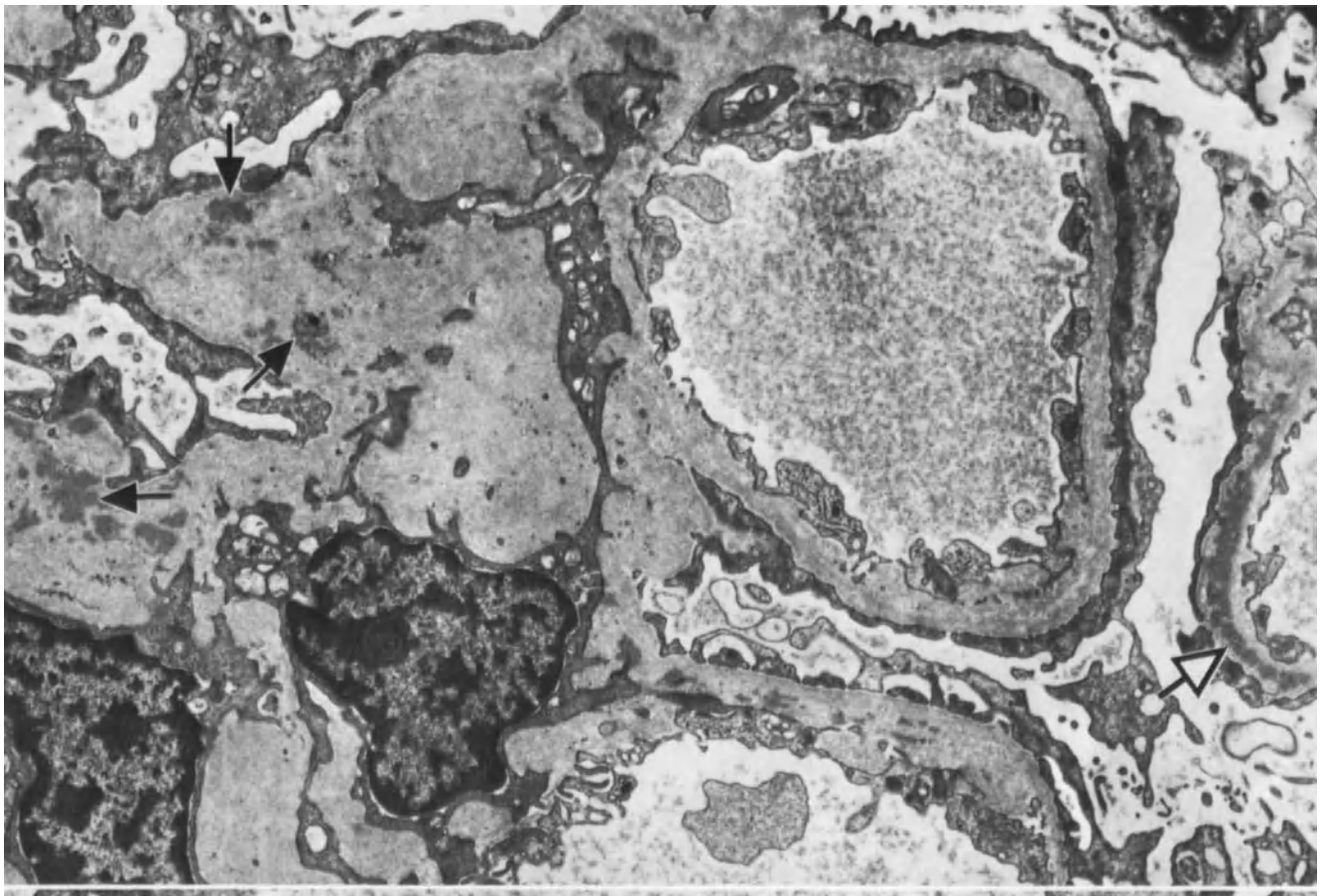
◁ **Fig. 23.24.** Secondary urate deposition chiefly in distal tubules after intensive treatment of myeloid leukemia. Schultz (× 140)

**Fig. 23.25.** Glomerular segmental sclerosis in clinically and EM-dignosed Alport's syndrome representing a later stage than in Figure 23.26. Incipient renal insufficiency. Male, 9 years. PAS (× 160)

**Fig. 23.26.** Glomerulus is shown with partially thickened glomerular capillary loop (→) in patient with familial hematuria. Since intramembranous (although not highly osmiophilic) deposits were found with EM, diagnosis of intramembranous GN was made. Subsequent renal biopsy of patient's 16-year-old sister revealed Alport's syndrome with EM.
Reexamination of the brother's biopsy resulted in revised diagnosis of Alport's syndrome with secondary deposits (cf. Fig. 23.29). Male, 18 years. PAS (× 500)

**Fig. 23.27.** Renal biopsy from a patient with typical clinical symptoms of Alport's syndrome which was confirmed with EM. Majority of tubules are not significantly altered. A few clusters of foam cells (→) and a large, unspecific interstitial infiltrate (*) are present. Male, 17 years. PAS (× 200)

The densa lamellae are 300–1000 Å thick, usually arranged in parallel or net-like (reticulation). Between these densa lamellae, two types of particles are found: 200–300 Å round and compact; 500–700 Å round and bulb-like (Fig. 23.31; see also [697, 283]). These BM changes were intimated in earlier publications [351, 438, 814, 915]. BM thinning nearly always accompanies the above described BM changes (12 out of 13:Z; [1401a]) but is usually more clearly recognizable in early disease stages where a thinning of isolated loops of the otherwise unaffected BM may be present.
BM thickening and splitting of the glomerular capsule (5 out of 13: Z) and of the tubules (3 out of 13: Z; [268]) have been observed, but they are nonspecific.
Scanty (8 out of 13: Z) or numerous (1 out of 13: Z) finely granular osmiophilic deposits have been observed within the lamina densa in severely changed BM segments (Figs. 23.25, 23.26, 23.27). A few of the deposits are surrounded by a light area as is seen with immunodeposits undergoing degradation.



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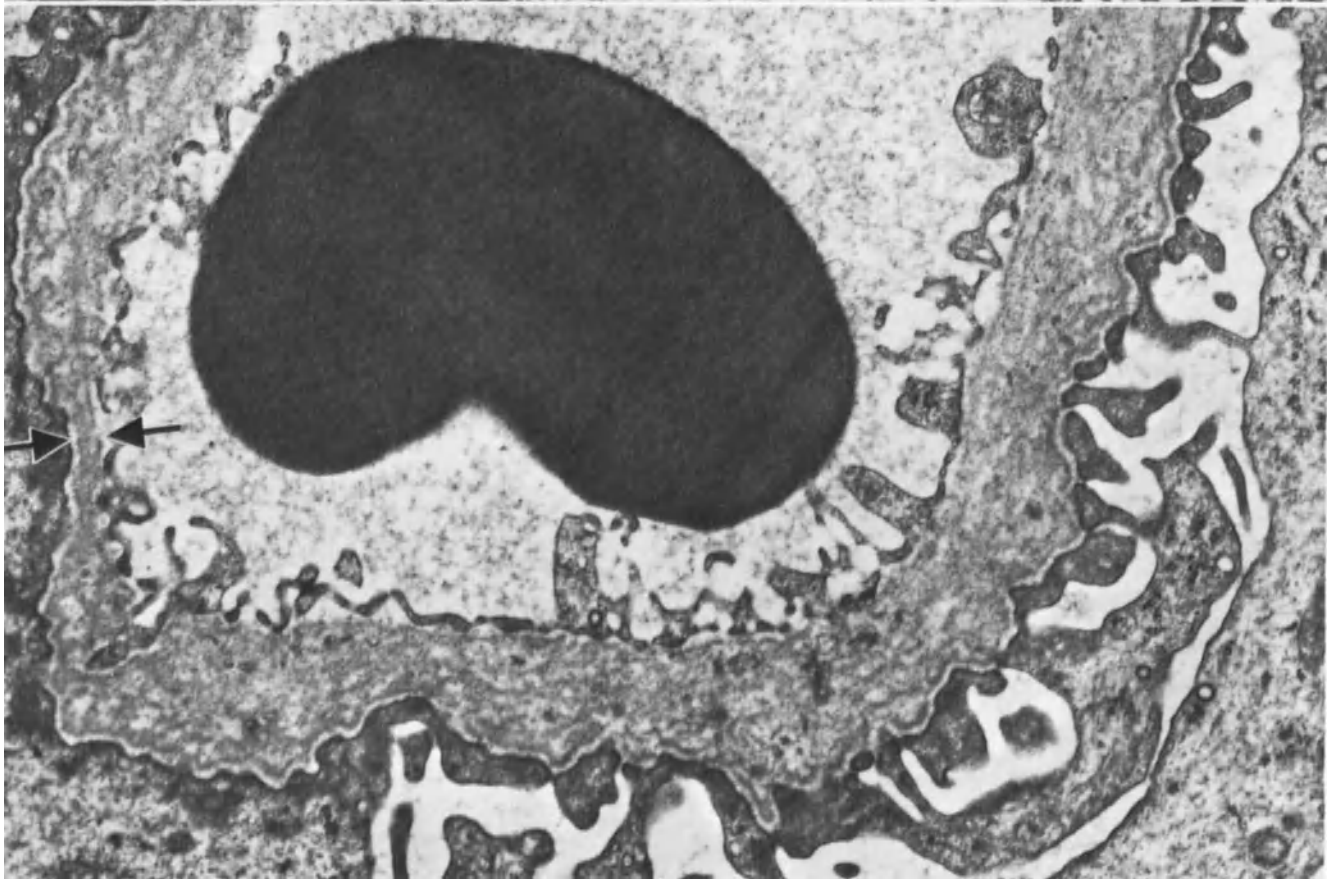

23.30

While we have observed these absolutely characteristic BM changes (EM only) in all of our Alport cases, other investigators have reported cases of hereditary nephritis without these BM changes [283, 697]. Further study will reveal whether those cases without BM changes belong to Alport's syndrome or benign familial hematuria (see p. 476) or even to other not yet clearly delimited forms of hereditary nephritis. Other investigators challenge the pathognomic significance of the described BM changes in general [695].

It has not been possible to follow the secondary proliferative reaction, assumedly arising from capillary loop injury, with EM in serial biopsies. In 10 out of 13 of our cases studied with EM, we found slight (Fig. 23.33) to very severe (Fig. 23.34) mesangial thickening with hypercellularity and increased matrix (Fig. 23.35); 8 out of 13 demonstrated endothelial hypertrophy, podocytic edema or hypertrophy and foot process fusion was present in all 13 (Fig. 23.32). Podocytes and endothelial cells are especially hypertrophied in the region of the considerably thickened BM [268]. In 4 out of 13 cases, capillary loop obsolescence was seen.

## Differential Diagnosis

LM differentiation of Alport's syndrome from glomerular minimal change, endotheliomesangial GN and sclerosing or proliferative FGN is impossible in the absence of adequate clinical data. Table 23.5 summarizes different morphologic parameters for elucidation of this differential diagnosis. Among LM parameters, only foam cells and fetal glomeruli are of limited help, but they are not present in all cases of Alport's syndrome. IF investigation is not contributory, whereas the EM parameters are of great importance: BM splitting is present in all cases of Alport's syndrome and BM thinning in more than 80%. Retrospectively, EM study of the original paraffin-embedded material permits clear recognition of these typical BM changes; this is also true for advanced cases reminiscent of membranoproliferative GN [1799]. Not all types of BM splitting indicate Alport's syndrome (Table 23.4; see also [872b]) for which there is only one specific type, as demonstrated in Fig. 23.36. In GN, there is usually a coarse lamellar splitting with large lucid BM defects, the outer and inner continuity of the densa lamellae is far better preserved than in Alport's syndrome, and at least one densa lamella is of normal thickness. In non-GN the densa lamellae are usually long, lamellated and slightly reticulated, while in Alport's syndrome the densa lamellae are short, fragmented, lamellated and reticulated.

## Prognosis

The prognosis is hopeless without transplantation. Men usually die earlier (between 10 and 40 years) than women (30–60 years), although the progression of the disease varies considerably in different families. We consider the appearance of segmental glomerular sclerosis as a prognostically significant morphologic change [697]. Between the beginning of the disease and the appearance of segmental glomerulosclerosis, there is a latent period averaging 13 years for men and 26 years for women.

◁ **Fig. 23.29.** Same case as in Figure 23.26. Peripheral glomerular capillary loop BM is thickened. There are irregularities of the lamina rara interna and externa. Osmiophilic intramembranous (→▷) and mesangial (→) deposits are present besides severe mesangial matrix increase. Male, 18 years. EM (×8400)

**Fig. 23.30.** Typical lamellation, reticulation and fragmentation of peripheral BM. Outer aspect of BM is irregular and there are foci of BM thinning (→). Osmiophilic substance in podocytes is increased. Initial clinical diagnosis was GN. Subsequent to biopsy, familial nature of the renal disease was proven. Male, 8 years. EM (×18,000)

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**Fig. 23.31.** Peripheral glomerular BM change in Alport's syndrome. Lamina densa predominantly shows reticulation with some loose osmiophilic deposits and degradation granules and thread-like structures. Irregularity of outer aspect of BM and isolated BM thinning (→) are present. Male, 3 years. EM (×32,300)

**Fig. 23.32.** Reticulated and irregularly thickened peripheral glomerular BM in Alport's syndrome. Small osmiophilic intramembranous deposits (→) and slight fusion of podocytic foot processes (*) are present. Male, 6 years. EM (×23,800)

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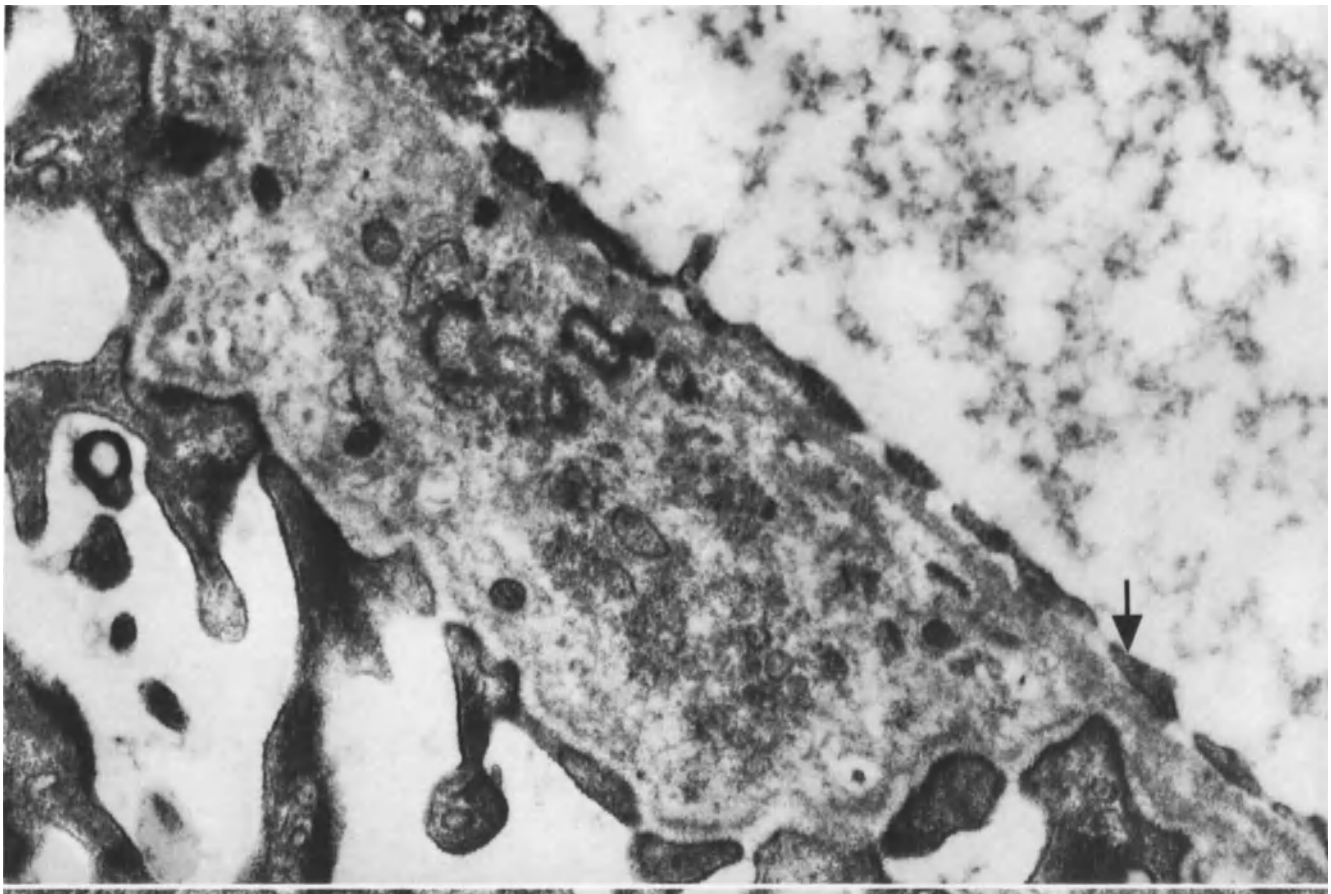
**Fig. 23.33.** Alport's syndrome in a 36-year-old woman. Obsolescent glomerular capillary loop and severe hypertrophy of podocytes. EM (×5430)

**Fig. 23.34.** Alport's syndrome with advanced mesangial sclerosis and intense cell increase and hypertrophy (poor fixation). Male, 6.5 years. EM (×3480)



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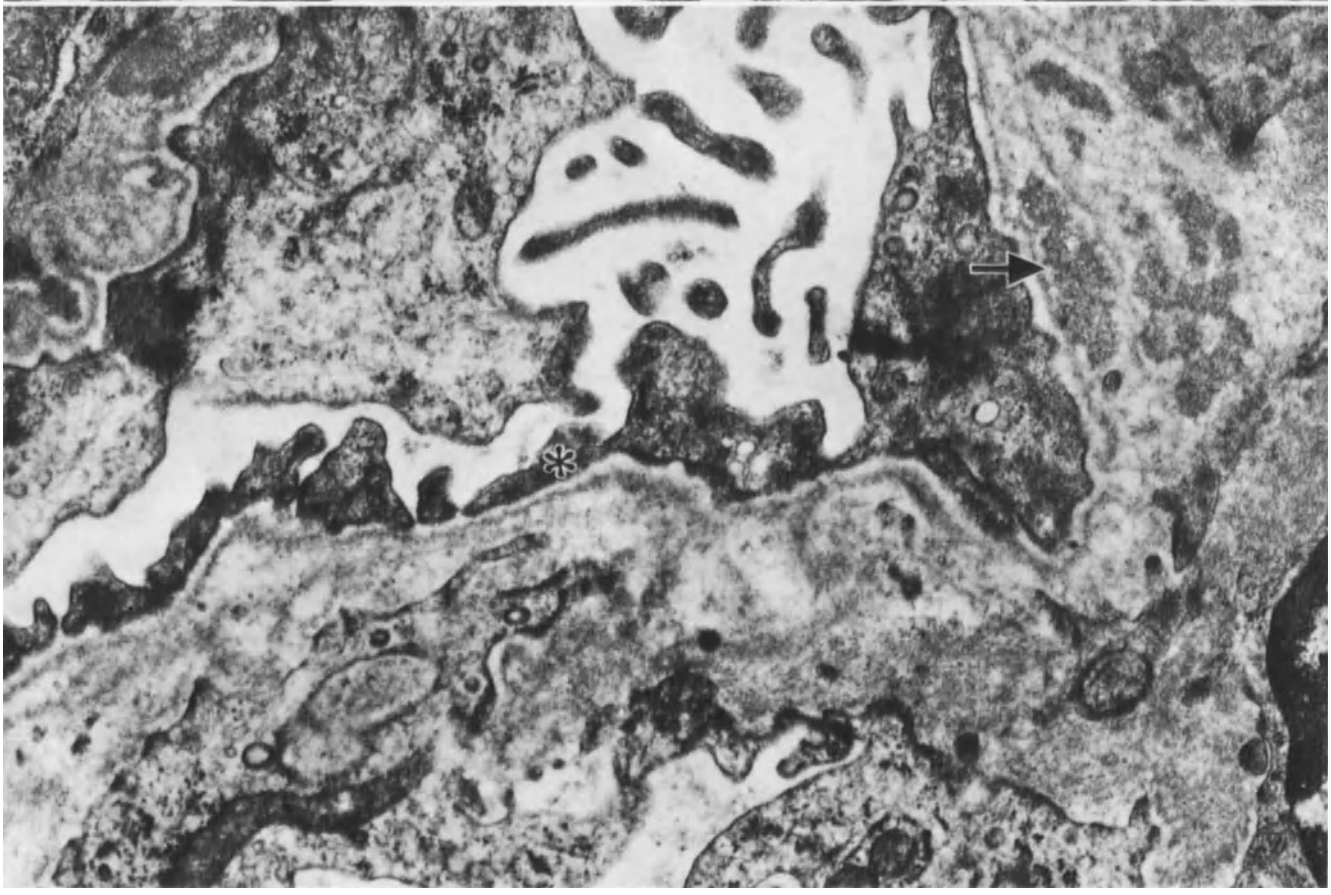

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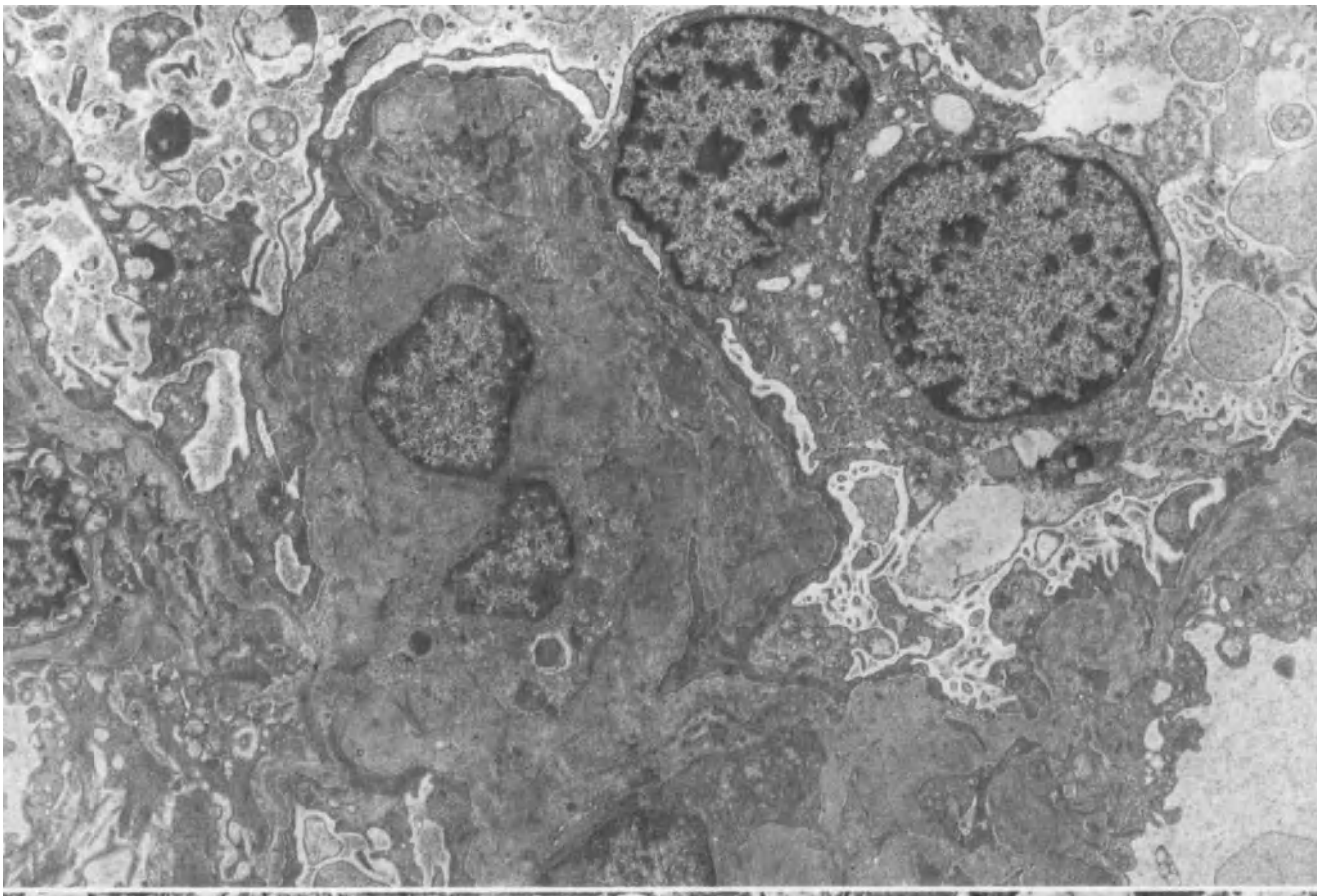

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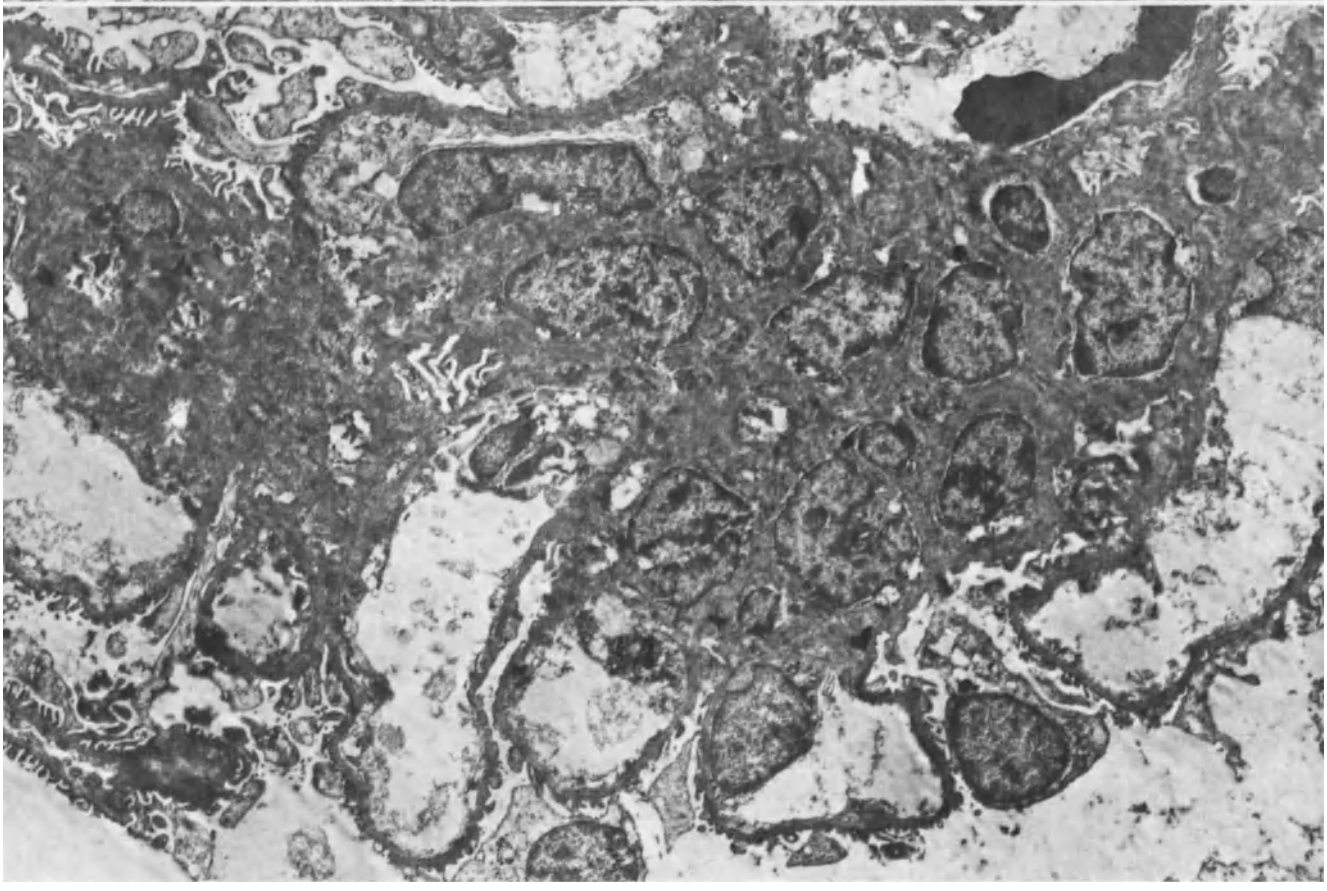

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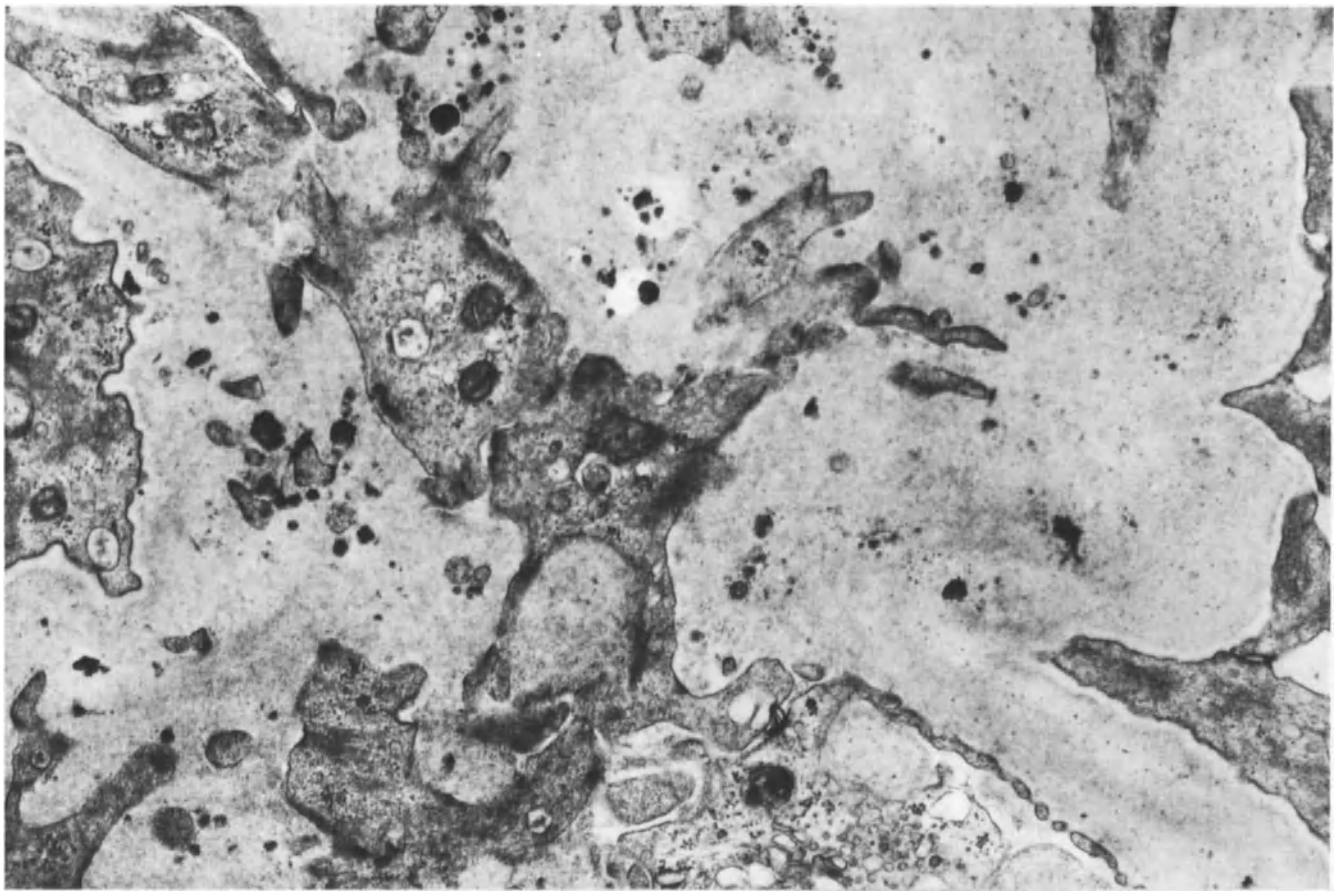


**Fig. 23.35.** Mesangial sclerosis in Alport's syndrome. Coarse and loosened matrix bars with masses of degradation granules. Male, 23 years. EM (×22,800)

Table 23.4. Differential diagnostic significance of morphologic parameters in Alport's syndrome with respect to GN and non-GN

| Morphologic parameter | | LM | | IF | EM basement membrane | |
|---|---|---|---|---|---|---|
| | | Foam cells | Fetal glomeruli | IF negative | Splitting | Thinning |
| Alport's syndrome | own cases[a] | n=40<br>25% | n=40<br>25% | n=20<br>15% | n=20<br>100% | n=20<br>95% |
| | total cases from literature [521, 695, 1401a] | n=114<br>35.9% | [b]n=57<br>38.5% | n=75<br>73% | [b]n=64<br>100% | [b]n=49<br>83.6% |
| Glomerulonephritis (own cases) | | n=200<br>5.6% | Unknown beyond 6 months of age except in congenital nephrotic syndrome | n=196<br>28.6% | n=340<br>14.4% | n=340<br>2.9% |
| Non-GN nephropathies (own cases) | | n=1100<br>0.2% | Unknown beyond 6 months of age except in cystinosis | n=76<br>55% | n=145<br>4.8% | n=145<br>0% |

[a] Including recent cases not referred to in text.
[b] Significantly more frequent than in GN or non-GN (chi-square-test: $p < 0.001$).
n Number of cases. % Percent of cases in which parameter present.

A decrease in creatinine clearance was found in cases with segmental glomerular sclerosis in 7 of 12 of our patients and in only 4 out of 24 without the change. Proteinuria is also more frequent in the group with segmental sclerosis (see also [521]). We observed a nephrotic syndrome exclusively in the group with segmental glomerular sclerosis as occurred in our only case with hypertension. Our concept of the morphogenesis and significance of morphologic findings is presented in Figure 23.37 (see also: [1837].).

**Pathogenesis**

The primary injury lies, morphologically, in the glomerular BM; it is not known how it occurs. We suppose that the underlying cause is to be found in a congenital enzyme deficiency—most likely of the podocytes—leading to formation of abnormal BM substance which is first discernable as a structural lamina densa change during the course of childhood.

The previously mentioned, and certainly inconstant disturbance in proline metabolism (see p. 467), could support this otherwise unproven supposition as could the finding that the BM is incapable of binding antiglomerular BM antiserum reacting with the BM in non-Alport patients [1044]. Seven cases of transplants—including one of our own—without relapse after months and years currently known also reinforce the above contention [268].

The BM change is implicated in hematuria as well as in other functional changes which, as in Fabry's disease, for example, trigger a proliferative and sclerosing reaction which cannot be qualitatively differentiated from

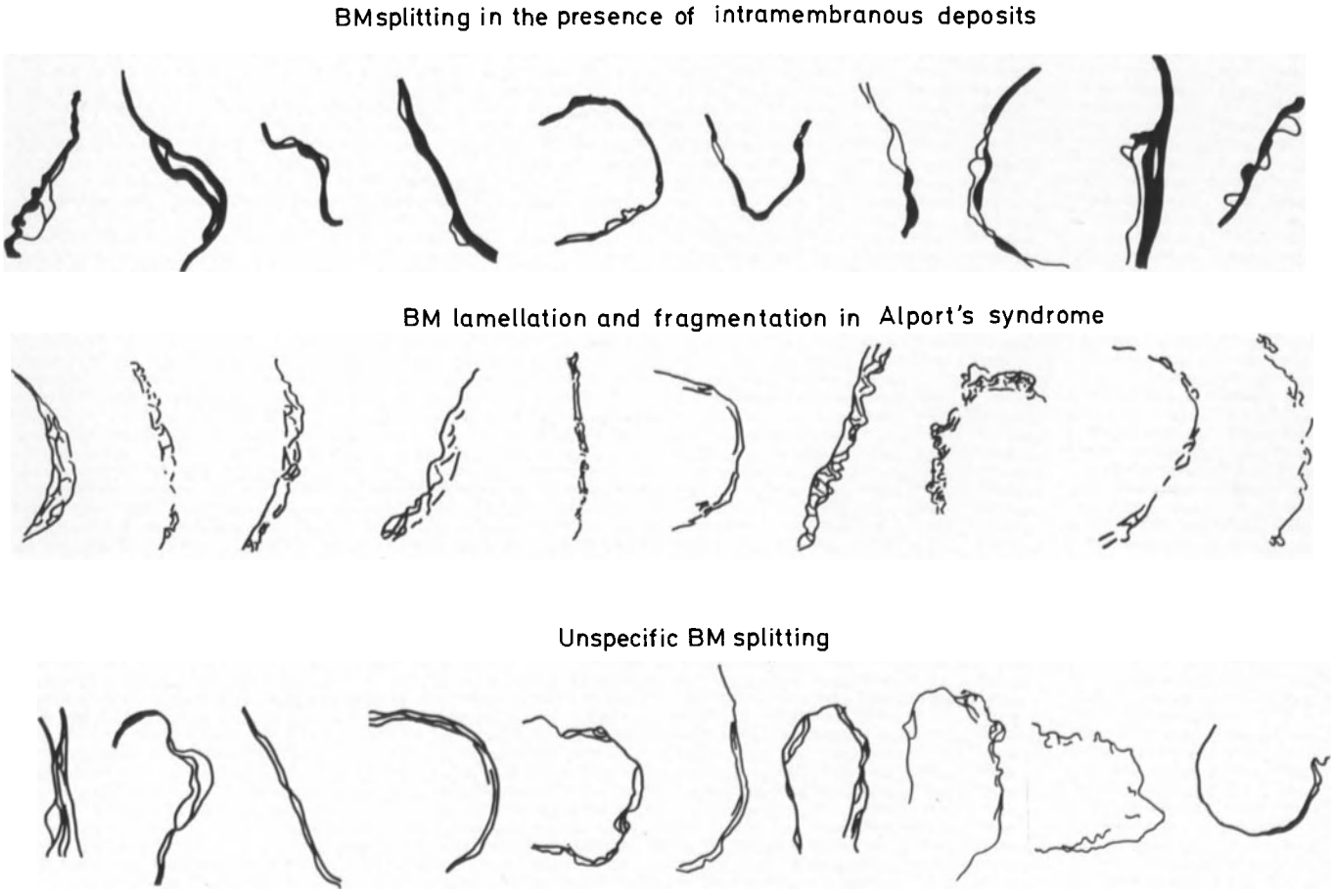



**Fig. 23.36.** Selection of the varying types of BM splitting in non-GN and GN kidney diseases and Alport's syndrome. Drawings—only of lamina densa of BM of the peripheral glomerular capillary loops—obtained by tracing lamina densa lamellae from electron micrographs from a group of 75 cases. Subdivision in the three groups indicated was done in single-blind fashion uniquely on the basis of their common configuration (i.e., without knowledge of the underlying disease, by persons without medical training). Unspecific BM splitting is found mainly in non-GN, whereas BM splitting in the presence of intramembranous deposits was chiefly encountered in GN

GN. We believe that the osmiophilic deposits quite frequently seen are due to insudation arising from BM permeability disturbances. They may play an essential role in progression of the disease (Fig. 23.37).
The origin of foam cells is the same as that which is operative in so called lipoid nephrosis, e.g., GN, glomerular minimal change, etc., whereby blood lipoproteins, reaching the renal filtrate due to glomerular injury are reabsorbed in the tubules and stored as cholesterol esters and given off to the interstitium. Such afflicted kidneys may contain 3.5–40 times the normal amount of renal cholesterol esters [1189].
Hereditary macrothrombocytopathia (with deafness and renal changes) is thought to be closely related to Alport's syndrome, but in this disease, girls are more afflicted than boys. Focal GN has been described in association with the disease. In EM, however, the typical BM changes are absent [438].

## Idiopathic and Benign Familial Hematuria

### Definition

The entity *idiopathic (essential) hematuria* is a disease in which morphologic (LM, EM and IF) findings are negative [655]. The same consideration is valid for *benign familial hematuria* in which, however, EM examination may show slight BM changes. Furthermore, EM is required for exclusion of Alport's disease which cannot be determined with LM alone.

### Incidence

The incidence of both entities is not well known. Among 29 cases of isolated hematuria studied with LM, only 10 out of 29 were idiopathic and 9 out of these familial [655].

### Clinical Findings

Microhematuria is relapsing and often occurs subsequent to respiratory tract infection [685, 995]. Hearing impairment or serum complement changes do not occur [909, 1039]. Familial stigmata must, of course, be especially sought in cases of microhematuria [1039].

### LM and IF Findings

In keeping with the definition, the findings are completely negative in benign familial and in idiopathic (essential) hematuria (LM: [1484, 1009, 1039]; IF: [1009]).

### EM Findings

In benign familial hematuria, a partially focal, partially diffuse BM thinning (Fig. 6.56) of up to 1040 Å [695, 1351], as well as the presence of numerous erythrocytes in the capsular space, are supposedly indicative of the disease. Perforations and other injuries to the BM have also been described [1351].
The description of BM splitting [695]—not confirmed by photographic evidence—arouses strong suspicion of Alport's syndrome whose inheritance pattern, moreover, appears to be the same as that of familial hematuria [1351].

### Differential Diagnosis

Differential diagnosis must be undertaken with great caution. As mentioned previously, LM, IF and EM findings are supposed to be negative. Additionally, a sufficient number of glomeruli must be present for study.
Examination of a large series of biopsies of purported idiopathic hematuria have almost always revealed the clear-cut pathologic findings of other diseases such as proliferative FGN [678, 995, 1242, 1544]. This suggests that idiopathic and familial hematuria are rare diseases. Some cases with negative morphologic findings may be diagnosed as idiopathic hematuria for years and, in the long run be shown to have been the consequence of a hemangioma, of a subpelvic cyst [973], or, of course, of a pyelonephritically induced fornix bleeding or even of a renal (pelvc) tumor. Formerly (without EM and IF), there was probably broad overlapping with IgA-GN.

### Prognosis

The prognosis of genuine idiopathic and familial hematuria appears to be absolutely benign. A few cases reported ending in uremia [995] were probably falsely diagnosed.

### Pathogenesis

The pathogenesis is obscure. The familial benign form may possibly be related to Alport's syndrome [1393].

## Nail-Patella Syndrome
[11]

The nail-patella syndrome is a very rare familial disease—apparently closely related to Alport's syndrome—characterized by nail dysplasia and osseous abnormalities (osteo-chondro-dystrophy: [421]) of the knee, elbow and ilium (iliac horns).

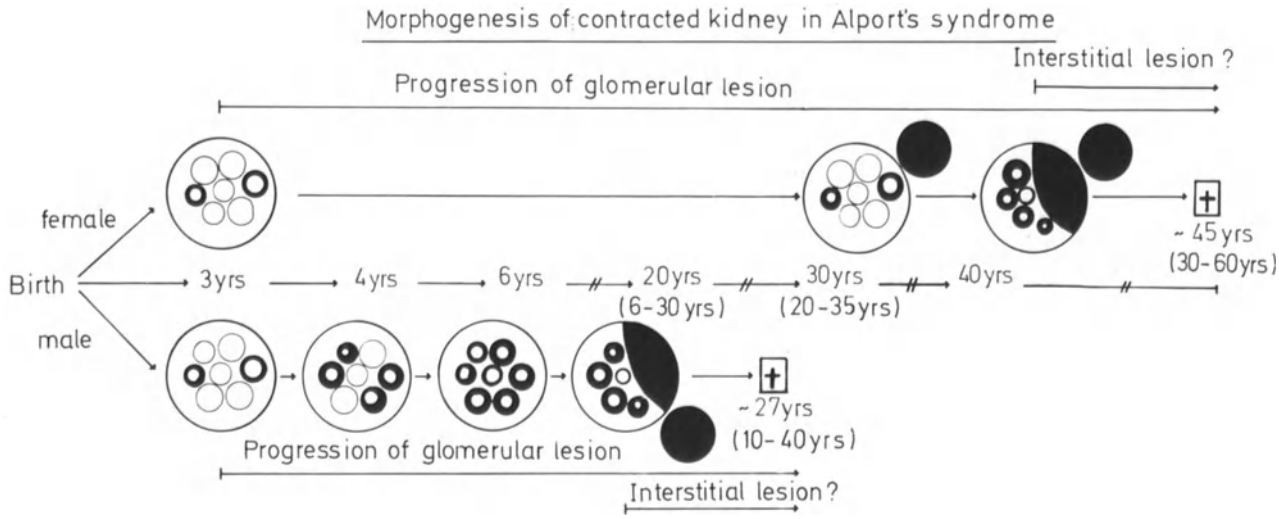



**Fig. 23.37.** Morphogenesis of contracted kidney in Alport's syndrome based on an analysis of our own cases. There is a progressive involvement—as seen under EM—of glomerular capillary loop BM within single glomerulus (and different glomeruli) which procedes more rapidly in the male than in the female, and which results in segmental glomerular sclerosis—on average at age 20 in the male and 40 in the female. Thereafter, development of contracted kidney probably proceedes very rapidly since death occurs in males on average at age 27 and in females at 45 years. Thus, we consider segmental glomerular sclerosis as an indication of a more rapid decrease of renal function during the following decade

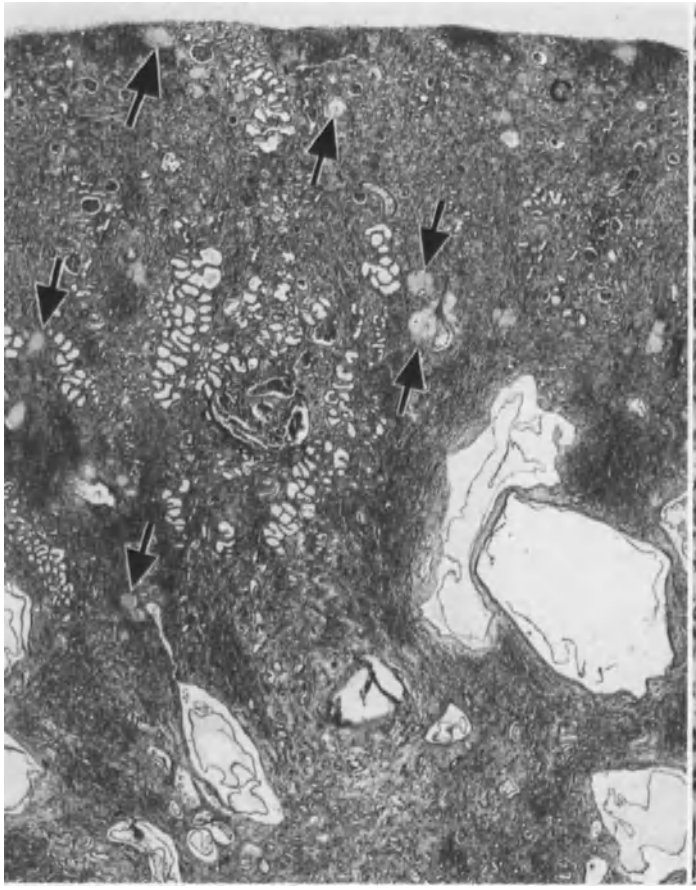


**Fig. 23.38.** Nephronophthisis in a 9-year-old girl. There are numerous small cysts at the corticomedullary junction. Dark foci represent inflammatory interstitial infiltrates. Tubules are severely atrophic, but a few demonstrate compensatory hypertrophy. Some of the glomeruli are completely obsolescent (→). HE (×15)

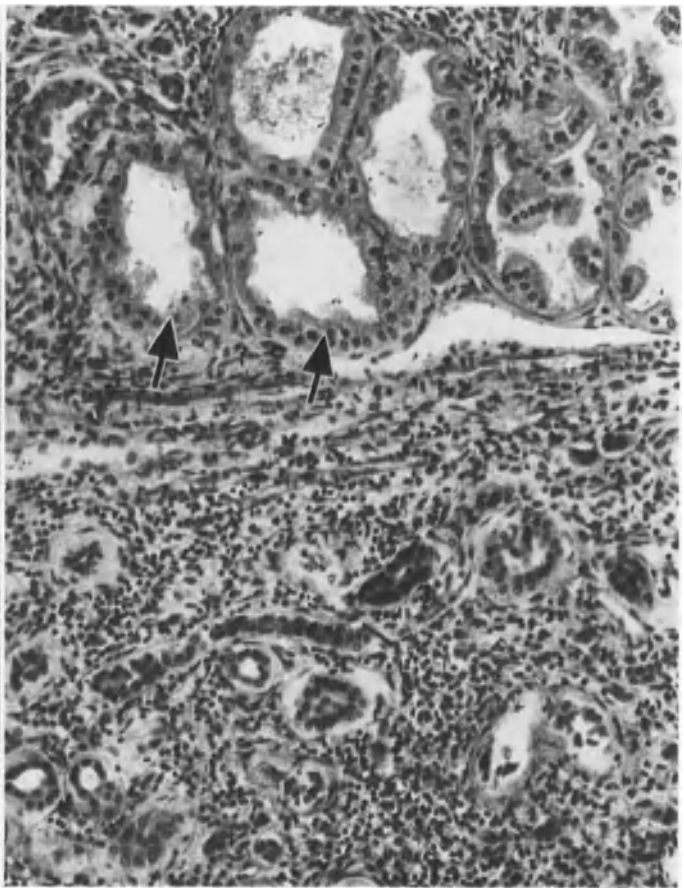


**Fig. 23.39.** Same case as in Figure 23.38. At the corticomedullary junction, most of the tubules are severely atrophic and show thickened BM; a few tubules evidence compensatory hypertrophy but are otherwise unchanged (→). Interstitium shows inflammatory infiltrates and sclerosis. Female, 9 years. HE (×180)

In one series of cases [117] 36 out of 72 patients showed renal symptoms: 17 proteinuria, 12 pathologic urinary sediment with erythrocytes, leukocytes and casts, 7 decreased concentration of urine, and 5 decreased creatinine clearance. Of the patients with the disease, 27% die due to renal impairment [117].
LM and IF findings are unspecific and similar to those described for Alport's syndrome. Podocytic giant cells may be present in EM. All family members demonstrating osseous lesions—also those without clinical renal involvement—show a deposition of collagenous material in the BM as well as irregular BM thickening (12 cases: [117]), with mothhole-like defects. These BM changes appear to be highly specific and may be even pathognomonic.
As a cause of the disease, a disturbance of structural carbohydrates or pathologic collagen formation have been proposed. A renal transplant in an 11 year old boy has remained free of relapse [421]—as in Alport's syndrome—which points to local cellular disturbance of the host kidney. In one case, nail-patella syndrome was complicated by Goodpasture's syndrome [1847].

## Primary Tubulopathy
[545, 1474, 1555]

LM, EM, histochemical studies as well as microdissections have, as yet, not revealed any pathognomonic findings in primary tubulopathy (Table 23.5) nor have they contributed to a better understanding of the disease.
In phosphate diabetes and renal tubular acidosis, the described morphologic changes appear to be more related to the secondarily developing nephrocalcinosis than to the basic disease. Currently available publications or morphologic examinations are summarized in Table 23.5.

Table 23.5. Primary tubulopathies

| Disease entity | Literature |
|---|---|
| Renal glucodiabetes (=glucosuria) | [1121, 1122, 1123, 1124, 1326] [940, 1276, 507] |
| Renal diabetes insipidus | [120, 249, 342, 850, 988, 1696] |
| Phosphate diabetes (=vitamin D-resistant rickets) | [1190, 1251, 1276, 1724] |
| Renal tubular acidosis (=Butler-Albright-Lightwood syndrome) | [11, 69, 583, 1423, 1762] |
| Hartnup syndrome | [347, 699, 711] |
| Lowe syndrome | [1218, 1390, 1405, 1645, 1754] |
| Primary congenital complete and incomplete Fanconi syndrome | [306, 316, 376, 735, 887, 1185, 1584, 1725, 1749, 590a, 1050] (Fig. 4.25) |

## Secondary Fanconi Syndrome

The secondary Fanconi syndrome has been described up to now in the following conditions: subsequent to heavy metal poisoning (many cases), in Wilson's disease, plasmocytoma, galactosemia, tyrosinosis, tetracycline poisoning and in relation to poisoning with numerous aromatic compounds [1474].

## Nephronophthisis
[655, 924]

### Definition

Nephronophthisis is a familial disease with autosomal-recessive inheritance (occasionally dominant: [146, 691]) which is not primarily a vascular or glomerular renal affliction. The entity leads to contracted kidney in childhood and is thought to be identical with medullary cystic disease of the kidney (see below).

### Incidence

The disease is very rare (2 out of 25,000 autopsies and 3 out of 2080 biopsies: Z; 69 cases: [457, 924]).

### Clinical Findings

82% of the cases are familial and usually of the autosomal-recessive inheritance type [924]. Boys and girls are equally afflicted in about the fourth year of life [1395]. The symptoms are: decreasing concentrating ability of the kidney, polyuria and polydipsia, anemia, and later, azotemia, salt loss, and imino-acid disturbances [118, 830a]. Other urinary findings are reported to be practically normal [457]. Hypertension is usually not present, or only terminally [456]. Renal X-ray abnormalities are frequent in the form of ectatic tubules and papillary blush [830a].
Retinal dystrophy may be present as well as cerebellar ataxia and skeletal hyperplasia [146] and, rarely, liver fibrosis [1299]. Death usually occurs between the fourth and 25th years of life (average: 11.2 years [551]). In the Senior-Loken syndrome, inflammatory tapetoretinal degeneration is present [479, 26a]. Allied diseases are probably the recessively inherited renal-retinal dysplasia [57a] and less-defined forms of familial interstitial nephritis [296b].

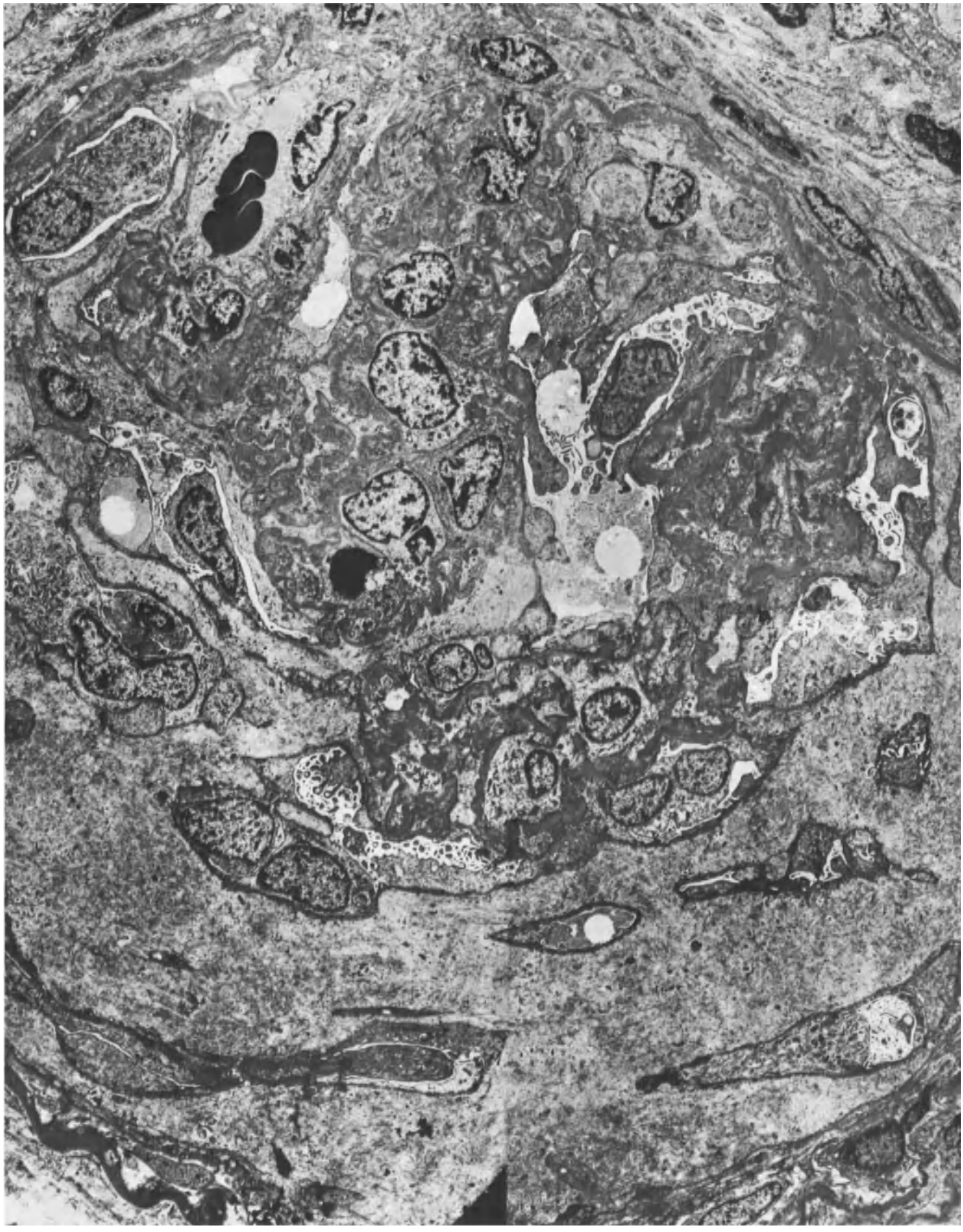


**Fig. 23.40.** By and large obsolescent glomerulus (collapse type) in nephronophthisis. Male, 5 years. EM ( $\times 2370$)

### LM Findings

At autopsy, small, uniformly contracted kidneys are found, each weighing 20–40 g [551]. At this advanced stage of the disease, the findings are scarcely decipherable. Nevertheless, an important finding is the presence of cysts of up to 10 mm in the outer medulla (Figs. 5.15, 23.38) which we have observed in 2 out of 5 of our autopsy cases (6 out of 15 cases: [924, 1395]) and which are usually not found in biopsies (0 out of 3 cases: Z). The cysts may also occur in the cortex [575, 691, 1350] and are said to arise from collecting ducts [691, 1495].

The high degree of parenchymal atrophy is considerably more extensive in the cortex than in the medulla. The glomeruli are mostly obsolescent (collapse type) and demonstrate thickening of Bowman's capsule [1358, 340] from which obsolescence is thought to procede [638]. Severe periglomerular fibrosis is also encountered [551, 1129, 1495].

Tubular BM is greatly thickened and the tubuli themselves are focally severely atrophic (Fig. 23.39; [638, 691, 755, 966, 1358]. Distal tubules are supposedly injured before the proximal ones [638, 1480]; contra: [551].

Thyroid-like foci have been occassionally described and illustrated [575, 638]. Unchanged or hypertrophic nephrons occur side by side with atrophic ones (Fig. 23.39; [146, 924]; 5 out of 5: Z). Microdissection has revealed tubular diverticulae [1495] and especially so in the descending branch of Henle's loop (15% of a series of cases: [476]). This finding is not specific.

The interstitium exhibits severe increase in connective tissue and almost always contains numerous lymphocytes (Fig. 5.15; [1480]) and occassionally plasma cells [638, 655, 1358], whose occurrence, however, has been denied [457]. The vessels are unchanged.

### IF Findings

The IF findings are negative (3 out of 3: Z; [1350]).

### EM Findings

Three of our biopsies demonstrated numerous collapse glomeruli in various stages of obsolescence (Figs. 23.40, 23.41). We have not uncovered evidence of a primary glomerular lesion. Severe atrophy of some of the tubules with extensive thickening of their BM (Fig. 23.42)—which is now and again split and vacuolized—(Fig. 23.43) are typical findings.

Thyroid-like tubules rarely occur and are always isolated (never in groups). In varying degrees, the epithelium is secondarily degeneratively changed (Fig. 23.44). Initially, vacuolization and foam cells are present followed by epithelial necrobiosis, detachment and total necrosis. In our cases, we found no deviation from the usual picture of tubular atrophy. We did not find changes in the tubules—which were still well preserved—indicative of a primary tubular lesion.

In all cases, the interstitium is severely broadened by very coarse bundles of collagenous fibrils (Fig. 23.42) between which relatively few phagocytes, a moderate number of small lymphocytes, and a very small number of plasma cells are found. Neither tubules, glomeruli, nor vascular adventitia evidence signs of inflammatory destruction. It is striking that the intertubular capillaries remain practically unchanged despite the presence of interstitial sclerosis (Fig. 23.42).

According to other investigators [1350], healthy family members of afflicted patients supposedly have focally laminar thickened tubular BM and sack-like evaginations.

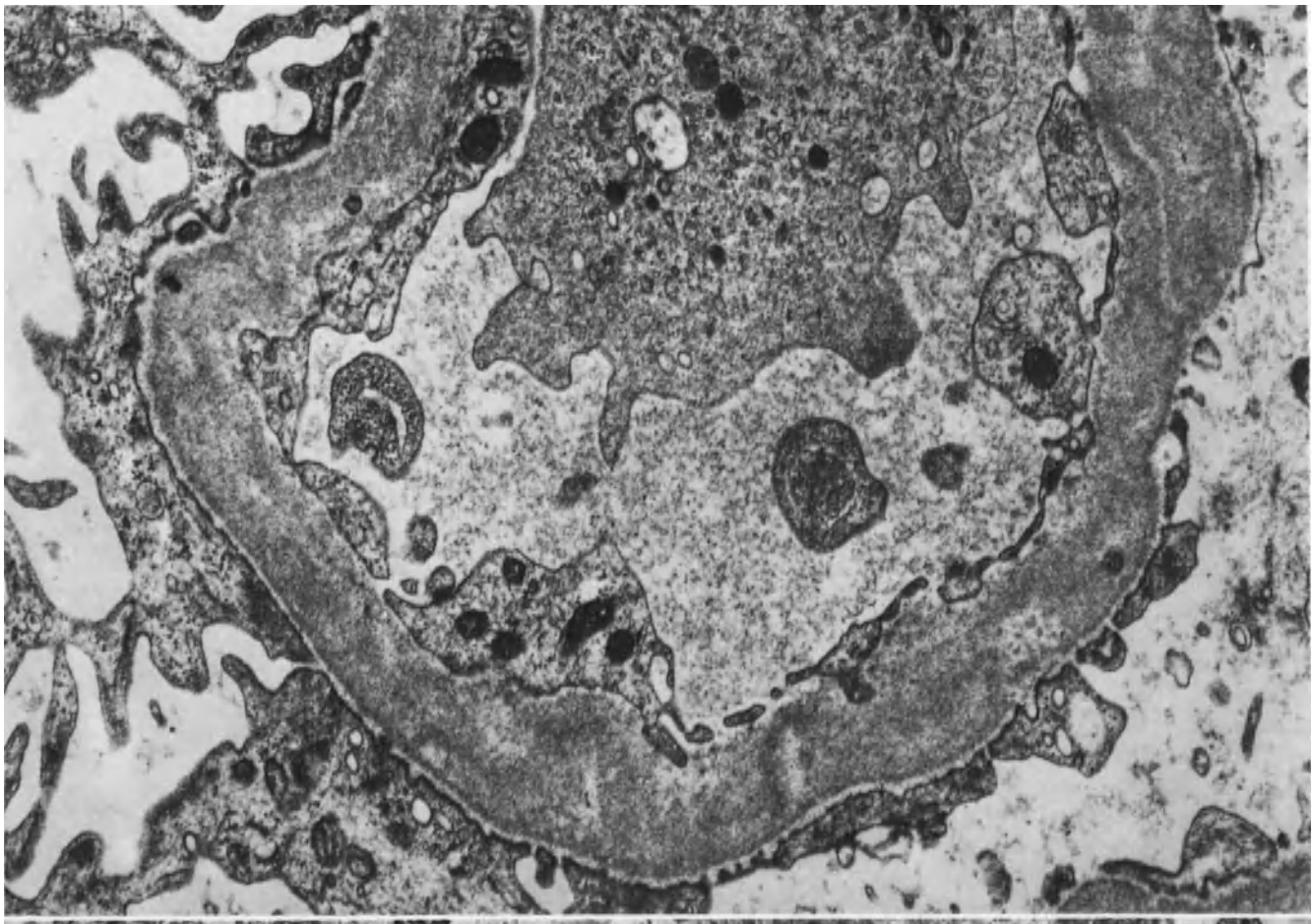
### Differential Diagnosis

Decisive for the diagnosis is the demonstration of a large number of cysts in the medulla. This demonstration is, unfortunately, difficult, since the cysts are rarely present in needle biopsy material.

The absence of destructive interstitial inflammatory foci justifies the exclusion of pyelonephritis. The hypertrophic tubuli encountered in PN—and especially in the early childhood form—must not be confused with cysts. In late disease stages, this differentiation may prove exceedingly difficult.

**Fig. 23.41.** Same case as in Figure 23.40, illustrating a slight collapse change of glomerular capillary loop BM in nephronophthisis. BM is wrinkled and partially somewhat loosened. Foot processes are fused. Male, 5 years. EM (×23,100) ▷

**Fig. 23.42.** Same case as in Figure 23.40, showing renal interstitium and tubules in nephronophthisis. Tubular atrophy with epithelial dedifferentiation and BM thickening predominate. Note isolated, unspecific foam cell formation (→). Interstitium is highly sclerosed and evidences loosely arranged infiltrates consisting of phagocytes, fibrocytes, and a few small lymphocytes. Intertubular capillaries are unchanged. Male, 5 years. EM (×1300)



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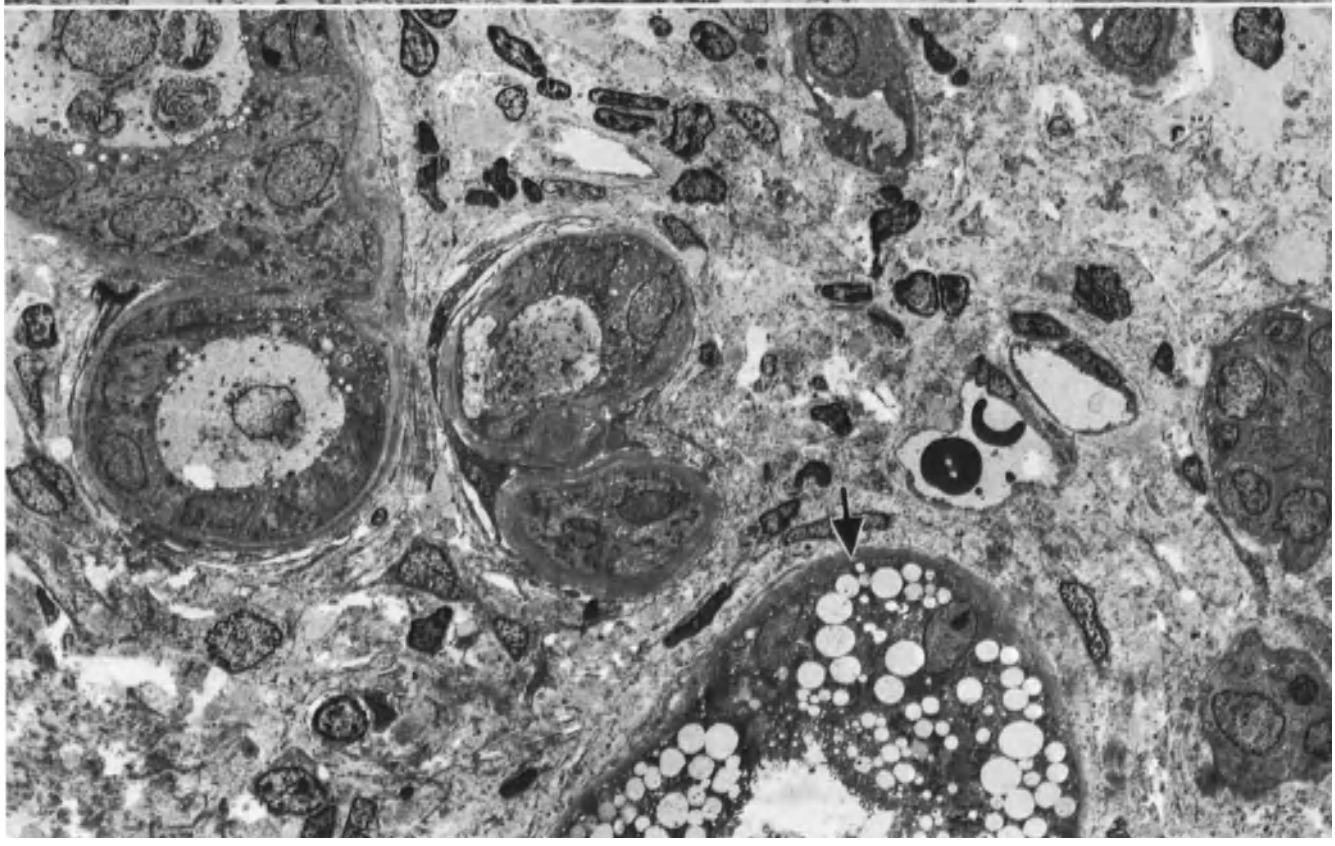

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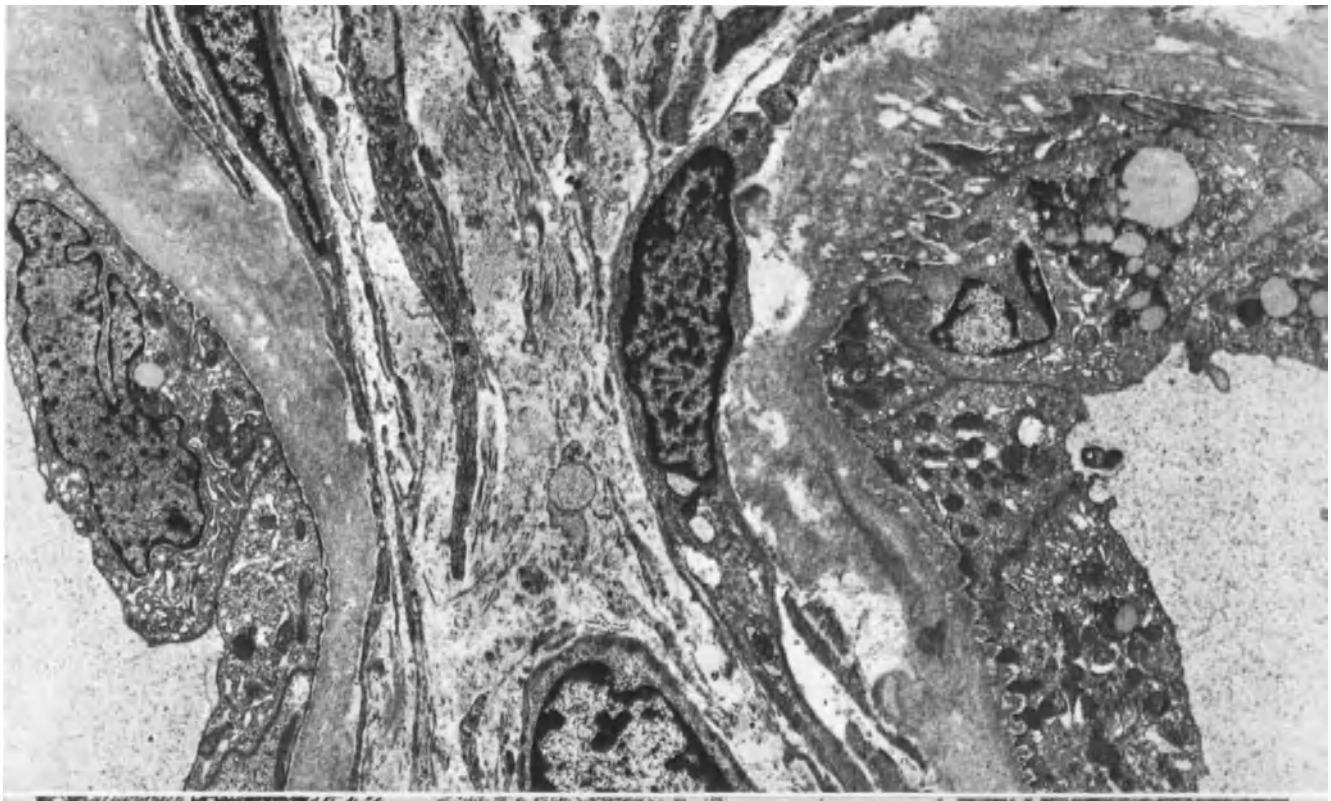
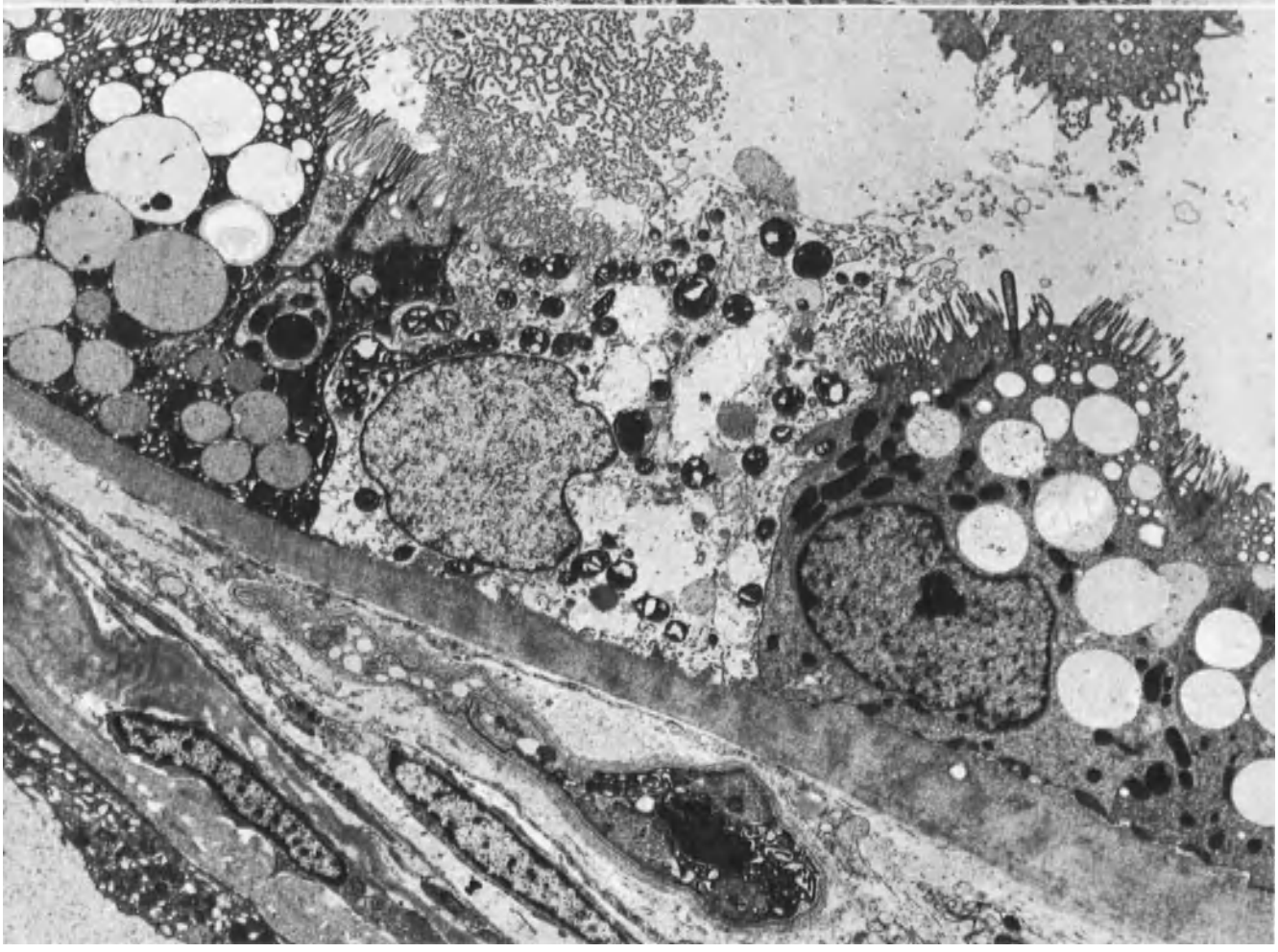


23.43



23.44

GN is often not easy to exclude. However, the type of glomerular obsolescence does not correspond to the GN type but to the collapse type.
We have not succeeded in differentiating nephronophthisis from nondestructive interstitial nephritis. It should always be borne in mind that cysts can develop secondarily in all forms of contracted kidney.
The medullary (papillary) sponge kidney does not exhibit severe cortical lesions. It can be unilateral, frequently lead to stone formation and, occasionally, to secondary pyelonephritis [239, 904, 1301, 1308].

### Prognosis

The prognosis is practically hopeless unless transplantation is carried i.e. no relapse of the disease occur in the transplant [691].

### Pathogenesis

In the first publication [456], the reporting pathologist considered the disease to be a chronic glomerulo-tubulonephrosis with interstitial nephritis, while the discoverer of the disease [456] viewed it as primary tubular destruction and the interstitial nephritis component as a secondary phenomenon. In general, Fanconi's view has prevailed [691, 1480]. Tubular damage is supposedly due to a familial metabolic disturbance (unknown nephrotoxic substance: [691, 1129]). In a later publication [457] Fanconi spoke of a developmental disturbance of the entire nephron.
The thickening of the tubular BM is thought to be due to injury to the tubular epithelium which, in turn, leads to impairment of permeability [1480].
We are not convinced that a primary tubular defect is the basic disease lesion, especially since completely unchanged nephrons are frequently found side by side with those evidencing severe changes. The extent to which medullary cysts due to impairment of urine flow may be responsible for the development of chronic interstitial nephritis—such as is possible in papillary necrosis—awaits further clarification.
In agreement with the majority of investigators, we are of the opinion that the *medullary cystic kidney* and *nephronphthisis* are one and the same disease entity [557, 684, 924, 1129, 1253, 1571].
With respect to this statement, it must be firmly realized that there are differences between *benign medullary* (better: *papillary*) *sponge kidney*—with involvement of, above all, the papilla—and *medullary cystic kidney* which are not always appreciated [425, 579, 1149, 1495]. The medullary (papillary) sponge kidney can be unilateral, frequently leads to stone formation and, occasionally, to secondary pyelonephritis [239, 904, 1301, 1308].
It is not known whether the autosomal dominantly inherited cystic kidney afflicting the corticomedullary zone—which appears during the fourth to fifth decades of life without concomitant anemia or salt loss [1761]—is or is not a mild form of the disease. In any event, the medullary (papillary) sponge kidney is also familial in 50% of the cases. This disease shows, in the majority of cases, an autosomal-recessive inheritance pattern and occurs—above all with anemia—around the twentieth year of life [924]. Diagnosis is usually made in two-thirds of the cases between the third and sixth decades of life. Clinically, differentiation between medullary cystic kidney and medullary (papillary) sponge kidney is not always easy [830a], but usually in the latter disease state radially arranged cysts can be demonstrated radiologically [602a].

◁ **Fig. 23.43.** Same case of nephronophthisis as in Figure 23.40. Tubular BM is severely thickened and occasionally split; tubular epithelium is dedifferentiated and atrophic. Tubules are surrounded by proliferated fibroblasts and interstitium is sclerosed. Male, 5 years. EM (× 5440)

**Fig. 23.44.** Same case as in Figure 23.40. Tubular changes in nephronophthisis. Tubular atrophy, dedifferentiation of epithelial cells, and masses of lysosomes are seen. A slight homogeneous BM thickening is present. Male, 5 years. EM (× 3840)

## Nephrocalcinosis
[263, 439, 655, 674, 967, 1791]

### Definition

Nephrocalcinosis, either metastatic or dystrophic, is a condition characterized by the deposition of calcium salts intracellularly and extracellularly in the kidney. Extracellularly, the salts occur as calcium casts in the tubular lumen and as calcium depositions in the BM and ground substance of the interstitial connective tissue.

### Incidence

A slight deposition of calcium salts in the papillary interstitium is found in 20–100% of autopsies [439, 642, 1717]. Marked nephrocalcinosis is considerably more rare (18 out of 2080 biopsies = 0.87%: Z).

### Clinical Findings

In the early stages of nephrocalcinosis, the symptoms of the underlying disease which lead to calcium deposition predominate. In the dystrophic form of the disease which follows tubular necrosis, acute renal failure is the main symptom. The early stage of the metastatic form occurring in hypercalcemia is characterized by an insufficiency in urine concentration. In the chronic state, this form can lead to progressive renal insufficiency occasionally accompanied by hypertension [674].

### LM Findings

Smaller, granular calcium deposits are very difficult to discern with the PAS stain (Fig. 23.45), so that thorough scanning of the HE-stained slides is extremely important.

In dystrophic calcification, the necrotic, calcified tubular epithelial cells are shed into the lumen (Fig. 23.46). It is sometimes possible to recognize the tubular origin of the epithelial cells from the form of the calcium deposits.

In metastatic calcification, intratubular calcium casts have a clumpy, stratified structure (Fig. 23.47). In this form too, it is sometimes possible to see the primary calcium deposits in the epithelial cells. Polysaccharide can often be demonstrated along with calcium salts in PAS-stains (possibly glycocalyx: [220, 1003]). In addition to amorphic calcium deposits, crystalline deposits are also observed (calcium oxalate, see p. 460).

With LM, intracellular calcium deposits cannot usually be unequivocally identified since they are limited to mitochondria or lysosomes (see below).

Interstitial calcium deposits are observed in the region of the collagen fibers or in the PAS-positive ground substance. Very rarely, calcification of tubular and glomerular BM occurs, but it may be excessive (Figs. 23.45, 23.48; [1356, 1370]).

### EM Findings

Since sufficient data for the different forms of nephrocalcinosis in humans are not available, the following discussion, accordingly includes data from animal experiments which should be viewed with appropriate reservation.

In metastatic calcification, calcium deposition starts, for example, following parathormone or vitamin D administration in probably previously injured mitochondria. This injury must not be massive however, since calcium accumulation is an active function of the mitochondria. Deposition occurs in the form of apatite crystals [258, 400, 543, 1428].

In the presence of magnesium deficiency, calcium is taken up in the lysosomes (Fig. 23.49; [220]).

Extracellular deposition on BM (Fig. 23.50) and on interstitial collagen fibers (Fig. 23.50) usually takes place in the form of amorphic masses of calcium carbonate [1370, 1356, 1501, 1717]. Calcium salts are primarily deposited in mitochondria—also in the dystrophic form of calcification—before the cells become necrotic and are shed (see p. 486).

### Prognosis

The prognosis usually depends on that of the underlying disease which leads to nephrocalcinosis. Accordingly, it is very poor for the extensive dystrophic calcification in cortical necrosis or in toxic tubulonecrosis, e.g., following mercury bichloride (sublimate) poisoning, because of the irreversible renal parenchymal injury (see p. 487).

If the cause of the hypercalcemia which leads to metastatic calcification is eliminated in time, no irreversible renal injury will occur. The associated concentrating insufficiency is reversible. When the hypercalcemia is of longer duration, however, the complications mentioned below can lead to a decrease of renal function and possibly even to hypertension. A recipient of a kidney transplant from a patient with idiopathic hypercalciuria did not show any disturbances of calcium metabolism [744].

### Complications

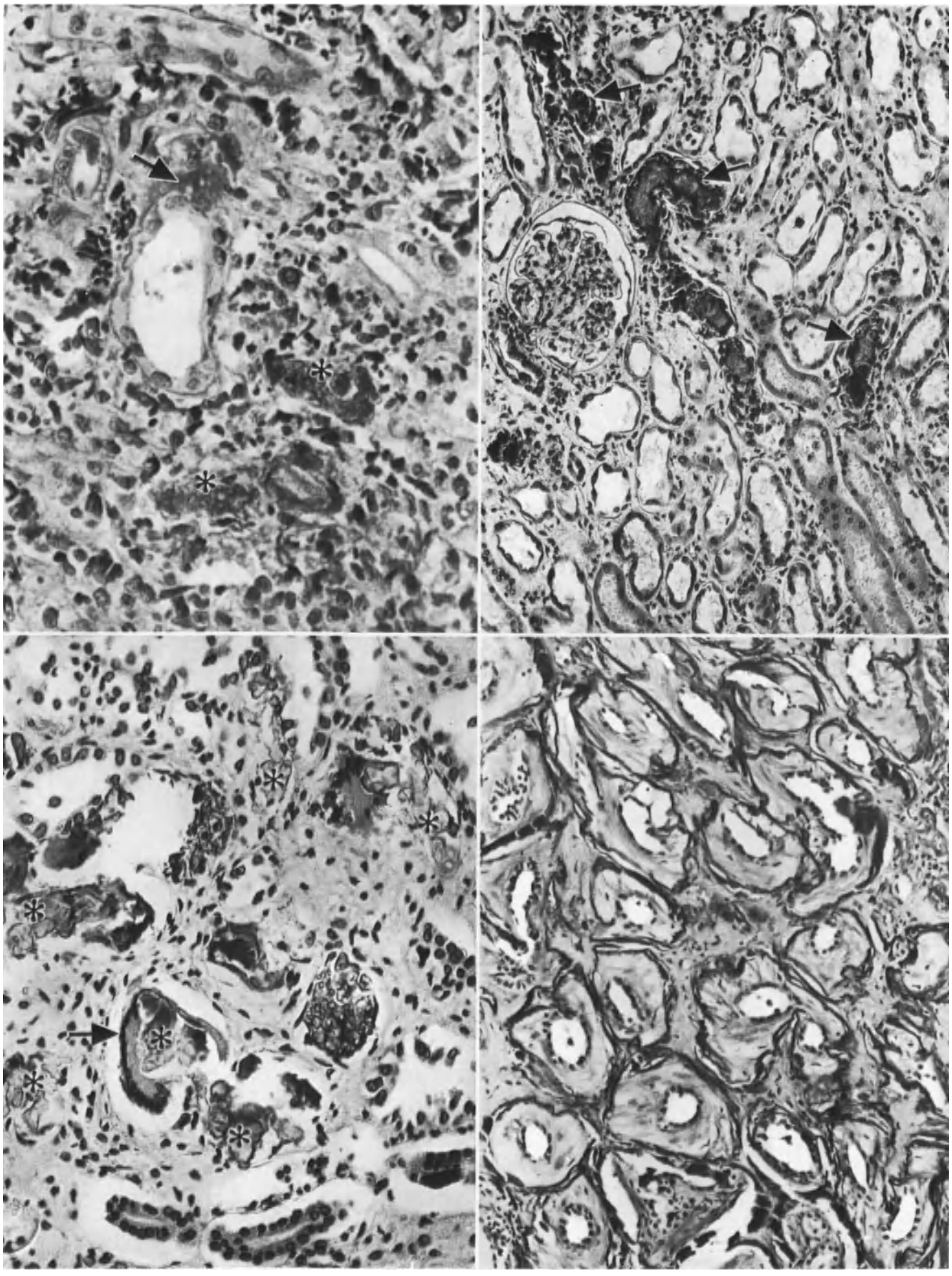
Calcium casts can cause nephrohydrosis, which in turn enhances the occurrence of PN. It is thought that extensive interstitial calcium deposits lead to fibrosis [642, 1717].

**Fig. 23.45.** Nephrocalcinosis in acute lymphatic leukemia. The ▷ rather massive calcium deposits (*) are poorly recognizable in this PAS stain, as are the focal tubular BM calcifications (→). Male, 3 years. (×550)

**Fig. 23.46.** Dystrophic calcification of necrotic tubular epithelium with cast formation (→). Biopsy was taken 7 days after a suicide attempt with mercuric chloride. Mild, nondestructive acute interstitial nephritis is present. There is severe flattening of proximal tubular epithelium. HE (×140)

**Fig. 23.47.** Nephrocalcinosis in idiopathic hypercalcemia. Massive clumps of calcium appear to be lying in the interstitium (*) and are surrounded by foreign body giant cells (→). Stroma is highly fibrosed and loosely infiltrated with inflammatory cells. Male, 2.5 years. HE (×270)

**Fig. 23.48.** Contracted kidney in nephrocalcinosis. There are massive calcium deposits in tubular BM. A wide mucoid layer has developed between tubular BM and epithelium. Male, 36 years. PAS (×90)



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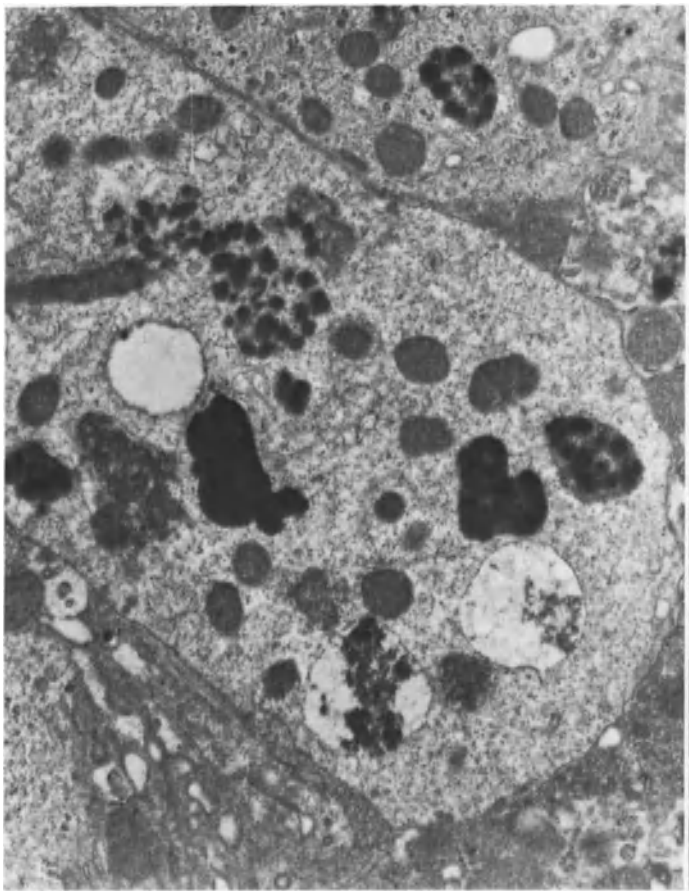


**Fig. 23.49.** Same case as in Figure 23.45. In proximal tubular cells, massive calcium deposits are present which are at least partly lying in mitochondria. Male, 3 years. EM (×12,340)

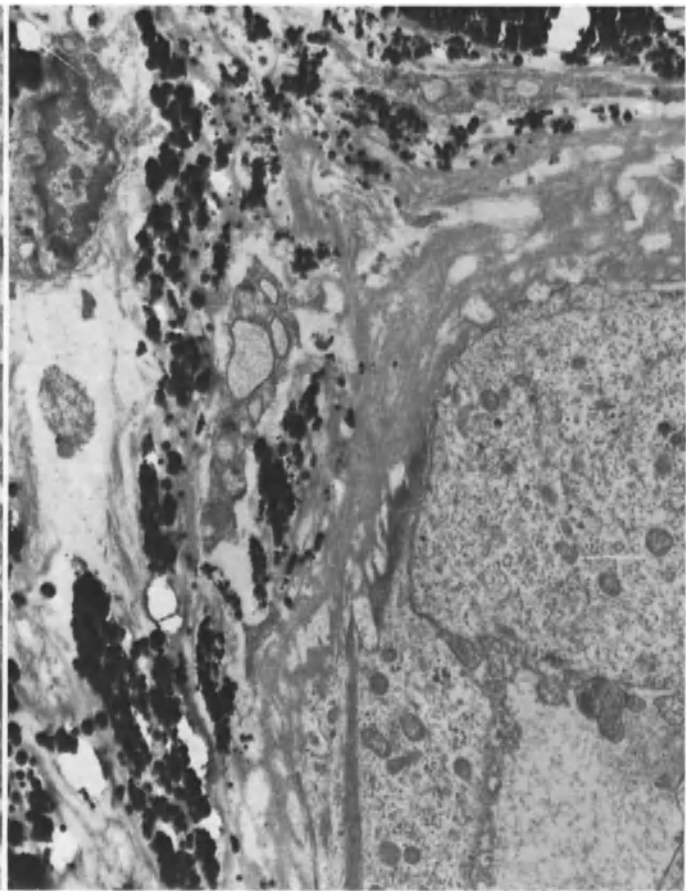


**Fig. 23.50.** Same case as in Figure 23.48 with massive calcium deposits in severely split tubular BM. EM (×6670)

## Etiology and Pathogenesis

In dystrophic calcification, calcium precipitation is enhanced by alkalinization of the tissue. A condition for the origination of nephrocalcinosis is the uninterrupted supply of calcium to the tissues from the blood. Therefore, calcification starts on the fringes of infarcted tissue and the central region (deprived of a blood supply) remains free of calcification for a considerable period of time [1315, 1501].

Metastatic calcification, which does not depend on tubulonecrosis, may be either associated with hypercalcemia or normocalcemia (Table 23.6; [674, 1739]). In the latter, it may be due to impaired proximal tubular calcium reabsorption or increased intestinal calcium absorption such as in idiopathic hypercalciuria [1192a].

Metastatic calcium deposition occurs predominantly in the renal medulla. This is explained by the fact that the medullary concentration of calcium is higher than in the cortex, even under physiologic conditions [1717]. A higher incidence of nephrocalcinosis in female animals obtained in experiments is due to their higher concentration of estrogen.

Nephrocalcinosis is also observed in primary or secondary oxalosis, in magnesium deficiency and in hypochloremia [220, 1419, 1591, 1791].

There is also evidence for sex differences in humans since men excrete more calcium under controlled calcium loading than women. Perhaps calcium resorption is more effective in women than in men [361, 537, 1142].

Predominantly experimental data are available relating to the renal zone for primary calcium deposition. Deposition may occur in the lumen (chloride deficiency: [1419]), intracellularly in mitochondria or lysosomes (vitamin D poisoning, parathormone poisoning, magnesium deficinency; calcium gluconate poisoning: [220, 258, 400, 1428]), in BM and in the interstitium [1356, 1370, 1717]. Precipitation occurs in contact with the mucoproteins or collagenous fibers of the ground substance. Chemical analysis of the calcium salts has shown the presence of hexosamines which correspond to those found in bone [537].

Table 23.6. Causes of hypercalciuria (modified from [674])

| Hypercalciuria associated with hypercalcemia | Hypercalciuria associated with normocalcemia |
|---|---|
| Primary hyperparathyroidism | Renal tubular acidosis |
| Malignant tumors | Fanconi's syndrome |
| Osteogenic tumors, skeletal metastasis of nonosseous tumors, following sex-hormone therapy | Interstitial nephritis |
| | Pyelonephritis |
| | Cushing's disease |
| | Cortisone therapy |
| Plasmocytoma | Osteoporosis (acute attack) |
| Hyperthyreosis | Diuretics |
| Vitamin D poisoning | (furosemide, ethacrynic acid) |
| Sarcoidosis | Idiopathic hypercalciuria |
| Paget's disease of the bone | Primary oxalosis |
| Immobilization | Magnesium deficiency |
| Fractures | |
| Progressive osteoporosis | |
| Idiopathic hypercalcemia of childhood | |
| Milk-alkali syndrome | |

## Toxic and Metabolic Tubulonephrosis [1094, 1448, 1791]

### Definition

Toxic tubulonephrosis results from direct injury to the tubular epithelium by exogenous or endogenous poisons. This does not include hypersensitivity responses which may be associated with acute, nondestructive interstitial nephritis (see p. 407).

### Incidence

There are no exact data from biopsy or autopsy material; the entity is rare.

### Clinical Findings

Renal involvement is usually manifested as acute renal failure. The symptoms of a secondary Fanconi syndrome are infrequently encountered [1091, 1448].

### LM Findings

The various morphologic forms of tubular injury observed are the result of the kind and amount of the causative noxious substance [1094].

***Fine Vacuolar Degeneration.*** This form, the so-called carbohydrate-storage kidney or osmotic nephrosis occurs following administration of various plasma expanders. In these situations, the kidney has usually undergone prior injury from impaired blood flow so that the transepithelial transport of the expanders is disturbed i.e. no longer possible (Figs. 8.16, 8.17, 8.18; see p. 126).

***Coarse Vacuolar Degeneration.*** This form afflicts the epithelium of the proximal tubules and occurs chiefly after glycol poisoning. It is also characteristically observed in hypokalemia as is noted following overdosage of diuretics or after therapy with amphotericin or neomycin (Fig. 8.21).

***Diffuse Lipid Deposition.*** A diffuse deposition of neutral fat—above all at the base of the proximal tubular cells—occurs simultaneously or consecutively with liver dystrophy following hepatitis, phosphorus or mushroom poisoning (Figs. 8.19, 8.20).

***Nuclear Inclusion Bodies.*** These are seen following lead or bismuth poisoning [585, 1084].

***Diffuse Tubulonecrosis.*** This is the most severe form of tubular injury. It is a characteristic finding in acute heavy metal poisoning (e.g., mercury). It is also observed in poisoning with organic solvents (e.g., carbon tetrachloride; Fig. 8.8) and following antibiotic therapy (e.g., viomycin, bacitracin, cephalothin, gentamicin: [1275a, 1765a, 1843, 1844]; Fig. 8.6). Following vitamin D overdosage, there occurs extensive calcification of necrotic tubular epithelium.

***Intratubular Precipitate.*** Precipitation of filtered or secreted substances is another form of tubular injury in which the distal nephrons are most affected.
After administration of poorly soluble sulfonamides—which are especially easily precipitable in an acid environment—a granulomatous inflammation develops around the precipitated crystals.
In the renal failure following methoxyflurane anesthesia, oxalate crystals (Fig. 23.15) are precipitated in the tubular lumen in addition to tubular injury caused by the released fluorine [274].

### EM Findings

There are only few reports in humans. In general, biopsy material is not available from the early phase of the disease, so that no information relating to the initial injury can be given [274, 480, 1094, 1763].
Experimentally, acute heavy metal poisoning has been best investigated. Following mercury poisoning, the earliest recognizable change is mitochondrial swelling, which is associated with a decrease in ATP synthesis, and acute transport insufficiency in the proximal tubules [708, 860, 1296, 1534].

Other investigators, giving higher doses of mercury, have found loss of the brush border and vacuolization of the endoplasmic reticulum to be the primary changes [527].
When administered to humans in the usual therapeutic doses (5 mg/kg/day), gentamicin leads to myelin figures and autolysosomes in the proximal tubules as well as to massive enzymuria [1719, 1843].
For EM findings in other toxic tubulonephroses, see p. 118.

### Differential Diagnosis

No reliable conclusions concerning the etiology of the changes can be drawn from the morphology of the tubules. Ischemic tubulonecrosis in the early stage can hardly be differentiated from that caused by poisons.
The localization of the injury in the nephron allows only conditional conclusions. Experimentally, both ischemia and poisons lead to necrosis, chiefly in the straight parts of the proximal tubules.

### Prognosis

Acute renal failure in cases of tubular necrosis currently enjoys a favorable prognosis due to the beneficial effects of dialysis. The Fanconi syndrome also undergoes remission following elimination of the poisons (for details and complications see p. 419).

### Etiology and Pathogenesis

Accidental poisoning is the most important cause of tubular necrosis e.g., poisoning with heavy metals, organic solvents, glycol, phosphorus, mushrooms and, formerly, diuretics.
Various antibiotics are also considered tubulotoxic [881, 1094, 1160]. Antibiotics are often given because of severe general infection which itself can lead to tubular injury and impairment of renal function [1275a]. The above statement indicates the difficulty encountered in attempting clarification of the pathogenesis of tubular injury. The direct tubulotoxicity of antibiotics, heavy metals and organic solvents has been proven in animal experiments [881, 1534, 1580].
Clinically, severe general illness is present, which is sometimes accompanied by acute liver insufficiency or shock, indicating that the pathogenesis of acute renal failure has a multifactorial basis. Impaired perfusion of the renal cortex apparently plays a significant role in the disease [19, 56, 709, 1275a].

# 24. Renal Changes Caused by Impairment of the Circulatory System

## Anoxic Glomerular Lesions

Unequivocal capillary loop necrosis (Fig. 24.1) occurs chiefly in arteriolonecrosis of the kidney or at the edge of infarcts.

Collapse glomeruli are far more frequent (Fig. 6.4; see p. 113). Massive fibrinoid deposits in capillary loops, which can even lead to their complete occlusion, are also often encountered (Fig. 24.3).

Under EM, the focal, translucent thickening of the lamina rara interna is characteristic of anoxic injury; it is, however, also seen in nonanoxic endothelial damage occurring with secondary plasma insudation (see p. 64). We have discussed the more severe changes on p. 113.

## Hemorrhage

Glomerular bleeding is observed in severe hypertension (Fig. 24.2) and especially so when anticoagulants are used. It is also observed in periarteritis nodosa, arteriolonecrosis and GN. Sickle cell anemia is often accompanied by occlusion of capillary loops with attendant necrosis and glomerular bleeding.

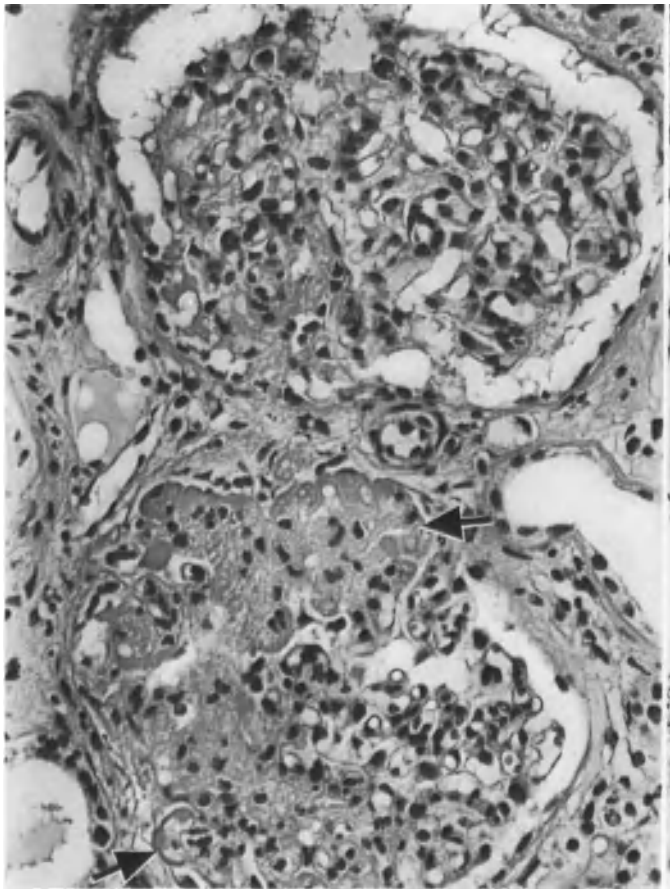


**Fig. 24.1.** Incipient anoxic glomerular capillary loop necrosis (→) in the outer zone of a fresh infarct. Male, 44 years. HE (×320)

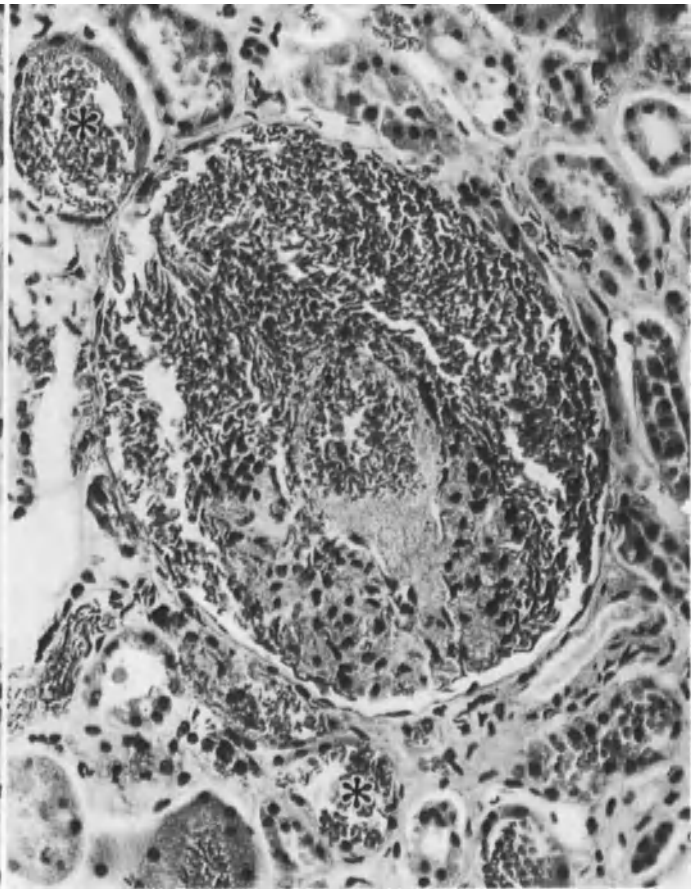


**Fig. 24.2.** Glomerular hemorrhage associated with hypertension of 350/170 mm Hg. Capsular space is filled with erythrocytes which can also be seen in the tubules (*). Male, 45 years. HE (×250)

Very massive parenchymal bleeding with rupture of the renal capsule (so-called spontaneous rupture of the kidney) is observed in transplants (see p. 610), in the macroform of periarteritis nodosa, other vascular diseases [1051, 1622] and occasionally in renal adenoma in the presence of anticoagulant therapy (own observation; see also [1716]).
The decisive initial factor in all these forms appears to be parenchymal necrosis with consecutive hemorrhage.

## Fat Emboli

These are, of course, rarely encountered in needle biopsy and they are very difficult to diagnose since the fat droplets are dissolved during the routine embedding procedure. Completely round, widened lumens of capillary loops which appear totally empty (Fig. 24.4) alone call attention to the possibility of fat emboli.

## Kidney in Shock

### Definition

The "shock kidney" is characterized by extensive widening of the tubular lumen (especially of the proximal tubules), by flattening of the epithelium, and by a more or less pronounced interstitial edema with or without lympho-plasmocytic infiltrates.

### Incidence

Shock kidney is encountered in 4–17% of autopsy material [226, 1453]. It is far more rarely observed in biopsy. This is explained by the fact that at autopsy, those cases are also included in which shock kidney develops in progressive terminal cardiac insufficiency. It is also recalled that acute renal insufficiency in cardiovascular shock is not an indication for renal biopsy.

### Clinical Findings

Due to the frequent overlapping of different etiologic factors, the clinical findings are presented on p. 407.

### LM Findings

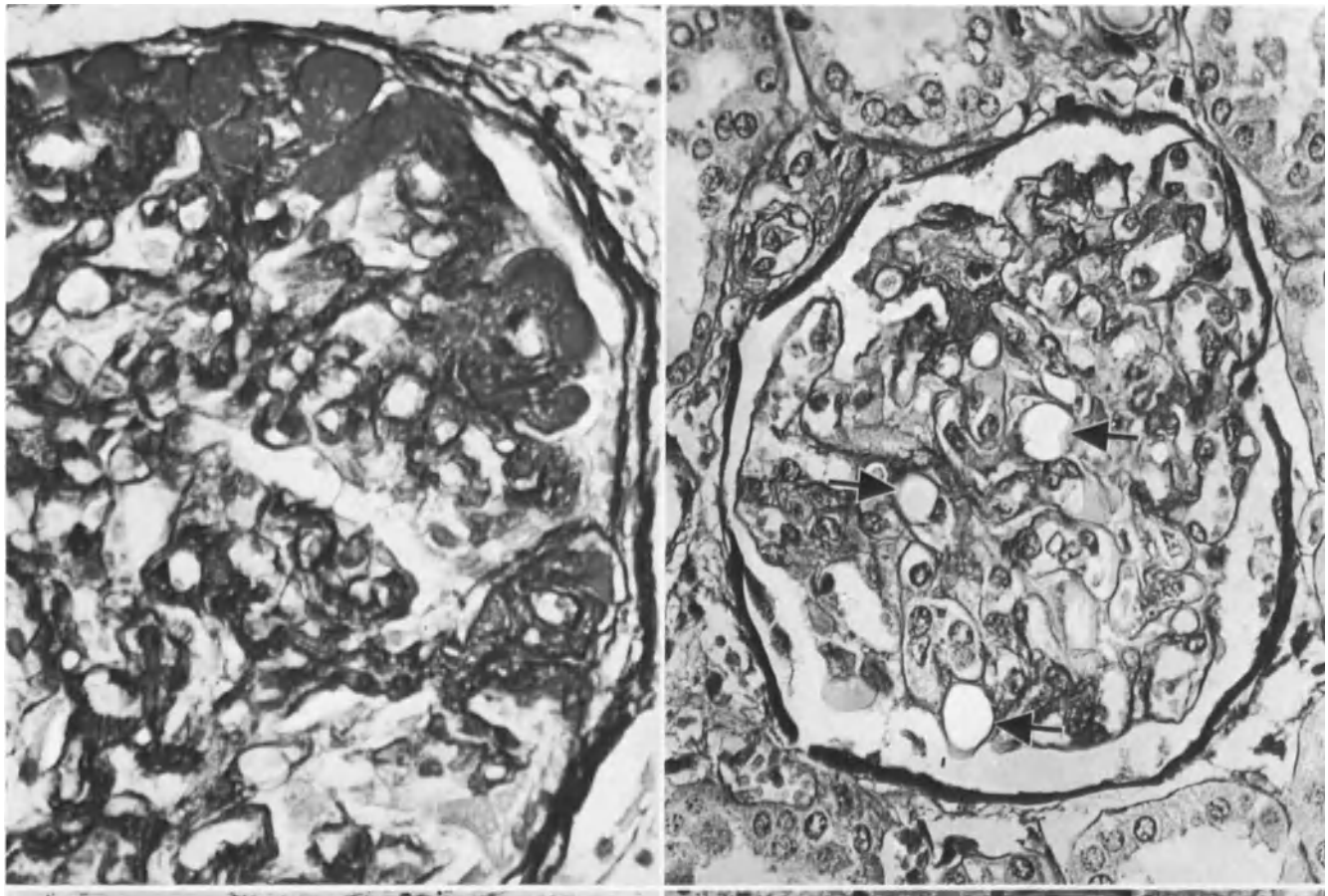
The characteristic sign in shock kidney is diffuse tubular dilatation with an increase of the outer and inner diameter and flattening of the epithelium (Fig. 24.5) which is partially dedifferentiated and shows cytoplasmic basophilia and loss of brush border. Tubulonecroses are rarely encountered and are restricted to small numbers of tubular cells.
Carbohydrate storage kidney is often observed (Fig. 24.6; see p. 125), It is caused by resorption of plasma expanders which, due to tubular transport insufficiency, can no longer be eliminated from the cells. The uptake of these materials (e.g., glucose, dextran, etc.) in the phagosomes with the subsequent inflow of water results in a fine, vacuolar transformation of the cytoplasm [313, 1213, 1791].
In the tubular lumens, especially in the distal parts, casts are regularly encountered which often consist of chromoprotein (Fig. 24.10) released, for example, by hemolysis attendant on shock in septicemia. More rarely, cell-casts of necrotic tubular epithelium are observed (Fig. 24.7).
The interstitium of the corticomedullary zone is widened by patchy edema and shows inflammatory infiltrates of lymphocytes, plasma cells, histiocytes and eosinophils, especially around veins (acute nondestructive IN, see p. 407; Fig. 24.8). A frequent finding in the bundles of dilated medullary vasa rectae is the accumulation of myeloid cells released from the bone marrow in shock (Fig. 20.4).
The glomeruli show no characteristic changes; capillary loop collapse is not obligatory. For intravasal coagulation, see p. 493.

**Fig. 24.3.** Anoxic glomerular capillary loop damage with fibrinoid deposits in anoxia associated with arteriolosclerosis. Male, 74 years. PAS (×840) ▷

**Fig. 24.4.** Fat emboli in post-traumatic anuria. Diagnosis can be made on the basis of scattered, severely dilated, optically empty (fat has been dissolved out) glomerular capillary loops (→). Male, 23 years. PAS (×500)

**Fig. 24.5.** Typical finding of so-called shock kidney as seen in biopsy 6 days after burn injury with anuria. Lumens of proximal tubules appear highly dilated due to severe flattening of proximal tubular epithelium due to ischemia. Outer tubular diameter is normal. Glomeruli are unchanged. Material was obtained at autopsy at which kidney weight was found to be 200 g. Male, 28 years. PAS (×50)

**Fig. 24.6.** "Overlapping" of tubular atrophy and swelling in shock kidney. Swelling of proximal tubular epithelium is due to carbohydrate storage; note delicate vacuolization (→). Coarse vacuoles of a few proximal tubular cells (*X*) are indicating hypokalemia. Patient suffered from severe shock following poisoning with formic acid. Female, 68 years. HE (×255)



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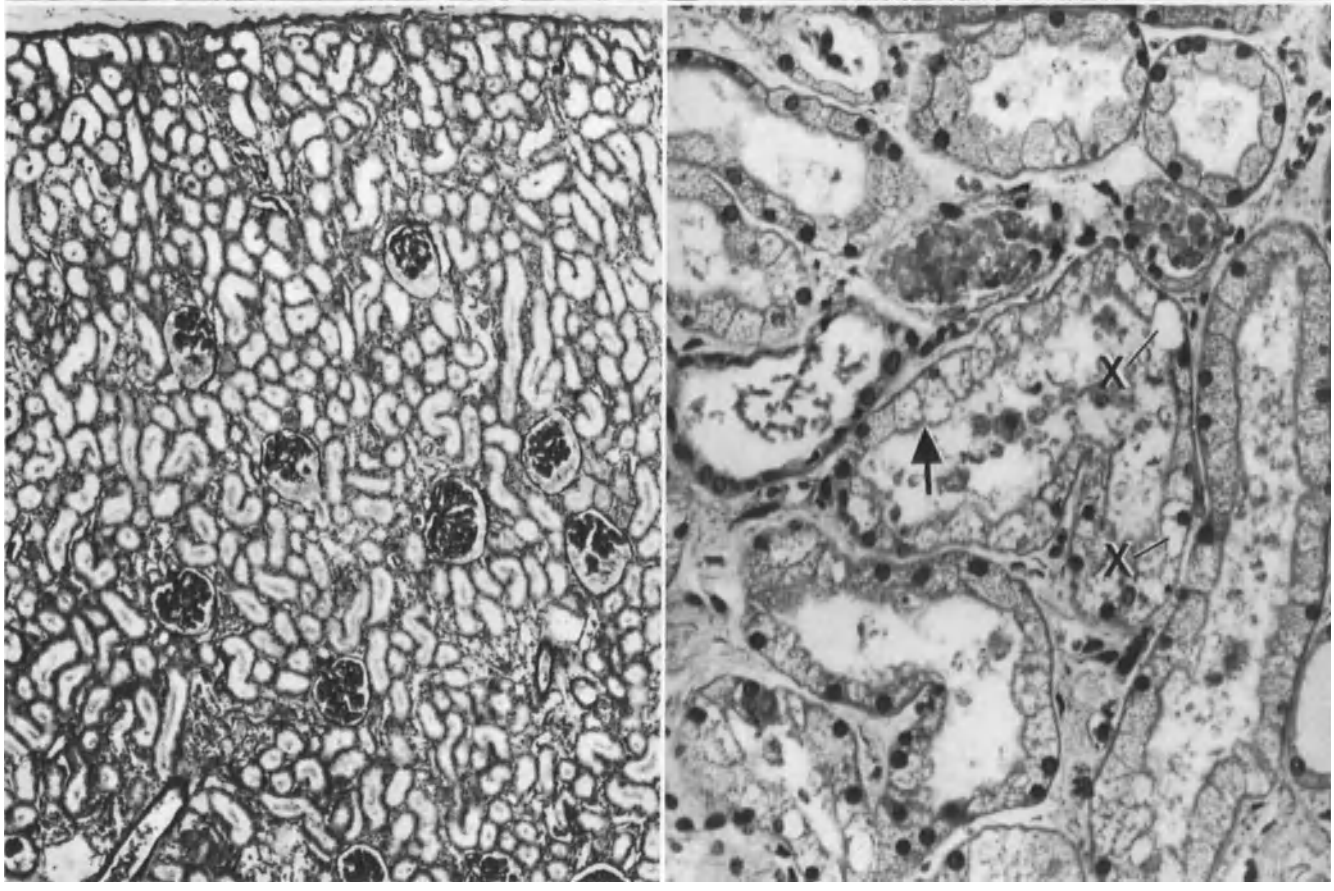

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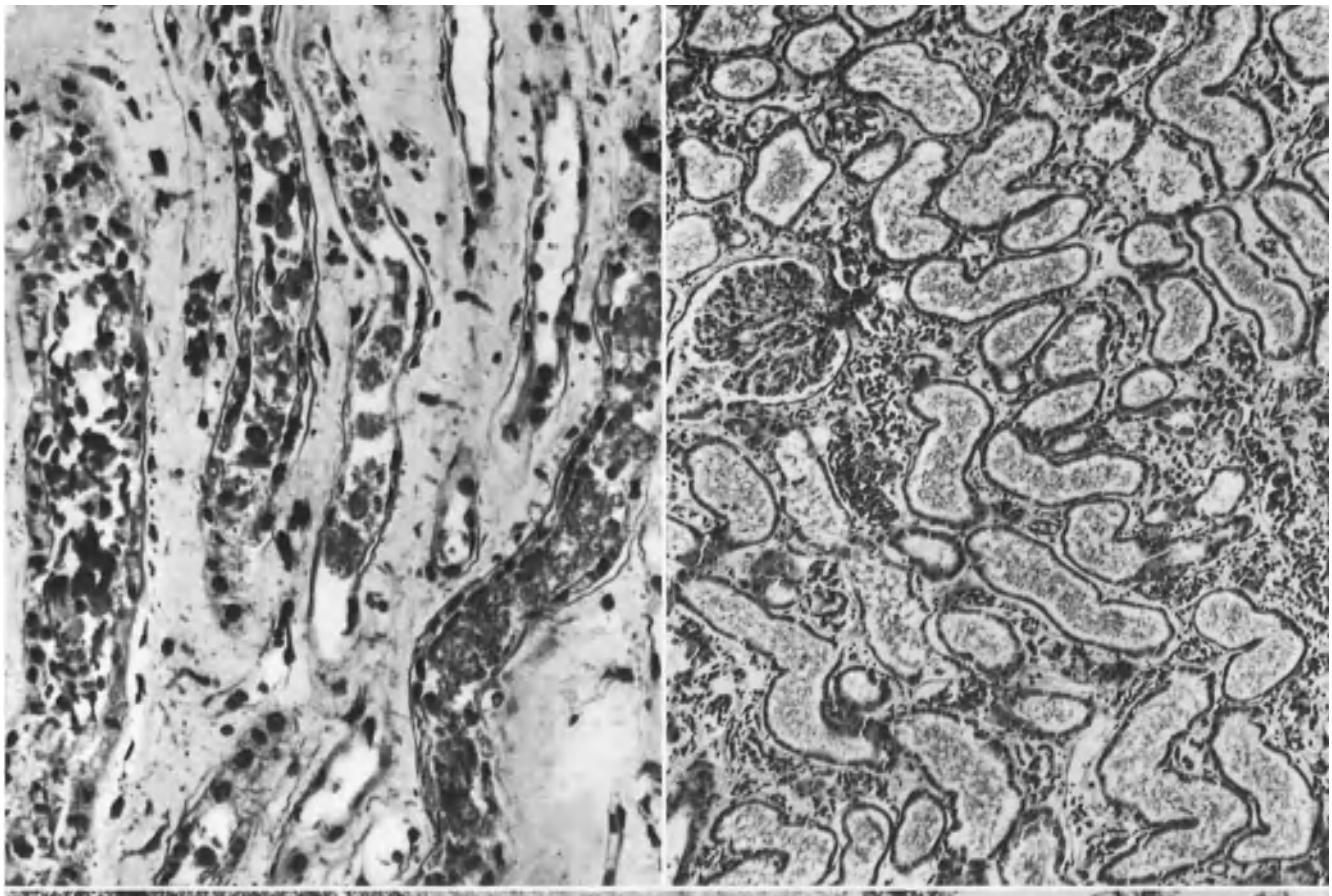

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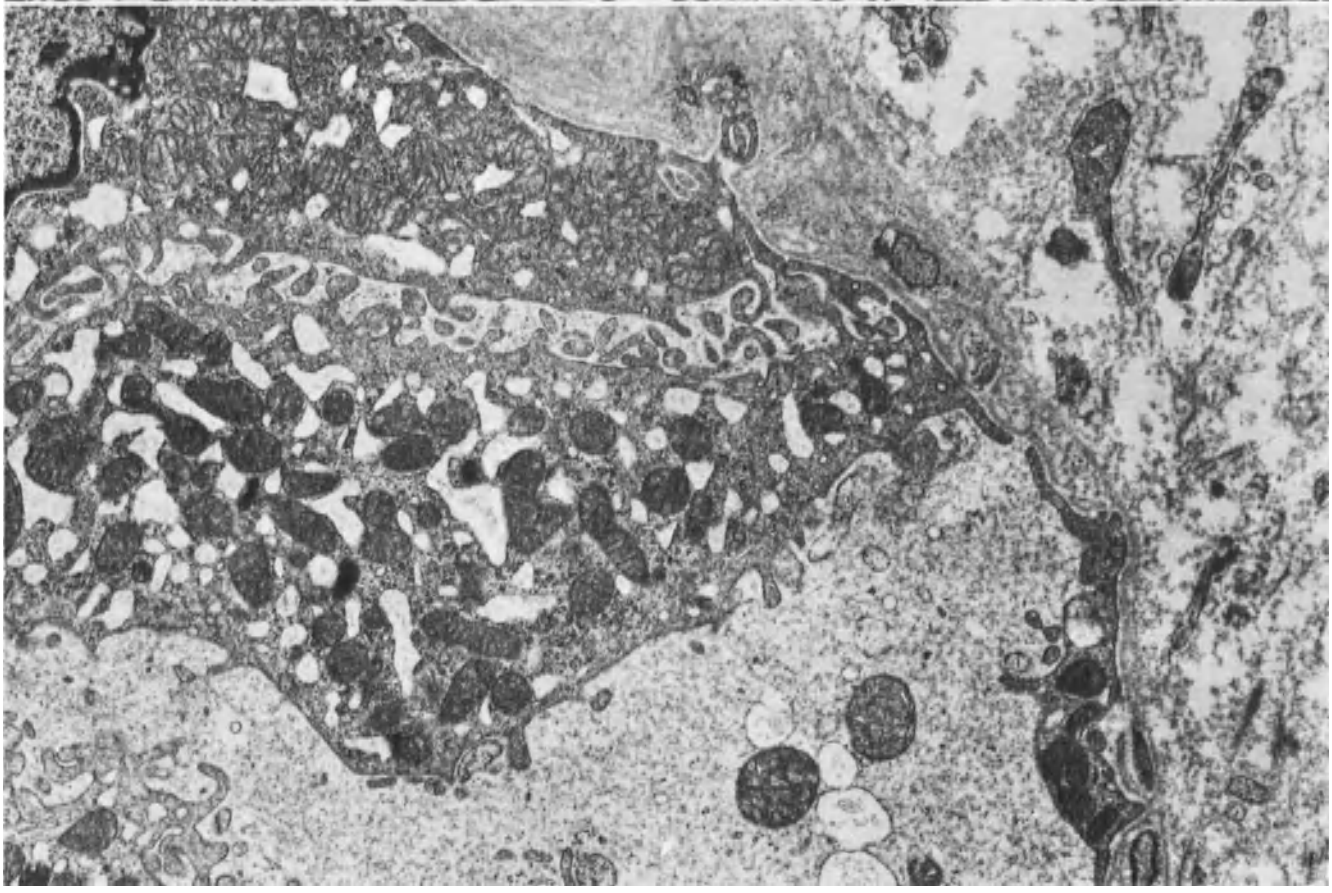


24.9

### IF Findings

We are unaware of any reports concerning shock kidney. In one own observation, there was a diffuse smooth linear staining of glomerular BM for IgG along with focal segmental granular deposits of IgM and C3.

### EM Findings

The main findings concern tubules and interstitium. Epithelial cells of the proximal tubules show cytologic characteristics of regeneration with increased polyribosomes and rough endoplasmatic and a decrease in the number of other organelles (especially mitochondria). The brush border and basal labyrinth are sometimes missing (Fig. 24.9). In the tubular casts, cellular organelles and granular, electron-opaque material corresponding to chromprotein are frequently recognized (Fig. 24.10). Interstitial changes are described under LM. With EM, glomerular collapse may be observed. The glomeruli often contain scattered fibrin thrombi and show focal endothelial defects [291].

### Differential Diagnosis

The LM findings are so typical that the diagnosis is usually made without difficulty. Similar findings do occur in acute nephrohydrosis due to impairment of urinary flow, but lymph vessel casts—although rarely found in needle biopsy—are usually present in this condition.
The early change in renal artery occlusion is characterized by severe blood stasis in intertubular capillaries and glomerular capillary loops. Difficulty may arise in acute vascular transplant rejection (see p. 573; [1804]).

◁ **Fig. 24.7.** Same case as in Figure 24.6. Distal tubules in medulla are filled with necrotic tubular cells. Female, 68 years. HE (×255)

**Fig. 24.8.** Shock kidney in colitis ulcerosa with hemorrhage and perforation of colon. Tubular epithelium is much flattened. There is nondestructive interstitial inflammation. Female, 63 years. HE (×100)

**Fig. 24.9.** Regenerating dedifferentiated cells of proximal tubule following shock-induced tubulonecrosis due to serious traffic accident 11 days prior to biopsy. Brush border and basal labyrinth are practically absent. Endoplasmatic reticulum is slightly dilated. Male, 33 years. EM (×11,600)

### Prognosis

In general, the acute renal failure attendant on shock is completely reversible; remnant damage may heal even after 1 year [23, 644, 953, 1845]. Some investigators have reported permanent reduction of the glomerular filtration rate to low normal values. Additionally, permanent concentrating insufficiency of urine has been observed in about 30% of patients [274, 953].
Interstitial fibrosis and nondestructive interstitial nephritis have been reported as the morphologic basis of irreversible functional impairment (see p. 418; [23, 953, 1791]). Acute renal failure is reported to enhance the occurrence of pyelonephritis which in turn can lead to permanent functional impairment [516].

### Etiology and Pathogenesis

Fundamentally, renal changes are due to ischemia which arise from decreased blood flow. The ischemia is a direct consequence of cardiovascular shock which results in a decrease of blood pressure in the renal artery. Additionally, constriction of the afferent vessels following activation of the intrarenal renin system can occur.
Further factors which may promote decreased renal blood flow in shock are intravasal coagulation or sludging of erythrocytes [171, 403, 502, 687, 1453, 1528, 1691, 1791]. Finally, (subtotal) occlusion of the renal artery may play a role.

## Disseminated Intravasal Coagulation Including Cortical Necrosis

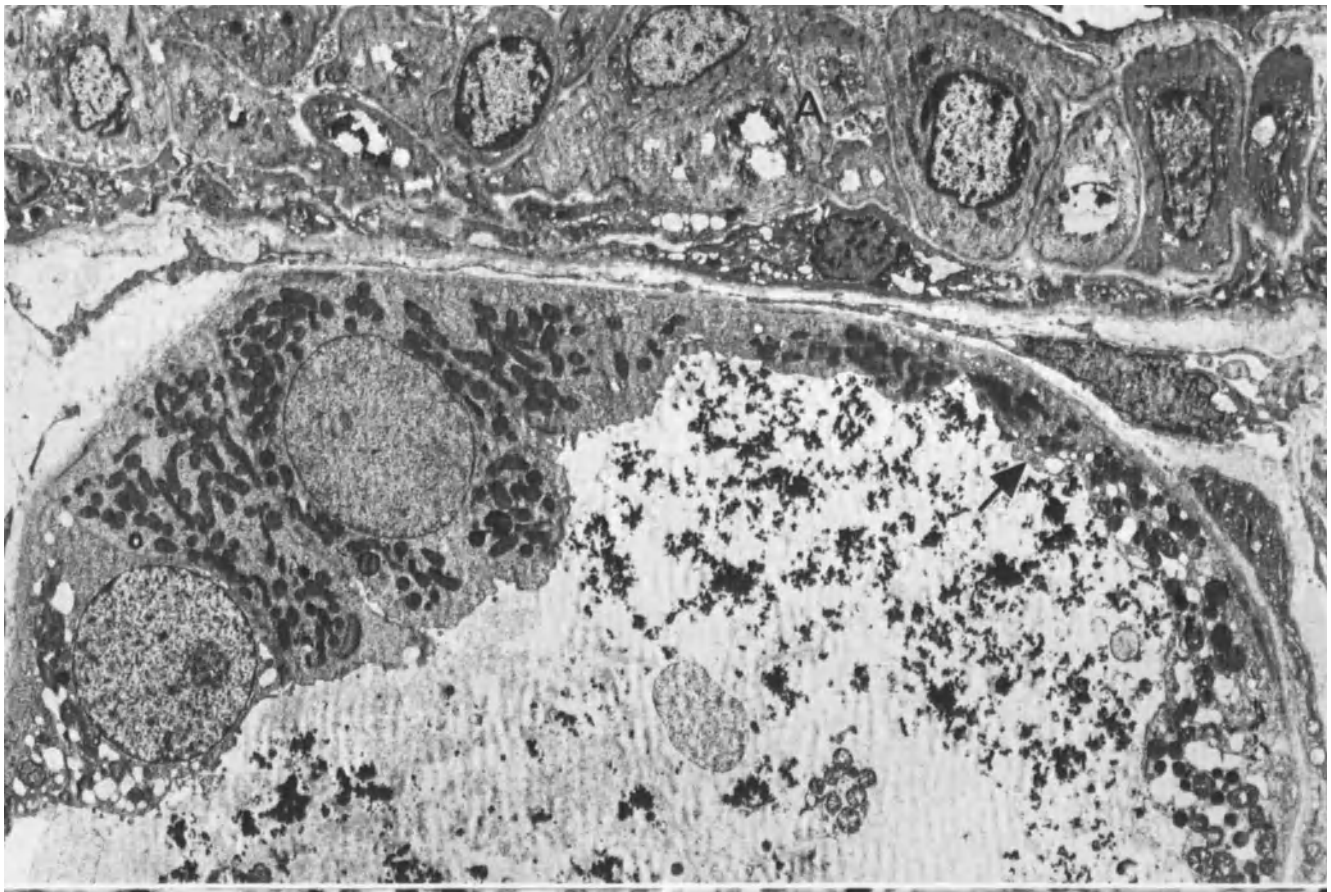
[191, 746, 1023]

## 1. Acute Disseminated Intravasal Coagulation

Acute disseminated intravasal coagulation—in its discrete form as occuring in shock and its massive form as seen in gram-negative speticemia (Sanarelli-Shwartzman phenomenon)—are discussed. Cortical necrosis and chronic forms of intravasal coagulation are presented on p. 499.

### Incidence

According to the latest clinical findings, acute disseminated intravasal coagulation is far more frequent than previously realized. It is thought to be an important co-factor in numerous renal diseases such as nephropathies in pregnancy, etc. [1060, 1690].

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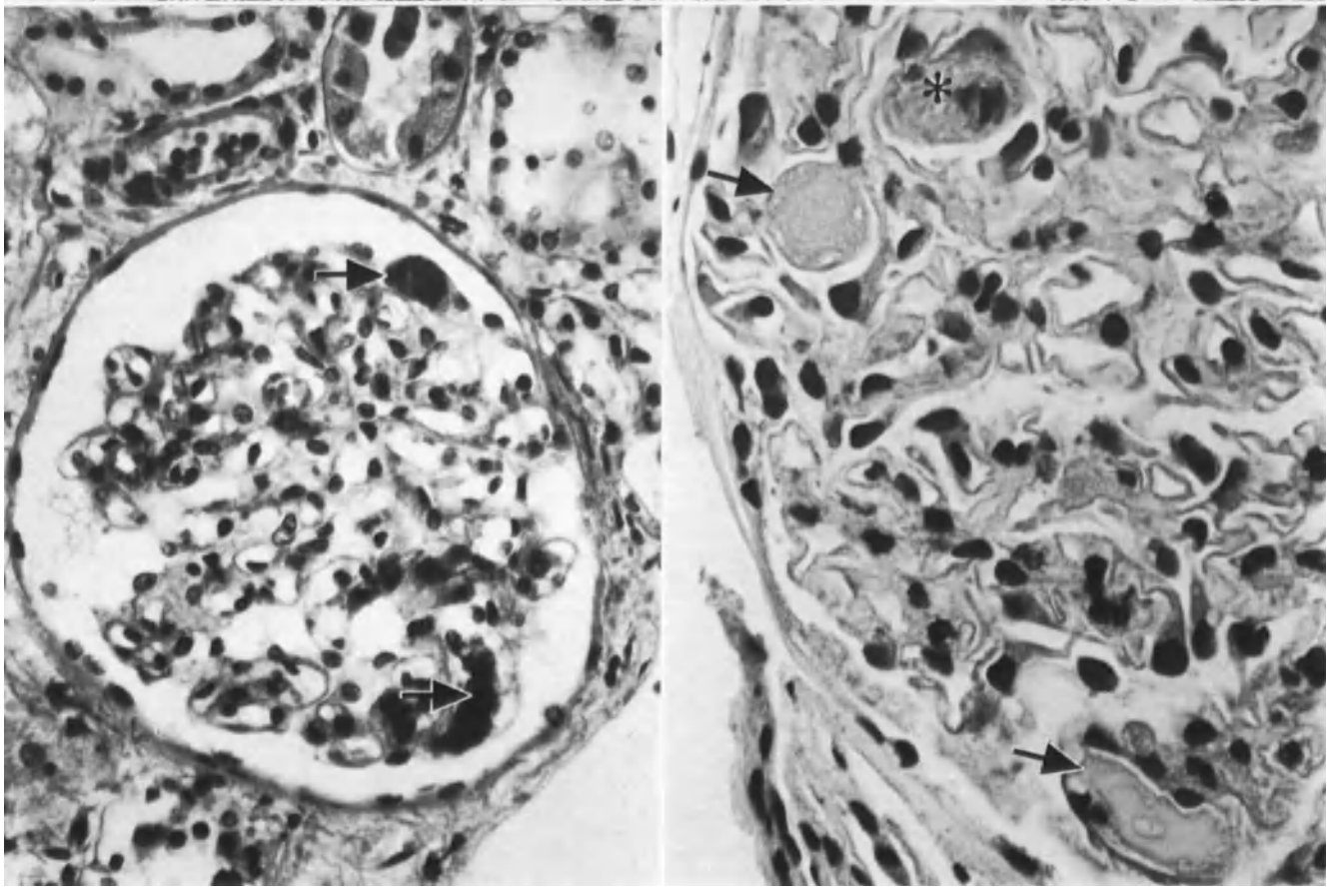

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At autopsy, the usually sparse microthrombi can easily be overlooked or were already dissolved beforehand.
In any event, because of its filtering function and large blood supply, the kidney is especially implicated in intravasal coagulation ([191]; 15 out of 22: [1343]). In 100 consecutive autopsies during which microthrombi with fibrin and thrombocytes were especially sought for, 45 were positive of which the kidney was afflicted nine times, e.g., 1 microthrombus/2.3 $cm^2$ of renal tissue [1515, 1516]. Microthrombi without corresponding clinical symptoms were found in 12% of 500 consecutive autopsies. They were, accordingly, considered to represent a terminal event [1173]. In 700 EM-examined biopsies, we found only 2 cases of clear-cut intravasal coagulation without concomitant renal insufficiency (110 out of 1368: [624]).
Diffuse cortical necrosis is extremely rare (12 out of 25,000 autopsies: Z). It sometimes occurs in children following massive loss of fluid from diarrhea or vomiting [1758].

## Clinical Findings

In addition to the basic disease (endotoxin or traumatic shock, nephropathy of pregnancy, etc.) consumption coagulopathy is present and is characterized by a reduction of serum fibrinogen, platelets and different clotting factors. Fibrin degradation products can be demonstrated in blood and urine.
In about 25% of cases, a discrete purpura is present. The mild form of the disease, however, is often inapparent or compensated [191]. Slight accompanying hemolysis with fragmentocytes in the blood smear are very often encountered [1060].

In the severe form of the disease, hypertension, anuria or oliguria and hematuria are usually present. Convulsions occur and occasionally vomiting, diarrhea, cyanosis, and finally, coma [1060].
In acute cortical necrosis, complete anuria and occasionally lumbar pain—in addition to the above-mentioned symptoms—are present.

## LM and EM Findings

The small thrombi consist of fibrin and platelets. They occur preferentially in the glomerular capillary loops (Figs 24.11, 24.12) and less frequently in the afferent vessels or larger arteries. Pure platelet thrombi (Fig. 24.13) are recognizable in the loops only during the earliest phases of the disease; they are rapidly replaced by fibrin thrombi (Fig. 24.14) and are transformed later into fibrinoid (hyaline) microthrombi which, in the HE stain, appear strongly eosinophilic and more or less compact (Fig. 24.12). With Masson's trichrome/AFOG stain, the thrombi are bright red (Fig. 24.11); they should not be confused with subendothelial deposits. The thrombi measure 2–40 μm. Under EM, they consist of an irregular dense network of fibrin strands with occasional periodicity (Fig. 24.14; [1516]). Circumscript necroses of the thrombosed capillary are observed in the subacute stage and severe forms [1515] but are mostly lacking in mild intravasal coagulation.
The above-mentioned and, to our knowledge, unique EM observation [1516] can be substantiated by experimental findings [1221, 1655]. Following thrombin infusion in rabbits, the thrombocytes clump and develop fine processes. Then their granules are released, the processes become coarse, and fibrin fibrils appear (Fig. 24.15). At this point, the thrombocytic processes become detached and remain as large, empty vesicles in the vascular lumen. Additionally the endothelium becomes hypertrophic or destroyed (Fig. 24.15).
The fibrin massively picks up intravenously administered India ink particles. It is thought that this is also true for plasma proteins which can lead to their limited local deposits [390].
In cortical necrosis, the LM finding is that of a typical infarct, i.e., of ischemic necrosis (Fig. 24.16). Now and again—especially in the early stages—massive bleeding and severely widened glomerular capillary loops with clumped erythrocytes are observed. Intravasal thrombi in the arteries and arterioles occur. Proximal tubular necrosis is seen under LM after 8 h. Glomerular necrosis is first clearly discernable after 48 h. Injury to the proximal tubules can be seen with EM as early as 5 h after onset. These changes consist of apical edema, loss of brush border, and vesicular transformation of organelles (rough endoplasmatic reticulum, lysosomes, Golgi apparatus, mitochondria) and basal labyrinth [1223].

◁ **Fig. 24.10.** Sectors of highly flattened tubular epithelium (→) without brush border and with vacuolar changes (regeneration or migration of neighboring epithelium for covering denuded BM) associated with tubular necrosis caused by carbon tetrachloride poisoning. Fine-granular chromoprotein masses are present in the tubular lumens. Wall of an arteriole (A). Female, 26 years. EM (×3260)

**Fig. 24.11.** A glomerulus in intravasal coagulation. Fibrin thrombi (→) are present in glomerular loops. There is still no reaction of the glomerulus or surrounding tissue. Male, 30 years. Picro-Mallory (×510)

**Fig. 24.12.** Not completely fresh intravasal coagulation of unknown etiology. There are three fibrillar glomerular capillary loop thrombi, two of which show fibrinoid transformation (→), and one of which evidences a cellular reaction (*). Female, 58 years. HE (×800)

Since in unilateral blood flow impairment cortical necrosis manifests itself only in the contralateral kidney, considerable difficulties can arise in interpreting needle biopsy [1456].

### Differential Diagnosis

Acute, generalized intravasal coagulation is so specific that it can hardly be confused with any other disease. In biopsy material, cortical necrosis can only be clearly differentiated from an infarct following thrombotic or embolic occlusion of the main renal artery or its chief branches when intravasal coagulation is present in the sections (Fig. 24.16).
Old cortical necrosis (associated with long-term dialysis) may evidence extensive calcification (Fig. 24.17).

### Prognosis

In acute disseminated intravasal coagulation, the prognosis depends completely on the underlying disease.
In the late stage of the disease (3 out of 25,000 autopsies: Z) we once observed (after 1 month) a severe inflammatory reaction of the glomeruli which was strongly reminiscent of membranoproliferative GN. This patient died of uremia, and small thrombi were still demonstrable. In a second case, a focal-segmental proliferative-sclerosing change was observed 2.5 months after onset of the disease. In LM, the glomerular changes could not be differentiated from those of proliferative FGN (Figs. 24.18, 24.19). We also observed a sclerosing stage of FGN 4 years after intravasal coagulation following heart surgery.
It is, accordingly conceivable—in at least some of these cases—that acute intravasal coagulation is the cause of the segmental-focal proliferative or sclerosing GN (see also [1047] and p. 287). Similar findings have been described in sickle cell anemia [430].
Bilateral cortical necrosis terminates fatally within some hours to 15 days without dialysis. After long-term dialysis, contracted kidney with severe calcification ensues [1791].

### Etiology and Pathogenesis
[1023, 1059]

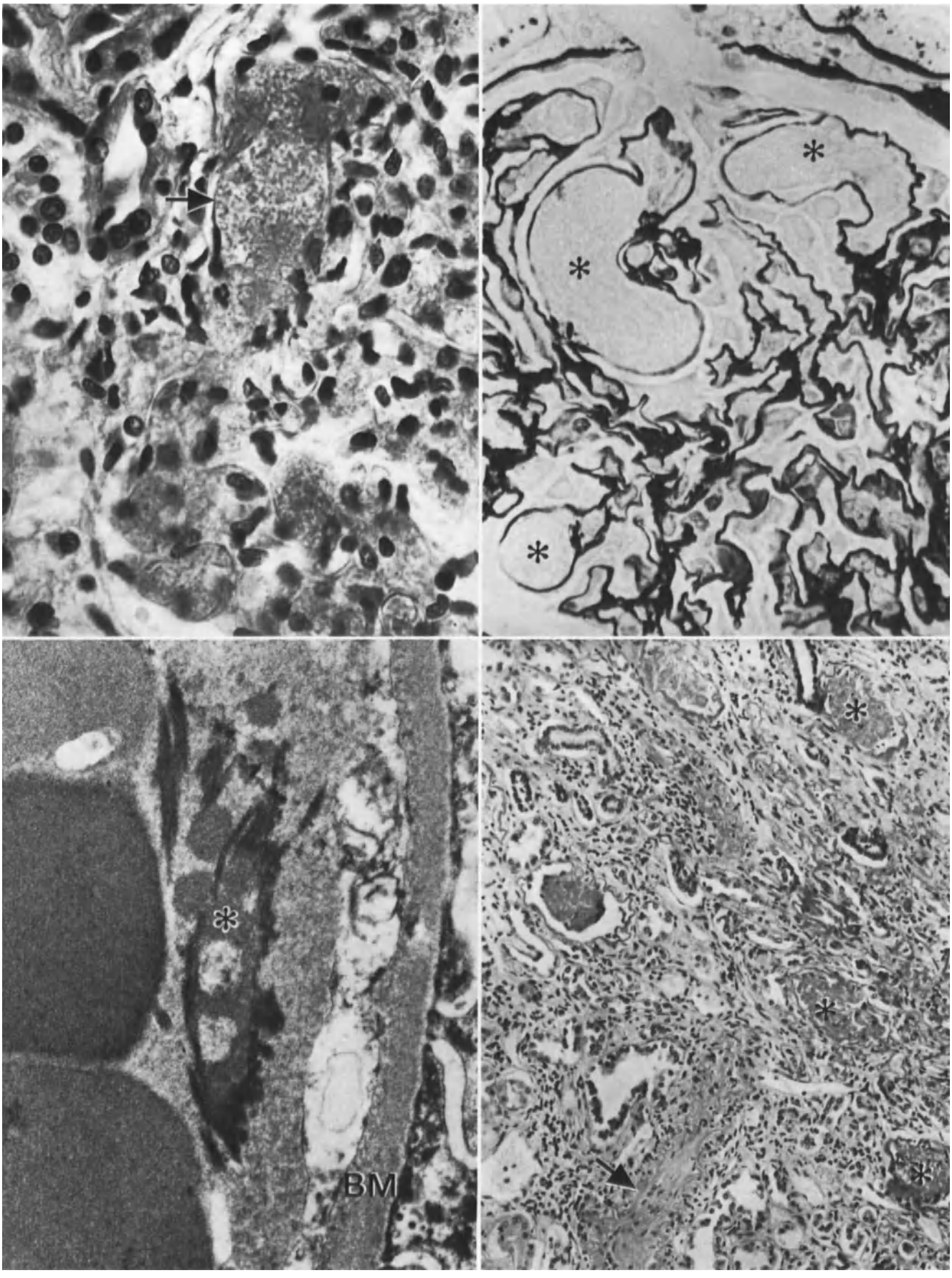
Intravasal coagulation may result from the massive release of coagulation-promoting factors into the circulation such as occurs in association with retroplacental hematoma, amniotic-fluid emboli, fat emboli, heat stroke, massive hemolysis, snake venom, gram-negative, or, more rarely, other forms of septicemia. Functional impairment of the RHS by excessive storage of any material and/or anoxia (e.g., during shock) are significant cofactors, especially for the severe form.
In hematological diseases, such as acute leukemia, mismatched transfusions, sickle cell anemia, etc., as well as in shock, it is thought that the endothelial lesion and the thereby caused reduction of fibrinolysis are pathogenetically decisive factors [1690]. Immunologic triggering of the disease by medication (e.g., pyrazolone: [97]) has also been considered as a causative factor.
In one of our own cases, liver dystrophy with severe disseminated intravasal coagulation followed halothane anesthesia. In another case, an anti-erythrocyte AB was demonstrable (Figs. 24.18, 24.19). The entity is occasionally observed in association with malignancies (see also [1068]). In two of our own cases, generalized Hodgkin's disease was present.
In cortical necrosis in children, extreme dehydration is, as previously mentioned, a predominating factor. Broncho-pneumonia attendant on circulatory disturbances is sufficient to bring about milder forms of the disease [1515]. The discrepancy between the number of thrombi, which is often not large, and the extensively developed cortical necrosis shows that vasospasms are a contributory factor. Vasospasm is thought to be caused by bradykinin released during platelet destruction.

**Fig. 24.13.** Fresh platelet thrombus (→) associated with fresh, ▷ generalized coagulation in colitis ulcerosa. Frozen section. Female, 55 years. HE (×800)

**Fig. 24.14.** Same case as in Figure 24.12. There is considerable distention of the glomerular capillary loops occluded by platelet thrombi (*). Female, 58 years. PASM (×620)

**Fig. 24.15.** Acute intravasal coagulation of unknown cause. Endothelium is by and large destroyed and numerous fibrin strands (*) are present in the plasma covering the damaged endothelium. Basement membrane (*BM*). Male, 36 years. EM (×20,800)

**Fig. 24.16.** Four-month-old renal cortical necrosis following rubella associated with severe shock. A small artery is occluded by an organized thrombus (→). There are numerous obsolescent glomeruli (*). Some of the tubules are still preserved. Female, 31 years. PAS (×150)

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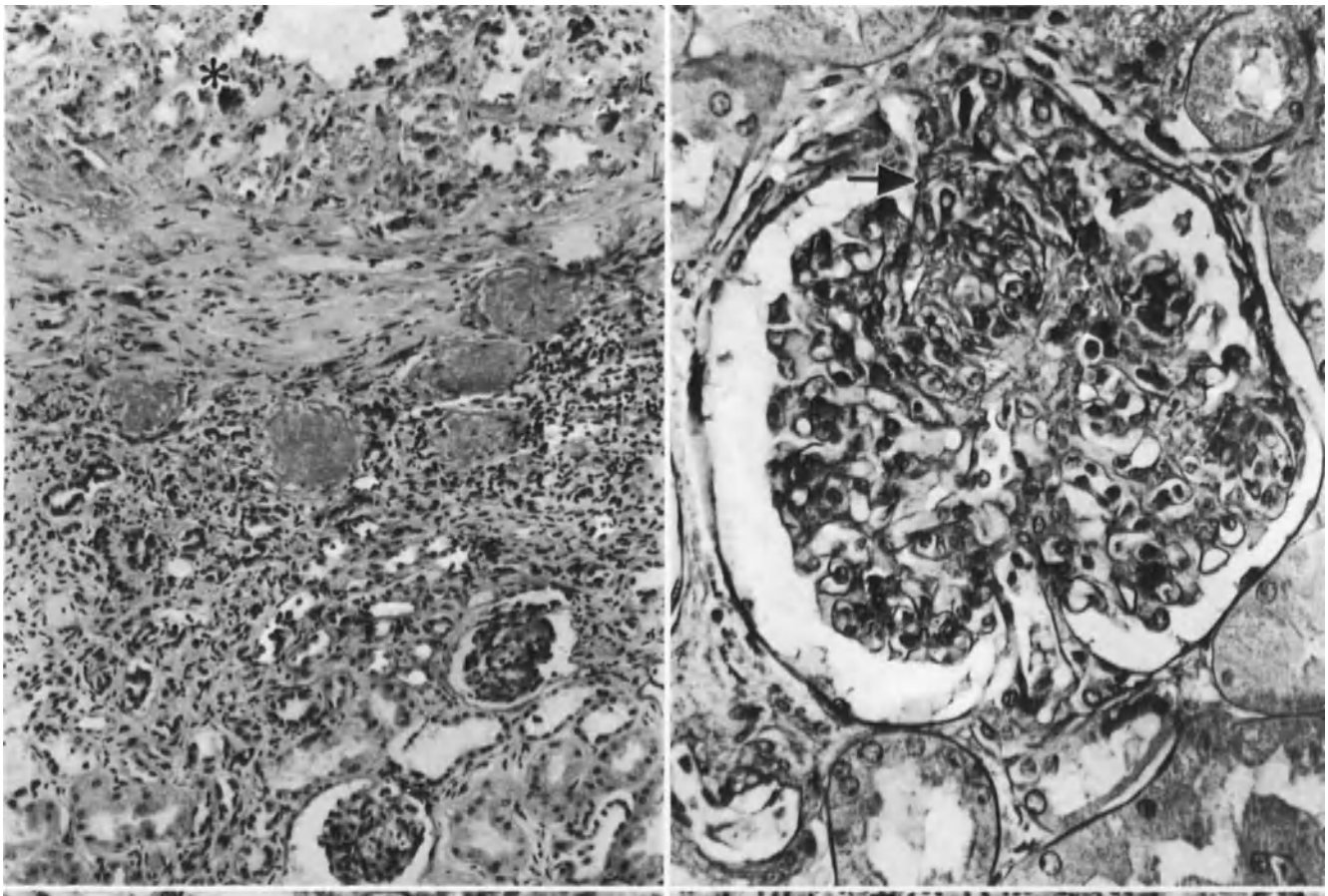

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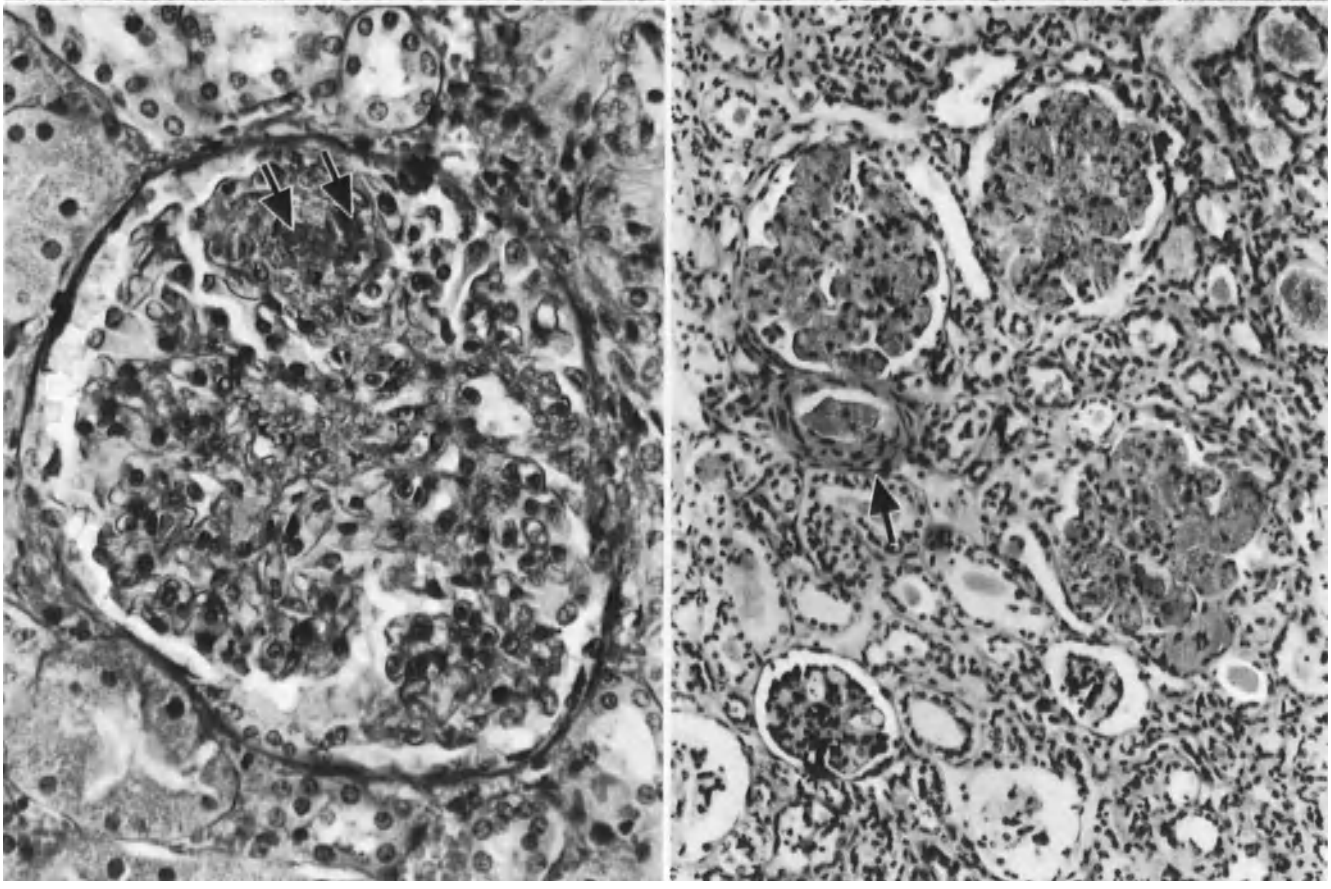

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## 2. Subacute and Chronic (Relapsing) Disseminated Intravasal Coagulation [1021, 1484, 1797]

The common basic phenomenon in these forms is the generalized intravasal coagulation which leads to proliferative inflammatory reactions in the glomeruli. The overall picture differs from that encountered in consumption coagulopathy in that there are several attacks of the disease over a considerable length of time.
The number of investigators who consider or tend to consider microangiopathy and the hemolytic-uremic syndrome as variations of one and the same disease, namely, of disseminated intravasal coagulation, is progressively increasing [191, 444, 1021, 1070, 1484, 1672, 1791].

## 3. The Hemolytic-Uremic Syndrome [550, 959, 1292, 1509a]

### Definition

This syndrome is defined as intravasal coagulation associated with hemolytic anemia, hemorrhagic diathesis and renal insufficiency.

***Synonym:*** Gasser's syndrome [533].

### Incidence

This is a rare syndrome (2 out of 25,000 autopsies: Z) which occurs more frequently in South America [550].
It usually appears before the fourth year of life and afflicts girls and boys equally ([444]; contra: female:male: 28 out of 13 [1021]). The disease usually develops in summer [1046]. Small epidemics have been reported [888].

◁ **Fig. 24.17.** Same case as in Figure 24.15. Old cortical necrosis is almost completely calcified (*). Male, 36 years. PAS (×180)

**Fig. 24.18.** Biopsy obtained 2.5 months after clinically-proven acute intravasal coagulation in a patient with anti-erythrocyte antibodies. An older glomerular focus (→) is seen with segmental proliferation and synechia. Male, 64 years. PAS (×500)

**Fig. 24.19.** Same case as in Figure 24.18. Dark-stained thrombi (→) in the proliferatively changed glomerulus are still recognizable. Male, 64 years. PAS (×500)

**Fig. 24.20.** Thrombocytopenic microangiopathy in an acute attack. Almost all glomerular capillary loops are severely distended and filled with fresh thrombi as is a small artery (→). HE (×280)

### Clinical Findings

Characteristically, from a few days up to 2 weeks following an infection of the upper respiratory tract or gastroenteritis, hemolytic anemia with slight jaundice, purpura, oliguria, and even unconsciousness and cramps [444] occur abruptly. The Coombs test is negative and serum complement level normal [888]. Of the patients, 85% evidence increased bleeding tendencies and melena is present in 65% [550].
Thrombocytopenia is always present. Serum fibrinogen level as well as clotting factors V and VIII are reduced. Fragmentocytes are a typical finding in the blood smear (see below). Frequently, oliguria or anuria occur in the acute attack (92% of cases: [444, 550]).
Hematuria is found in all cases. In the late stages, uremia develops insidiously and often with hypertension (50% of cases: [444]). Subacute and chronic cases with bilateral cortical necrosis have been reported (9 out of 31: [550]). Acute death has been observed in 10–50% of a series of cases [1292].

Morphologic particulars are described in the next section on microangiopathy.

## 4. Thrombotic Microangiopathy [1588]

### Definition

Microangiopathy is defined as usually recurrent generalized intravasal coagulation with endovascular thrombus organization.

***Synonyms:*** Idiopathic postpartal renal failure [1588], Moschkowitz's syndrome [1150].

### Incidence

In general, the condition is very rare. The lesion, first described by Moschkowitz in 1925 [1150], afflicts women between 10 and 40 years of age much more frequently than men and, in this respect, it differs from the hemolytic-uremic syndrome.

### Clinical Findings

Psychiatric and neurologic symptoms (unconsciousness, cramps, hemiplegia) dominate the clinical picture in addition to fever, nausea, abdominal pain, headache, myalgia and purpura. In women, the disease develops sometimes immediately after giving birth, or weeks or months thereafter [920, 1736]. Epidemics are unknown.

The disease can lead to renal insufficiency [1552]. In one of our own cases, it developed shortly after acute tonsillitis and smallpox vaccination. This patient showed a precipitous fall of thrombocyte number to 3000/mm$^3$, a decrease of fibrinogen to 140 mg%, hemolysis, jaundice (bilirubin 10.4 mg%), purpura, hematuria, and hemoglobin casts. The serum creatinine rose to a maximal value of 2.6 mg% and this patient finally died in generalized cramps.

Postpartum hemolytic anemia is typically associated with oliguria or anuria, often hypertension, and terminal cardiac failure [1736]. With careful clinical examination, hemolysis can often be demonstrated [1060]. Other symptoms are similar to those encountered in the hemolytic-uremic syndrome. We feel that the morphologic changes of the two entities are identical. Both evidence erythrocytic anomalies in smears: pointed burr cells, fragmentocytes, schizocytes [888, 994] respectively, cellules en casque [191] as well as thrombocytopenia. In both conditions, fibrin-split products are demonstrable in the urine [1553].

### LM Findings

The early changes are scarcely distinguishable from those encountered in ordinary intravasal coagulation (see p. 493). The outstanding finding is the occurrence of extensive partially focal, partially diffuse glomerular capillar loop thrombi (Fig. 24.20; see p. 60) which disappear in about 30 days [550]. They are usually accompanied by local necroses of the afflicted loop wall. In postpartal cases, they may be absent due to increased fibrinolysis [922]. Thrombi often extend from the afferent arteriole to the glomerular capillary loops [1070]. Numerous polymorphonuclear leukocytes are found in the vicinity of such glomeruli. Small segmental crescents and collapse glomeruli may be seen. Other loops may be aneurysmatically distended and the nuclei poorly defined (so-called glomerular infarct: [1068]).

Frequently, small infarcts which can lead to total cortical necrosis are seen (80% of postpartal fatalities in a series of cases [1672]). Thrombi in arterioles are usually accompanied by inflammation. In arteries, thrombi are much more scanty and only partially obstructing. Occasionally, only a subendothelial fibrin layer can be demonstrated.

Late changes are found after 2 to 6 weeks. In this phase, capillary loop thrombi are considerably less predominant and either segmental-focal glomerular proliferation with segmental crescents [1588] or – especially in children – affliction of all glomeruli are found (Fig. 24.22). The inflammatory nature of these glomerular changes is rarely doubted [1361]. We have seen similar changes after ordinary intravasal coagulation (Fig. 24.24; see p. 287).

In addition to fresh thrombi, subacute phases are also present and characterized by severely deforming capillary loop inflammation which is usually focal-segmental (Fig. 24.22) and accompanied by fibrinoid degeneration of the loop wall. In the chronic phase, hyaline, segmental-focal scars can be demonstrated (Fig. 24.21); [262, 1701, 1791]) and interposition of mesangial cells – as in membranoproliferative GN – may occasionally develop [100]. Some of the glomerular loops are aneurysmatically widened with thickened, fibrin-impregnated walls (Fig. 24.23).

In the vessels, the thrombi are frequently recovered with endothelium. Subendothelial fibrin is replaced by connective tissue (Fig. 24.25) which appears mucoid [1070, 1588, 1736].

In the late phases of the condition, these changes lead to severe intimal proliferation which can appear very similar to that encountered in malignant nephrosclerosis [1068].

Granulomas around the especially frequently afflicted afferent arteriole are designated as glomeruloid structures [1642]. Occasionally, intramural thrombi have been described [471].

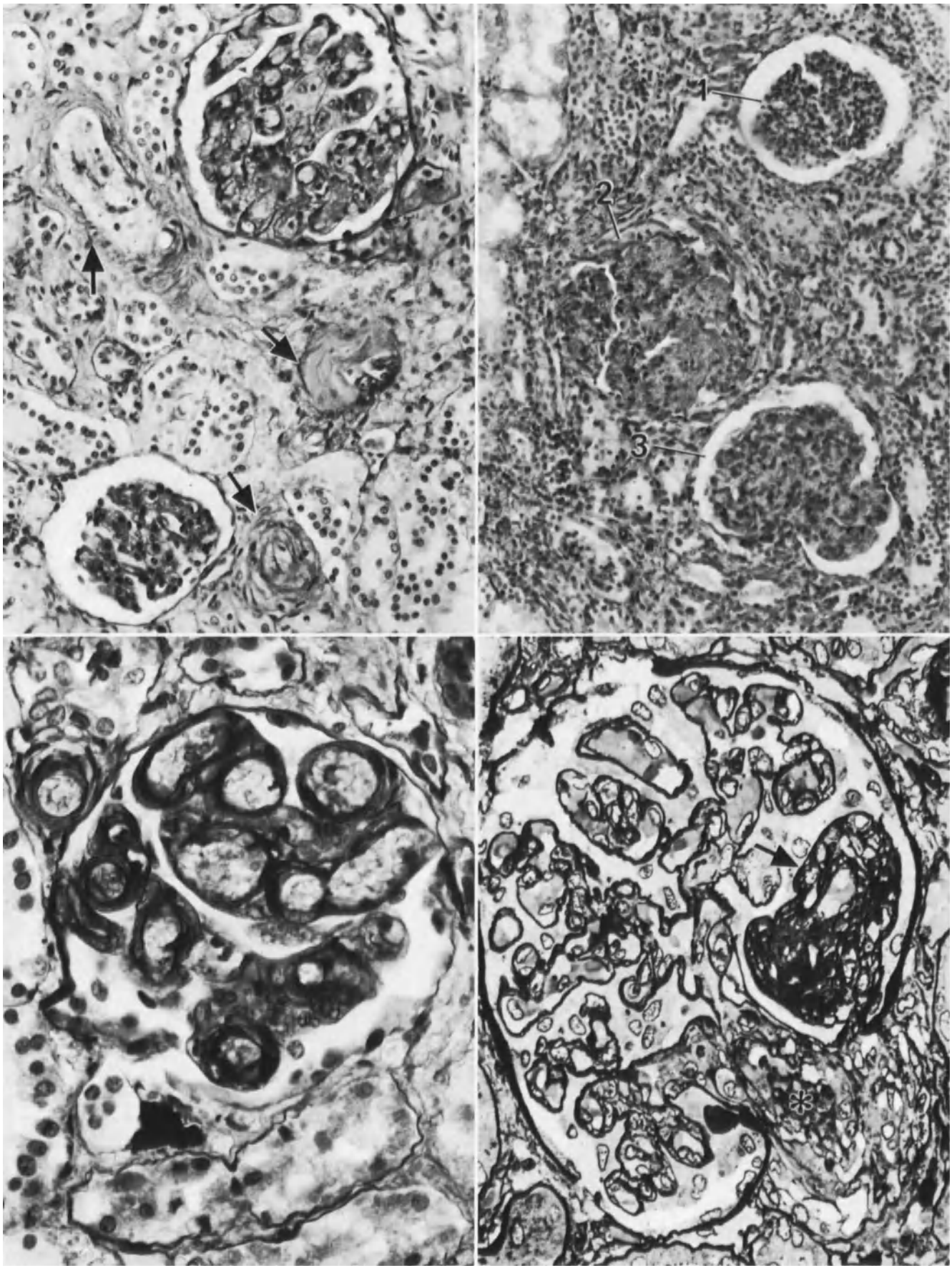
As a consequence of renal hypertension, arteriolosclerosis may develop in addition [1484]. In some cases, only the kidney is implicated; in others, there is generalized involvement of the vascular system [1021]. General involvement is often termed thrombotic-thrombocytopenic microangiopathy and involvement limited to the kidney as hemolytic uremic syndrome.

**Fig. 24.21.** Same case as in Figure 24.22. Old microangiopathy ▷ (hemolytic – uremic syndrome) at autopsy. In one glomerulus, capillary loops are distended and proliferatively changed. Changes due to repair are very evident in three small arteries and arterioles respectively (→). Male, 8 years. PAS (×480)

**Fig. 24.22.** Hemolytic – uremic syndrome. One glomerulus (*1*) is collapsed, and the second (*2*) evidences a rather fresh attack with glomerular capillary loop thrombi, fresh proliferation and synechia. Third glomerulus (*3*) shows only proliferative changes and a small synechia. Frozen section. Male, 8 years. HE (×310)

**Fig. 24.23.** Same case as in Figure 24.22. Obvious thickening and splitting of glomerular BM in distended loops are seen. Upper glomerulus from Figure 24.21. Male, 8 years, PAS (×420)

**Fig. 24.24.** Findings 1 month after acute intravasal coagulation associated with severe shock. Renal biopsy was performed because of persistent anuria. In addition to an organized glomerular capillary loop thrombus (→), an obliterating, proliferative change of the vas afferens (*) is also present. Male, 28 years. PASM (×600)

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### IF Findings

Granular deposits in the glomerulus of IgA, IgG, IgM, complement, and fibrin(-ogen) [1021, 471] or IgG respectively only in 4 out of 9 cases without complement [444] have been reported. In one of our own cases, we found granular deposits of IgG, IgM, C3 , and fibrin(-ogen) in the mesangium. Fibrin(-ogen) was demonstrable in arteries, arterioles and in the capsular space (see also [2]). In the vessels, fibrin and IgG have been reported to be strongly positive subendothelially from 7 weeks to 14 months after an acute attack [471].

### EM Findings

Afflicted glomerular loops contain granular or fibrillar material which, however often does not demonstrate the typical periodicity of fibrin [1672]. IF demonstration of fibrin(-ogen)—without electron microscopical correlates—are considered to consist entirely of fibrinogen [640]. In general, only a few platelets are demonstrable [285, 1021] since they are quickly destroyed [202].
As early as the seventh day of the disease, a few endothelial or mesangial foam cells are found which are thought to originate from resorption of platelet lipids [1361].
The endothelium under the thrombi is partially absent [504] or shows frank proliferation [1021]. The erythrocytes in the loops are polyhedric [1021], a finding which is thought to be analogous to the fragmentocytes seen in blood smears.
The BM is thickened [96]—usually due to a thickening of the lamina rara interna [482, 1736]; experimental findings: [1654]. In our case, the BM was unchanged. We doubt that the described lamina rara interna change is the consequence of immunocomplex deposition [920, 1021]; we feel, on the contrary, that it is the result of plasma protein insudation arising in the presence of endothelial injury.
Oval particles in the lamina densa have been interpreted as suggestive of virus particles [627], we feel, rather, that they are degradation granules. Both the mesangial cells and matrix are slightly increased [1736]. The matrix is permeated by a proteinaceous and a fibrin-like material similar to that found in glomerular loops [1497b]. In cases of severe mesangial affliction, segmental tuft necrosis may ensue [1497b].
The segmental crescents, which could be shown to overlay BM interruptions [1497b], as well as the mesangial and podocytic changes do not deviate from those occurring in GN.

### Differential Diagnosis

In the presence of fresh thrombi, the differential diagnosis is not difficult. Actually, only FGN in subacute bacterial endocarditis must be considered. In this disease, however, severe involvement of blood vessels is never seen. If the thrombi have disappeared and if the clinical data are not conclusive, an accurate diagnosis may be difficult.
In these cases, delineation from rapidly progressing scleroderma [929] as well as malignant nephrosclerosis may be impossible although, in less advanced cases, the lack or only minimal presence of thrombi will hinder misinterpretation with the before-mentioned diseases. Hypersensitivity angitis primarily shows a pronounced inflammation and necrosis of the vascular wall with secondary nonobligatory thrombosis. The glomerular changes are not of a thrombotic nature. Hemolysis is also usually absent [1552].
The very acute, severe membranoproliferative GN with extensive subendothelial fibrinoid deposits may cause difficulties since these deposits give positive results with Masson's trichrome/AFOG stain (Fig. 6.15; see p. 63). However, the arteries and arterioles in acute GN are practically unchanged.

### Prognosis

The prognosis is better in the hemolytic-uremic syndrome of childhood (40% mortality, 10% persistence of renal symptoms) than it is in the generalized microangiopathy of adulthood (75% mortality within the first 3 months: [444]; 100% mortality: [1046]). It is noted that there was a mortality of only 6.25% (50% persisting renal symptoms) in 678 cases reported from Argentina [550].
Children usually die from uremia [1701, 1841] and adults predominantly from cerebral injury.
Long-term survivors in childhood occasionally develop a contracted kidney, which in the late phase, hardly allows etiologic classification [1047]. After removal of the host kidney, the disease does not appear to recur in the transplant [261, 419]. Cure has been described following anticoagulative therapy [994] and biopsies have shown endovascular scarring [1283] as result of successful organization of the thrombi.

### Pathogenesis

It is not yet known for certain whether intravasal coagulation or endothelial injury is primary or if both conditions occur simultaneously. We believe that the endothelial injury [504] may be the consequence of primary vasculitis [1642] due to immunocomplex deposition.
In many cases, there is substantial evidence of toxic/anoxic endothelial injury (possibly bacterial or viral neuramidase: [1292]) which could be caused by anti-endothelial AB [1690]. Injury to the endothelium, leads to reduction of its fibrinolytic activity [1690] as well as to direct

exposure of collagen of the vascular wall to platelets. Both of these factors trigger consumption coagulopathy (see also [922]) whereby fibrin, by formation of "inflammatory spikes" [182]) at the vascular surface, causes vascular narrowing [182, 1130] which leads, in turn, to mechanical destruction of erythrocytes and thrombocytes [203]. Thus, hemolysis is a secondary phenomenon [171, 1690].
The earlier assumption of primary hemolysis, whereby intravasal coagulation was thought to be triggered by the thromboplastic activity of the erythrocytic stroma and by RHS blockage (see also [1701]), appears to be outdated.

### Etiology

The epidemic occurrence of the disease reported from Argentina [549, 550] points to the possibility of an infectious origin, e.g., viral [444, 550, 1642]. Actually, different viruses were isolated in 11 out of 25 patients [1046]. In one, rickettsiae were demonstrated which were transmitted by ticks. The rickettsiae have been reported to produce a similar disease in monkeys [1088]. It must be noted that the condition has also been observed in 12% of cases in typhoid fever. Endotoxin of *S. typhi* is thought to act as the trigger mechanism for intravasal coagulation [70].
The following factors have also been considered as causative: drug allergy (e.g., penicillamine: [142; 1797]), metastatic carcinoma (mucus-forming gastric carcinoma [178]); prostate and bronchus carcinoma [1233]); pregnancy, and contraceptive drugs ([203, 929, 1842] (see also p. 503); 3 out of 18 cases: [156]), antilymphocytic globulin therapy [334].
Presumably, microangiopathy is a specific reaction which can be elicited by numerous, completely unspecific noxious substances.

## Renal Vein Thrombosis
[1367]

### Definition

We define renal vein thrombosis (RVT) as primary in the absence of any prior renal disease and as secondary in its presence.
Acute means a few days old and chronic at least several weeks old. Contracted kidney is defined on p. 526.

### Incidence

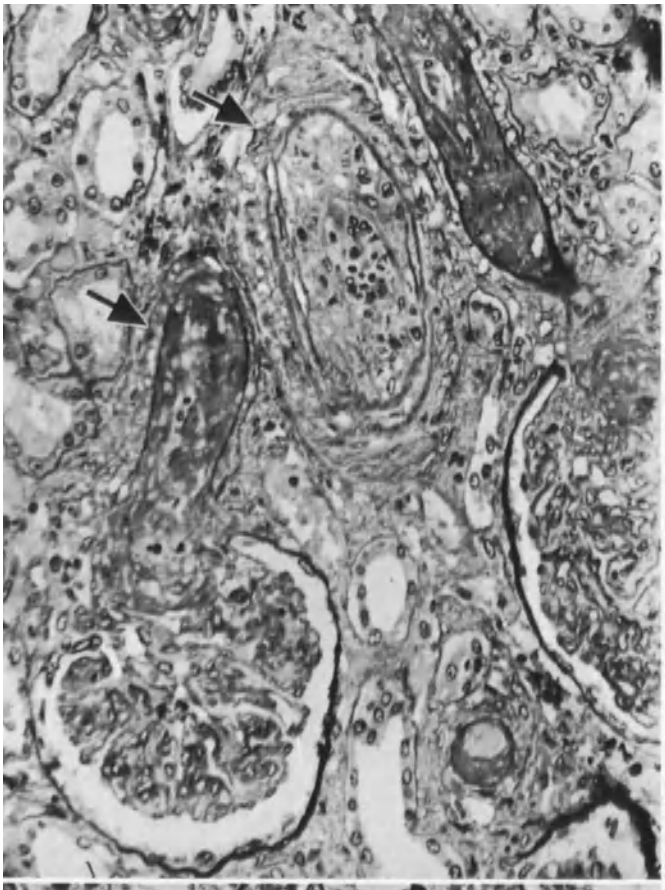
Acute RVT with severe bilateral parenchymal damage and uremia usually occurs in young children and chiefly in infants (6 children and 4 adults out of 28,000 autopsies: Z; [46]).
We observed the lesion as a terminal event (without parenchymal injury) in 22 out of 25,000 autopsies.
Chronic RVT is found almost exclusively in adults (9 out of 25,000 autopsies: Z). It clearly shows increased incidence in the presence of prior nephrotic syndrome. We observed venothrombotic contracted kidney in 4 out of 25,000 autopsies.

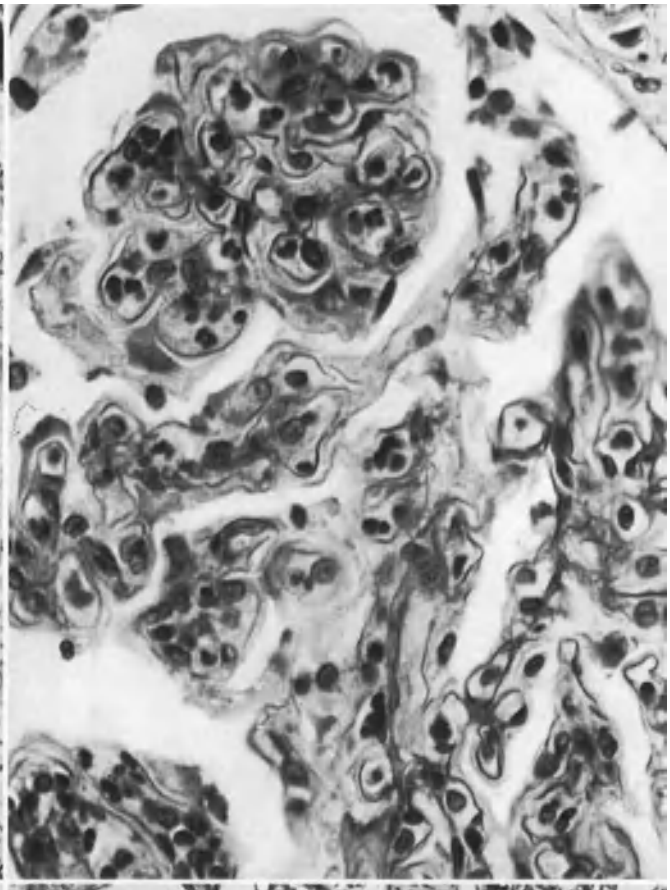
### Clinical Findings

Characteristically, renal vein thrombosis manifests itself clinically with severe flank pain, hematuria, proteinuria and, frequently, pulmonary emboli. In the event of bilateral affliction, precipitous oliguria and uremia occur.
In stepwise occlusion of the renal vein, a venous collateral circulation may develop along the ureter which is demonstrable by angiography.
If adequate collateral circulation is present, massive proteinuria or even a nephrotic syndrome may develop (experimental evidence: [1006, 1357]), which is often the case in unilateral, chronic renal vein thrombosis (9 out of 11 cases: [1131]).
Hypertension is usally absent except in the extremely rare cases of venothrombotic contracted kidney [1791].

### LM Findings

In acute RVT, the glomeruli are relatively large and show very prominent dilatation of capillary loops which demonstrate numerous polymorphonuclear leukocytes (Fig. 24.26). The interstitium is strikingly widened, due to edema, but without significant inflammatory infiltrates.
The discrepancy between the extensive widening of the interstitium and the slight or absent inflammatory infiltrates is highly characteristic for acute RVT.
After some time, the tubules demonstrate a slight atrophy. Full scale lipoid nephrosis may develop. Rarely, and only in infants after massive dehydration, instead of typical RVT changes, hemorrhagic necrosis may be seen.
In chronic RVT, glomerular changes as found in the acute stage—but without polymorphonuclear leukocyte margination—are still present. The mesangium is somewhat enlarged, but without cellular increase. The glomerular BM appears unchanged (Fig. 24.27).
Numerous other investigators have reported massive glomerular changes such as in amyloidosis, diabetic glomerulosclerosis, plasmocytoma [493] and epimembranous GN [1468]. We feel that cause and effect in these instances have been confused [see p. 261].





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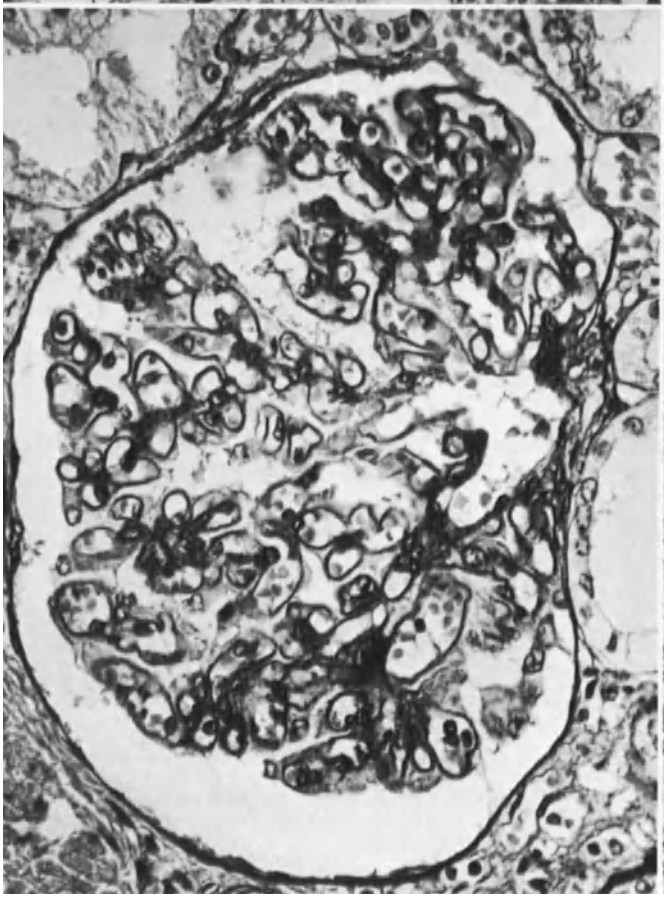

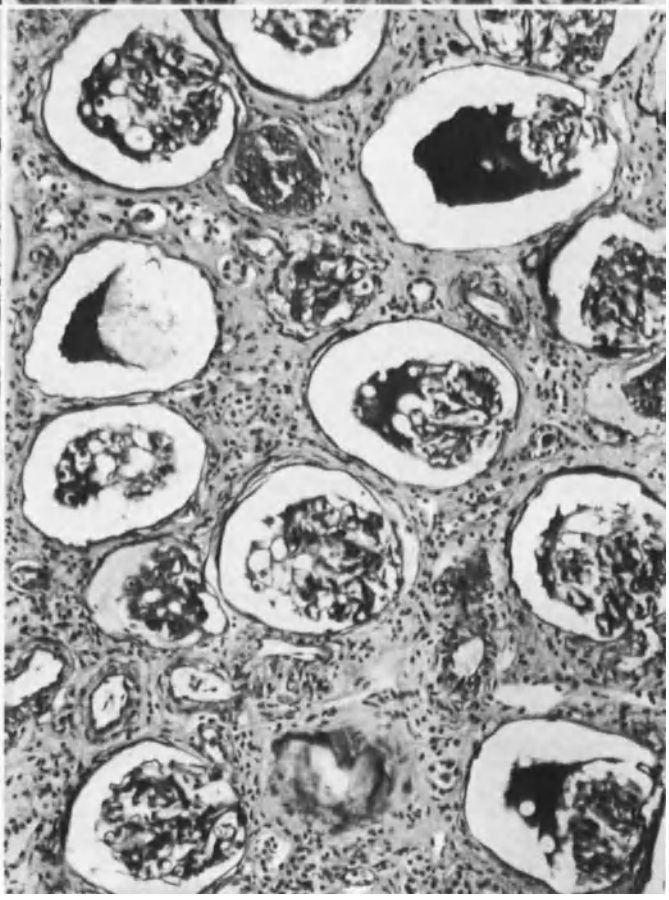

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24.28

In the rare venothrombotic contracted kidney, the glomeruli are strikingly well preserved, but the capsular spaces are considerably widened (Fig. 24.28). Severe interstitial fibrosis is present and the tubules have nearly disappeared.

### IF Findings

In chronic RVT without GN, the finding is either negative, or only fibrin [398] or gamma globulin [665] are found.
In primary GN, the entire picture is dominated by the IF mosaic of the underlying basic disease [1468].

### EM Findings

In primary chronic RVT, there are no inflammatory changes or osmiophilic deposits. The BM is thickened (experimental findings: [665]; see also [1367, 398]) or irregularly shaped [398], whereas in acute RVT, BM thickness appears to be normal [775].
Severe foot process fusion is already present during the early stages of the disease. Mesangial matrix is clearly increased. Focal sclerosing GN was encountered once in a biopsy 2 weeks after an otherwise typical acute RVT biopsy finding [398]. It is not known whether organized capillary loop thrombi, which we have never observed, or overload glomerulitis (see p. 308), which we saw in 3 out of 39 rats with experimental RVT and contralateral nephrectomy [1006], are responsible for the condition.

◁ **Fig. 24.25.** Same case as in Figure 24.24. Organized thrombi in an artery and two arterioles (→) are clearly discernible. Vascular lumens are almost completely occluded. The process in the artery appears to be considerably older. Thrombus masses, appearing dark, are still present in the arterioles. Male, 28 years. PAS (×280)

**Fig. 24.26.** Fresh renal vein thrombosis associated with thrombosis of the inferior vena cava. Glomerular capillary loops are obviously distended and contain numerous polymorphonuclear leukocytes. Female, 62 years. PAS (×580)

**Fig. 24.27.** Old renal vein thrombosis with nephrotic syndrome. There is no evidence, however, for epimembranous GN. The mesangium is delicate. Female, 56 years. PAS (×500)

**Fig. 24.28.** Venothrombotic contracted kidney. Surgically removed kidney weighed 35 g. Blood pressure preoperatively 240/130 mm Hg decreased to 135/85 mm Hg after nephrectomy. Glomeruli are strikingly well preserved. Capsular spaces are severely distended and occasionally contain exudate. Tubules have completely disappeared. Interstitium is sclerotic. Female, 47 years. PAS (×125)

### Differential Diagnosis

In needle biopsy, it is very difficult to differentiate the early phase of a subinfarct from an infarct due to acute RVT. In the early phase of infarcts, interstitial bleeding is usually already present which is not encountered in RVT.
In chronic RVT, the considerably widened sclerosed interstitium contains far fewer infiltrates than are found in chronic interstitial nephritis. Since destructive changes are absent, pyelonephritis can be excluded.
Venothrombotic contracted kidney cannot be differentiated from contracted kidney caused by central arterial stenosis unless large thrombosed veins and, in addition, cystoid widened glomerular spaces are present in the biopsy.
RVT is easily differentiated from Montaldo's pyelonephritis in which a chronic interstitial destruction is present (see p. 440).

### Etiology

Renal vein thrombosis arises by impaired venous flow as in renal cell carcinoma, tumors in retroperitoneal lymph nodes, right cardiac insufficiency, and, more rarely, following abdominal trauma, surgical procedures, and thrombophlebitis. During childhood, RVT usually develops in association with dehydration.
The simultaneous occurrence of epimembranous GN and RVT has given rise to controversy (2 out of 8 cases: [1770]; 1 out of 69 cases: [1167]). Although some investigators—mainly from the US—see RVT as primary and epimembranous GN as its consequence [1131, 1233a], we feel that there is more evidence against than for this concept. As far as we know, there is only one experimental finding (guinea pig with cardiopathy and severe, chronic venous stasis) showing BM thickening, loosening of the matrix and a few isolated subepithelial deposits [251]. In all other experimental findings of which we are aware, there are no reports of RVT—induced epimembranous GN [493, 1006, 1357, 1484]. The IF demonstration of fibrin deposits in biopsy is probably attributable to pure insudation arising from severe venous stasis.
It has, however, been known for quite some time that secondary RVT occurs with increased frequency in the presence of a long-lasting nephrotic syndrome (amyloidosis, etc.) and especially so with epimembranous GN. It is noted further that chronic RVT is unilateral and epimembranous GN bilateral [278]. It has been suggested [815a] that the low antithrombin III level—typical for nephrotic syndrome—enhances secondary RVT. Furthermore, in experimental Heymann nephritis, RVT occurs in 20% of the cases [856]. In acute RVT of children—arising through dehydration—no change reminiscent of epimembranous GN is observable with EM. A

proposed mechanism whereby renal tubular antigen—set free by thrombosis—induces antibody formation and circulates thereafter as immunocomplex and, as such, damages the kidney [1131, 1233a] is suggested by the demonstration of renal tubular antigen in the immunodeposits of epimembranous GN.
Nevertheless, we believe that RVT is, in the overwhelming majority of cases, a complication of the chronic nephrotic syndrome in association, amongst other lesions, with primary epimembranous GN (see also [39b, 88, 89, 195, 398, 918a, 1131, 1359, 1468, 1612, 1770]).

### Prognosis

Acute RVT, usually encountered in infants after massive dehydration, is usually a fatal complication.
In chronic RVT, prognosis depends, in the secondary form, usually on that of the underlying disease (e.g., GN, etc.). In the primary form, prognosis is usually good, as long as thrombosis does not progress into the vena cava and result in fatal embolic complications. In the venothrombotic contracted kidney, hypertension can develop and which determines prognosis. Hypertension can be cured by nephrectomy [1791].

### Pathogenesis

Capillary loop dilatation is ascribable to the severe venous stasis. We consider the BM and mesangial changes observed in primary chronic RVT to be a consequence of anoxia (see also [729, 1367]). The peculiar cystoid glomeruli (found only in venothrombotic contracted kidney and Montaldo's PN—see p. 440) are possibly the expression of venous flow still functioning via renal capsular veins which are usually patent in RVT. This is apparently only rarely so in chronic PN, but, if present, the picture of Montaldo's PN arises.

## Kidney Infarct

### Definition

Kidney infarct is an ischemic necrosis caused by arterial obstruction. Hemorrhagic necrosis (so-called hemorrhagic infarction) is seen almost exclusively in infants with venous thrombosis, and it plays no role in biopsy.

### Incidence

We have observed renal infarcts in about 4% of our autopsy material [1791]. Predominant pathogenetic causes in our material are myocardial infarction (19%), endocarditis (19%) and cardiac insufficiency with endocardial thrombi (29%).
With the exception of transplants, renal infarct does not play a significant role in biopsy (0.46%: Z). In one case, an infarct arose from prior needle biopsy which resulted in thrombosis of a large renal artery. In another case, there was embolic occlusion of the renal artery in a patient with unilateral renal agenesis.
The other infarcts were the consequence of traumatic kidney rupture or repeated surgery for congenital malformations of the urinary tract.
In the transplant biopsies, renal infarcts are strikingly frequent (11.5% of 131 biopsies: Z) and are chiefly due to transplantation vasculopathy (see p. 596).

### Clinical Findings

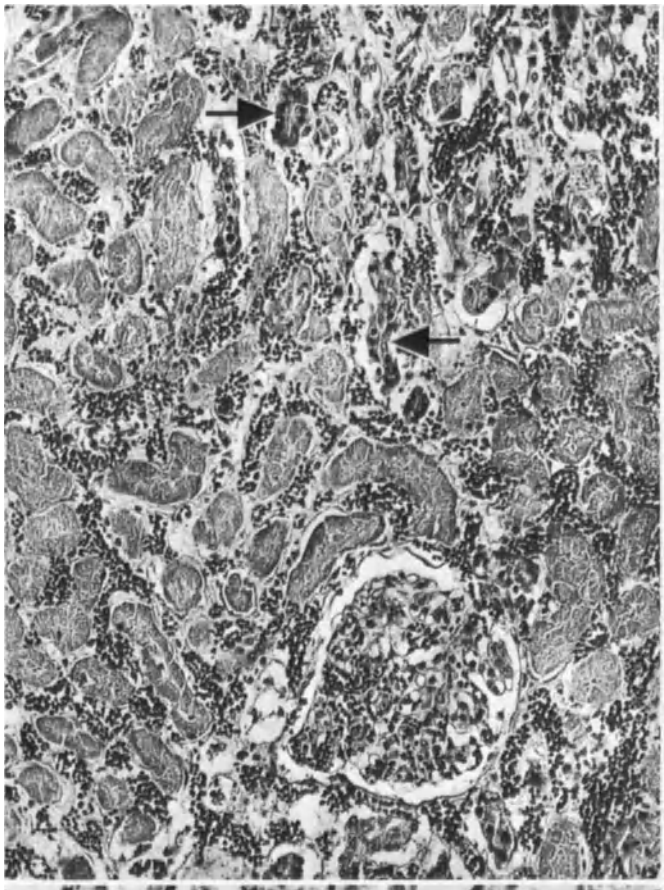
Flank pain is present in the majority of cases, fever in 30–70%, proteinuria in 50% and micro-or macrohematuria in 30–80% [1758, 1791]. In large infarcts, transitory hypertension is sometimes observed after 4 to 8 days [1758]. In case of persistent hypertension, nephrectomy will result in cure [1118]. Acute anuria occurs with infarction in individuals with only one kidney and in the event of bilateral arterial occlusion.

**Fig. 24.29.** Bordering zone of a fresh cortical infarct. Glomeruli ▷ even more clearly recognizable, intertubular capillaries—from which some extravasation occurs—are filled with blood. Proximal tubules are fully necrotic. A few distal tubules are preserved (→). HE (×150)

**Fig. 24.30.** Partial glomerular capillary loop necrosis (→) with sludging and homogenization of erythrocytes in a fresh infarct. Disintegrated erythrocytes and some fibrin are present in the capsular space. Female, 62 years. PAS (×480)

**Fig. 24.31.** Bordering zone of a not completely fresh infarct. Isolated necrotic tubules (*N*) are present. A glomerulus with capillary loop collapse and reactive crescent formation can be seen. Autopsy specimen. HE (×250)

**Fig. 24.32.** An old renal cortical infarct with the bordering zone. Glomeruli are fully obsolescent and completely fill the unchanged capsular spaces. Stroma is broadened, homogenous and almost free of nuclei. PAS (×100)



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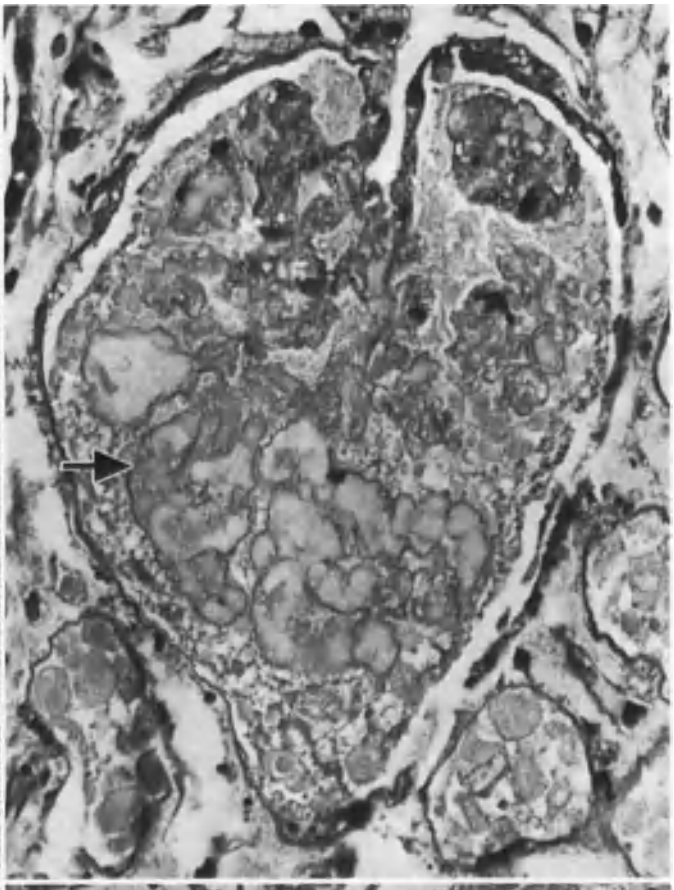

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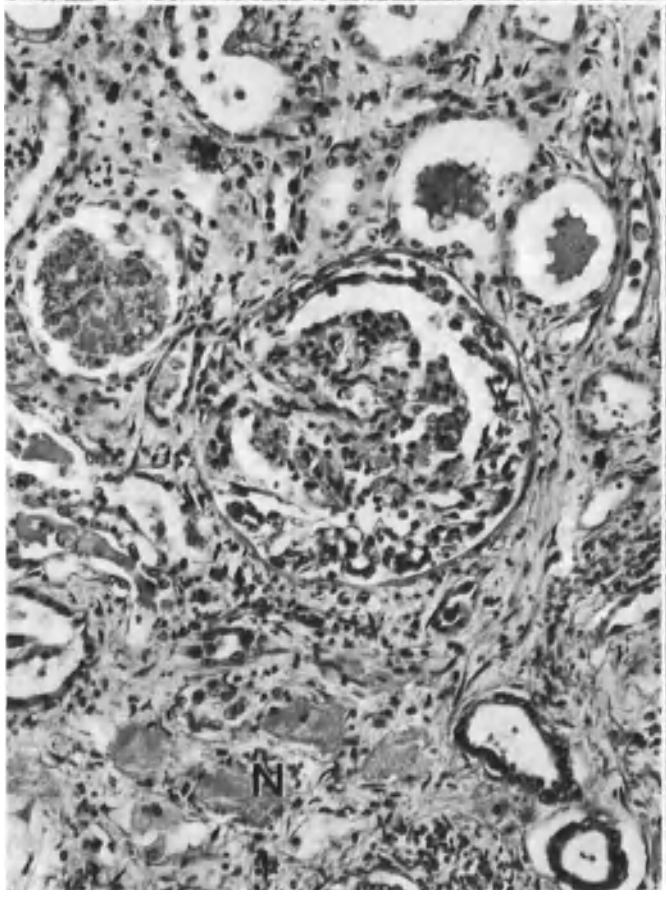


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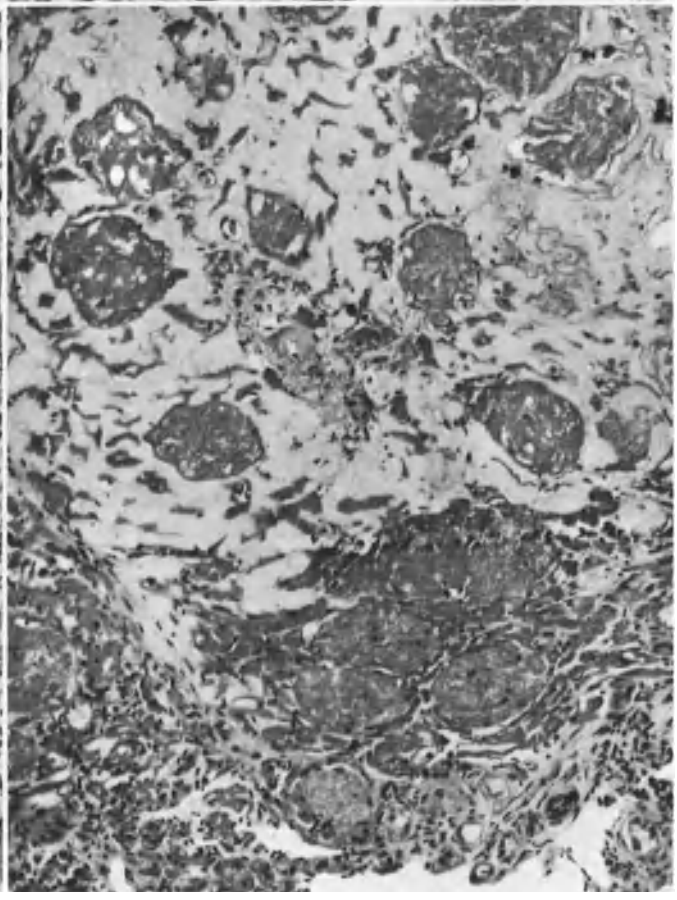

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### LM Findings

In infarcts of a few hours up to a few days old, the glomeruli are enlarged and the loops filled up with clumped erythrocytes (Fig. 24.29).
Corresponding to the topography of the nephrons, necrosis with jigsaw puzzle-like borders are found (Fig. 5.2; p. 47) and intensely eosinophilic tubules with vanishing nuclei are present. The distal tubules and the glomeruli are longer preserved (Fig. 24.29) than the other parts of the nephron. Necrotic areas are sharply demarcated from the intact parenchyma. In this phase, the interstitium is slightly edematous and often permeated with blood (Fig. 24.29).
As in other organs, renal infarct a few days old exhibits a cockade pattern. Therefore, if the biopsy needle penetrates the infarct area tangentially, difficulties in interpretation may arise.
In the center of the infarct, the tubules and some of the glomeruli are completely necrotic. A few better-preserved glomeruli show partial capillary loop necroses which are flooded with blood (Fig. 24.30). This central part of the cockade is followed by a usually small, dense fringe of leukocytes which, in turn, is surrounded by a hyperemic zone with rapidly emerging fibroblasts.
Exterior to hyperemic zone, the sensitive proximal tubules evidence necrobiotic injury while the glomeruli usually show no changes except for hyperemia. In other cases, the glomeruli in the fringe zone are strikingly large with dilated capillary loops full of erythrocytes and have no—or very few—nuclei. This finding is explained by the presence of minimally maintained (possibly restored) blood flow. As a rule, the arteries in the region of an infarct are contracted. They almost never contain thrombi.
An infarct scar (Fig. 5.3; p. 48) is characterized by a necrotic, very lipid-rich center in which the original structures—especially the glomeruli—can still be recognized as shadows (Figs. 6.113, 24.32). The glomeruli appear as hyaline spheres (van Gieson stain: yellow) without any capsular reaction (see also [1068]). This form of obsolescence is a consequence of abruptly—occurring ischemia, blood stasis and necrosis. In the region bordering the infarct, a few more or less old crescents in glomeruli can be seen (Fig. 24.31). The interstitial stroma is fibrosed.

### EM Findings

The glomeruli evidence either complete collapse or severe loop dilatation with clumped erythrocytes in their lumen, and endothelial necrosis and detachment (Fig. 30.38; see p. 585). The tubules show beginning or completely developed necrosis (Fig. 24.33). The interstitium is usually somewhat edematous and often contains numerous erythrocytes.

### Differential Diagnosis

The differentiation between an infarct and cortical necrosis caused by intravasal coagulation is of decisive significance. In cortical necrosis, parietal fibrin thrombi are found in the peripheral vessels and in glomeruli to a degree not present in infarcts.

### Etiology

It is scarcely possible to reach etiologic conclusions on the basis of needle biopsy findings. Biopsy material obtained by surgery permits identification of thrombotic or embolic occlusion of larger arteries. Special attention should be given to identifying atheromatous emboli which are recognizable by their whetstone-shaped hollows arising by dissolution of cholesterol crystals (Fig. 24.34). These crystals are usually surrounded by a granulation tissue containing foreign body giant cells (8 out of 755 biopsies: [785]; 6 out of 690 biopsies: [744]).

## Subinfarct
[1808]

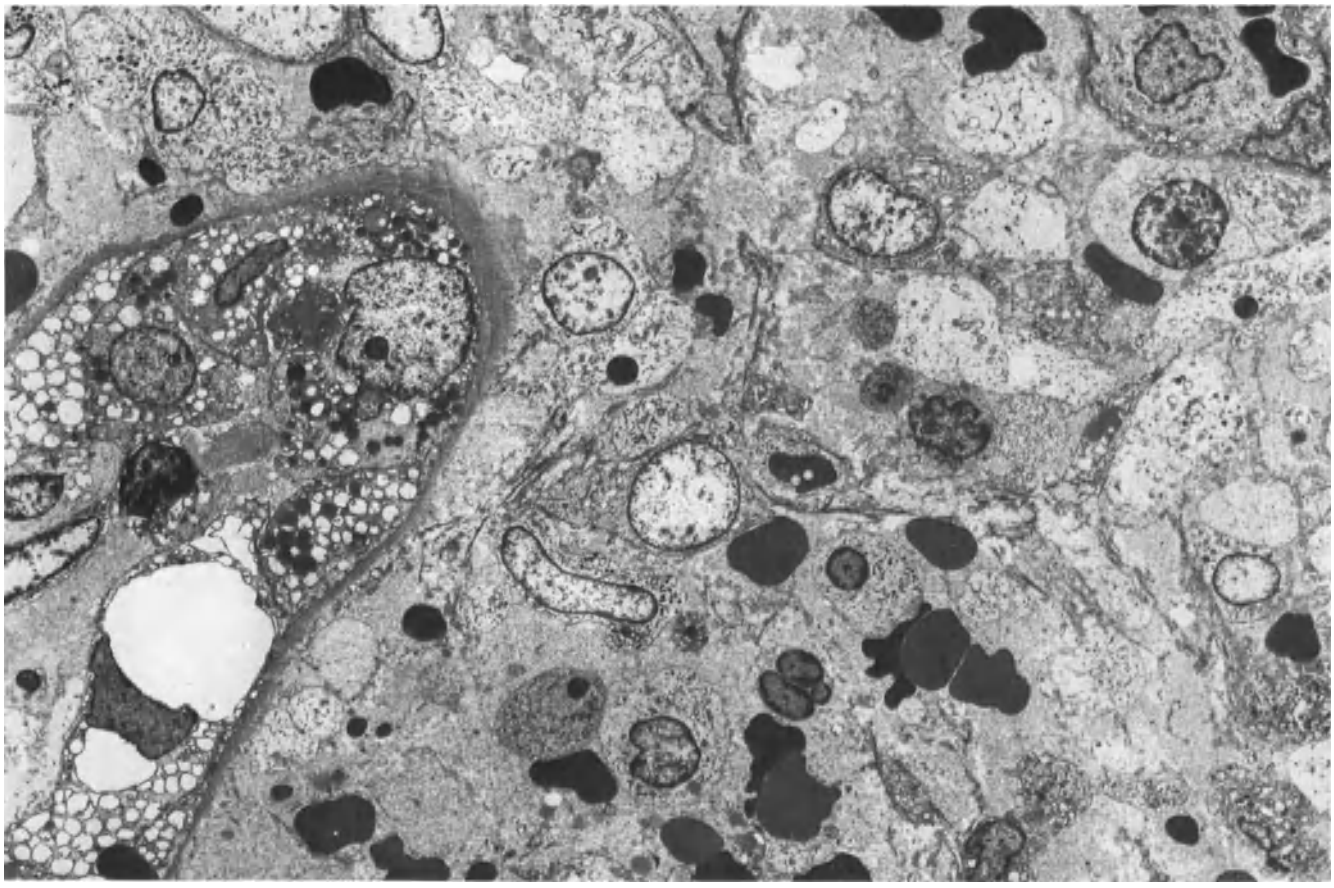
### Definition

The subinfarct is a characteristic renal parenchymal atrophy associated with subtotal arterial obstruction. We arbitrarily designate parenchymal areas larger than 3 cm as subinfarcts and those smaller as arteriosclerotic cortical scars.

***Synonyms:*** Ischemic contracted kidney, incomplete renal infarct, central arterial contracted kidney.

### Incidence

In 25,000 autopsies, we encountered small subinfarcts (larger than 3 cm) in 92 cases of which 18 were associated with hypertension, 148 middle-sized subinfarcts (at least one-third of the kidney) of which 104 were associated with hypertension, 293 subtotal subinfarcts, 228 of which were associated with hypertension. Contracted kidney caused by central artery stenosis was found in 64 cases (54 out of 64 with hypertension).
The subinfarct plays a minor role in biopsy (0.67%: Z). There are no reliable data relating to age distribution. Since vascular lesions become manifest predominantly in the aged, it is probable that subinfarcts usually occur among the older age groups. The incidence between males and females is about the same.



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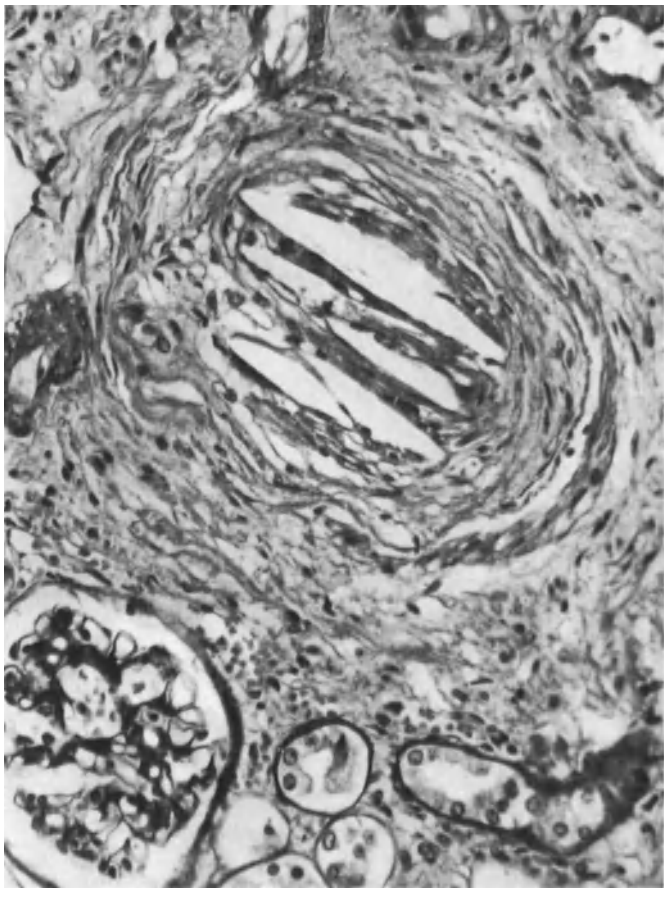

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**Fig. 24.33.** Very acute infarct predominantly evidencing swelling of interstitial cells—chiefly phagocytes—and extravasation of erythrocytes. Proximal tubules appear to be still vital but they do show severe swelling of their organelles. Twelve-day-old transplant associated with arterial thrombosis at site of suture. Male, 35 years. EM ( $\times$ 1500)

**Fig. 24.34.** Cholesterol crystal emboli in a small renal artery due to massive ulcerative aortic arteriosclerosis. Renal biopsy, performed because of persistent hematuria, demonstrated a large infarct. Female, 56 years. PAS ( $\times$ 500)

### Clinical Findings

The case history is silent with the exception of complaints related to hypertension which we found present in 84% of cases evidencing central arterial contracted kidney. This incidence is three times greater than that of essential hypertension occurring in a control group of the same age [1808].
On the other hand, renal artery stenosis has been reported to be the cause of hypertension in 5–15% of a group of hypertensive patients (literature relating to clinical findings: [320]). It is not known why hypertension is absent in a small number of cases with severe stenosis of the renal artery (see also [320, 1137]); perhaps functional adrenal insufficiency, cardiac insufficiency or ischemic–induced impairment of renin formation may be involved. In some cases with severe hypertension, proteinuria is present (12 out of 33: [1137]) but rarely a nephrotic syndrome which then can be eliminated with antihypertensive therapy [131].
In central arterial contracted kidney a unilateral small "silent" kidney is present. There are no clinical data reporting on the frequency of hypertension in the presence of small and middle-sized subinfarcts [1239].

### LM Findings

Affected cortical sectors are highly atrophic (Fig. 5.5; p. 46). There is a marked discrepancy between the relatively well-preserved glomeruli and the severely atrophic tubules (Figs. 8.9, 24.35). The glomeruli are very close to each other. Whereas there are normally 2.5 glomerular sections per $mm^2$, in subinfarcts there are 6 [1808]. Collapse glomeruli are found in various numbers. Completely obsolescent glomeruli are quite rare.
The number of nuclei, mesangial volume and mesangial nuclear volume are slightly increased [1808]. The juxtaglomerular apparatus is clearly hypertrophic in 50% of the glomeruli. Morphometrically, the tubular volume is considerably decreased. In LM, it is seen that the tubular outer diameter is severely decreased, the lumen narrowed or partially or entirely absent (Figs. 24.35, 24.36, 24.37).
In the region of the proximal tubules, the epithelium is abnormally clear and dedifferentiated (Fig. 24.36). The tubular BM is usually considerably thickened (Figs. 24.36, 24.37), occasionally thinned or completely absent (Fig. 24.37).
The cortical interstitium is focally slightly thickened and sclerosed while that of the medulla is diffusely and severely so. There is a scanty sprinkling of lymphocytes and phagocytes in the interstitium but no destruction of tubules, glomeruli or blood vessels due to inflammation or to scar tissue arising from inflammation is present. Blood vessels in the subinfarct are characterized by severe adaptive intimal fibrosis (Fig. 24.37).

### EM Findings

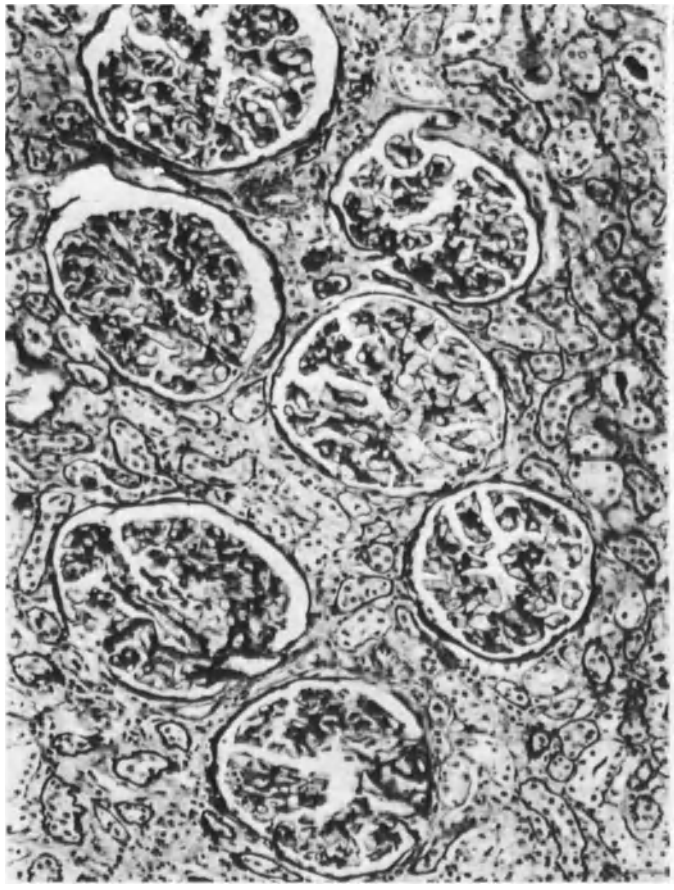
Slight glomerular collapse is far more frequently encountered than with LM [1808]. Dedifferentiation of tubular cells with attendant decrease in the number of organelles is very marked (Figs. 24.38, 24.39).
The tubular BM is either thickened and split (Fig. 24.39) or clearly thinned (Fig. 24.38). It is occasionally penetrated by dedifferentiated tubular cells which come to lie free in the interstitium (Fig. 24.39; [1808]).

### Differential Diagnosis

In infarct scars, the structural elements (e.g., glomeruli, etc.) are discernible for months or years as shadows. A zone of a subinfarct may border an infarct scar. In the case of infarct, however, the interstitium shows more extensive fibrosis in the bordering zone as a result of perifocal inflammatory response than is ever seen in pure subinfarcts.
Glomerular atrophy–often accompanied by periglomerular fibrosis–is much more extensive in pyelonephritic scars, as are fibrotic changes and inflammatory infiltrates. Signs of destruction of tubules, glomeruli and small vessels are always present in chronic pyelonephritis.
Hypogenetic foci (see p. 547) are easy to differentiate from subinfarct in which the normally structured parenchyma is recognizable and fetal tubules, cartilagenous elements, etc., are never seen.

### Prognosis

Prognosis is exclusively dependent on secondary hypertension which can be eliminated by resection of the afflicted renal tissue or by total nephrectomy and, in many cases, by arterioplasty (25 out of 29: [1147]). The success of surgical procedures is dictated chiefly by the presence of arteriolosclerosis (hypertensive vasculopathy) of the contralateral kidney. If severe arteriolosclerosis is present and serum creatinine elevated as result of contralateral renal damage, no success can be expected.
Bilateral pre-or intraoperative renal biopsy has not proven to be of great value for predicting postoperative success in reducing hypertension, although quantitative bilateral JGA evaluation does allow such a prediction with some degree of reliability [330, 448]. Semiquantitative evaluation of bilateral renal biopsy shows no correla-



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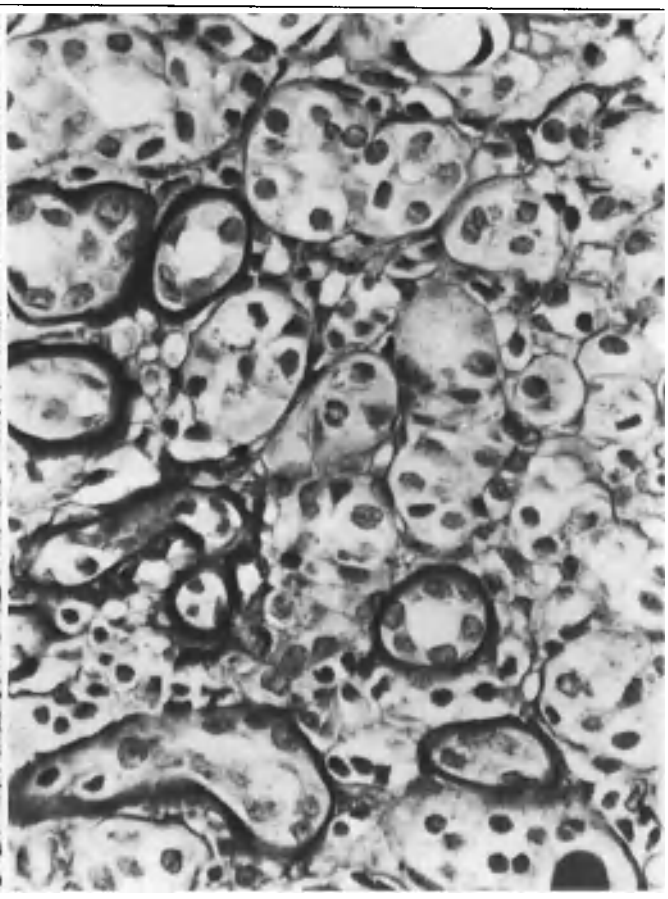

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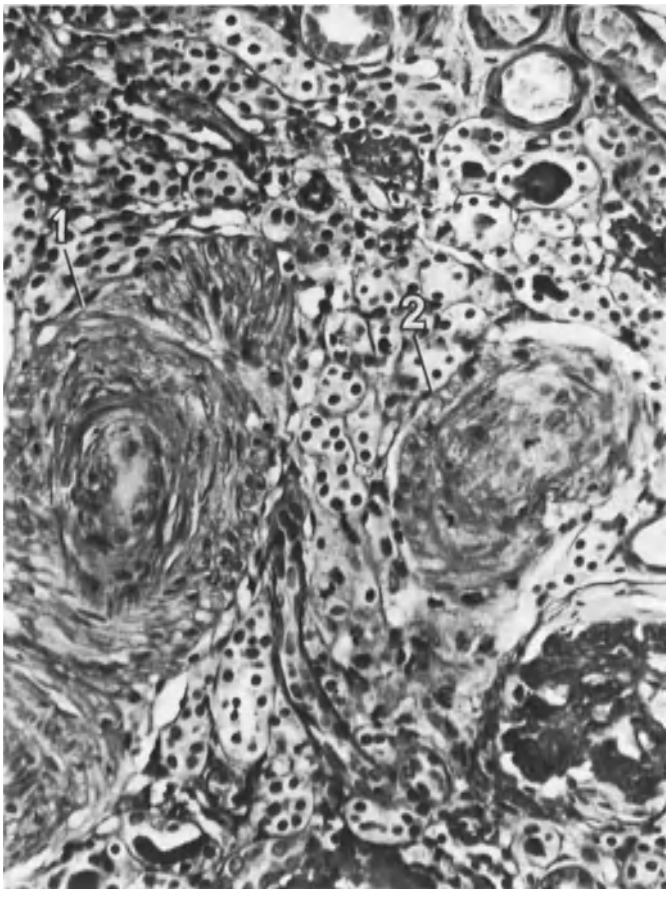


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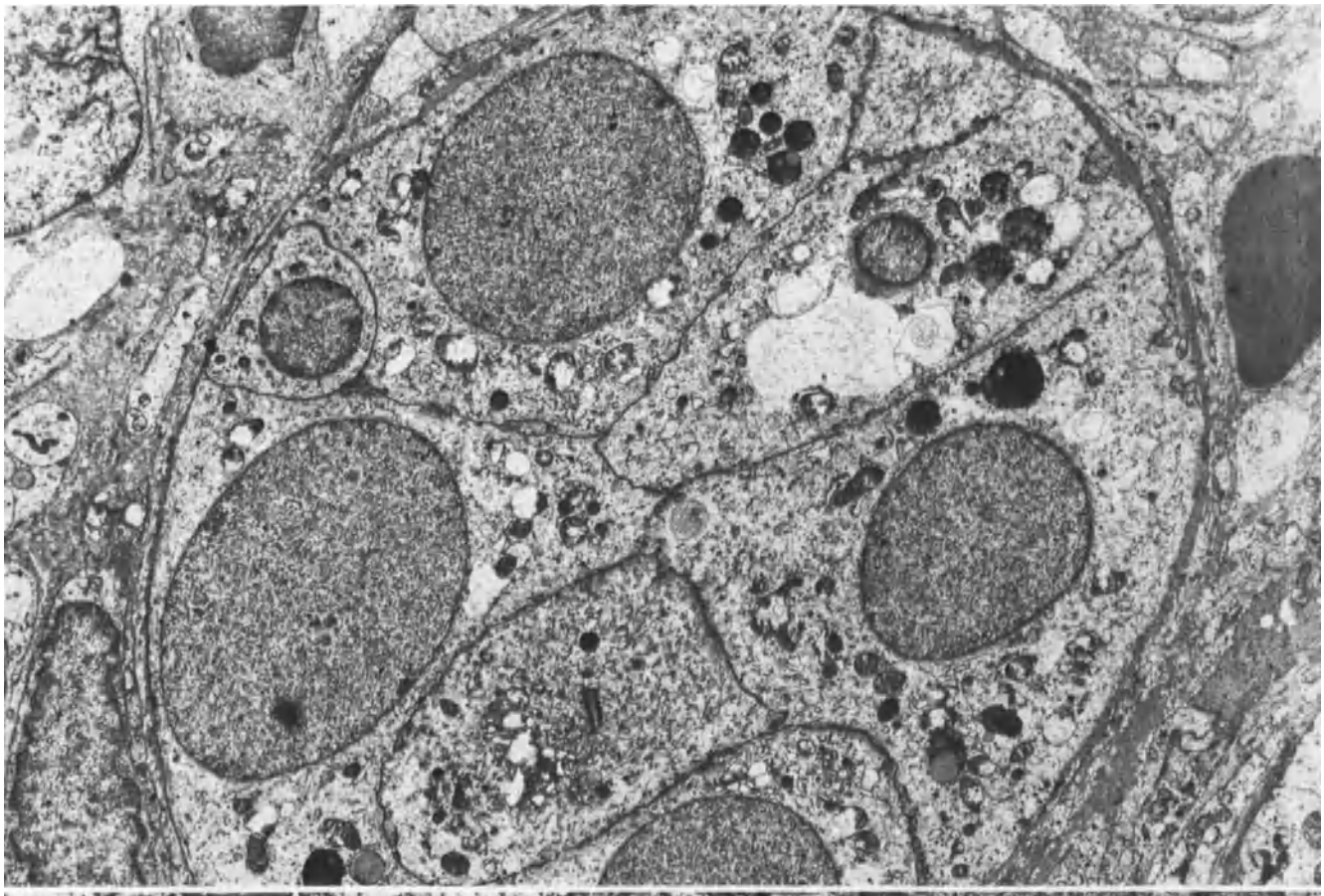
**Fig. 24.35.** So-called central arterial contracted kidney (due to stenosis of renal artery) associated with hypertension. Glomeruli appear unchanged but are closely packed together. Tubules are severely diminished in size and are dedifferentiated, i.e., appear clear. Their lumens have completely disappeared. The interstitium is unchanged. Male, 50 years. PAS (×170)

**Fig. 24.36.** Same case as in Figure 24.35. Dedifferentiation of the tubules (note clear cytoplasm) is now very obvious. Tubular BM is at times delicate and at times very severely thickened. These findings correspond to the so-called endocrine kidney. Male, 50 years. PAS (×600)

**Fig. 24.37.** So-called central arterial contracted kidney (due to stenosis of renal artery with kidney weight of 21 g) associated with severe hypertension. One glomerulus evidences collapse obsolescence; vessels show adaptive intimal fibrosis. Artery (*1*) with adaptive intimal fibrosis, arteriole (*2*) also with adaptive intimal fibrosis in which lumen appears to be completely occluded. Here and there, dedifferentiated tubules can be recognized. Male, 43 years. PAS (×180)



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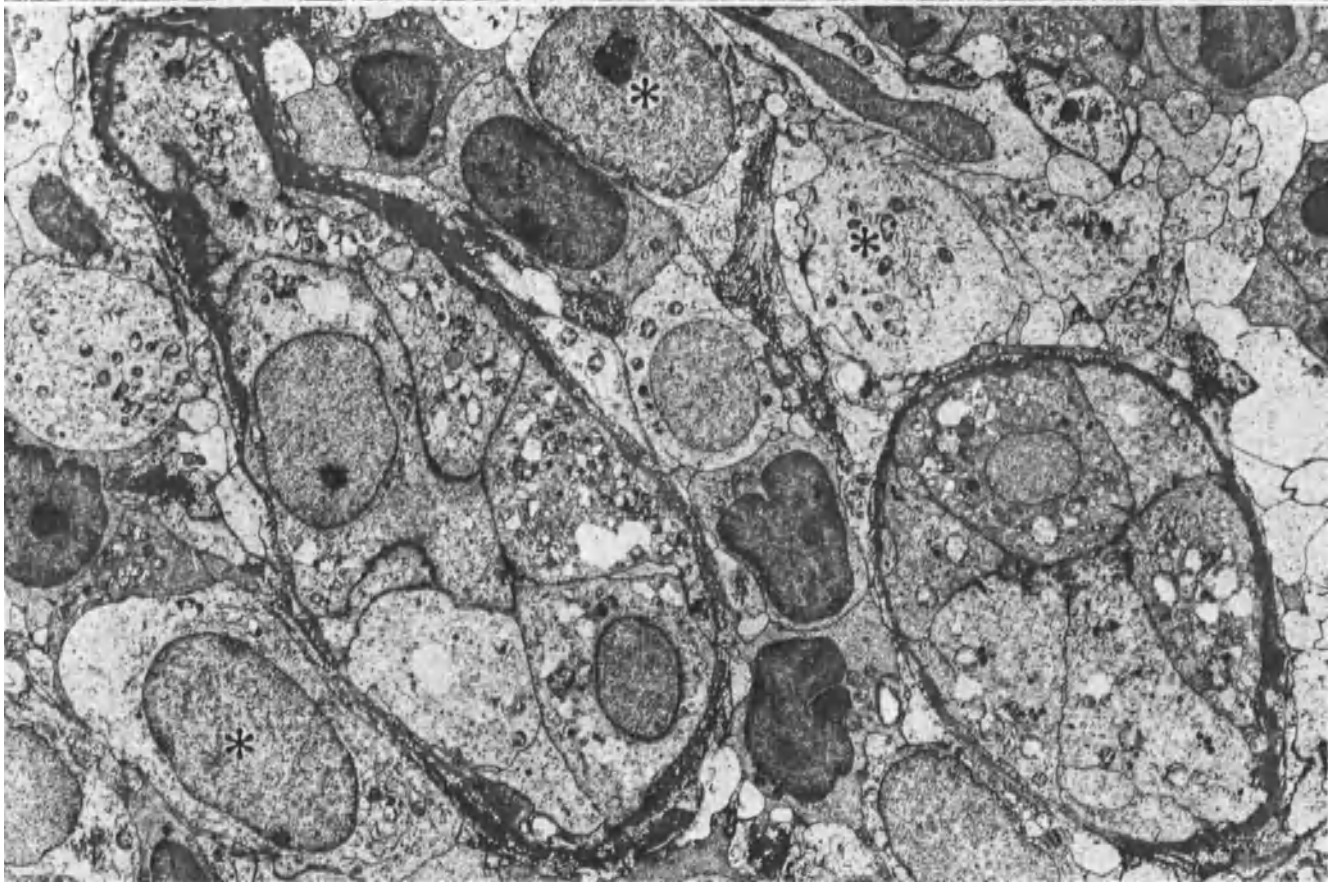


24.39

tion relating to the prediction of operative success as does evaluation of nephrectomy material [81]. The disadvantages and problems of preoperative bioptic methods can be overcome by renin estimation in both renal veins and arteries as well as in the peripheral blood [1656a] which is said to allow prediction of surgical success or failure in all cases [1656a].

**Pathogenesis**

Renal changes are the consequence of reduction of blood flow to a minimum allowing preservation of structure but not of excretory function. Renin formation (incretory function) is increased, so that renal hypertension may ensue.
Cases healed operatively have confirmed the renal origin of the blood pressure increase (see p. 541). In this connection, it must be emphasized that hypertension is directly dependent on the degree of renal blood flow impairment. This means that even in cases with minor or no subinfarct changes, hypertension may be present. Therefore, even discrete subinfarct changes in needle biopsy can be of significance.

**Etiology**

In almost all cases, impairment of renal blood flow is the consequence of severe arteriosclerotic stenosis which is not infrequently accompanied by thrombosis. Patients with aberrant renal pole vessels are especially frequently afflicted [1345, 1791].
A totally obstructing embolus does not lead to subinfarct as does one causing partial obstruction, which after a while, cannot be differentiated from a thrombus.
Other vascular lesions are extremely rare causes of subinfarcts.

◁ **Fig. 24.38.** Same case as in Figure 24.35. Dedifferentiated tubule is seen with increase in lysosomes whereas the number of other cell organelles is reduced. Tubular BM is partly thinned and partly dissolved. Male, 50 years. EM (×4900)

**Fig. 24.39.** Same case as in Figure 24.35. Partial thickening and splitting or thinning of the tubular BM are now far more evident. Occasionally, cells with the characteristics of tubular cells (*) are recognizable free in the interstitium. A few scattered large lymphocytes are present. Male, 50 years. EM (×3900)

# 25. Renal Changes Caused by Vascular Disease

Renal vascular changes are strikingly common. Very often they arise secondarily in association with other renal diseases and lead to further parenchymal damage so that very complex findings are generated.
Accordingly, knowledge of the various vascular lesions and their consequences is of great importance. Arteriosclerosis will not be discussed.

## Arteriolosclerosis
[552, 1509a]

### Definition

Arteriolosclerosis is a lesion in which fibrinoid (hyaline) deposits occur between the endothelium and media of arterioles without significant media change.

### Incidence

A few arteriolosclerotic vessels are frequently found in needle biopsies of older patients. In older patients with hypertension of long duration, almost all the arterioles are more or less severely afflicted (see Fig. 25.1).
Arteriolosclerotic contracted kidney (=red granular atrophy or benign nephrosclerosis) is rare (0.12% of a series of autopsies: [1791]). The incidence is the same for men and women.

### Clinical Findings

In cases of extensive arteriolosclerosis, hypertension is the predominant finding. Although clinical data on hypertension may be absent at autopsy, the autopsy findings themselves usually give ample evidence of hypertensive disease.
Proteinuria is usually slight, about 1–2 gm/day [1239, 1325]. In moderately severe to severe arteriolosclerosis, 71.4% of our biopsy cases evidence hypertension of $\geqq$160/100 mm Hg. In mild arteriolosclerosis, 41.2% of biopsy cases have a history of hypertension. The absence of arteriolosclerosis in needle biopsy (30% of our own cases with hypertension) does not exclude hypertension (Fig. 25.1). A similar and almost equally good correlation is also present for the IF-demonstrated arteriolar insudation with IgM and/or complement (Fig. 25.1).

### LM Findings

The cortical tissue, especially that lying immediately subcapsularly, demonstrates fine, radial strip-shaped subinfarcts (Fig. 5.6) which, depending on the area included in biopsy material, may or may not be present. Complete obsolescence of the glomeruli (collapse type) is more frequent in these regions than it is in large subinfarcts.
The arteriolar change in needle biopsy is readily discernable with Masson's trichrome/AFOG and PAS stain (see also [1530]). We give special attention to the afferent vessels and to the arterioles at the point where they issue from interlobular arteries (Fig. 25.2). Severe involvement of the efferent vessels indicates diabetes mellitus.
In transverse sections, an annular, strongly eosinophilic homogenous fibrinoid deposition lies between the endothelium and media (Fig. 25.3).
The deposits are sudanophilic, yellow in van Gieson's stain, strongly PAS positive, red in Masson's trichrome/AFOG stain, and PASM negative.
The elastic lamina of prearterioles lies outside of the deposits (Fig. 25.4). It is only fragmented or absent in severe cases in which the fibrinoid deposits lead to severe stenosis of the arteriolar lumen. In this condition, the media is frankly atrophic and, especially in severe hypertension and in relatively young patients, it can also demonstrate a slight fibrinoid muscle cell necrosis ([1791]; see also p. 521). The focal character of the lesion is best discernible (Fig. 25.5) in longitudinal sections. The arteries may, but need not, demonstrate arteriosclerosis.
The tubules associated with the changed arterioles—occasionally of only one nephron—often exhibit hyaline casts, severe atrophy and lipid deposition with slight birefringence in lipid stains, but we have never observed thyroid-like tubules. The interstitial changes correspond to those encountered in subinfarcts.
In the glomeruli, there occurs a slight increase of the mesangial matrix [75] as well as anoxic injury, i.e., collapse with a few severely thickened capillary loops which

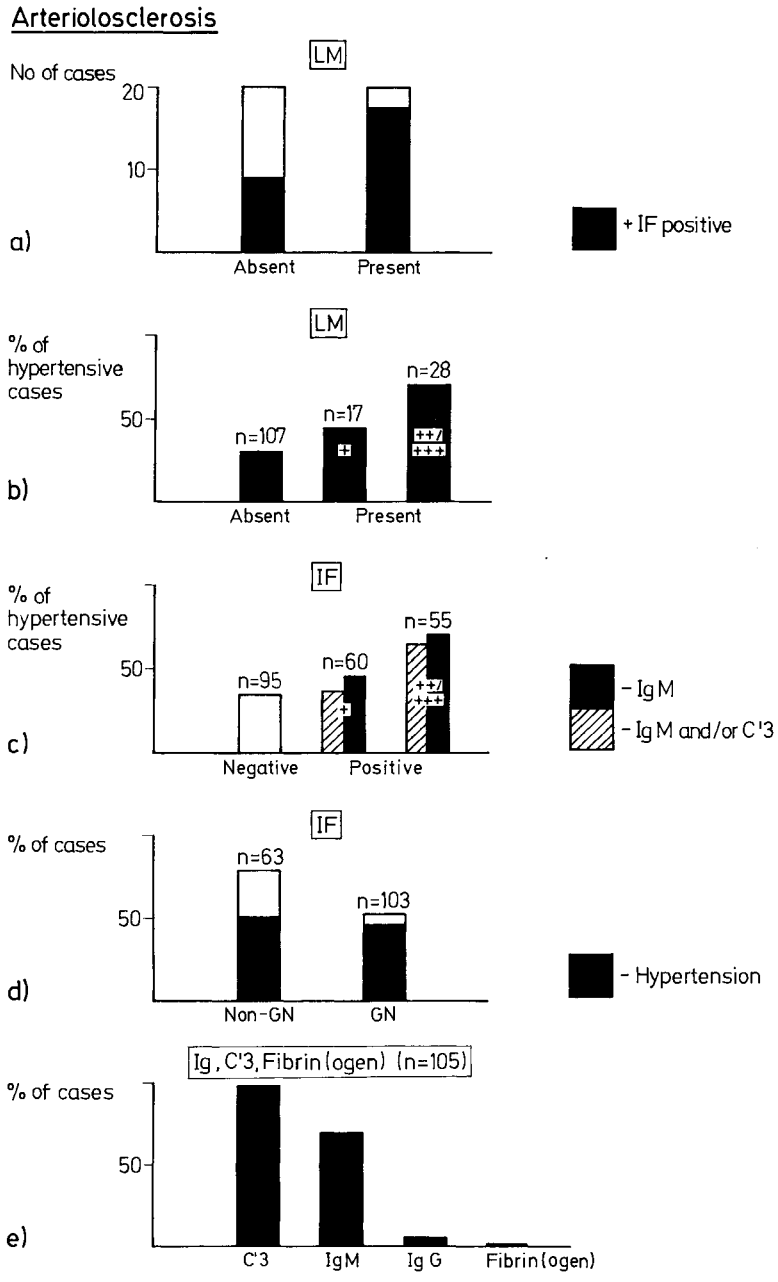



**Fig. 25.1a–e.** LM and IF arteriolar findings as related to hypertension (BP≧160/100 mm Hg). (a) Relationship between arteriolosclerosis as identified by LM and IF. Note: Arteriolosclerosis is more often found by IF than by LM, even if the LM material is serially sectioned. In cases of arteriolosclerosis identified by LM, IF is nearly always positive. (b) Relative frequency of hypertension in cases with and without arteriolosclerosis under LM. Note: even in the absence of arteriolosclerosis with LM (left column), nearly 30% of cases disclose hypertension. Percentage increases in cases with severe (*right column*) arteriolosclerosis with LM to more than 70%. (c) Relative frequency of hypertension in IF arteriolar findings. Note: 35% of patients negative in IF (*left column*) disclose hypertension. Percentage increases in marked IF positivity to 70% (*right column*). (d) Relative frequency of IF arteriolar findings in non-GN and GN. Note: 80% of patients with non-GN have positive arteriolar findings, vs. only 55% with GN. Percentage of hypertension in both groups of renal disease is nearly the same. (e) Relative frequency of immunoglobulins in 105 cases with positive arteriolar findings in IF

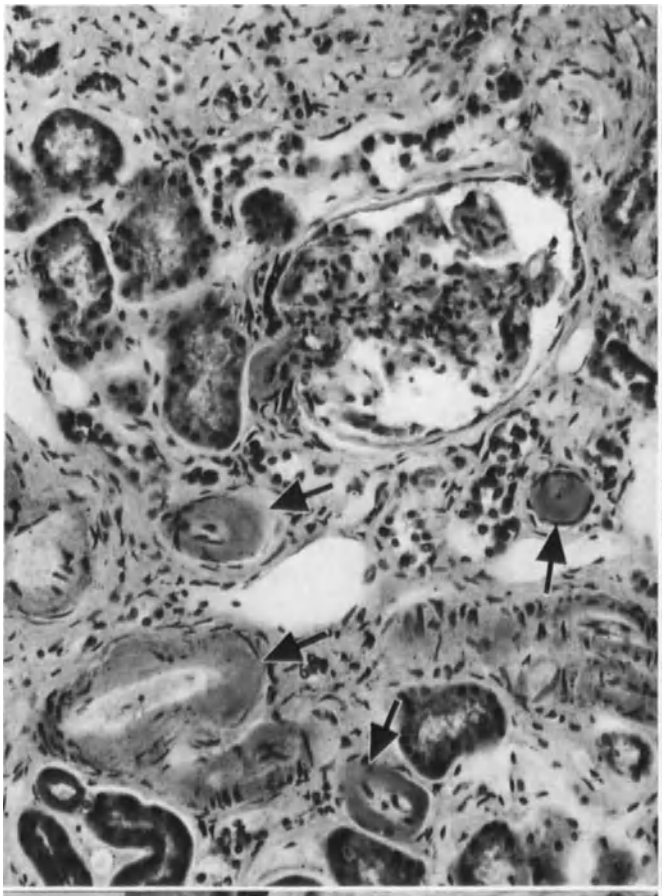
may demonstrate fibrinoid masses. The changes slowly develop into segmental loop obsolescence (Fig. 25.6) with synechiae and striking thickening and splitting of the glomerular capsule (Figs. 6.112; 25.6). Complete glomerular obsolescence finally occurs.

The above-described parenchymal changes may be completely absent in mild arteriolosclerosis, even though hypertension is present. Accordingly, the arteriolar changes are the significant ones and not those of the parenchyma (see also [81]).

JGA changes are described on p. 116.

## IF Findings

A statistically significant correlation exists between IF findings of plasma protein insudation of the arteriolar wall (Fig. 25.1) and the LM finding of arteriolosclerosis. This can be only demonstrated when all arterioles in serial sections are very carefully examined with LM (Fig. 25.1). The focal character of arteriolosclerosis in the beginning explains the discrepancy between LM and IF findings (Fig. 25.1). Among 105 positive IF findings in arterioles, we found complement (C3) in 97%, IgM



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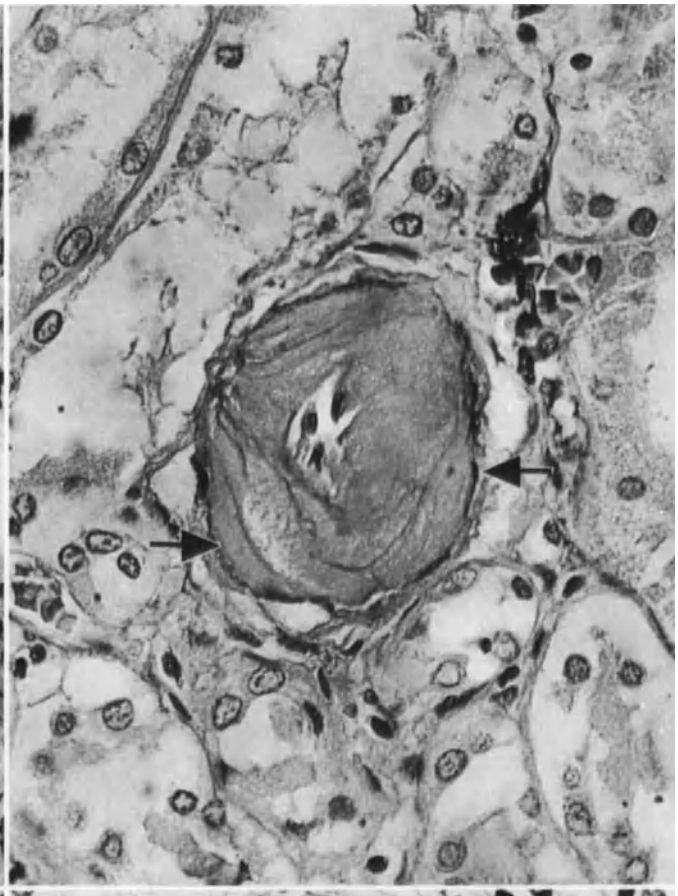

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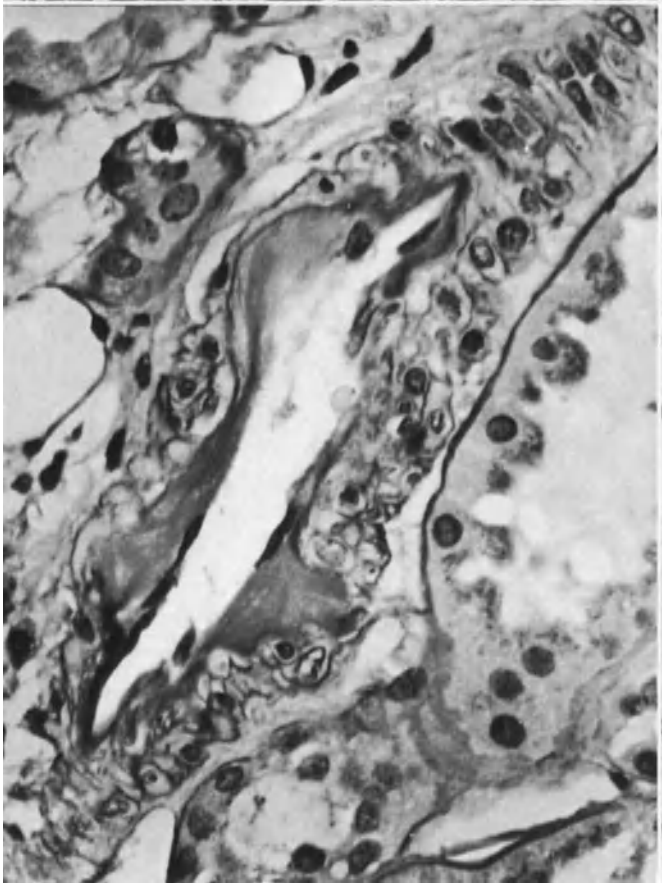

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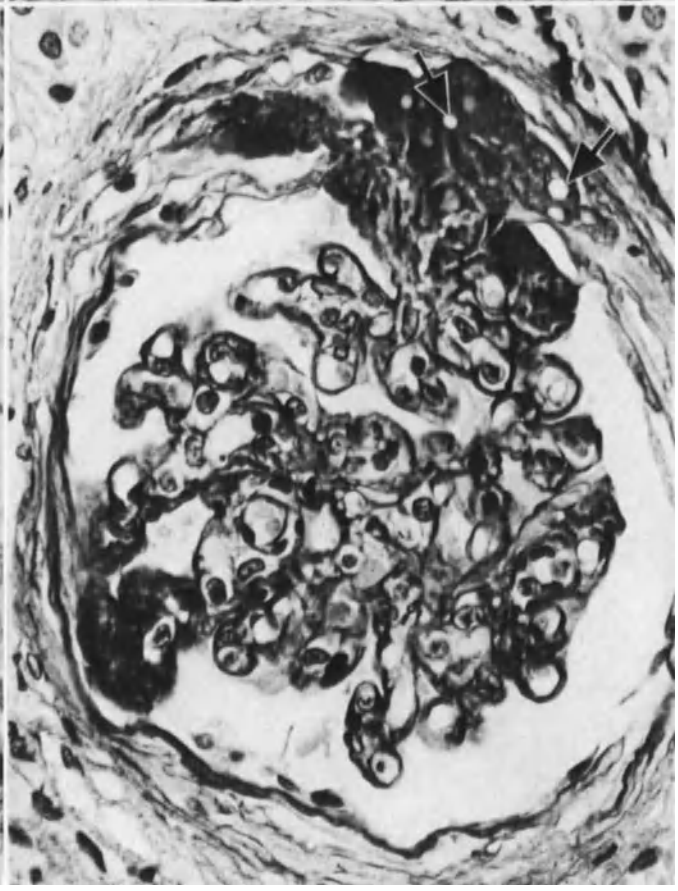

25.5

in 72%, IgG in 5% (mainly in GN) and fibrin in 2%. All other immunoglobulins were always negative.
In 5 out of 11 of our cases, the glomeruli demonstrated deposits of IgM and/or C3 in focal or diffuse but always in segmental distribution in the mesangium and/or in the periphery (Figs. 11.8, 11.21, 25.7). In 10% of the cases with arteriolar changes, a slight focal insudation in the walls of the arteries (positive for IgM, C3 or IgG) was present. IgG, however, was demonstrated only in the presence of attendant GN.

### EM Findings

In EM, arteriolosclerosis differs from arteriolonecrosis more quantitatively than qualitatively in that in arteriolosclerosis, ground substance formation predominates (due to myocytic transformation) and in arteriolonecrosis, myocytolysis [783]. Overlapping of both findings can be observed (Fig. 25.15; see p. 524; see also [576]).
In arteriolosclerosis, endothelial necrosis and widening of the normally slit-shaped cell junctions between the endothelial cells are frequent. The subendothelial space is enormously widened and filled with a finely granular osmiophilic mass with a cloudy, patchy arrangement (LM: fibrinoid = eosinophilic noncellular subendothelial hyaline: [1274a]; Figs. 25.8, 25.9). In this condition, the BM and elastica are split and partially impregnated with osmiophilic masses (Figs. 25.8, 25.10).

In arteriolosclerosis, there is no significant intermyocytic separation caused by osmiophilic material (i.e., no permeation of the media). A few scattered elastic aggregates frequently lie in the immediate vicinity of the myocytes. The myocytes may show a spider-shaped transformation and an increase in organelles (mesenchymally transformed myocytes, "moth-hole cells" [1591c]) or they may be rounded, thickened and vacuolized, i.e., early degeneration of myocytes leading to myocytolysis (Figs. 25.8, 25.9). The myocytic injury continues and procedes centrifugally from the lumen. There remains cellular detritus—with minimal mineral deposition—which demonstrates vesicular structure. The latter-described myocytic changes already indicate arteriolonecrosis (for histograms on glomerular EM findings see Figs. 6.9, 6.22, 6.34, 6.57, 6.64, 6.80, 6.88).

◁ **Fig. 25.2.** Arteriolosclerosis due to severe hypertension. Homogeneous fibrinoid masses are present between the endothelium and media (→). Glomerulus depicted demonstrates obvious collapse. Arteriolosclerosis is also present in the vas afferens. Female, 62 years. HE (×250)

**Fig. 25.3.** Same case as in Figure 25.2. Elastica of an arteriole is still recognizable (→). Endothelium is also preserved. Between l. elastica and endothelium homogenous masses are present which are occasionally slightly lamellated. Female, 62 years. Van Gieson elastin (×540)

**Fig. 25.4.** Arteriolosclerosis in pyelonephritis and hypertension. Fibrinoid homogeneous masses are clearly focally deposited in the subendothelial space. Media overlying the deposits is atrophic. Male, 72 years. Van Gieson elastin (×540)

**Fig. 25.5.** Segmental obsolescence of glomerular capillary loops with fibrinoid (giant) deposits containing lipid vacuoles (→). There are obvious synechiae in the region of occluded glomerular capillary loops. BM of the other capillary loops shows slight wrinkling, e.g., collapse. A case of severe renal arteriolosclerosis associated with hypertension. Female, 71 years. PAS (×600)

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**Fig. 25.6.** Same case as in Figure 25.5. Ischemic injury is far more advanced. In addition to capsular thickening, segmental glomerular sclerosis is present. Female, 71 years. PAS (×280)

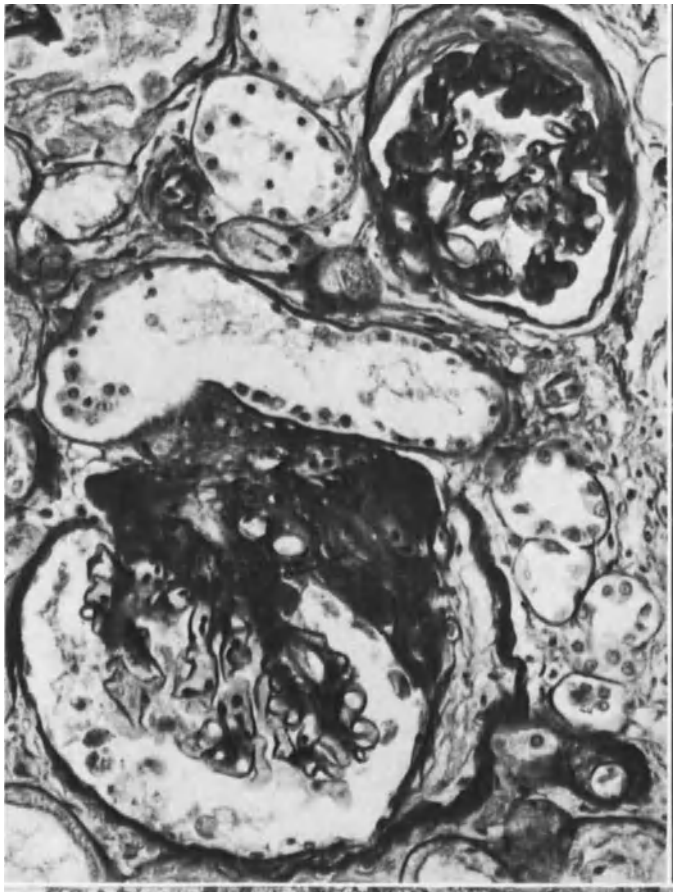
**Fig. 25.7.** Immunofluorescent findings in arteriolosclerosis due to hypertension. IgM deposits—which are narrowing the lumen of the arteriole—are present. There is also segmental, granular deposition in the mesangium and glomerular loops. Female, 52 years. IF (×600)

**Fig. 25.8.** Slight arteriolosclerosis in chronic pyelonephritis. Fine-grained osmiophilic masses (*) are present in the highly thickened BM and lamina elastica interna. Endothelium shows only slight vacuolar changes. Massive vacuoles are present in myocytes. Adventitia is unchanged. Female, 58 years. EM (×5460)

Page 519

**Fig. 25.9.** Severe arteriolosclerosis in a 29-year-old woman. Contralateral kidney was removed and diagnosed as early childhood pyelonephritic contracted kidney and weighed 30 g. Preoperative hypertension was cured by nephrectomy. In contrast to Figure 25.8, extensive osmiophilic deposits in cloud-like and clumpy form are present in the subendothelial space. A few myocytes have been destroyed and removed. EM (×3600)

**Fig. 25.10.** Same case as in Figure 25.9. Part of the wall of a renal arteriole shows only slight sclerosis. BM is highly thickened and split and contains a fine-granular osmiophilic deposit (*D*) with a few thread-like structures (→) as is also found in older glomerular immunodeposits (see p. 96). Endothelium (*E*), myocyte (*MC*) with a large vacuole (*). Female, 29 years. EM (×24,800)



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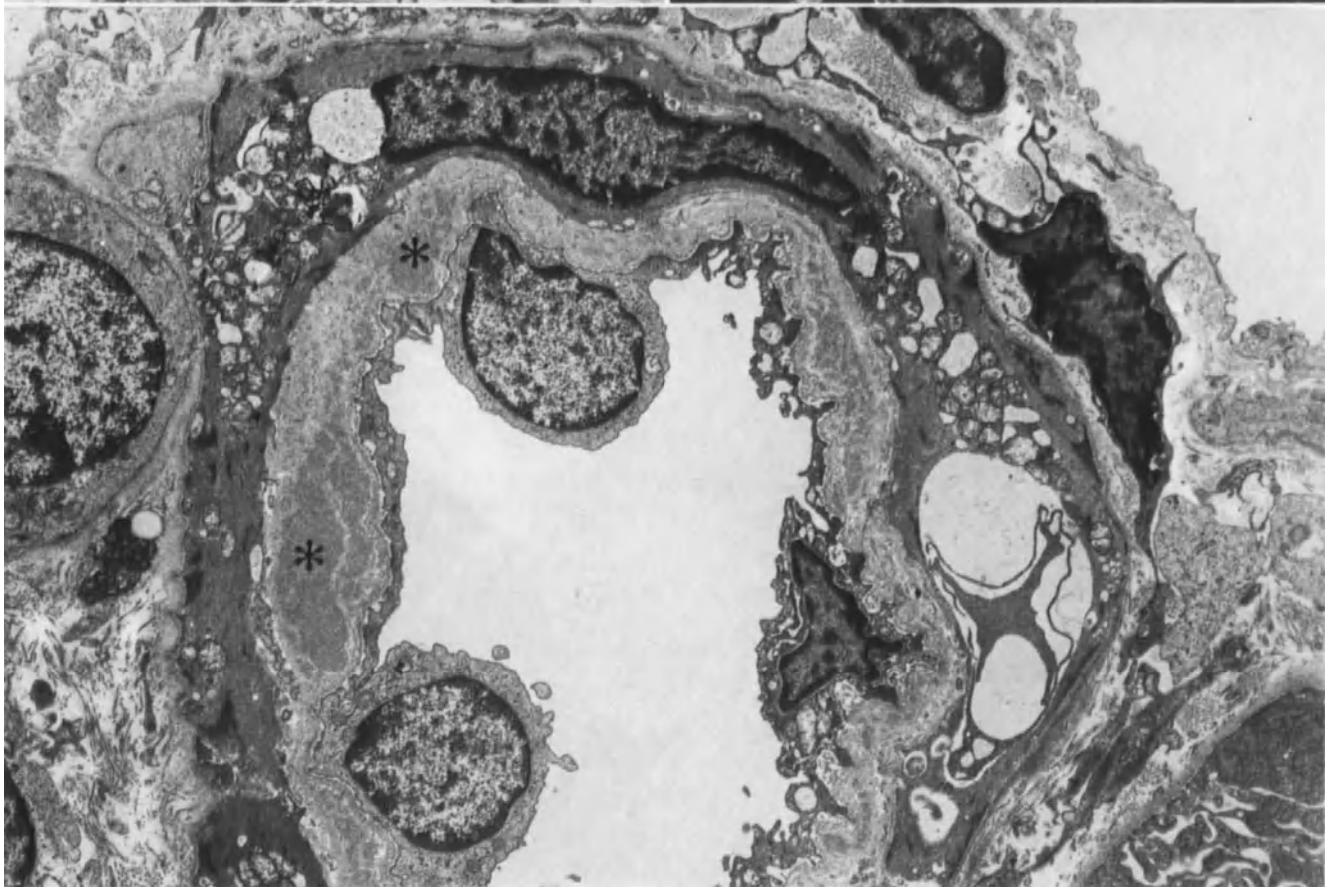


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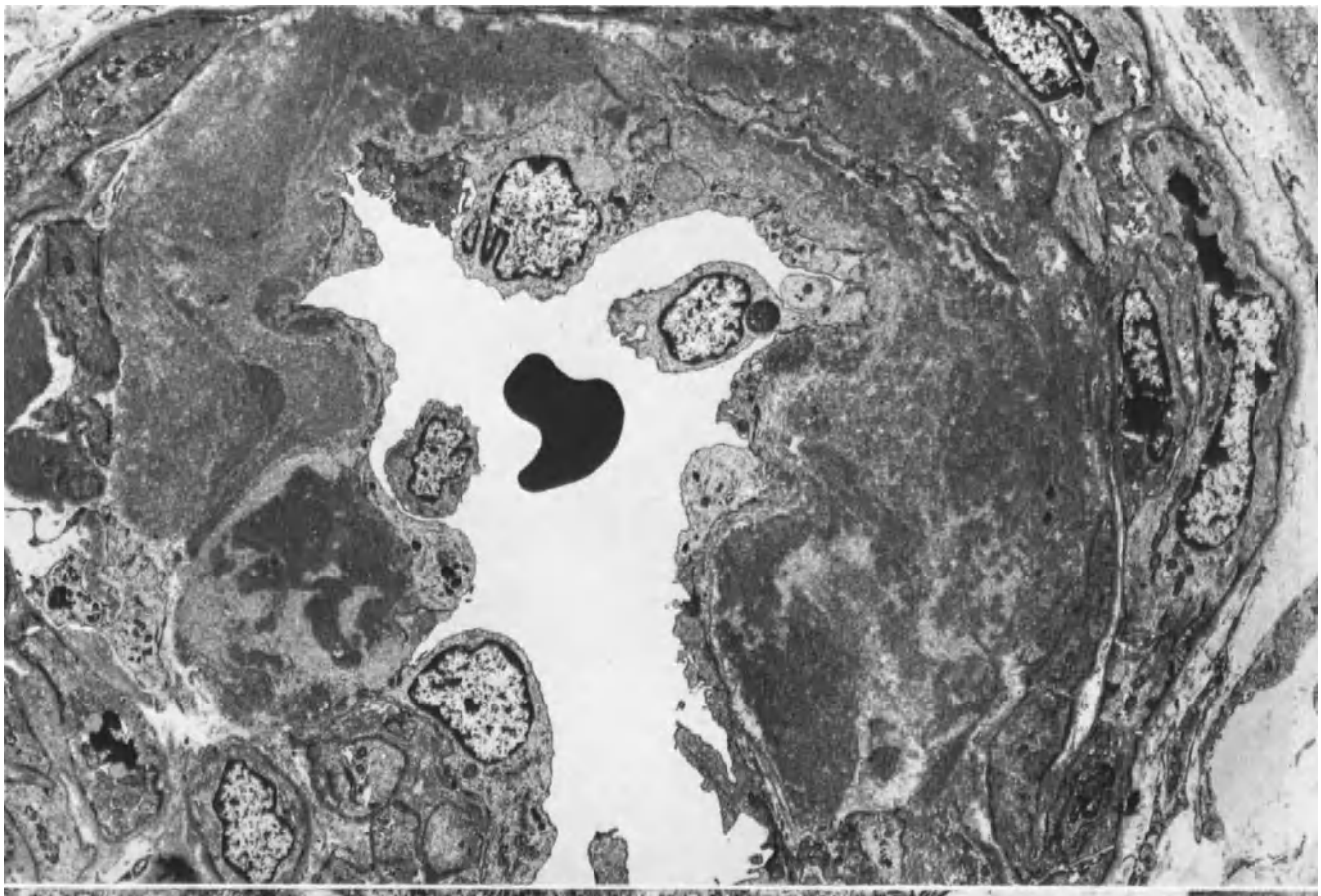

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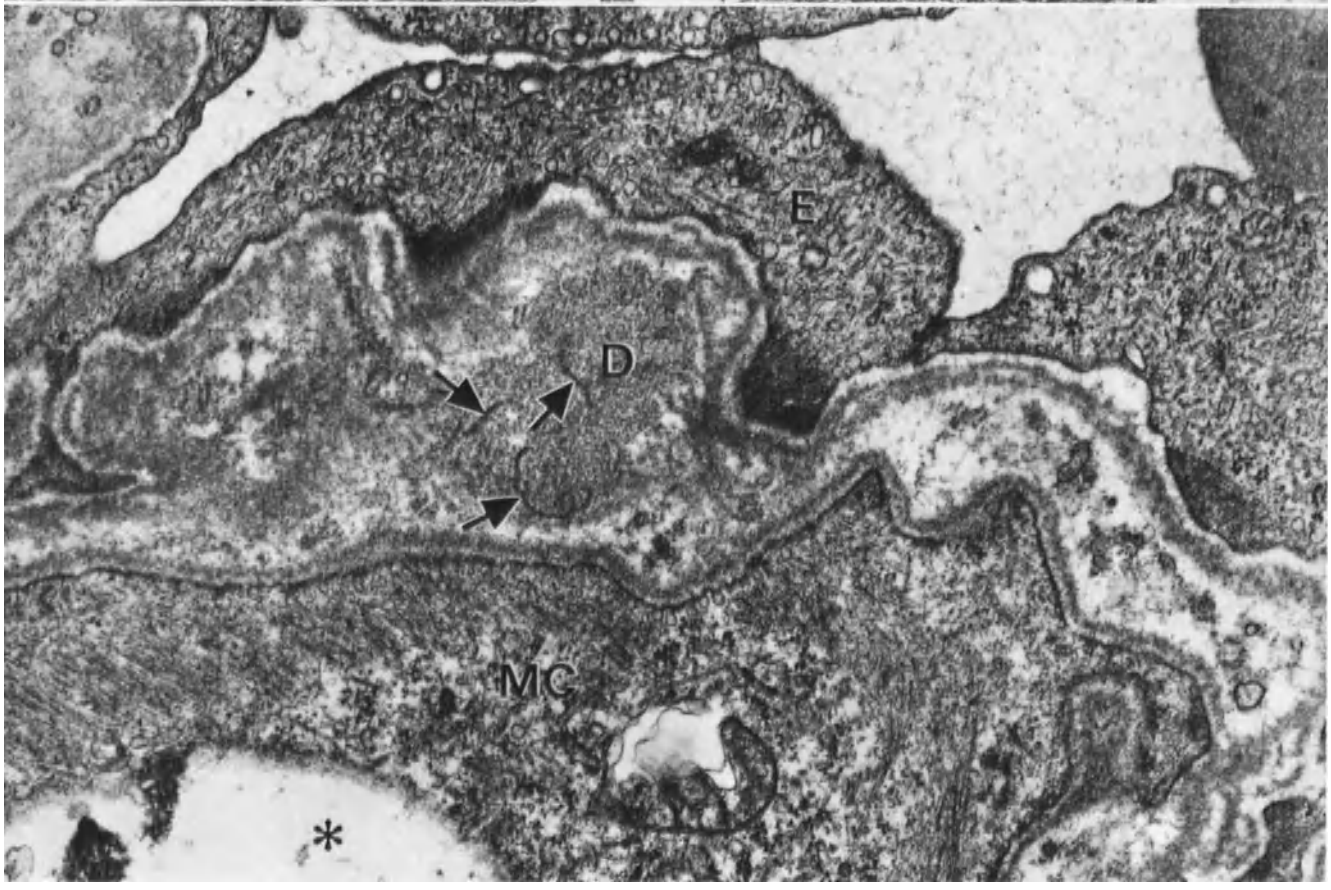



25.10

### Differential Diagnosis

The absence of significant necrosis and inflammatory reaction allow exclusion of arteriolonecrosis. This is even more valid for allergic vasculitis which is characterized by inflammatory infiltrates.

### Prognosis

The prognosis is decisively dependent on the degree of hypertension. If hypertension is eliminated through medication or surgery, the arteriolar changes can undergo remission as we have noted in sequential lymph node biopsies (experimental findings: [17]). Subendothelially, new elastic material is formed and the fibrinoid transudate is replaced by a fibromuscular tissue which contains elastic fibers. Untreated patients usually die from hypertension (only 2% from uremia).

### Pathogenesis

Fibrinoid deposition is a consequence of insudation of plasma elements and especially of C3 and IgM (experimental findings with India ink as label: [552]).
Most investigators consider hypertension—irrespective of etiology—in the peripheral circulatory system to be the cause of insudation, especially so in the presence of severe and generalized arteriolosclerosis ([1790]; literature with opposing views: [1239]). In this process, spasms of the larger arteries appear to play a significant role [65a, 1064, 1591c]. Despite normal general blood pressure, a considerable pressure increase may occur in the kidneys (see also [552, 1758]). This finding explains, in some cases, the presence of severe arteriolosclerosis in the absence of generalized hypertension (Fig. 25.1).
Edema of the vascular wall caused by hypernatremia may possibly play an additional role [536]. Other insudation-enhancing factors, such as ischemia and metabolic disturbances (e.g. diabetes mellitus) should also be recognized as factors in causing slight—and usually circumscript—arteriolosclerosis. Thus, in our case material of non-GN renal diseases examined with IF (acute and chronic PN, hydronephrosis, unspecific GNo etc.), we found insudation of IgM and/or complement in 80% of the cases, but in GN in only 55%. In both disease groups, hypertension was present in about 50% of the cases (Fig. 25.1, see also [1068]). Despite this finding, these cases do not play a significant role in needle biopsy interpretation if the quantitative relationships are borne in mind, since the presence of one arteriolosclerotic vessel must not be interpreted as proof for hypertensive vasculopathy.
Generalized arteriolosclerosis, on the other hand, is almost always the consequence of hypertension and, by impairment of blood flow in normal renal tissue, further increases the severity of the hypertension. Needle biopsy of the non-affected kidney in the presence of unilateral renal disease can often clarify the extent of arteriolosclerotically-induced blood flow impairment. Recently, association of hypertension and arteriolosclerosis with ovulation inhibitors has been reported [556].

## Arteriolonecrosis
[1791, 1509a]

### Definition

Arteriolonecrosis is characterized by severe fibrinoid insudates of the arterioles with media necrosis accompanied by unspecific inflammatory reaction.
The *symptomatic form* (secondary form: [166]) is the consequence of chronic renal or extrarenal hypertension. In the *idiopathic form* (primary form: [166]) hypertension is absent or only very mild.

***Synonyms:*** Malignant nephrosclerosis, malignant hypertension, musculomucoid intimal hyperplasia [1275].

### Incidence

In 0.33% of our autopsy material, we found arteriolonecrosis without primary, diffuse renal disease. Biopsy is rarely used (0.91% of 2080 biopsies: Z; for a contrary opinion, see [843]) because of danger of hemorrhage. Of patients with essential hypertension, 1% [843] to 8% [1239] are said to finally develop renal arteriolonecrosis. In this group, young patients are more frequently observed than they are in arteriolosclerosis (maximum age: 30–50 years).
In our autopsy material, the average age was 43 for women and 47 for males; in our biopsy material 38.5 years (23–41 years). The ratio of men to women was 5:4.
In the very rare idiopathic form which occurs without hypertension (2 out of 25,000 autopsy cases: Z), the incidence is considerably greater for women.
The average duration of hypertension at the time of biopsy was 7.8 years. At autopsy, we have never encountered arteriolosclerosis in children, but we have encountered severe arteriolonecrosis in a few cases.

### Clinical Findings

The term "malignant hypertension" is not equivalent to arteriolonecrosis. It encompasses massive generalized

arteriolonecrosis (17% of patients with malignant hypertension: [676]) as well as the closely related form of severe arteriolosclerosis (83% of cases). Arteriolonecrosis seems to be rather infrequent in blacks with malignant hypertension [1274a].

Clinical symptoms include optic papillary edema, rapidly progressive renal insufficiency, and cardiac and CNS symptoms [1239]. Diastolic blood pressure lies between 110 and 170 mm Hg, while systolic values are not essentially higher than those encountered in benign essential hypertension [843]. In our biopsied patients, the average systolic pressure was $230 \pm 25$ mm Hg and the diastolic $143 \pm 25$ mm Hg. A few cases which were not hypertensive have been reported (idiopathic form: [157, 1239, 1677]).

In 50% of cases reported in the literature, death occurs within one year. Of these deaths, 50% are due to uremia, which accounts for the designation, "malignant nephrosclerosis". Occasionally, renal insufficiency may emerge in the form of an acute attack [1552]—especially in the idiopathic form—and may be accompanied by signs of hemolysis and intravasal coagulation [166, 515, 1024, 1158, 1483, 1552].

The remaining clinical symptoms include proteinuria, often more than 2 gm/day (0.5–5.4 gm/day in 6 out of 13 biopsies: Z), polyuria and isosthenuria. Urinary findings often suggest the presence of a primary glomerular disease [1325]. Plasma renin values are massively increased.

### LM Findings

The small-strip, radial subinfarcts may be similar to those seen in arteriolosclerosis; in arteriolonecrosis, however, the boundaries of the anoxic regions are far less sharply demarcated and less pronounced. The arteriolar lesion also afflicts the glomeruli more severely (Fig. 25.11). A few glomerular loops or – even entire glomeruli—can be necrotic ("alterative glomerulitis": [1068]) and sometimes show slight partial capsular epithelial proliferation (Fig. 25.12). Collapse glomeruli are frequent (Fig. 25.16).

Arterioles (see also [1462]) are difficult to identify since their media is strongly split and permeated with cells and fibrinoid masses (Fig. 25.11). The fibrinoid masses stain similar to those in arteriolosclerosis, but they are less strongly sudanophilic and more granular (Fig. 25.13). The masses often contain cellular detritus (Fig. 25.13). They occasionally extend not only to the media but also to the adventitia and can reach the surrounding stroma, in which case they are surrounded granuloma-like by lymphocytes, histiocytes, and plasma cells (Fig. 25.14). Splitting of the vessel wall is more clearly demonstrable with the PASM stain (Fig. 25.12) than it is in the HE stain (Fig. 25.13). A few investigators describe these findings as "proliferative arteriolitis" [843, 1239].

A pad-like granuloma formation is frequently found around the especially afflicted afferent vessels (Fig. 25.11). Erythrocytes may occasionally be found within the vascular wall. The lumen in the region of endothelial necrosis may be entirely occluded. Endothelial proliferation at the site of intact lumens is frequent, a finding supposedly very pronounced in the idiopathic form and especially so in the afferent vessels [166].

The wall of the interlobular arteries is split onion bulb-like and thickened by myxoid material (Fig. 25.16; see also [1274a]). Media necroses are extremely rare and the lumen is greatly narrowed. This change is also described as "proliferative endarteritis" [166, 1068]. Subendothelially, concentrically arranged increased connective tissue and deposition of myxoid or mucoid substances are found.

The elastica interna is usually split.

Arteriosclerosis of the larger vessels is not obligatory. Adaptive intimal fibrosis can develop with long-term dialysis.

The interstitium is far more fibrosed than in arteriolosclerosis; it is often edematous and contains extensive lympho-plasmocytic infiltrates. Tubular atrophy is less pronounced than it is in arteriolosclerosis, and JGA changes are analogous to those found in arteriolosclerosis.

### IF Findings

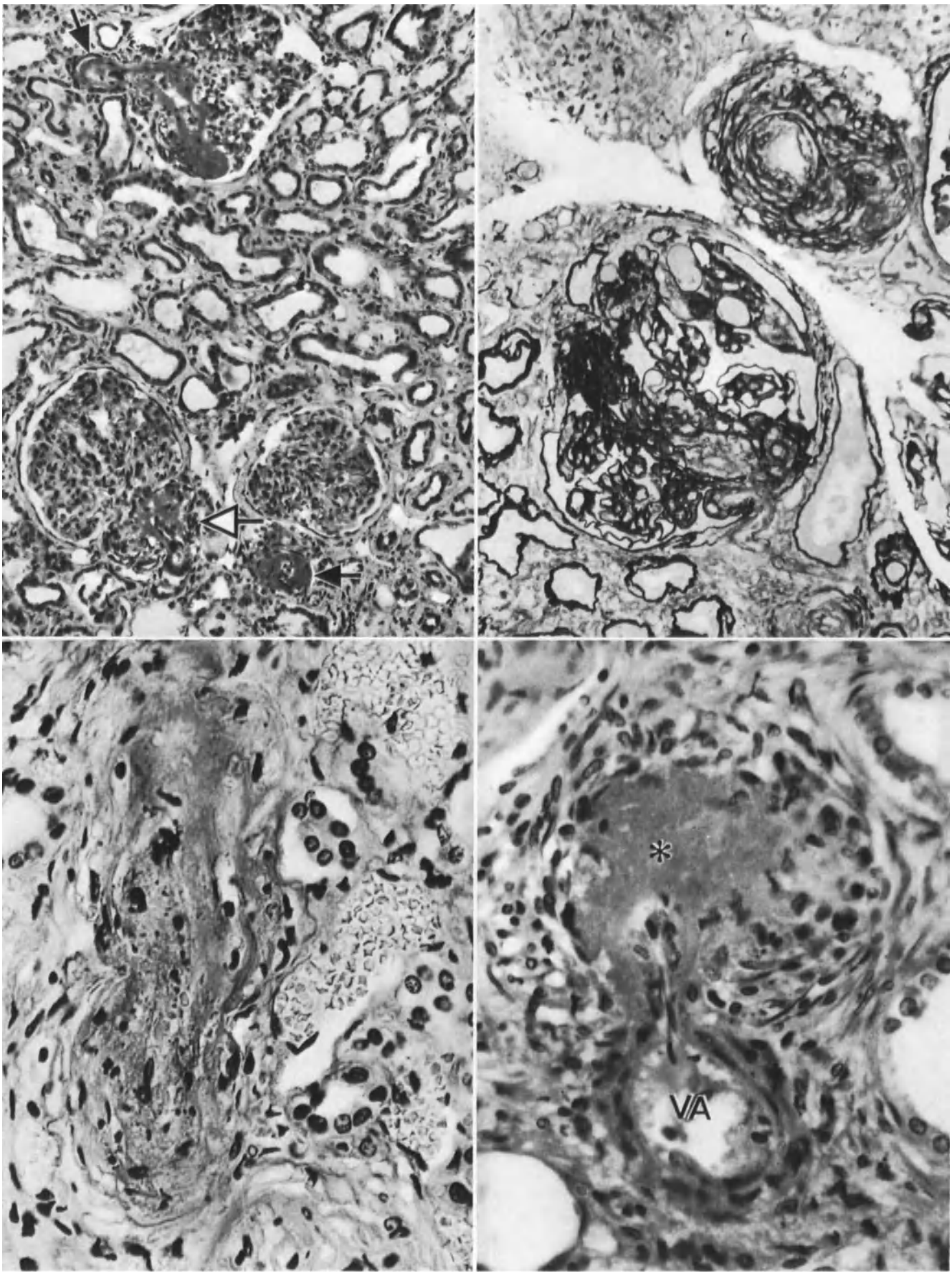
Fibrin(-ogen) is said to be always present, a finding thought to indicate secondary intravasal coagulation [1552]. We see this rather as an expression of plasma insudation, since ferritin and IgG can be demonstrated as well [489]. In two of our own cases we found C3 and IgM in glomeruli and arterioles, but not fibrin(-ogen).

### EM Findings

In addition to arteriolosclerotic changes, the arterioles demonstrate severe permeation of the media with osmophilic masses which may spill out into the surroundings (Figs. 25.15, 25.17) where an inflammatory reaction is usually present.

Subintimal myocytes are severely damaged and may even show necrosis. In less severe injury, progressive myocytolysis leads to a transformation of all the media myocytes in the larger vessels (see also [1275]) which, in turn, gives rise to an onion peel-like sclerosis of the entire vascular wall (see above and Fig. 25.16).

Ischemic injury is present in the glomeruli. Finely granular osmiophilic deposits can be demonstrated in the subendothelial space, the mesangium and sometimes in the capsular BM (experimental findings: [109]).




25.11
25.12

25.13
25.14

In the idiopathic form, fresh thrombi and those undergoing organization—chiefly in the interlobular arteries, more rarely in the arterioles, and in very isolated cases in the glomerular loops—appear to be very characteristic. These thrombi may occur as a result of concomitant intravasal coagulation.

"Accelerated obsolescence" is described as being by and large characteristic for renal arteriolonecrosis [783] in which a new (second) BM is supposed to be formed without interposition of mesangial cells within the very severely thickened lamina rara interna. This finding corresponds considerably to that occurring in scleroderma (see p. 528). We have not encountered this change in our scanty case material on arteriolonecrosis. In a few instances, however, we have seen unspecific new formation of lamina densa-like material subepithelially (Fig. 25.18).

### Differential Diagnosis

Differentiation from arteriolosclerosis has been discussed on p. 520. It must be pointed out that both lesions can occur side by side on the same slide (Fig. 25.19). The differentiation between arteriolonecrosis caused by essential hypertension and that by hypertension due to focal renal lesions often cannot be discerned on the basis of needle biopsy findings described above.

Difficulty may also be experienced in differentiating forms caused by essential hypertension from secondary arteriolonecrosis occurring in diffuse renal lesions. This is especially true if numerous capillary loop necroses tend to obscure the findings of GN. Knowledge of the quantitative distribution and extent of changed elements (vessels, glomeruli) is usually helpful in the final diagnosis.

Without knowledge of the clinical findings, differential diagnosis from kidney in scleroderma may be very difficult and even impossible (see p. 528).

◁ **Fig. 25.11.** Arteriolonecrosis in malignant nephrosclerosis. Arterioles, especially the vasa afferentia (→) exhibit severe fibrinoid necrosis with an obvious pole granuloma (⇾). Tubular epithelium is flattened due to ischemia. Female, 20 years. HE (× 160)

**Fig. 25.12.** Arteriolonecrosis with splitting of a small arterial/arteriolar wall which is permeated with fibrinoid. Glomerular capillary loops evidence similar changes and synechiae. Male, 44 years. PASM (× 300)

**Fig. 25.13.** Arteriolonecrosis. Arteriolar wall shows fibrinoid necrosis with numerous nuclear fragments. Adventitia is edematous and demonstrates slight cell proliferation. Female, 58 years. Van Gieson (× 400)

**Fig. 25.14.** Same case of renal arteriolonecrosis as in Figure 25.11. A pole granuloma is shown. Vas afferens (*VA*) is considerably narrowed and exhibits fibrinoid permeation (*) which, in turn, is surrounded by a granuloma. Frozen section. Female, 20 years. HE (× 380)

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**Fig. 25.15.** Incipient arteriolonecrosis associated with contralateral pyelonephritic contracted kidney. There are unclearly delimited osmiophilic masses in the highly thickened BM (*). These masses occasionally penetrate between the myocytes (→), which are severely atrophic or occasionally which have even disappeared. Female, 58 years. EM (× 3260)

**Fig. 25.16.** Onion bulb-like splitting of an interlobular artery in malignant nephrosclerosis. Arterial lumen is severely narrowed. Collapse changes are present in the glomerulus. PAS (× 250)

**Fig. 25.17.** Same case as in Figure 25.15. In this preparation there is an accumulation of osmiophilic masses, especially in the adventitia (*). Subendothelial space is broadened and loosened. Note degeneration and transformation of myocytes. Female, 58 years. EM (× 2710)

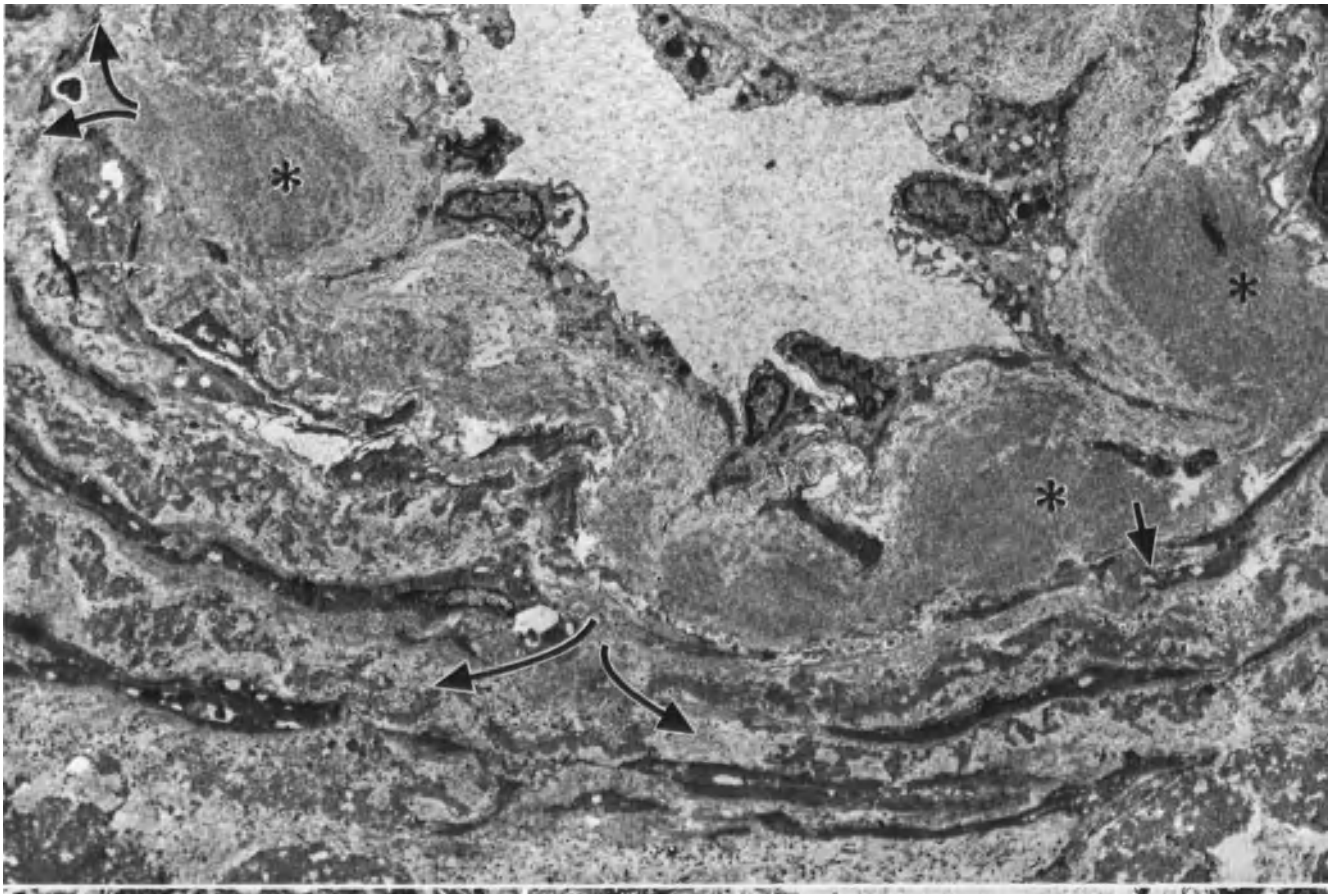
Page 525

**Fig. 25.18.** Glomerular capillary loop changes in arteriolonecrosis. Fine-granular, only slightly dense masses (→) are deposited between a podocyte (*P*) and lamina densa of BM. Masses are sharply delimited from the podocyte. There is typical collapse change of BM present. Endothelial nucleus (*E*). Male, 43 years. EM (× 9200)

**Fig. 25.19.** Simultaneous occurrence of arteriolosclerosis (*1*) and arteriolonecrosis (*2*). PAS (× 530)

**Fig. 25.20.** Idiopathic form of malignant nephrosclerosis associated with hemolysis. There is severe widening of the cell-poor subintimal space of a small artery. Residual lumen is highly narrowed. (This case was kindly provided by Dr. Wegmann, Liestal, Switzerland.) Female, 22 years. HE (× 140)

**Fig. 25.21.** Same case as in Figure 25.20. Note analogous arteriolar (→) and glomerular capillary loop (*) changes associated with thrombotic masses undergoing organization. Female, 22 years. HE (× 140)



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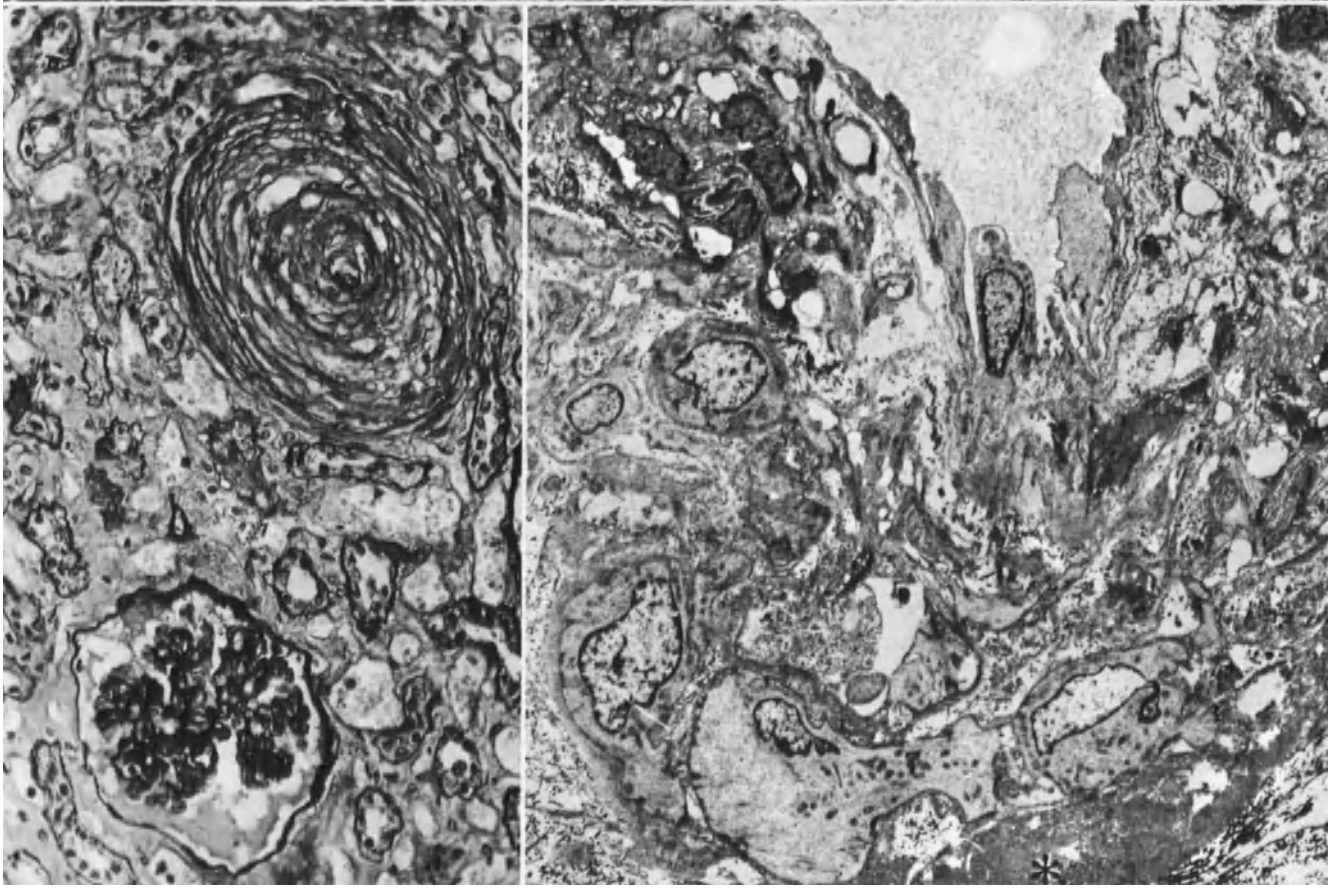

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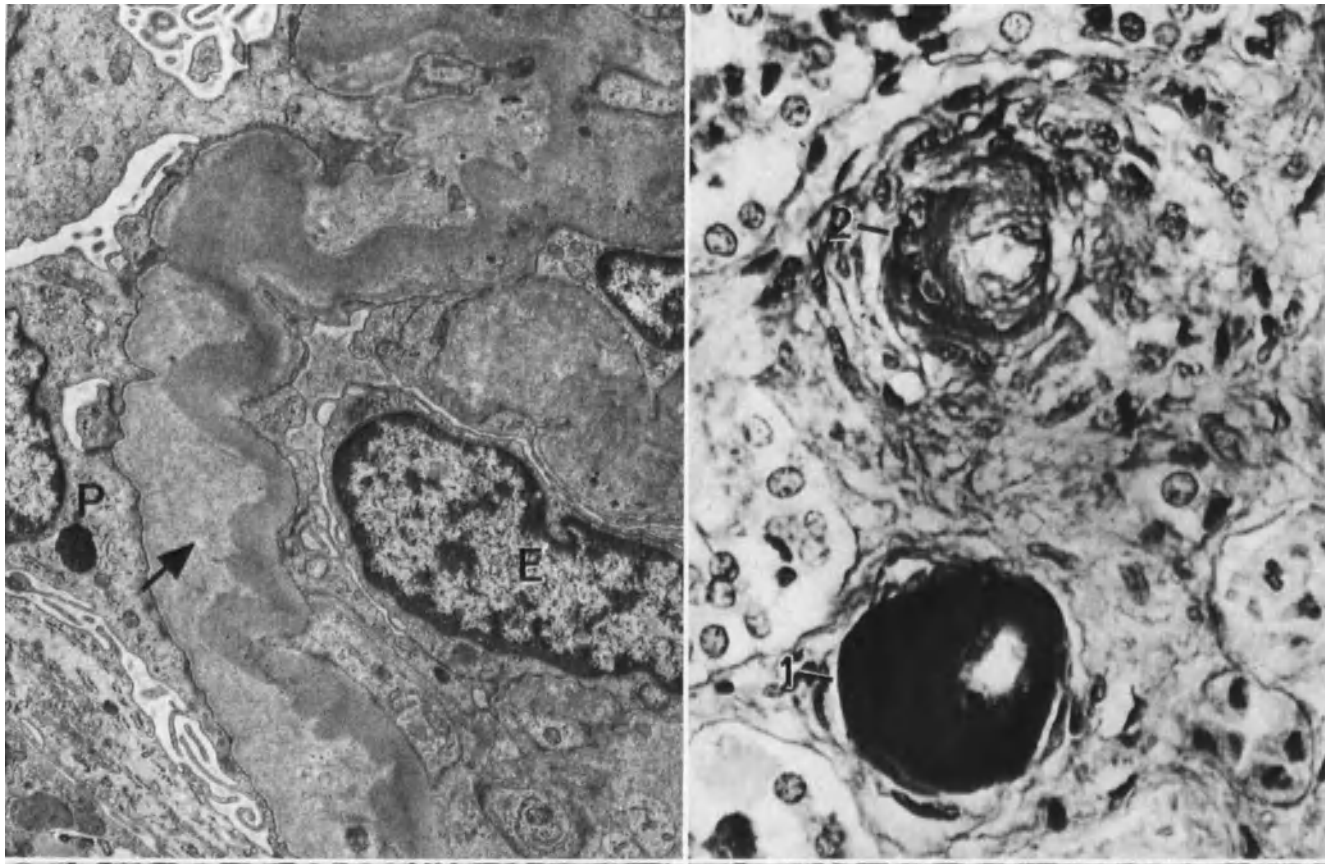


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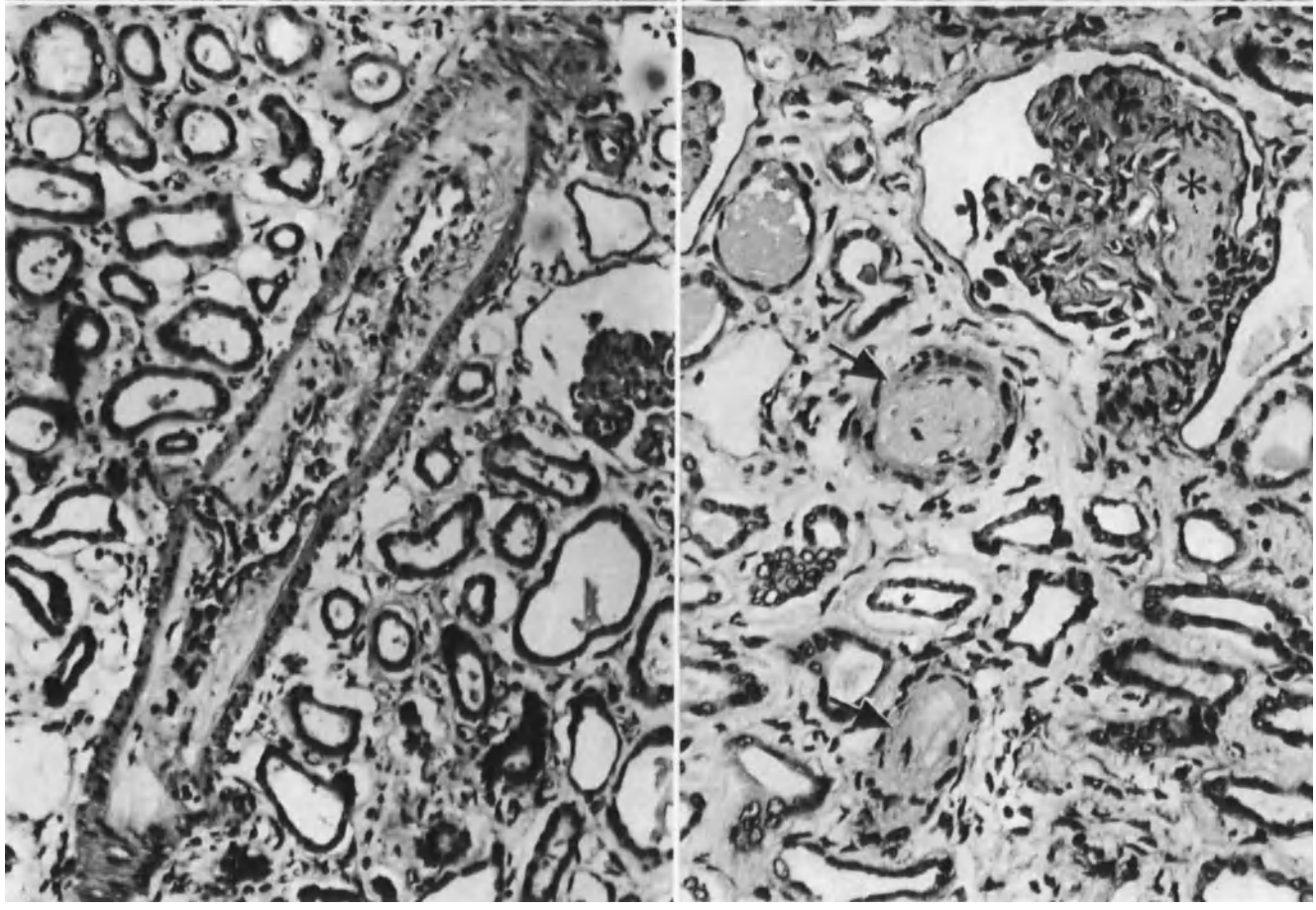



25.20
25.21

Differentiation from radiation injury and from the hypersensitivity angitis is not difficult when the changes in other renal elements (tubules, glomeruli etc.) and the distributional type and the severity of necrotic injury are given appropriate attention (see also [1068]).
The so-called idiopathic form of malignant nephrosclerosis, which may also be accompanied by hemolysis [166], cannot be morphologically differentiated from adult hemolytic-uremic syndrome, as we have confirmed in one of our own cases (Figs. 25.20, 25.25; [166, 1068, 1842], see p. 502).

### Prognosis

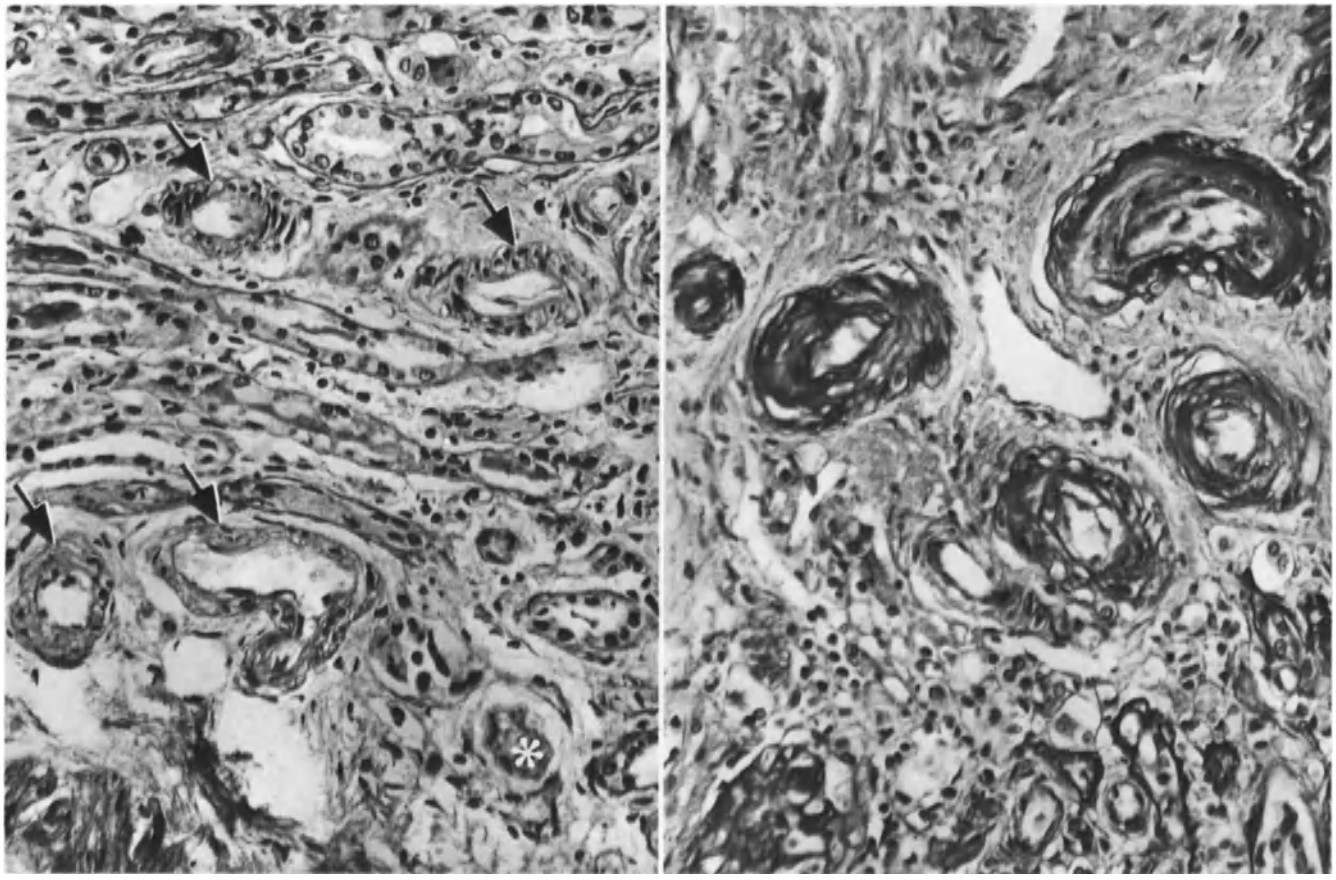
In general, the prognosis is poor. In 13 of our cases followed catamnestically, 8 died within 12 months, 7 of whom in uremia; 5 are still alive with an average survival period of 7.6 years (2.5–12). When antihypertensive therapy is pursued (medication, bilateral nephrectomy and transplantation) life expectancy may be increased considerably.
Total reversibility of the vascular changes following normalization of blood pressure is improbable because of the severe injury to the vascular wall and the frequently accompanying inflammatory changes. We are not, however, aware of objective data relating to this problem.
In one of our autopsy cases, we encountered malignant nephrosclerosis in which unilateral thrombosis of the renal artery developed secondarily. In this kidney, fibrinoid necrosis of the arterioles had been totally replaced by scar tissue (Figs. 25.22, 25.23).

### Pathogenesis and Etiology

Numerous arguments point to insudation of the arteriolar wall with plasma elements—e.g., in arteriolonecrosis—as the basic pathogenetic disturbance which occurs under the influence of elevated blood pressure and vasospasm (see p. 520; [1790]). This is confirmed by the fact that unilateral reduction of blood flow protects the kidney from vascular lesions [452, 765, 1034]. Thus, in eight subinfarcts, we have never encountered arteriolonecrosis despite extensive arteriolonecrosis in remnant parenchyma.
In a large series encompassing 124 cases, essential hypertension was present in 41.9%, GN in 15.3% and in 21.8%, another cause for hypertension was observed [843]. In 25 of our biopsy cases, essential hypertension was present in 19, pyelonephritis in 4 and GN in 2.
The pathogenesis of the disease process in those rare patients with idiopathic renal arteriolonecrosis without prior severe hypertension remains unexplained. Five postpartal cases with arteriolonecrosis limited to the kidney [515, 1677, 1840] and 6 in association with ovulation inhibitors [157, 555a, 1842] have been described (see p. 503). Hormonal factors acting in association with an activated coagulatory system have been implicated. Immediate normalization of blood pressure following bilateral nephrectomy has been reported [157].
In our case of a 22-year-old female, the typical disease pattern accompanied by severe hemolysis developed 2 years after spontaneous abortion and subsequent use of ovulation inhibitors (we thank Dr. Wegmann, Liestal, Switzerland, for referring this case to us). Idiopathic arteriolonecrosis was described in three siblings and a cousin 24–31 years of age [603]. In all four, proteinuria without hypertension had been present for years.
A biopsy from one of these patients in this phase showed C3, IgG and subepithelial deposits in the glomeruli. Bilateral nephrectomy in three patients resulted in cure. Pathogenetically, it was assumed that the presence of primary renal disease led secondarily to hemolysis and intravasal coagulation [603]. Other investigators attribute the disease to intravasal coagulation with secondary permeability disturbance of the vessels [166] or to a primary acute vascular disease with secondary, local coagulation [515]. We consider the endothelial lesion to be responsible for the hemolysis.

## Fibroelastosis
[1336]

This very common arterial disease occurs almost exclusively in the kidney. It chiefly afflicts the renal artery, but also its branches as far as the arcuate arteries. Accordingly, it can occasionally be seen in needle or open surgical biopsy.
The lesion consists of a mildly nodular and lamellar thickening of the media. In the affected region, there occurs a decrease of muscle cells with attendant increase of collagen and elastin (Fig. 25.24). The elastica interna shows a few isolated defects. The intima is slightly fibrosed and fills in the wavy depressions between the individual nodular thickenings.
Apparently, the pathologic change is attributable to abnormal attrition and to consecutive degeneration of the myocytes, the cause of which is not clear (possibly shock, spasms, stress). These effects lead to degeneration of the myocytes which become either necrotic or undergo a functional change whereby they produce more ground substance, collagen, and elastin. The change begins in both sexes in the second decade of life and constantly increases in severity with age. Dissecting aneurysm is the only complication of the disease; its occurrence is extremely rare. The lesion is apparently not identical with fibromuscular dysplasia [666] which will not be discussed since it is only found in the renal artery and as such is not accessible to needle biopsy. Adaptive intimal fibrosis is described on p. 151.



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25.24

**Fig. 25.22.** Healing of arteriolonecrosis associated with secondary arterial thrombosis in this kidney (see text for details). Arterioles have become very thin-walled (→). Only one arteriole, which apparently has a fully occluded lumen, has not healed (*). Female, 63 years. PAS (×290)

**Fig. 25.23.** Same case as in Figure 25.22. Arterioles in contralateral kidney—which is not protected from arterial thrombosis—shows severe arterilonecrotic changes. Female, 63 years. PAS (×290)

**Fig. 25.24.** Degenerative fibroelastosis of a renal artery. There are numerous lumpy elastin fragments in the media (*). Lamina elastica externa is more or less intact, but the interna exhibits numerous interruptions (→). Larger foci of degeneration without elastic fibers are present in the media (*0*). Intima exhibits severe fibrotic thickening. Surgical biopsy. Female, 48 years. Van Gieson elastin (×40)

## Scleroderma
[31, 1683, 1509a]

### Definition

Scleroderma is a systemic disease characterized by fibrotic interstitial changes afflicting various organs.

***Synonym:*** Systemic sclerosis.

### Incidence

Scleroderma is a rare disease (39 out of 25,000 autopsies: Z; 2 out of 2080 biopsies (0.19%)). The incidence has been reported to be 2.5 times greater in women than in men [31]. It is possible, however, that the disease is more frequent in that there are many patients with predominant visceral involvement (lung, stomach, intestine, esophagus, heart, kidney) and no or minimal skin changes.
In assured scleroderma, the kidneys have been reported to be involved clinically in 2.6% [1252] to 36% [250] and at autopsy, in 27 out of 39 (Z) respectively in 90% of cases [250].

### Clinical Findings

Typical scleroderma is characterized at onset by Raynaud's phenomenon or symmetrical swelling and stiffness of fingers. Later, skin changes as well as gastrointestinal symptoms, polyarthritis, muscle atrophy, dyspnea, arrhythmia, heart insufficiency and renal symptoms may develop (for various clinical forms see [1751]).
Hypertension is not obligatory (2 out of 5 cases: [903]; 2 out of 8 cases: [1241]; 6 out of 15 cases: [31]; 2 out of 7: Z; 24% of cases: [250]). In a series of patients [250] 7% suffered from malignant hypertension with hyperazotemia, a symptom which appears to occur more frequently following intensive corticoid therapy [1791].
Proteinuria is very frequent; uremia, however, is uncommon despite the severity of renal disease (15 out of 38: [31]; 4 out of 27 autopsy cases: Z). Antinuclear factors can be demonstrated in serum (renal tissue: [1053]) in more than half of the cases and rheumatic factor in about one fourth.

### LM Findings

At autopsy, the parenchyma of kidneys severely afflicted with the disease appears seeded with foci of subinfarcts as well as of fresh and older infarcts. These foci occur in areas supplied by the interlobular arteries or their branches.

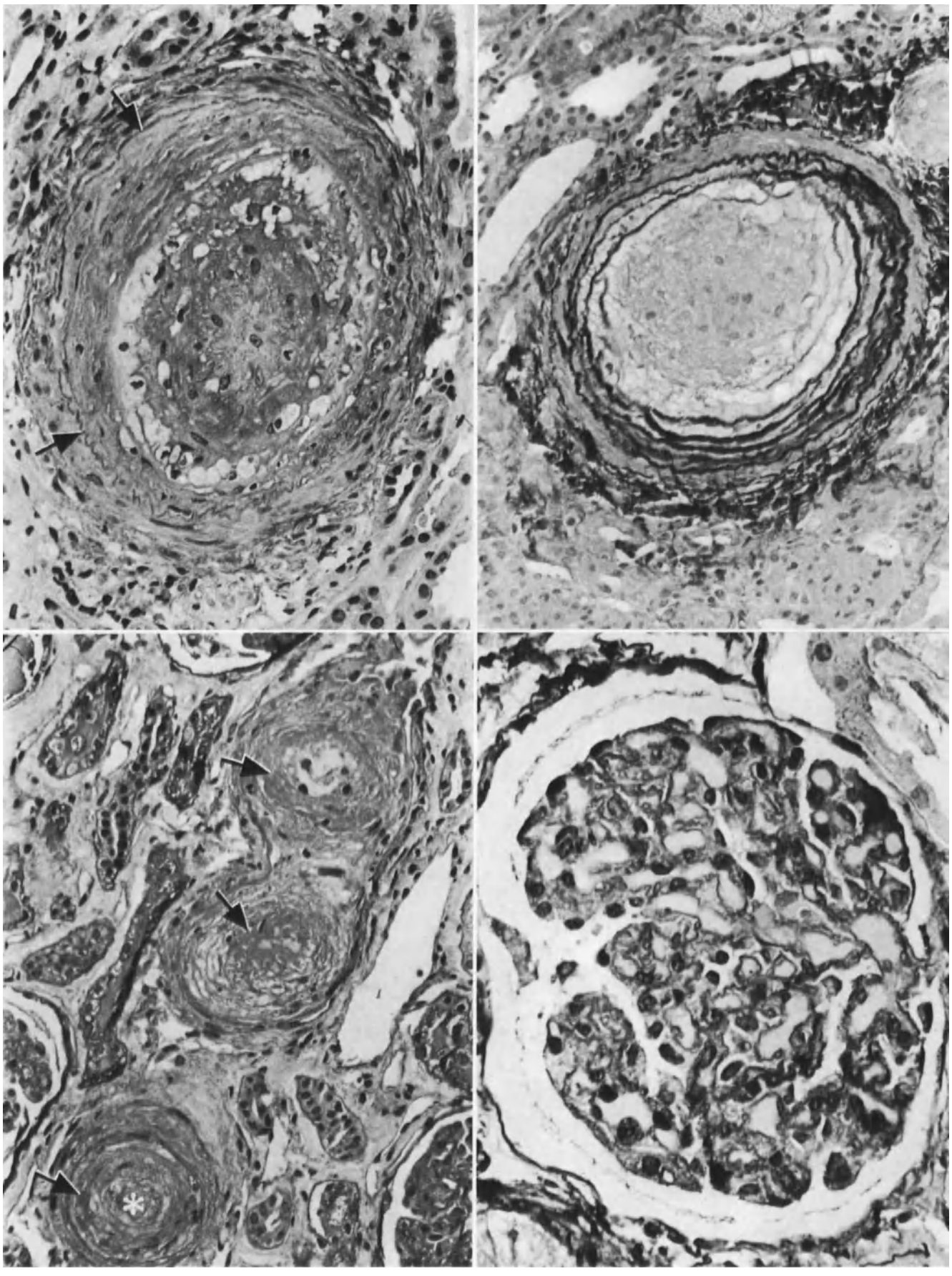
Capillaries are reported to be more frequently obstructed than arterioles and arteries least of all [1195]. We found the main lesions in the interlobular arteries and their branches. This change, referred to as the so-called onion-bulb interlobular artery, is characterized by marked thickening of the wall and severe narrowing of the lumen which occasionally becomes completely occluded (Figs. 25.25, 25.26, 25.27).
The wall thickening is characteristically due to splitting and proliferation of muscular and, chiefly, of connective tissue elements and of the elastica interna (Fig. 10.11, 25.26). Furthermore, the affected vessels are permeated with acid mucopolysaccharides which show a strongly positive reaction to the alcian blue stain (Fig. 25.25), especially in the subendothelial space.
The media is more or less atrophic (Fig. 25.26), whereas the adventitia is unchanged. The endothelium occasionally is slightly proliferated. The changes are as frequent in nonhypertensive cases as in hypertensive ones. Infarcts distal from completeley occluded arteries are frequent.
Of our autopsy cases without hypertension, 8 out of 27 showed arteriolonecrosis (Fig. 25.27) with segmental involvement of the glomeruli and 3 out of 27 mild arteriolosclerosis. In the presence of hypertension, arteriolonecrosis is extremely severe and more frequent than in nonhypertensive cases in which, however, it can also occur (8 out of 15: [31]; [903]). In a very few cases, the necrosis also involves the branches of the interlobular arteries.
The glomerular capillary loop walls are slightly thickened and coarsely wrinkled in about one-third of our cases (Fig. 25.28). Signs of capillary loop necrosis are said to be present [1068], a finding which we have not been able to confirm as is true for wire loops reported by others in 32% of their cases [31].

**Fig. 25.25.** Middle-sized renal artery in scleroderma. A very loosely organized tissue – appearing blue in this stain – is present inside the elastica interna (→). Lumen of the vessel is almost totally occluded. Female, 62 years. Alcian blue (×420) ▷

**Fig. 25.26.** Same vessel as in Figure 25.25. There is frank splitting of lamina elastica interna but there are no elastic fibers in thickened intima. Adventitia is normal and media is atrophic. Female, 62 years. Van Gieson elastin (×420)

**Fig. 25.27.** Same case as in Figure 25.25. Arterioles in scleroderma: arteriolar walls are highly split and thickened onion peel-like and occasionally exhibit embedded fibrinoid masses (→) and necrosis. Female, 62 years. PAS (×280)

**Fig. 25.28.** Same case as in Figure 25.25. Capillary loops of glomerulus depicted are thickened (cf. Fig. 25.31). Female, 62 years. PAS (×580)



25.25
25.26

25.27
25.28

We encountered loop thrombi only in cases in which glomeruli were damaged by severe ischemia. The JGA is greatly enlarged in a few cases [1569]. The interstitium and tubules demonstrate ischemic changes due to circulatory disturbances in the form of subinfarct or infarct.

### IF Findings

In one of our cases, all antiserea tested—IgG, IgM, IgA, IgE, C3, fibrin(-ogen) and nuclear factors—were negative. Other investigators, however, have described in 2 out of 2 cases, granular deposits of IgG, IgA, most predominantly IgM and some complement, and in 7 out of 7 other cases IgM, Clq, C4, and C3 respectively [1053]; see also [541, 1041]). In 7 patients, IF of the blood vessels was positive for IgM, Clq, C4, and C3 in all [1045a].

### EM Findings

In our case, the BM of the glomerular capillary loops was sometimes moderately wrinkled, i.e., collapsed (Figs. 6.27, 25.31, 25.32). The unchanged endothelium was, nevertheless, stretched, and the widened subendothelial spaces were filled in by a loose, coarsely granular material (Fig. 6.27, 25.32) which contained a few isolated collagenous fibrils (compare: [1509a]).
An analogous glomerular change has been described in renal arteriolonecrosis and designated as "accelerated obsolescence" [783]. This peculiar glomerular lesion has also been reported in nonhypertensive cases by other investigators who have suspected the granular material to consist of ferritin [1241], a finding which we cannot confirm. Similar deposits have been described in vessels of skeletal muscle [1195, 1194]. We found them in renal vessels (Figs. 25.29, 25.30).
Except for slight mesangial thickening without cellular increase and very mild fusion of foot processes, no significant glomerular changes occur. It is noted, however, that the number of EM investigated cases is still insufficient to permit firm conclusions on this subject. The changes of the blood vessels are said [1509a] to be indistinguishable from those of malignant hypertension.

### Differential Diagnosis

Great difficulty is encountered in differentiating sclerodermic renal changes from symptomatic and especially idiopathic, arteriolonecrosis (malignant nephrosclerosis, see p. 523). It may prove almost impossible in biopsy and even in autopsy material [903, 1068, 1241]. We have found the alcian blue stain to be of great help in resolving this problem.
With this stain, the interspaces of the onion-bulb interlobular arteries are much larger and stain more intensively blue in scleroderma than in arteriolonecrosis. In nonhypertensive cases, the discrepancy between the slight arteriolar lesions and the severity of the advanced arterial changes (onion-bulb interlobular arteries) speaks in favor of scleroderma. Both of these parameters, however, are only quantitative in nature and often cannot be relied upon when dealing with the idiopathic form of arteriolonecrosis. Accordingly, the clinical findings alone will, in some cases, allow a definite decision.
The subendothelial "deposits" in vessels and glomeruli, when present sufficiently for evaluation, are characteristic—even though not specific—of scleroderma. In any event, they are fundamentally different from the very dense finely granular and highly osmophilic IF positive deposits found in arteriolosclerosis and arteriolonecrosis.

### Prognosis

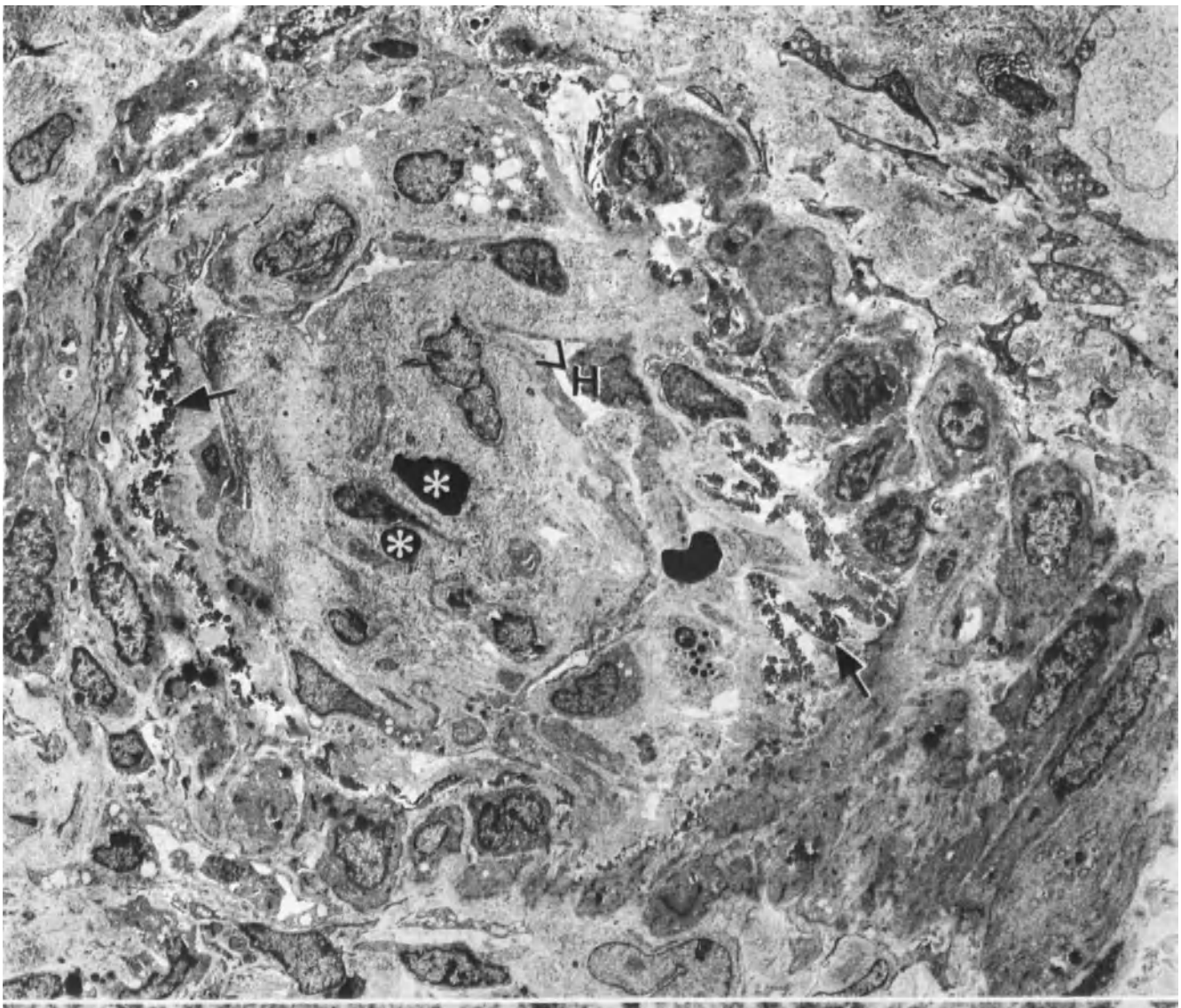
The average survival time after diagnosis is 6 years. After appearence of significant clinical renal symptoms, and, especially, of hypertension [250], it is reduced to a few months. In another series of cases [31], the average survival time following diagnosis was 13 months (46 months after appearence of symptoms). In some cases, the disease recurs in the kidney transplant [1045a, 1836].

### Pathogenesis and Etiology

Both pathogenesis and etiology of the disease remain unclear. For the development of secondary arteriolonecrosis, other factors must be considered besides hypertension, since the necrosis also occurs in nonhypertensive cases. It arises most likely as the consequence of especially serious anoxic injury due to severe impairment of blood flow to the region supplied by the onion-bulb interlobular arteries. The peculiar glomerular and arteriolar subendothelial deposits may be viewed as occurring analogously, i.e., as the consequence of anoxia.

**Fig. 25.29.** Same case as in Figure 25.25, showing arteriolar changes in scleroderma. Lumen (L) is slit-shaped. Isolated extravasated erythrocytes (*) are seen in the severely fine-granular thickened intima in addition to phagocytes. Lamina elastica interna is thickened, wavy and fragmented (→). Myocytes are not obviously changed. Female, 62 years. EM (× 1630)

**Fig. 25.30.** Same case as in Figure 25.29. Part of intima in an arteriole in scleroderma. Intima consists of a fine-granular and partly fibrillar material in which vacuolized processes can occasionally be recognized. Endothelium (*E*), myocyte (*MC*). Female, 62 years. EM (× 13,400)

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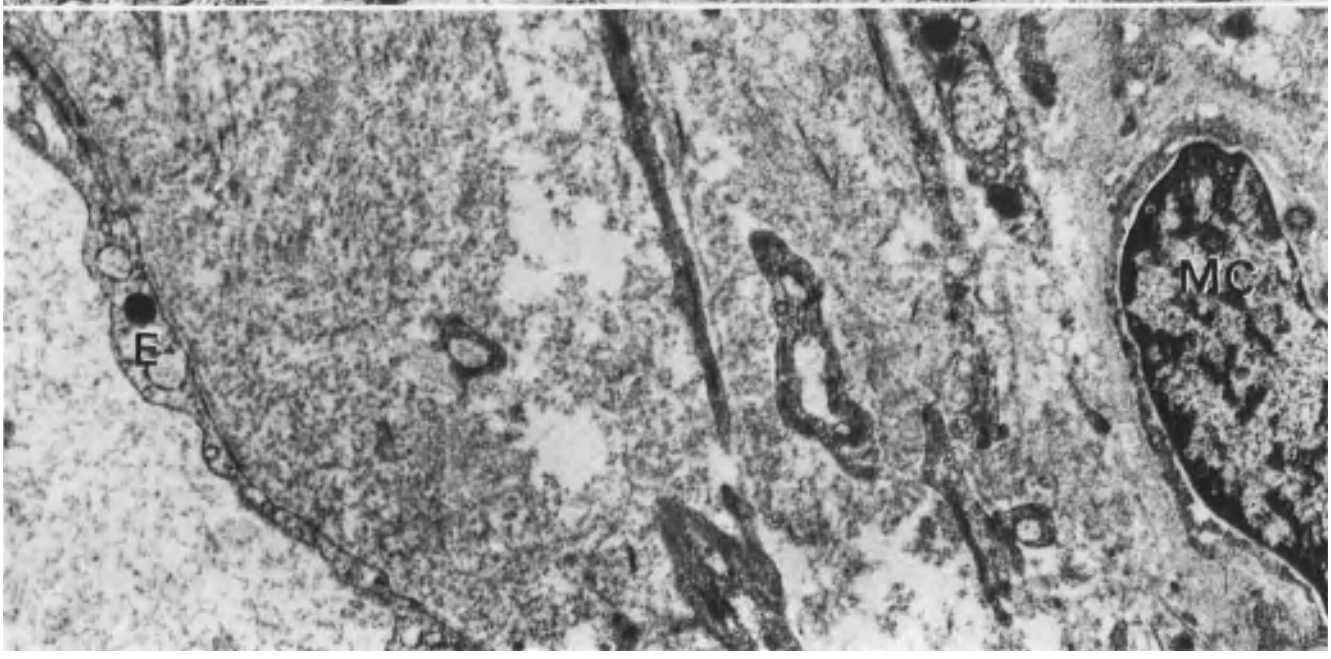


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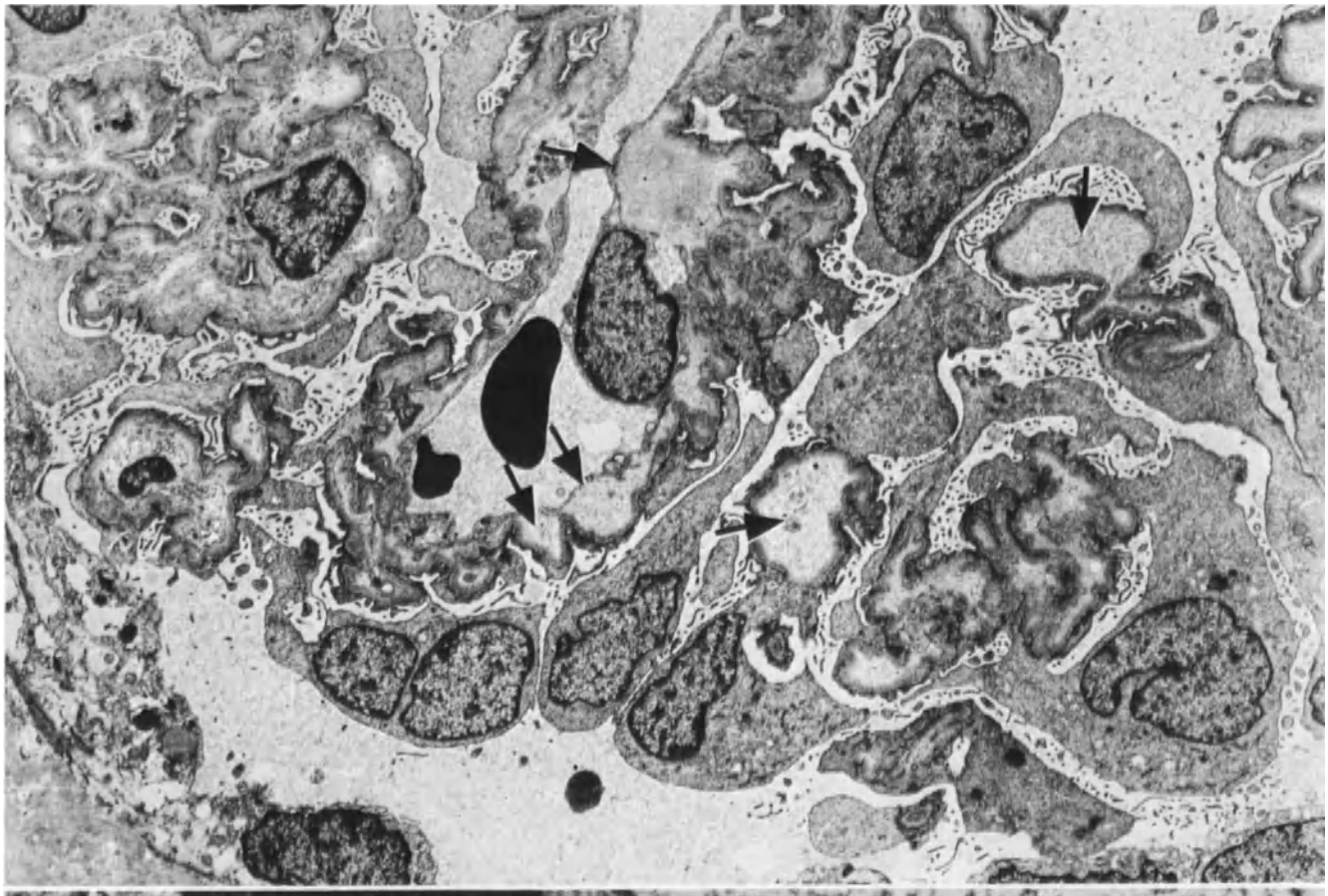

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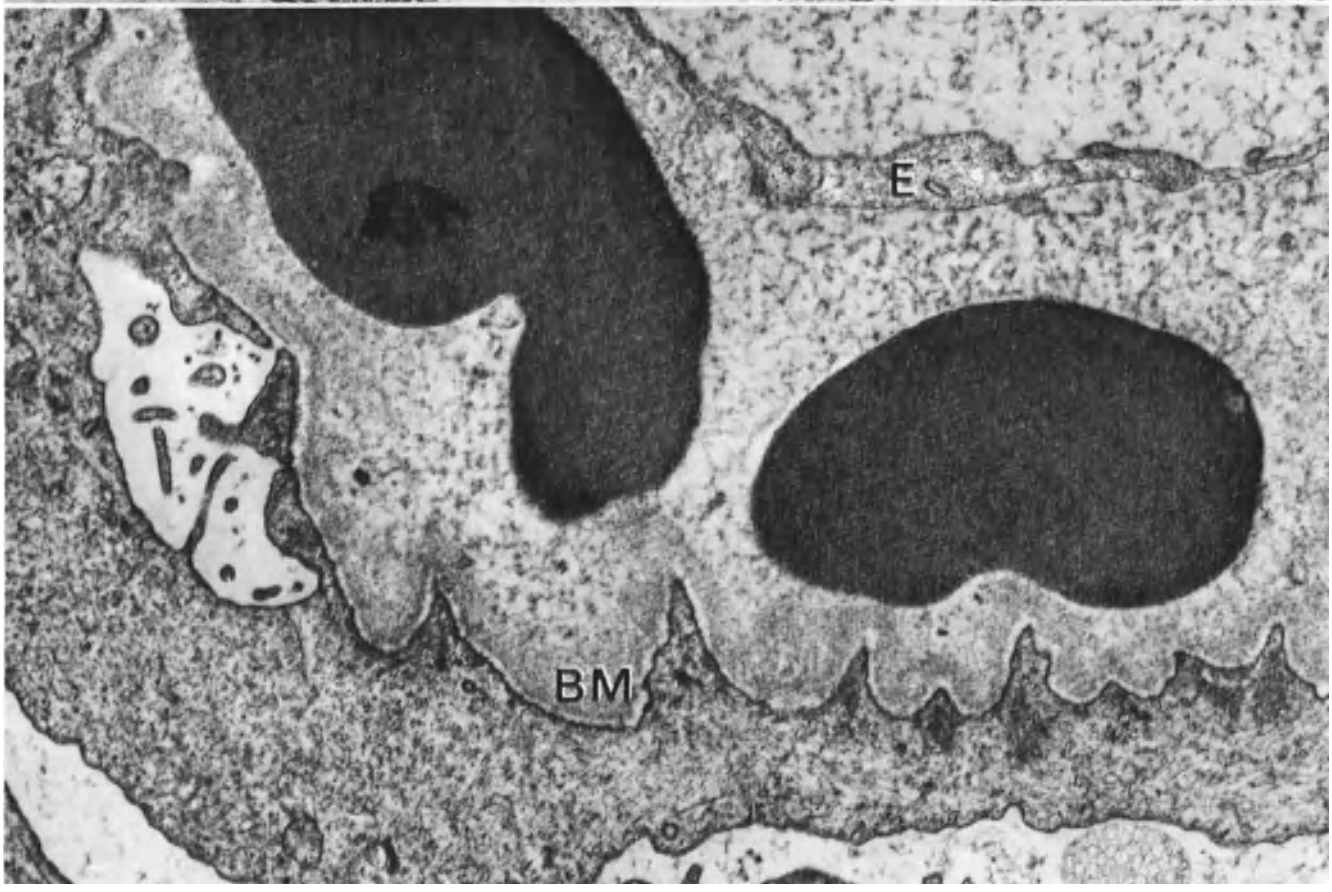


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We interpret the scattered positive IF findings as the result of insudation rather than as the expression of immunocomplex disease (contra: [1053, 1045, 1041, 541]). It is not known whether or not a genetic defect is basically responsible for scleroderma [1751].

## Arterial Intimal Proliferation Associated With Female Hormones

Severe arterial intimal proliferation without obvious inflammation can develop in response to the action of female hormones originating from ingestion of ovulation inhibitors or arising in pregnancy. The proliferation is occassionally associated with thrombi and can, rarely, lead to uremia [751].

## Neurofibromatosis
[181, 1087]

Involvement of renal vessels in generalized neurofibromatosis (von Recklinghausen's disease) is extremely rare, and only 30 cases have been described in the literature [1087]. Nevertheless, in the presence of hypertension in children without renal symptoms, the possibility of neurofibromatosis should be considered and appropriate attention should be directed to pathologic pigmentation and, of course, to neurofibromatosis of the skin.
The average age at which neurofibromatic renal hypertension was discovered was 15; the youngest known case was diagnosed in an infant 9 months old.

### LM Findings

The arteries (especially the interlobulars) demonstrate a peculiar intimal proliferation with formation of cell-rich pads and of a mild, loosely organized fibrosis of the subendothelial tissue. No reactive inflammation is present (Fig. 25.33; [1324, 181]). Cell proliferation has also been found occasionally in the media and has been interpreted as being neurofibromatic tissue (see also [1520]).

◁ **Fig. 25.31.** Same case as in Figure 25.29. This preparation shows a glomerulus in scleroderma. There is wrinkling of peripheral capillary loop BM. Resultant troughs in BM are filled in with a fine-granular material (→). Female, 62 years. EM (×3070)

**Fig. 25.32.** Same case as in Figure 25.29. Part of a peripheral capillary loop. Lamina rara interna is highly thickened, loosely granular and contains two erythrocytes. There is total foot process fusion. Endothelium (*E*), original basement membrane (*BM*). Female, 62 years. EM (×17,700)

However, even with LM it can be seen that these medial elements were strikingly similar to muscle cells (Fig. 25.34) and with EM, it was shown that the elements in question did consist unquestionably of myocytes [591]. In two of our own cases, there was a striking thickening of the periadventitial mesenchyma.
Pathogenetically, neurofibromatic transformation of vascular neural tissue [1098] or dysplasia of smooth muscule [591] are discussed in the literature.
Analysis of tissue and cells will prevent misinterpretation with respect to malignant mesenchymal tissue.

## Inflammatory Vascular Diseases
[225, 1791]

### Definition

Inflammatory vascular diseases of the kidney are—in contrast to arteriolonecrosis, etc.—primary inflammatory lesions.
Transplant vasculopathy is discussed separately on p. 596.

## 1. Unspecific Arteritis

Inflammatory arterial disease not arising in conjunction with systemic disease is extremely rare in the kidney. According to our experience, it occurs almost exclusively in pyelonephritis, especially when abscesses are present, or as a consequence of massive bacterial dissemination.

## 2. Periarteritis Nodosa

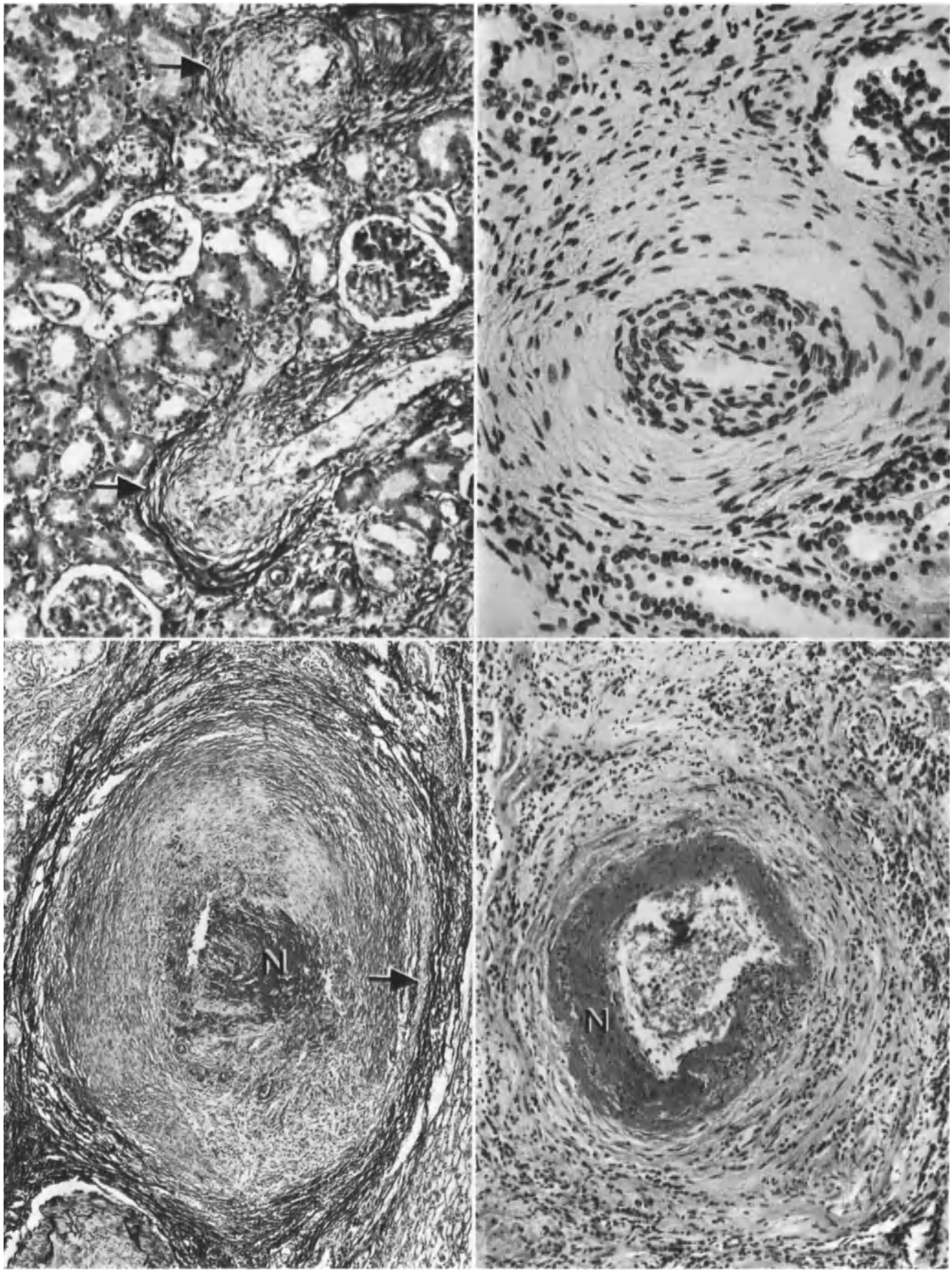
### Definition

Periarteritis nodosa is a chronically relapsing necrotizing granulomatous inflammation of the middle-sized arteries. It should be differentiated from hypersensitivity angitis (see p. 536).

***Synonyms:*** Panarteritis nodosa, polyarteritis nodosa, periarteritis nodosa: macroform, macropolyarteritis [403a].

### Incidence

According to the criteria of our definition, we have found a frequency of 0.57% for the disease in our autopsy

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material; we have never seen it in biopsy. Patients demonstrating the disease are usually between 20 and 50 years of age [789]. Periarteritis nodosa is extremely rare in children (20 cases: [1344]).
Renal involvement has been reported in 75–87% for adults [130, 1791], in 34 out of 56 cases [1151] and in 11 out of 20 cases respectively in children [1344]. Males are afflicted 4–5 times more frequently than females [789].

## Clinical Findings

Repeated attacks of fever and other signs of inflammation such as leukocytosis (often with eosinophilia), markedly raised sedimentation rate, etc., are usually present for weeks, months or even for years. Polyneuritis or better: mononeuritis multiplex (bioptically demonstrable), weight loss, and anemia, as well as myalgia, skin involvement and pleurisy, coronary heart disease and gastrointestinal symptoms are frequently encountered. Proteinuria and/or hematuria occur in more than 50% of the patients as well as uremia. Acute oligoanuric renal failure is a rare complication. Hypertension emerges chiefly after long-term corticoid therapy and renal involvement; its appearence may herald a new attack [1310]. About 15% of cases are reported to manifest changes in skin, a biopsy of which permits the diagnosis [1310]. In children, the disease manifets itself as erythema or uticaria, conjunctivitis, symptoms relating to the central nervous system and/or respiratory system, as well as cardiac insufficiency arising from very severe involvement of the coronary arteries [1344].

◁ **Fig. 25.33.** Neurofibromatosis of von Recklinghausen. A clear-cell tissue has caused nodular distention of two small renal arteries (→). Female 5.5 years. Van Gieson elastin (×130)

**Fig. 25.34.** Same case of neurofibromatosis as in Figure 25.33. In the artery shown, a cellular cover has developed between strikingly loose media and endothelium. Constituents of this intra-arterial cell cover are suggestive of undifferentiated myocytes. Female, 5.5 years. HE (×500)

**Fig. 25.35.** Periarteritis nodosa associated with hepatitis-B virus infection. Note the sector-shaped fibrinoid necrosis of the vascular wall (*N*). In this region, a severe inflammatory proliferation has developed which is leading to intense narrowing of vessel lumen. Media (→) is highly atrophic. Female, 48 years. HE (×37)

**Fig. 25.36.** Fresh attack of periarteritis nodosa in an artery previously afflicted. Arterial layers are fibrotic, split, and permeated with inflammatory elements; a sector of the vessel wall exhibits fibrinoid necrosis (N). HE (×150)

## LM Findings

The interlobular arteries exhibit focal and circular fibrinoid necrosis, while those of the middle-sized arteries are affected sector-like or circularly; there is, in any case, accompanying granuloma formation (Figs. 25.35, 25.36). Points of vessel branching are predominantly involved. In acute attacks, the vessel wall may be completely necrotic and the lumen narrowed by parietal thrombi. Later, the necroses are replaced by unspecific granulation tissue which consists of lymphocytes, plasma cells, histiocytes, and fibroblasts. In our material, eosinophilic leukocytes are not increased. In resolving foci, granulation tissue rich in fibrocytes and poor in histiocytes replaces the entire vascular wall, and goes on to finally develop into sclerotic scar tissue poor in cells (Fig. 25.37). In this phase, the elastica is mostly destroyed. Aneurysms may develop and the parietal thrombi undergo organization.
The concomitant occurrence of fresh and older scarifying foci in the vessels is characteristic of periarteritis nodosa, but is encountered in needle biopsy only exceptionally. Foci undergoing organization as well as scared vessels are more frequently found after intensive corticoid therapy.
Parenchyma nourished by afflicted vessels show, as a rule, infarcts of various age at autopsy. Additionally, anoxic tubular changes, collapse glomeruli, and moderately pronounced nondestructive interstitial nephritis are also present which may be quite distant from the vascular lesions. We have only once observed periarteritis nodosa combined with membranoproliferative GN in a case of hepatitis B. All other cases showed no inflammatory glomerular changes (see also [1054, 794a]).

## IF Findings

IgG, fibrin and complement have been reported to be present in blood vessels ([1246]; see also [794a]).

## Differential Diagnosis

The chronic relapsing course with the simultaneous occurrence of various phases of the disease, the larger size of the vessels afflicted, and the absence of pulmonary symptoms, involvement of the veins in periarteritis nodosa and especially the absence of glomerular involvement differentiate it from hypersensitivity angitis (contra: overlapping of both forms: [403a]; see also: [1855]. These differentiating factors are not always demonstrable in needle biopsy due to the few blood vessels (see also [1068]) contained therein.
Giant cells, which occur in allergic granulomatous angitis, are absent (see p. 538). Necroses are rarely seen in Buerger's disease, in Takayasu's arteritis and arteritis associated with SLE.

### Prognosis

The prognosis is very poor and rarely exceeds a 20% 5-years survival rate in untreated patients. Corticoid therapy slows disease progression considerably. Renal hypertension usually develops when the vascular lesions are already highly advanced at the time of therapy begin.

### Complications

According to the literature, the most important complication appears to be FGN. We feel, however, that this complication is not involved with the macroform of periarteritis nodosa but with hypersensitivity angitis. In any event, it was not present in any of our 140 autopsy cases (see also [794a]).
Renal parenchymal injury combined with massive bleeding can lead to spontaneous kidney rupture [1619].

### Pathogenesis

Periarteritis nodosa is probably an immunocomplex disease [955, 1848, 1849] caused by poorly soluble complexes [544]. Drugs are chiefly thought to be the source of AG in addition to bacteria and virus (e.g., hepatitis B antigen: [1016, 1848, 1849]—two cases of our own). Nevertheless, antigen demonstration is exceptional.

## 3. Hypersensitivity Angitis
[103, 1306]

### Definition

Hypersensitivity angitis is an allergic inflammation of the small arteries with a rapid, fatal course, and frequent involvement of the lungs, kidneys, and heart [1772, 1773].

***Synonym:*** Periarteritis nodosa, microform; micropolyarteritis [403a].

### Incidence

This generalized vascular disease is rare. It constituted 0.32% of the cases in an autopsy series and 6 out of 56 biopsies of renal arteritis [1151]. The disease shows no preference for age. Women are less afflicted than men (6:15: [509]; contra: [789]).

### Clinical Findings

Symptoms involving the lungs (pleurisy and hemorrhage: [1306]), gastrointestinal tract (hemorrhage and pain), heart (pericarditis and myocarditis) and skin purpura are frequently present. Renal involvement is reported in 50% of cases and uremia in 25% [103]. Blood eosinophilia may be present but it is not obligatory, and when present, it is not as pronounced as in allergic granulomatous arteritis. Neutrophilic leukocytes are often fragmented. The disease has been reported to be triggered by corticoid therapy in lupus erythematosus disseminatus [103] or in PCP [1151].

### LM Findings

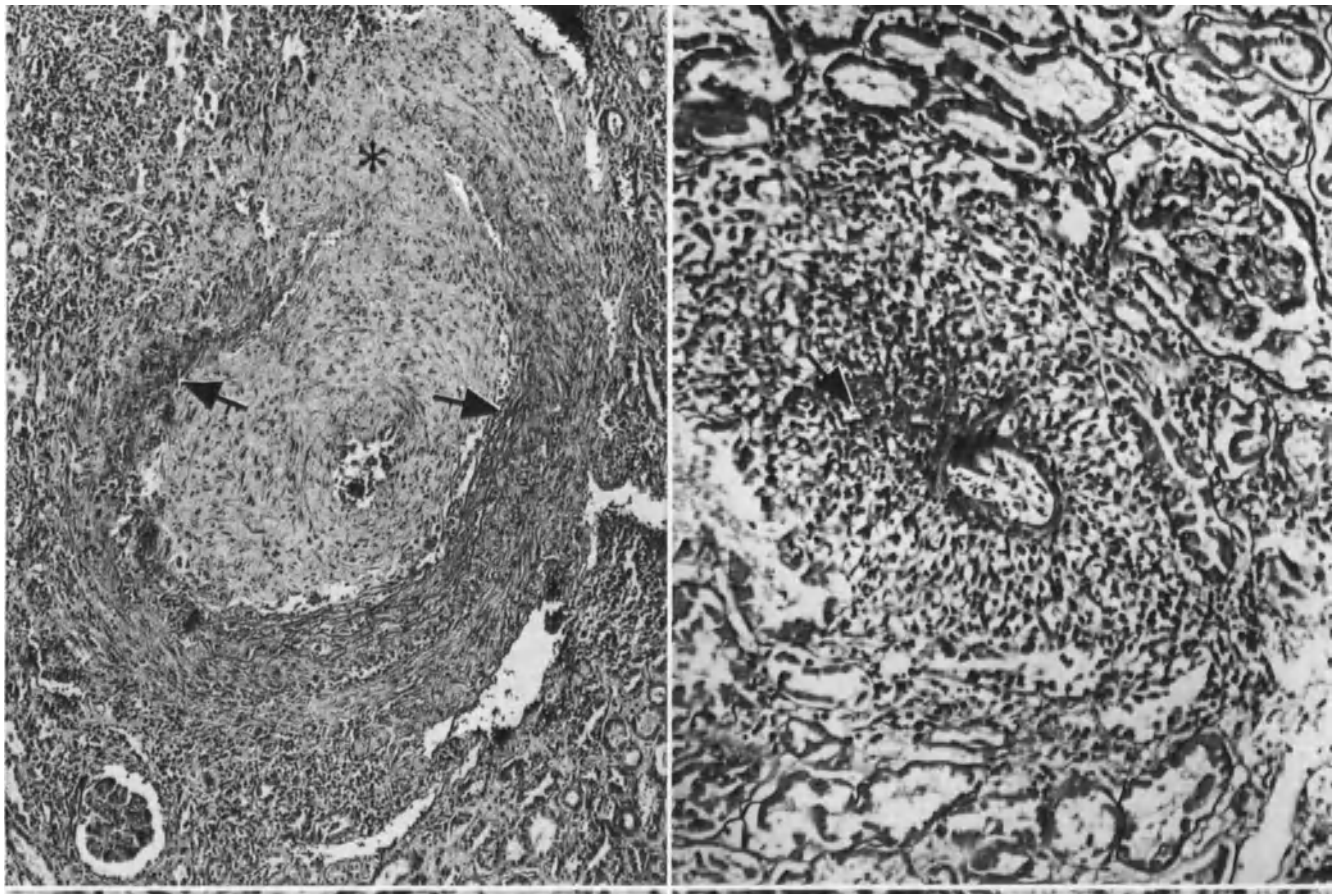
The walls of the smaller arteries, arterioles and, on occasion, of the capillaries and veins, are destroyed and replaced by a circularly arranged granulation tissue featuring numerous eosinophilic leukocytes and fibrin strands (Fig. 25.38). This change often occupies large areas of the afflicted vessel. Massive fibrinoid necroses are rare (Fig. 25.39). All foci are of about the same age. The glomeruli are frequently implicated in the inflammatory process in the form of focally accentuated GN often accompanied by extracapillary crescents (Fig. 25.40; see also [794a]).
We are not aware of any EM investigations.

**Fig. 25.37.** Old (scarred) periarteritis nodosa. Vascular lumen ▷ is nearly occluded by scar tissue between media (→) and endothelium. One sector (*) of media has been completely destroyed and replaced by scar tissue. Periarterial inflammatory infiltration is present. HE (×80)

**Fig. 25.38.** Hypersensitivity angitis of unknown etiology: analogous vascular changes are present in practically all of the inner organs. Only the most internal vascular layer is partly intact; all others are replaced by a radially arranged granulation tissue in which fibrinoid necroses are also occasionally encountered (→). Female, 72 years. PAS (×150)

**Fig. 25.39.** Same case of hypersensitivity angitis as in Figure 25.38. Fibrinoid necrosis is the predominant finding in this small artery. Lumen is almost completely occluded. Female, 72 years. HE (×290)

**Fig. 25.40.** Segmental-focal glomerulonephritis in same case of hypersensitivity angitis as in Figure 25.38. Necrotizing segmental glomerulitis with extracapillary involvement is present. Fibrin is seen in one glomerular capillary loop (→). Female, 72 years. Masson's trichrome (×500)



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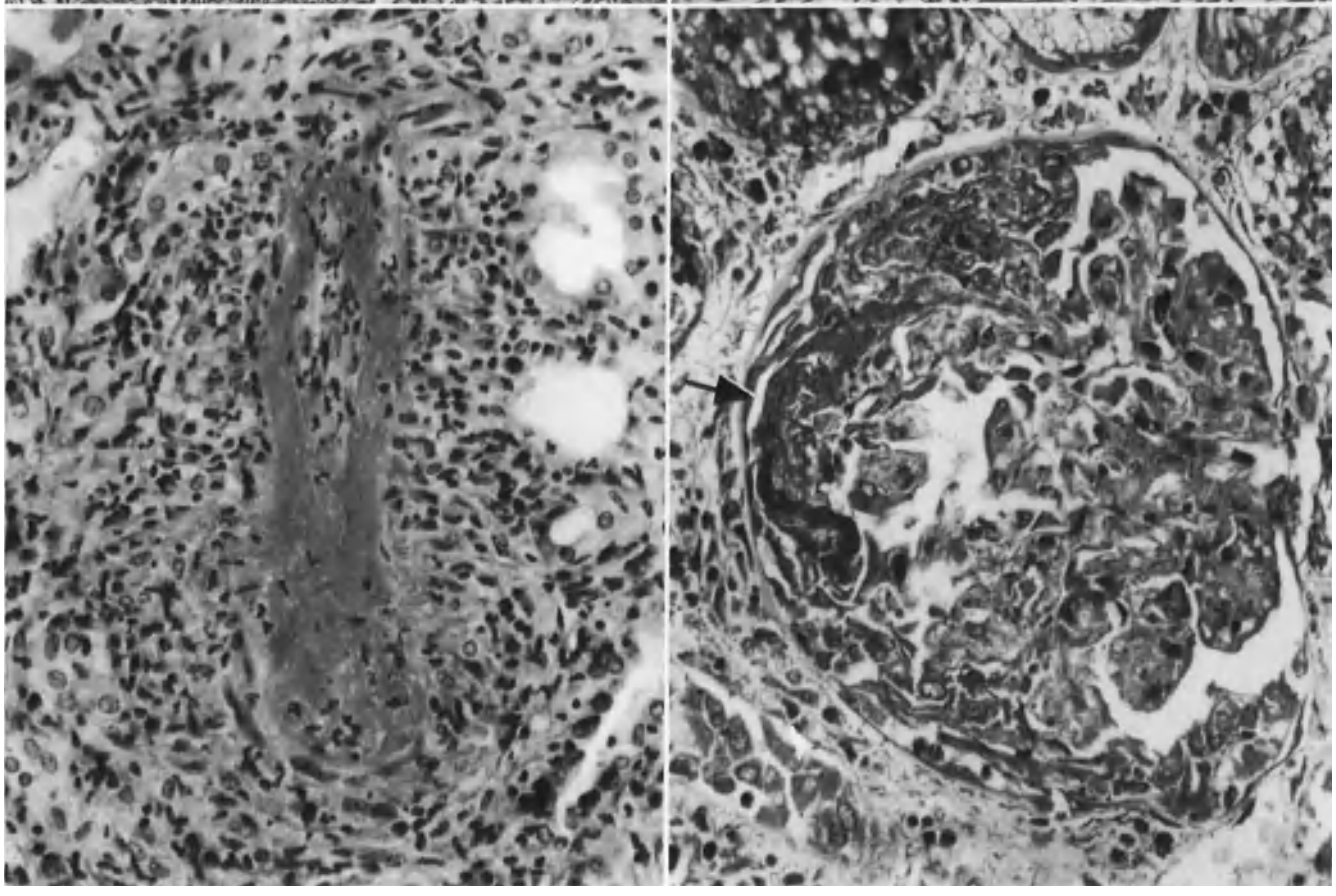

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### IF Findings

In one case [128], only fibrin was found, and in another [1246] complement and gamma globulins were also present. In another series, IgG was present in 3 out of 5 cases, C3 in 2 out of 5 and fibrin(-ogen) in all cases [794a].

### Complications

Glomerulitis, usually necrotizing and focally accentuated, occurs relatively frequently [103, 358, 509, 685, 794a, 1306, 1772]; see also p. 349. In 3 out of 7 of our cases we found extracapillary and usually proliferative FGN. Capillary loop necroses (Fig. 25.40; [1068]) were present in only 2 of our cases.

### Differential Diagnosis

Difficulty is mainly encountered in relation to the FGN which often accompanies this disease. Severe destructive glomerulitis with periglomerulitis is indicative of Wegener's syndrome, whereas the vascular changes in Wegener's syndrome are considered by some investigators as belonging to hypersensitivity angitis [103, 1772, 1855]. Pronounced hypertensive vasculopathy (arteriolonecrosis) in children can appear very similar to hypersensitivity angitis. It is noted, however, that inflammatory changes in arteriolonecrosis are much more discrete, and that this disease features frank hypertrophy of the media of unaffected vessels. The clinical course of the two diseases is also different.
Schönlein-Henoch's purpura is said to cause vascular changes similar to those in hypersensitivity angitis [325, 1855], a finding which we cannot confirm (p. 320). Hypersensitivity angitis usually afflicts smaller vessels than is the case in SLE and hematoxylin bodies are not found.
Pulmonary bleeding can occasionally direct attention to Goodpasture's syndrome in which, however, the glomerular changes are far more destructive, the periglomerulitis far more pronounced, the vascular changes far less pronounced, and in which anti-BM AB can be demonstrated in serum and kidney. For periarteritis nodosa, see p. 533.

### Prognosis

The prognosis appears to be very poor, even with corticoid therapy [103].
The disease usually leads to death within a few days or, at most, in a few months. One group of investigators, however, reported 11 out of 21 survivors [509] which possibly included patients with periarteritis nodosa (macroform).

### Pathogenesis and Etiology

In general, the disease is thought to result from an abnormal immunologic response to bacteria, drugs (sulfonamides: [1306]; Madribon® = sulfadimethoxine: [325]) and possibly to virus e.g. hepatitis B antigen [1848]. Poorly soluble immunocomplexes can cause the vascular lesions [544] which are also typically observed in serum sickness.
Finally, it has been observed that massive corticoid therapy for other diseases, e.g., SLE or rheumatoid arthritis, appears to trigger hypersensitivity angitis [103, 1151].

## 4. Other Inflammatory Diseases of the Renal Arteries

### Allergic Granulomatous Arteritis (Churg and Strauss)

This is a very rare disease (Z: 3 out of 25,000 autopsies: [284]). It runs a chronic course lasting many months with acute episodes of fever, bronchial asthma, severe blood eosinophilia and occasionally with eosinophilic pulmonary infiltrates and an increase in serum IgE [301a].
Extensive granulomas in arteries and veins [574] are found in many organs including the kidneys. The granulomas are in various stages of development and consist of eosinophilic leukocytes, epitheloid and giant cells (Figs. 25.41, 25.42). Tuberculoid arteritis [1791] belongs to this disease which has many similarities to Wegener's granulomatosis except for the characteristic glomerular lesions noted in the latter ([1773]; contra: [1054]).

### Rheumatic Arteritis

Rheumatic arteritis [103] rarely occurs in acute rheumatic joint disease (2 out of 25,000 autopsies: Z). It manifests itself in the middle-sized and small arteries in the form of a granulomatous, periarteritic, unspecific inflammation [210] or in the form of Aschoff's granulomas (Fig. 25.43; [863, 1773]).
Later in the course of the disease, fibrinoid medial necrosis and microabscesses can develop [673]. This form of the arteritis is reported to be morphologically very similar to that occurring in SLE which is further substan-

tiated by the presence of antinuclear antibodies (specific, however, only for native DNA) and rheumatoid factors in the serum [1068]. When corticoid is administered in high doses, extensive necrosis in the center of the granulomas may develop [705a].

**Thrombendangitis (Buerger-Winiwater Disease)**
[946, 1791]

This disease is rarely observed in renal arteries and it can, in rare cases, even afflict the arcuate arteries. Patients with this disease are usually men under 40 years of age who suffer from occluding arterio- and venopathy. Hypertension is frequently encountered when the renal arteries are involved.
LM study demonstrates cell-rich intimal pads with giant cells and, occasionally, with fibrinoid necrosis and tuberculoid granulomas in arteries as well as veins(!) with secondary thrombosis.
The thrombi are unusually rich in cells and considerably vascularized. In contrast to other arteritic diseases, thrombendangitis is characterized by the very slight lymphocytic infiltration of the media and adventitia. In the late phase of the disease, the tissue becomes sclerosed and may show secondary lipoid deposition.

Differential diagnosis with respect to arteriosclerosis is only possible in the acute phase and when sufficient clinical data are available.

**Giant Cell Arteritis (Horton's Temporal Arteritis)**

This disease, in rare cases, assumes a generalized form in which the kidneys may also be implicated and which can lead to uremia [707]. The disease usually attacks elderly people of either sex.
Prodromal symptoms, such as rheumatic complaints, headache, and visual disturbances, may last for a considerable period of time. The temporal artery is painful on pressure and the tissue surrounding the artery is reddish. Corticoid therapy prevents threatening blindness. It appears that allergic degeneration of the elastica interna (no further clarification currently available) is present. The media undergoes secondary replacement by granuloma tissue consisting of lymphocytes, histiocytes, plasma cells, neutrophilic leukocytes, and giant cells containing elastin fragments.
EM study [350] suggests that the myocytes are primarily affected (possibly disturbance of synthesizing ability). They show decreased numbers of myofibrils and fuse to form giant cells.

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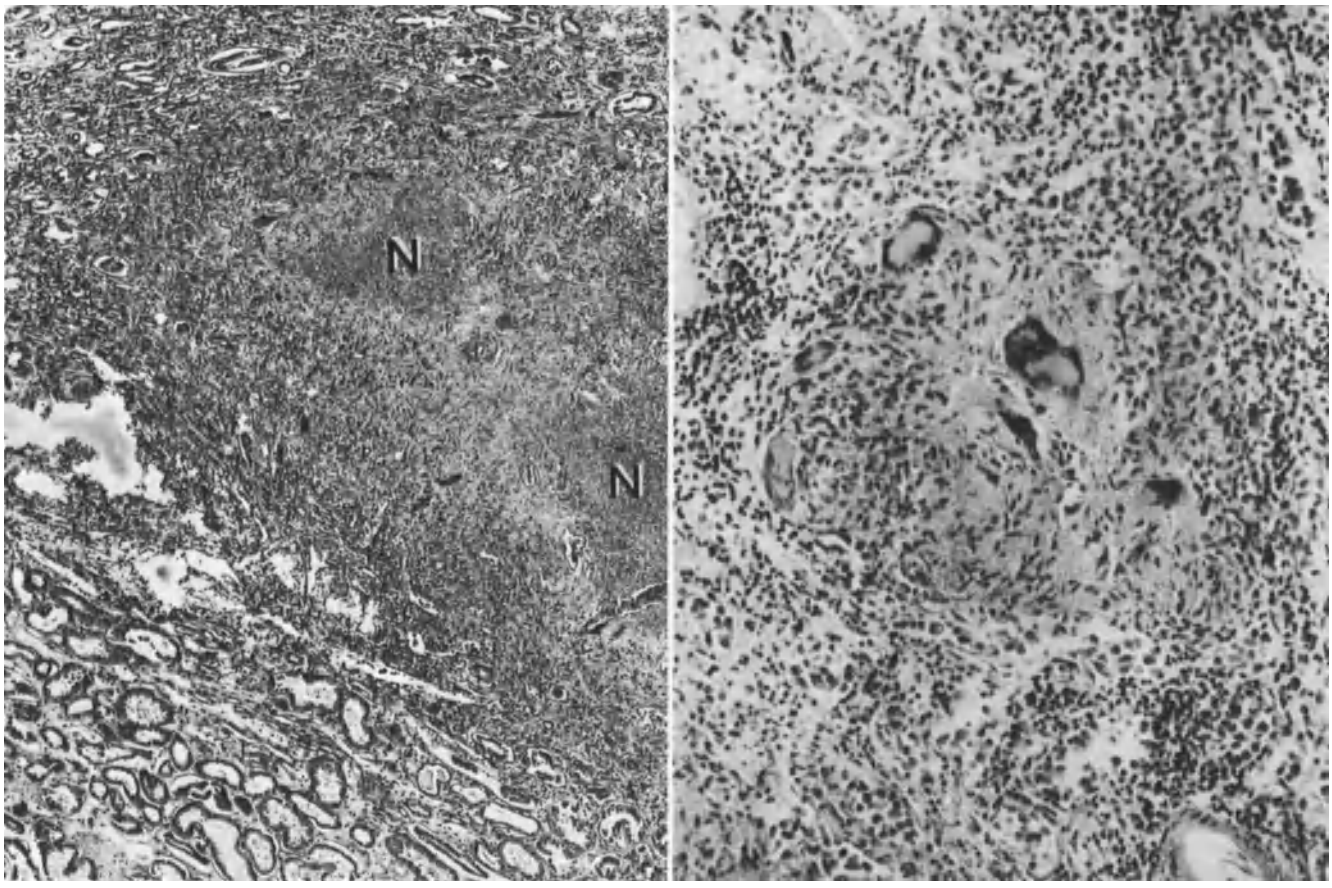


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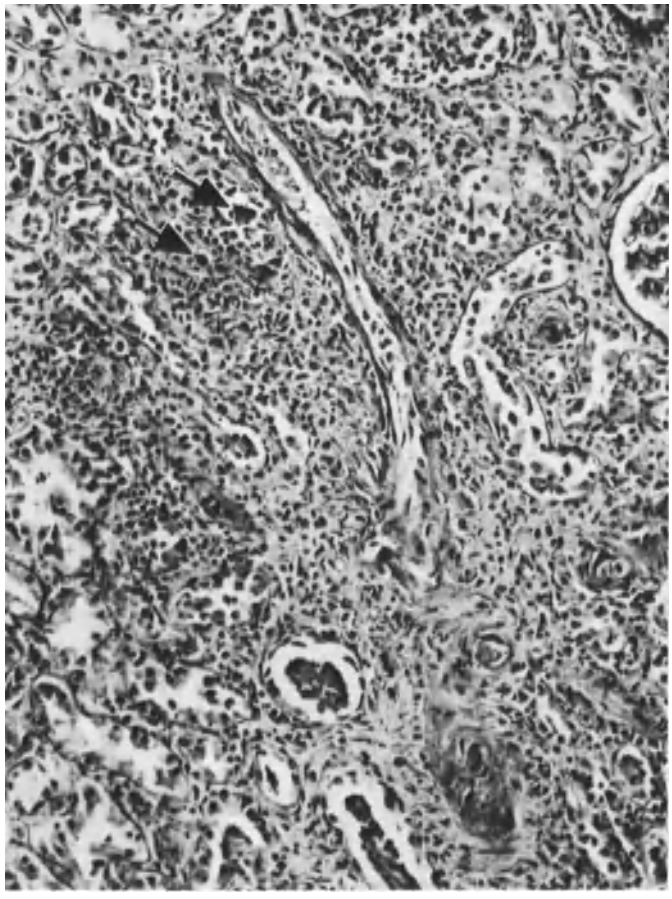


**Fig. 25.41.** Allergic granulomatous arteritis of unknown etiology. Artery is no longer recognizable as such, but periarterial tuberculoid granuloma with extensive central necroses (*N*) can be easily identified. Female, 64 years. HE ( × 33)

**Fig. 25.42.** Same case of allergic granulomatous arteritis as in Figure 25.41. Tuberculoid character of granuloma with its Langhans's giant cells, epitheloid cells, and lymphocytic rim is especially clearly recognizable. Female, 64 years. HE ( × 155)

**Fig. 25.43.** Rheumatoid arteritis of kidney in a case in which heart was also afflicted. Periarterial granuloma with isolated cell giants (→). Female, 85 years. PAS ( × 155)

# 26. Unilateral Contracted Kidney and Renal Hypertension

[1262, 1487, 1791]

## Definition

We define unilateral contracted kidney as a kidney weighing less than 90 g and showing a weight difference from the contralateral kidney of at least 50 g in adults. Hypertension is defined as a blood pressure of $\geqq$160/100 mm Hg. For differentiation from hypoplasia see p. 547.

## Incidence

Using the above-mentioned criteria, the frequency of unilateral contracted kidney at autopsy has been reported as 1.72% [1072] from which only 8.1% were present in patients under 50 years of age. In material obtained by surgery, the age of patients is, of course, much lower, and children are included.

As shown in our own autopsy material, the incidence of hypertension in patients with unilateral contracted kidney is much greater than in a corresponding age-matched control group (42%: 29%). The various forms of unilateral contracted kidney with respect to pathogenesis demonstrate the following incidence of hypertension: ischemic contracted kidney: 84% [1808], pyelonephritic unilateral contracted kidney: 33.3% [1791], 64.6% (Z); 16% [1262]; early childhood form of PN contracted kidney: 65% (Z); hydronephrotic contracted kidney 41% (Z); tuberculous putty kidney: 3–4% [908, 1466, 1783]; all other diseases leading to unilateral contracted kidney are rare. Thus, unilateral contracted kidney frequently, but not necessarily leads to hypertension, apparently via the renin mechanism [919].

## Biopsy Findings

The unilateral contracted kidney itself is rarely biopsied in contrast to the contralateral kidney in which the presence or absence of any diffuse or focal renal disease is of interest, as is the degree of hypertensive vasculopathy which more or less determines the prognosis relating to successful operative antihypertensive treatment. The possibility of vasculopathy arising from essential hypertension cannot, of course, be excluded.

Hypertrophy of the JGA can be observed in all forms of contracted kidney. We found this hypertrophy to be diffuse in central arterial ischemic contracted kidney and focal in PN contracted kidney with predominance in the scarred areas. In cases of extensive parenchymal damage, reliable evaluation of the JGA is no longer possible (4 out of 40: Z).

## Prognosis

The prognosis, as related to operative antihypertensive therapy, is said to be all the better the shorter the duration of the hypertension, the lower the blood pressure, and the younger the patient [908].

Table 26.1. Course of hypertension in relation to various statistically significant+ parameters in hypertensive unilateral contracted kidney ($\geqq$160/100 mm Hg)

| Parameter | Total No. of cases | Follow-up[a] | | |
|---|---|---|---|---|
| | | Normalization without therapy | Improved | Unchanged |
| *Postoperative blood pressure* | | | | |
| Normalization within 2–14 days postoperatively without therapy | 40 | 15 | 3 | 3 |
| No normalization | | 6 | 4 | 9 |
| *Arteriolosclerosis* | | | | |
| 0–+ | 39 | 17 | 5 | 5 |
| + + – + + + (semiquantitative) | | 3 | 2 | 7 |
| *Enlargement of JGA* | | | | |
| 0–+ | 36 | 4 | 3 | 8 |
| + + – + + + (semiquantitative) | | 14 | 5 | 2 |
| *Diagnosis of contracted kidney* | 40 | | | |
| Ischemic (central arterial stenosis) | | 9 | 5 | 1 |
| Pyelonephritic | | 10 | 3 | 7 |
| Hydronephrotic | | 1 | 0 | 4 |

[a] Follow-up time: mean 5.7 years (range 1–15 years).
+ m × n test: $p < 0.05$.

A favorable prognosis is associated with a large difference between the renin values of the two kidneys as demonstrated by bilateral renal vein blood examination [1669], especially when venous renin concentration of the contralateral kidney is lower than in peripheral blood.

Statistical evaluation of 40 of our own cases of unilateral contracted kidney revealed no significant relationship between postoperative blood pressure and age, sex, preoperative blood pressure, duration of hypertension, preoperative renal function and kidney weight.

A statistically significant correlation was found, however, in relation to immediate postoperative blood pressure behavior and to the extent of arteriolosclerosis and JGA hypertrophy in the diseased kidney as ascertained by semiquantitative analysis (Table 26.1, contra: [81]; see also [215a]).

Diagnostic methods for establishing indication for operation are intravenous pyelogram (with early X-rays), arteriography and separate determination of renal vein, artery and peripheral blood renin ([1656a]; see p. 541). The latter technique is said to enable 100% prediction of success or failure [1656a]. Less frequently used nowadays are renal function tests done separately for each kidney and the angiotensin test (see also [320, 1487]).

Various values for cure and improvement of hypertension in unilateral contracted kidney are reported. Thus, cure has been reported as 50% [908], 38% cure and 12% improvement [979], 75% cure and improvement in 9% [1262]. Cure or improvement in another series was 36% [1487] and 15 out of 42 [1676]. In our series of nephrectomies, 20 out of 40 were cured and 8 out of 40 were improved (Table 26.1).

Cases of ischemic contracted kidney appear to have a fairly favorable prognosis as indicated by 9 out of 15 cured and 5 out of 15 improved (Table 26.1; 56.7% cured, 30% improved [1424]; and 86.2% cured [1147]; 66% cured, 19% improved [215a]).

The following data are available on PN contracted kidney: 8 out of 14 cured [1676] and 10 out of 20 cured, 3 out of 20 improved (Table 26.1).

Nephrectomy has the least effect in hydronephrotic contracted kidney: only 1 out of 5 cases was cured (Table 26.1). Favorable results are also obtained with nephrectomy in the rare hypertensive unilateral tuberculous putty kidney (see p. 443).

In bilateral contracted kidney, increase of fluid volume with inadequate excretion of salt and water is, in the majority of cases, the cause of hypertension. Only a small group of these patients (8 out of 43: [1669]) were hypertensive due to the renin mechanism.

# 27. The Kidney in Radiation Injury

[981, 1152, 1791]

### Definition

Renal changes resulting from exposure of the kidney to ionizing irradiation.

### Nosology and Clinical Findings

Data relating to the frequency of radiation injury are not available.

Basically, six clinical conditions are recognizable [981]:

1. Acute radiation nephritis (better designated as radiation nephropathy). It occurs about 6 months after exposure in adults and 3–9 months in children [44]. The lesion manifests istself as proteinuria and edema, anemia and, rather frequently, as hypertension.
2. Secondary, chronic radiation nephropathy, which develops from the acute condition. Clinically, the lesion is characterized by proteinuria, anemia, hypostenuria, hypertension and intermittent impairment of excretory function.
3. Primary chronic radiation nephropathy, which first demonstrates clinical symptoms years after exposure without the occurrence of the acute condition. Symptoms are the same as in the secondary chronic form.
4. Asymptomatic proteinuria, which occurs on average 17 years after exposure.
5. Benign hypertension, which appears 6–8 months after exposure.
6. Late malignant hypertension, which occurs in one-fourth of all patients who have suffered irradiation injury to the kidney. Hypertension is the only symptom which is frequently encountered in cases of thorotrast storage in the kidney. Hypertension has also been produced experimentally by exogenous irradiation [1791].

   In general, the latent period between exposure and manifestation of symptoms is highly variable and is not uniquely dependent on the radiation dosage. It is possible that pre-existing inflammatory changes—which increase the sensitivity of the tissue to irradiation—could play a significant role.

### LM Findings

In the acute phase, endothelial swelling [817] and scattered capillary loop necroses followed by capsular epithelial proliferation are seen. Splitting of the glomerular capillary wall—reminiscent of membranoproliferative GN—frequently occurs [817]. Capsular BM is thickened. Somewhat later, a pronounced cellular swelling develops, especially of the proximal tubules as well as the characteristic nuclear polymorphism (Fig. 27.1; p. 129) which is also present, but less marked, in podocytes.

The number of glomerular cells decreases progressively. Widening of the capillary loops (aneurysms) are frequent (Fig. 27.2). The mesangium demonstrates a very considerable increase of a strikingly finely fibrillar mesangial matrix with reduction in the number of nuclei (Figs. 27.2,

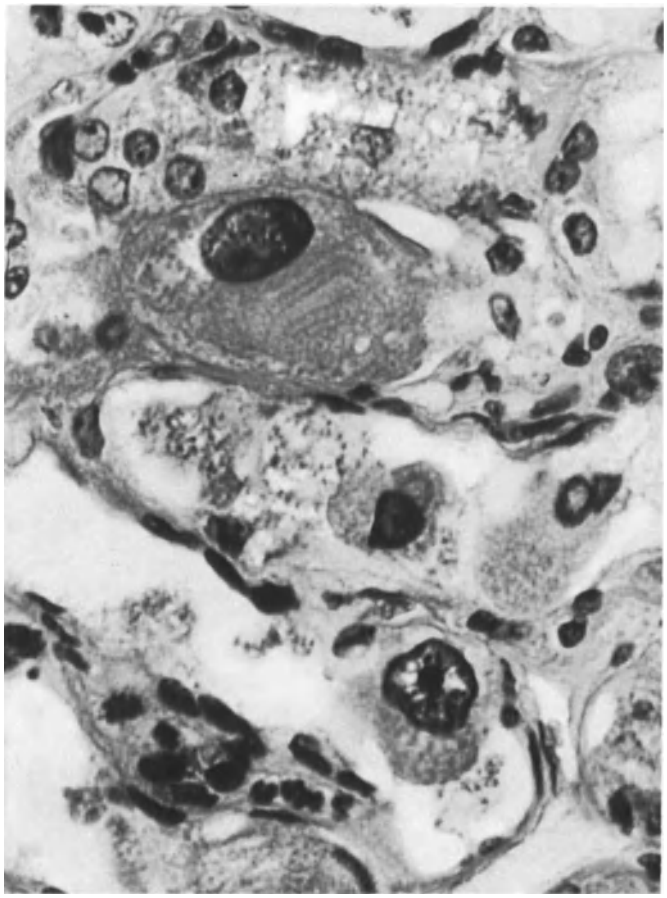


**Fig. 27.1.** Tubular cell giants with giant nuclei in a kidney irradiated with 2800 rads 3 years prior to biopsy. Male, 12 years. HE (×500)

27.3). The JGA, at least in acute experiments [965], shows reduction of granules in the irradiated kidney and an increase in the contralateral (nonirradiated) kidney [488]. Besides the above-instanced nuclear changes, the tubules are frankly atrophic (Fig. 27.3). Experimentally, tubular necrosis evidencing increased lipofuscin granules can be produced [993]. The very marked interstitial fibrosis with coarse fibers and very scanty nuclei (Fig. 27.3) is striking in both humans and animals.

The arterioles usually do not demonstrate the typical findings of massive radiation vasculopathy [1798], namely, endothelial injury followed by insudation of fibrinoid material, and inflammatory reaction with transition to sclerosis. Teleangiectasis of capillaries and veins is rare, while subendothelial foam cells are very frequent. Capillary changes may appear years after exposure if additional injury (e.g., PN, etc.) afflicts the already damaged cells [1798]. Thus, renal radiation vasculopathy is quantitatively considerably less prominent than corresponding changes in the skin.

In thorotrast-damaged kidneys, groups of large phagocytes occur arranged predominantly perivascularly, in addition to the changes described above. These phagocytes contain numerous strongly refractile thorotrast particles staining red with the glycogen stain (Best's carmine) (Fig. 27.4).

We are unaware of any IF findings.

## EM Findings

The early changes (of a few weeks) consist of the known consequences of cellular membrane injury which manifest themselves in cystoidal widening of the basal labyrinth (Fig. 27.5) as well as in cystoid transformation of other organelles (Figs. 27.6, 27.8). Additionally, endothelial edema and necrosis as well as detachment of cytoplasmic elements in the form of balloons typically occur (Fig. 27.7). The same swelling is also manifested by the mitochondria and the cystoid-widened podocytic endoplasmic reticulum. Simultaneous thickening of the lamina rara interna of capillary loop BM is also present. Mesangial cells show signs of hypertrophy [1362].

Late changes, among others, are reported to consist, of splitting and lamellation of the glomerular capillary loop BM [1362, 1269]. The BM is often described as being wrinkled [992, 993] as a result of collapse. This is not at all surprising in view of the vascular injury.

Endothelial detachment, along with decrease of cytoplasmic organelles in this phase [993, 1363] as well as deposits [993], have been described. The mesangial matrix has been reported as being considerably thickened [1269]. The mesangial cells demonstrate increased residual bodies, myelin figures and other signs of degeneration, i.e., progressive atrophy [1362].

## Prognosis

In a series of 22 cases of acute radiation nephropathy, 12 died chiefly of hypertension and, more rarely, of uremia [981]. Of 13 patients with primary chronic radiation nephropathy, 7 died as a direct result of the radiation.

## Pathogenesis

Radiation nephropathy follows therapeutic abdominal irradiation for such conditions as metastases of seminoma, cancer of the ovary or kidney or neighbouring structures such as tumors of the vertebral column, etc. It is thought that a radiation dosage of 1200 rads is sufficient to produce irradiation nephropathy, which may be enhanced by increased cellular activity as is associated with inflammation at the time of irradiation.

More than 2300 rads are necessary to produce primary chronic radiation nephropathy [981].

Endothelial injury is the most significant change from the pathogenetic viewpoint [1152, 991]. This must be recognized for irradiation injury in general [1791]. The tubuli are injured directly as well as indirectly by blood vessel damage.

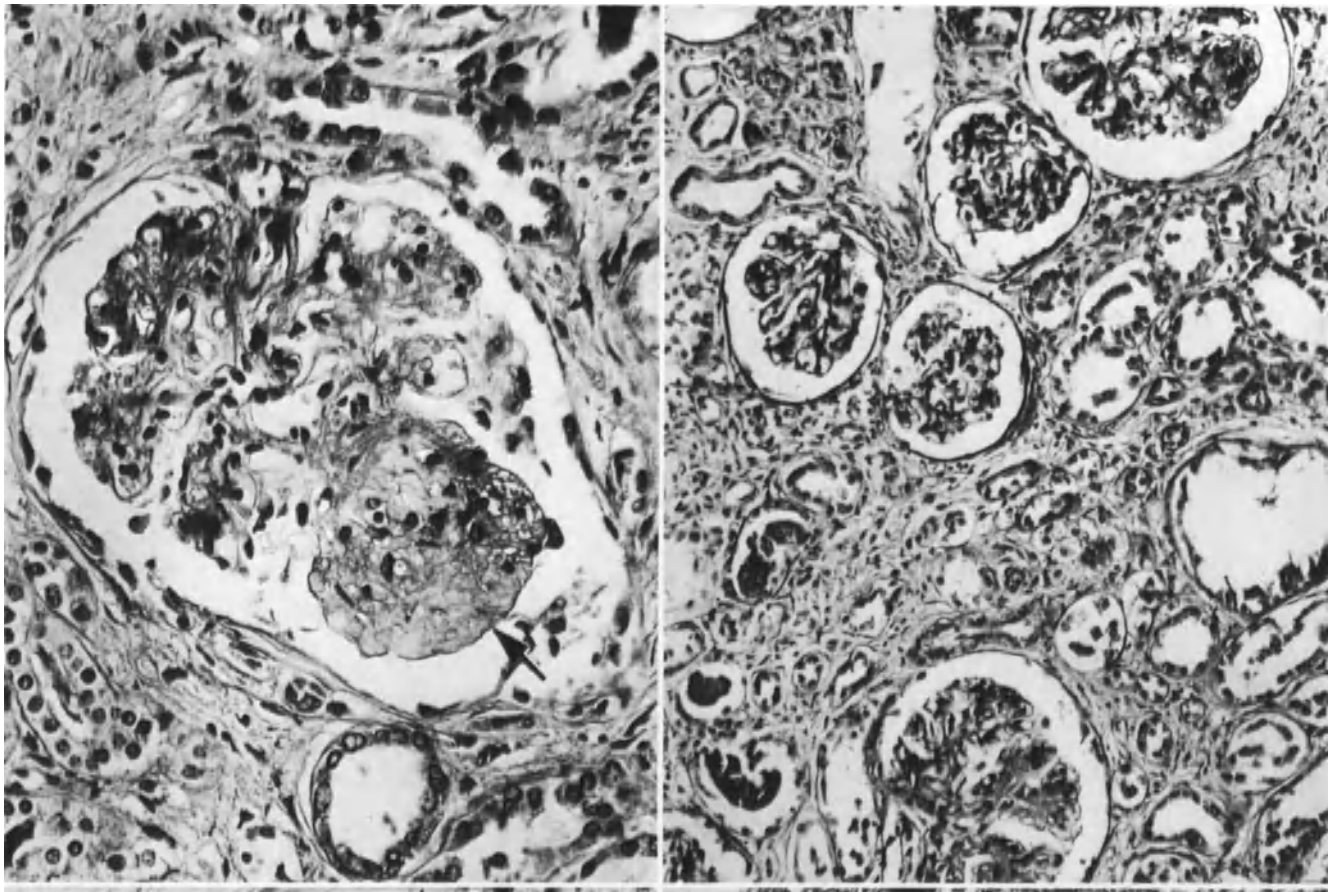
In addition, direct nuclear injury occurs which manifests itself in the form of nuclear polymorphy in the tubules and gradual cell decrease in the glomeruli. In any event, the term nephritis should not be used in describing the condition but, rather, nephrosis or nephropathy [1152]. The lesion appears to be worsened upon administration of actinomycine D (complex formation with DNA) and vincristine (impairment of regeneration: [44]).

**Fig. 27.2.** Aneurysm-like distention of a glomerular capillary loop (→). Biopsy was carried out 1 year after irradiation of kidney with 3000 rad. Male, 47 years. PAS (×290) ▷

**Fig. 27.3.** Same case as in Figure 27.2. In two glomeruli, mesangium is seen to be obviously enlarged but does not exhibit a significant cell increase. Interstitium evidences fibrosis with only a very few inflammatory cells. Tubules are atrophic. Male, 47 years. Autopsy, PAS (×140)

**Fig. 27.4.** Thorotrast storage in renal phagocytes. Note severe arteriolar necrosis (published [1791]). HE (×340)

**Fig. 27.5.** Acute radiation renal lesions 4 weeks after tumor irradiation of kidney with 4500 rad because of renal carcinoma. Basal labyrinth of proximal tubular epithelium is distended as is endoplasmatic reticulum. Mitochondria are seen to be slightly swollen. Brush border (*BB*). Female, 65 years. EM (×10,300)



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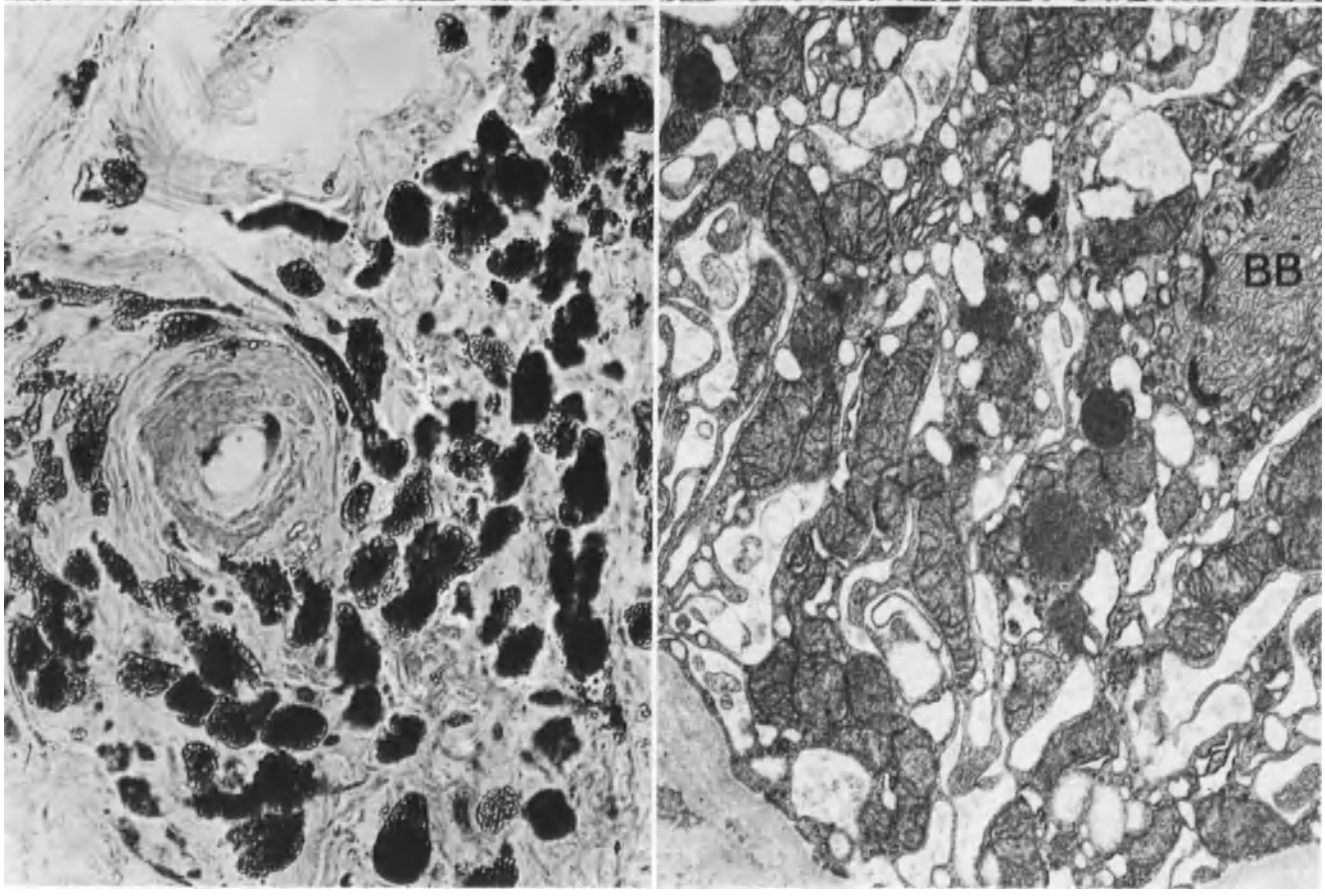


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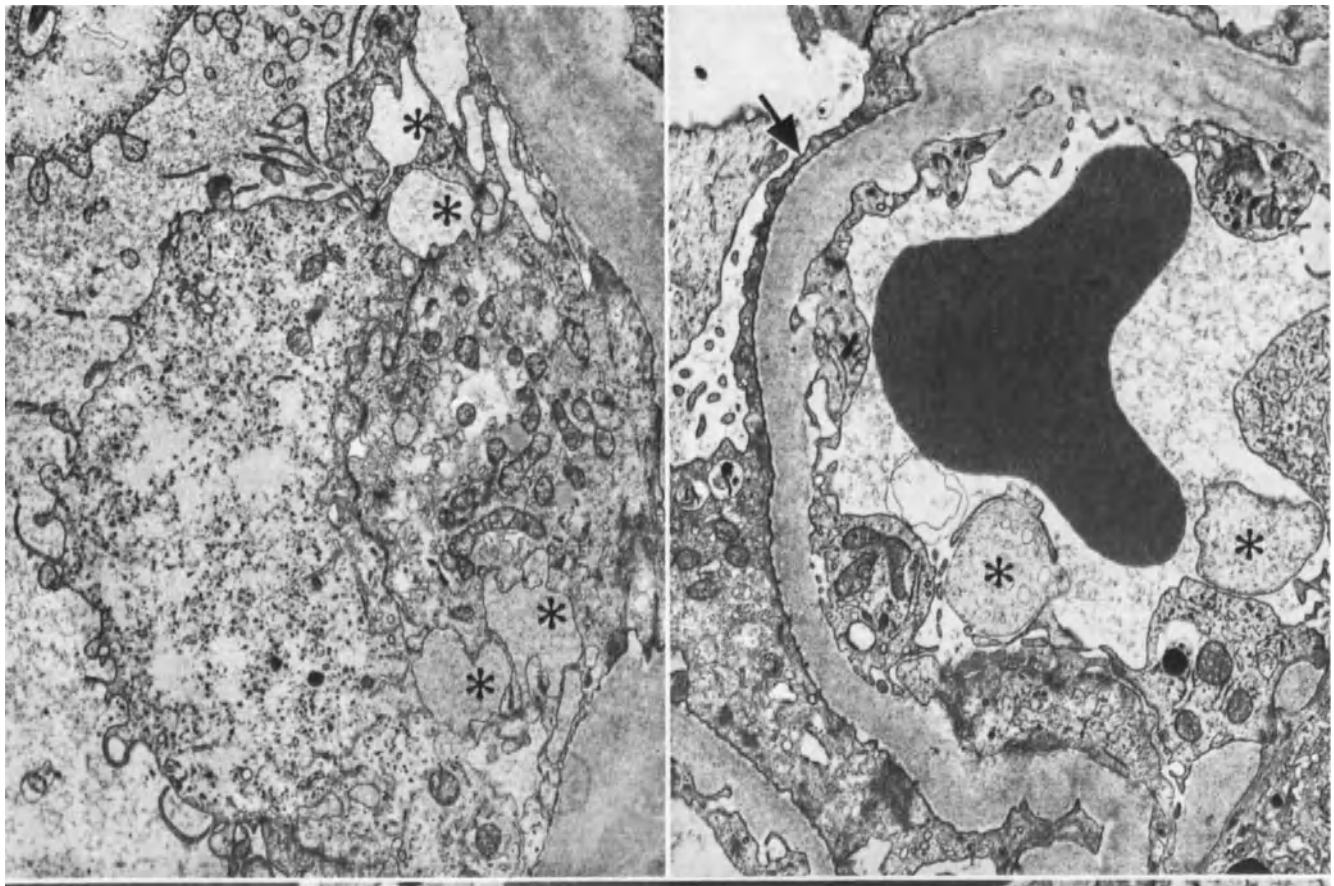

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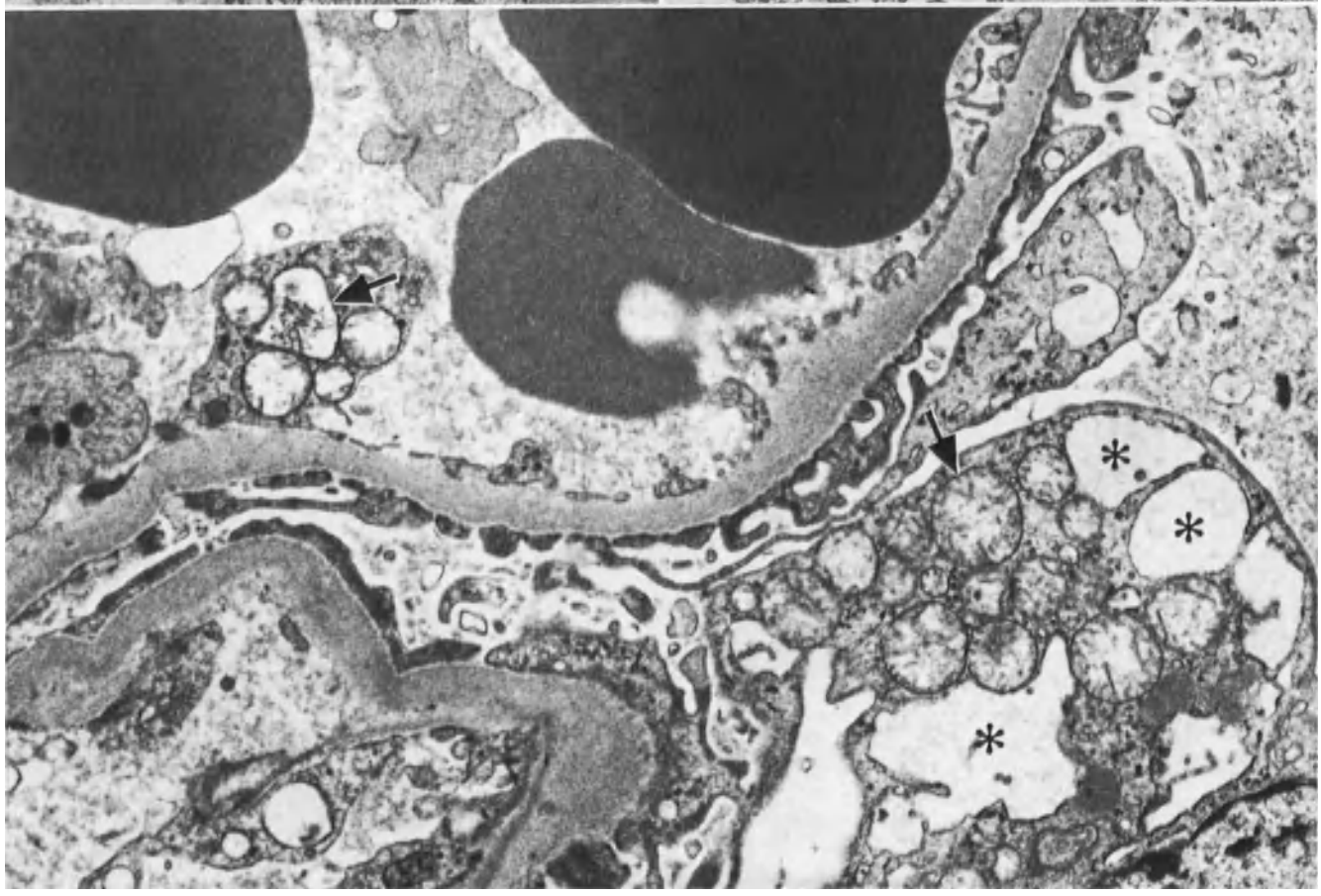

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# 28. Malformations of the Kidney

In contrast to the relatively frequent occurrence of renal malformation at autopsy (e.g., cysts) analogous findings are rare in biopsy. When they are present, however, they can give rise to great diagnostic difficulty.

## Primary Hypoplasia

Primary (genuine) hypoplasia which is manifested by a reduction of the number of papillae cannot, of course, be diagnosed in biopsy. It is extremely rare.

## Secondary Hypoplasia

Secondary hypoplasia, also considered as arrest of kidney development in early childhood PN, was present radiologically in 4% of 800 children suffering from infection of the urinary bladder [982] which was present three times more frequently in girls than in boys.
We are of the opinion that these kidneys always show PN changes and demonstrate a few hypogenetic—or at least underdeveloped—fetal nephrons. The change can also be produced experimentally [8].

◁ **Fig. 27.6.** Same case as in Figure 27.5. Completely dedifferentiated distal tubular epithelium shows severe cystoid widening of basal labyrinth (*) and highly swollen cytoplasm. Female, 65 years. EM (×7800)

**Fig. 27.7.** Same case as in Figure 25.5. There is extensive podocytic foot process fusion (→) as well as swelling and occasional ballooning (*) of endothelium. Female, 65 years. EM (×11,600)

**Fig. 27.8.** Same case as in Figure 25.5. There is severe swelling of mitochondria—with occasional loss of cristae and matrix—in podocytes and endothelium (→). Podocytic vacuolar degeneration is also present (*). Female, 65 years. EM (×13,000)

## Dysplasia

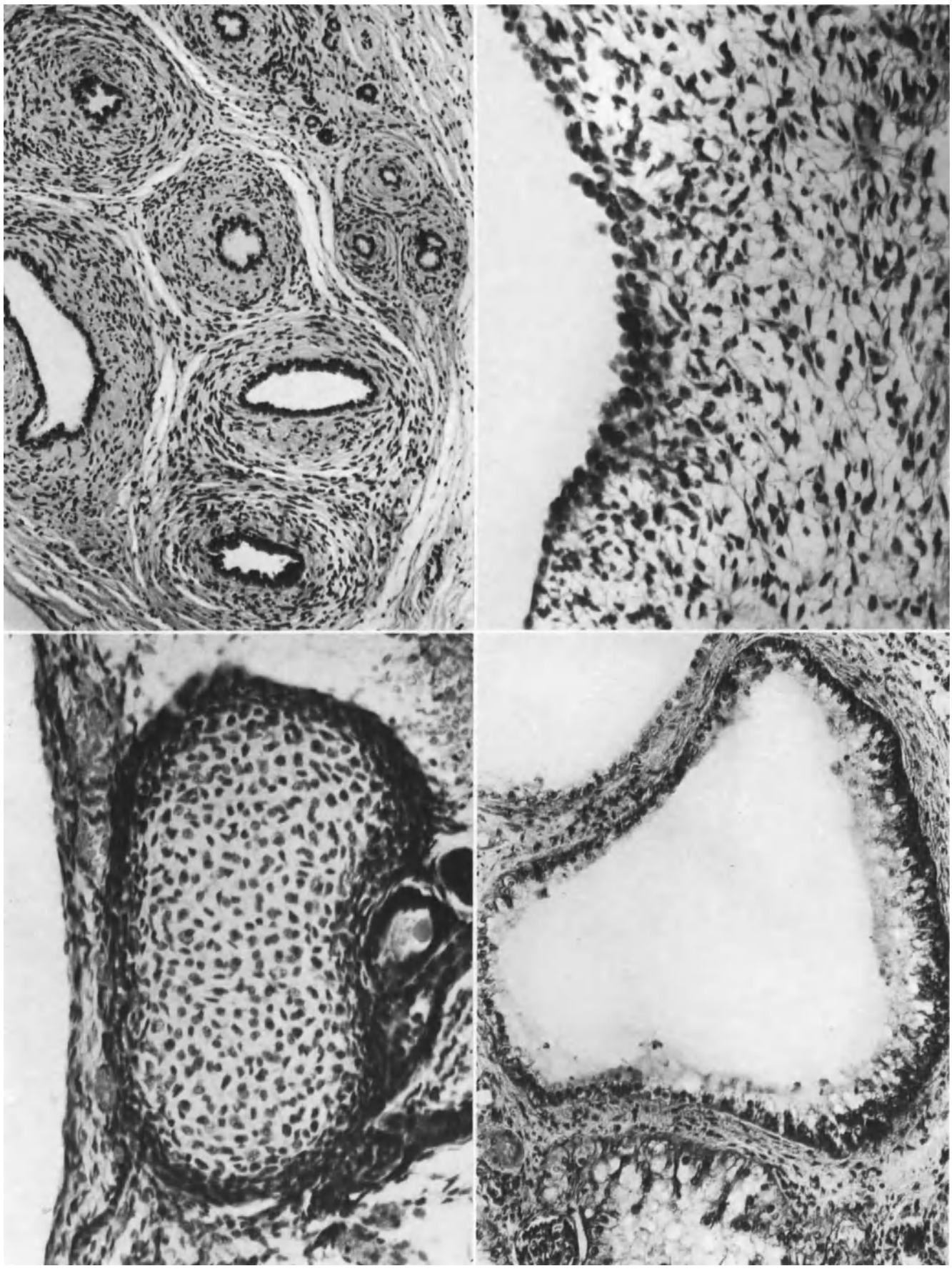
In dysplasia, which arises by faulty inductive action of the ureter on metanephrogenic tissue, primitive glandular tubules with a prismatic epithelial lining are surrounded by a concentrically layered connective tissue interspersed with smooth muscle cells. These changes are termed "ureteral buds". They were present in 0.15% of general autopsies and in 3.7% of children's autopsies up to the age of 3 months [1298].
Three forms of dysplasia are recognized:

1. The total compact form, consisting of a malformed dwarf-like kidney weighing only a few grams, which is probably never encountered in biopsy.
2. The total cystic form, in which the tubules are highly cystically widened. It can be differentiated from other cystic kidneys by the occurrence of foci with the typical circular arrangement of connective tissue elements with interspersed smooth muscle cells (Figs. 28.1, 28.2).
3. The partial form, in which dysplastic foci are usually arranged in sectors with or without cyst formation (Fig. 5.13).

Dysplasia is of significance in that secondary pyelonephritis arises relatively frequently. Moreover, the contralateral kidney is also dysplastic in 3% of the cases and even agenic in 16% [1298].
Hypertension occurs only when dysplasia is complicated by severe pyelonephritis [1298, 1791]. It is also important to note that 57% of children with dysplasia evidence other malformations of ureteral ostia, bladder, colliculus seminalis or urethra [1298].
Dysplastic foci contain cartilage in one-third to one-fourth of the cases (Fig. 28.3). We have never encountered foci of cartilage in completely unchanged kidneys (contra: [1601]).

## Kidney Cysts and Cystic Kidneys
[139, 1224, 1791]

Although needle biopsy is hardly ever used in the presence of diagnosed cystic renal disease, it now and again



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is a chance finding which may result in considerable difficulties in interpretation.

## Nosology

Our nosology for cystic renal changes is listed below:

1. Bilateral polycystic renal change.
   a) Adult form
   b) Childhood form: very rarely developing from 1.c [1393]; often with congenital cystic liver fibrosis with ascites, splenomegaly, and esophageal varices [139, 1547).
   c) Neonatal form (not to be confused with 4.a or 4.b).
2. Cystic dysplasia, partial or total (see p. 547).
3. Bilateral, multicystic kidneys (benign cystic nephroma: [139]; cystadenoma: [1547]). Also observed in tuberous brain sclerosis (Fig. 28.4; [1393, 389]). In our opinion, this entity is identical to cystic dysplasia.
4. Medullary cystic kidney.
   a) Pure medullary (papillary) cystic kidney = papillary sponge kidney [239] (Fig. 28.5) may be accompanied by leiomyomatosis and focal-sclerosing glomerulopathy [949].
   b) Multiple cysts of the corticomedullary junction = medullary cystic kidney = cystic degeneration of medullary-cortical junction = nephronophthisis (see p. 478).
5. Solitary or multiple renal cysts in an otherwise unchanged kidney.
6. Solitary or multiple (acquired) kidney cysts.
   a) Adult form: in severely contracted kidneys.
   b) Childhood form: subcapsular cysts as a consequence of urethral obstruction.
7. Dermoid cysts.

◁ **Fig. 28.1.** Dysplastic focus in renal cortex (associated with pyelonephritis). Fetal tubules evidence a cylindrical epithelium, poor in cytoplasm, which is surrounded by a ring of myocytes. Male, 8 years. HE (×150)

**Fig. 28.2.** Part of a cyst in cystic dysplasia. Epithelium is very much flattened and poor in cytoplasm. Under the epithelium, a mesenchymal tissue is found rich in cells and intercellular substance which appears clear in the preparation. Male, 4 months. HE (×290)

**Fig. 28.3.** Isolated focus of hyaline cartilage (a sign of dysplasia) in kidney of a 4-year-old boy with pyelonephritis. PAS (×316)

**Fig. 28.4.** Renal cyst in tuberous sclerosis. Note strikingly tall cylindrical epithelium lining the cyst. There are no muscle cells surrounding the cyst; this is a diagnostic criterion against dysplasia. Newborn male. HE (×100)

## Clinical Findings and Incidence

Bilateral polycystic kidney disease was present in 2.3% of our autopsy series.

In 40% of the cases, bilateral polycystic renal changes are manifested by lumbar or abdominal pain and by frequently relapsing hematuria [655]. Of our cases, 52% died in uremia, and hypertension was present in 50% (8.4%: [655]; see also [1791]).

Page 550

**Fig. 28.5.** Papillary sponge kidney associated with nephrolithiasis. Renal cortex and outer medulla are normal. Masses of densely packed cysts are present in papilla. Male, 46 years. HE (×6)

**Fig. 28.6.** Cystic kidney with acute interstitial nephritis (*). Tubular epithelium is flattened. A large cyst (→) is seen filled with phagocytes and lymphocytes. Stroma evidences fibroblastic proliferation. HE (×110)

**Fig. 28.7.** Kidney cyst with a highly sclerosed wall (▷) under which a loosely organized granulation tissue with numerous hemosiderin-containing phagocytes (→) can be recognized. Center of cyst is occupied by thin crystal lacunae (→) and a giant cell-containing granulation tissue as the result of hemorrhage into cyst. Female, 63 years. HE (×140)

**Fig. 28.8.** Cholesteatoma of the kidney. Patient underwent surgery because of suspicion of tumor. Dermoid cyst is lined with keratinizing squamous epithelium. Female, 32 years. HE (×150)

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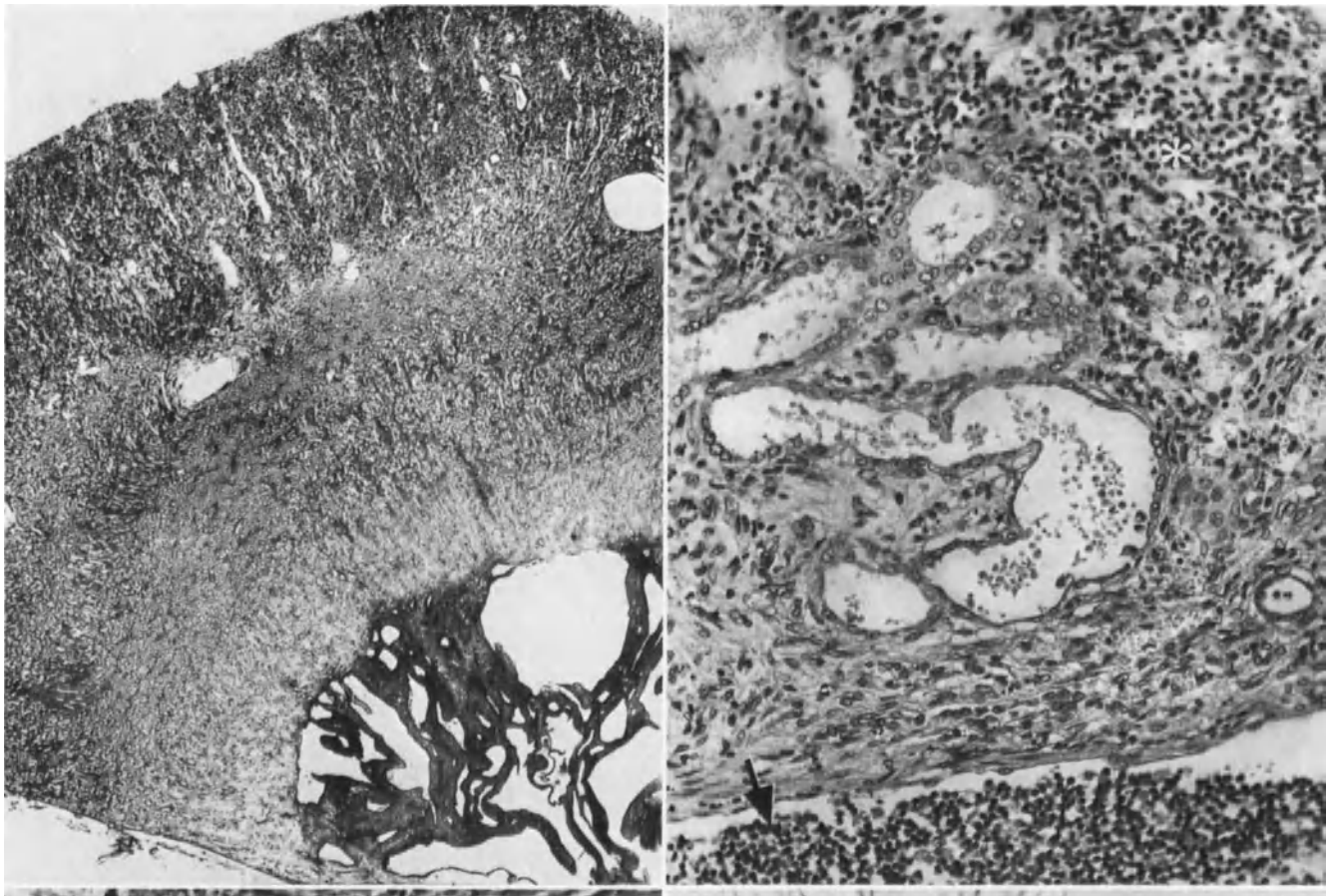
**Fig. 28.9.** Renal cyst, probably secondary in a case of chronic pyelonephritis. Cyst contains granular material (*) and epithelial lining of cyst is very much flattened. A dense, inflammatory infiltrate is present in surrounding area. Remnants of a disintegrated tubule (→). Male 37 years. EM (×1850)

**Fig. 28.10.** Secondary formation of concrements in adult-type of congenital cystic kidney with uremia. Autopsy case (published [1791]). Female, 58 years. HE (×28)

**Fig. 28.11.** Multilocular unilateral cystic kidney. Epithelium lining cyst is usually missing (possibly due to inappropriate handling of nephrectomy specimen). Stroma consists of mesenchymal tissue. Female, 45 years. HE (×150)

**Fig. 28.12.** Thick fibrous wall (*) of a renal cyst thought to be of congenital origin. Overlying renal tissue is extremely atrophic and evidences glomerular obsolescence (*G*) and almost complete obliteration of its arteries and arterioles (*A*). Note circular strips (→) consisting of smooth muscle. Inflammatory infiltrates are present in interstitium. Male, 34 years. HE (×150)



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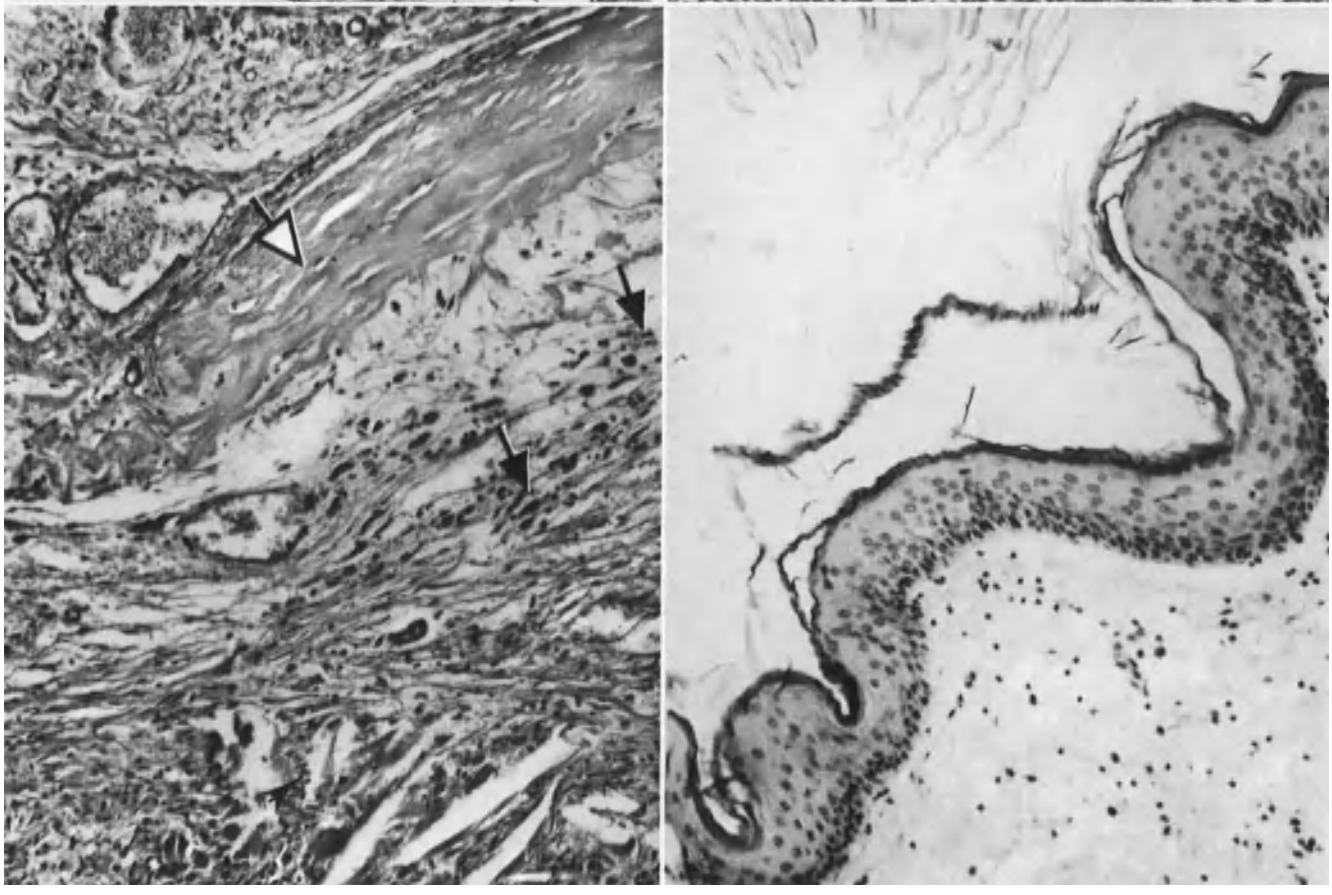

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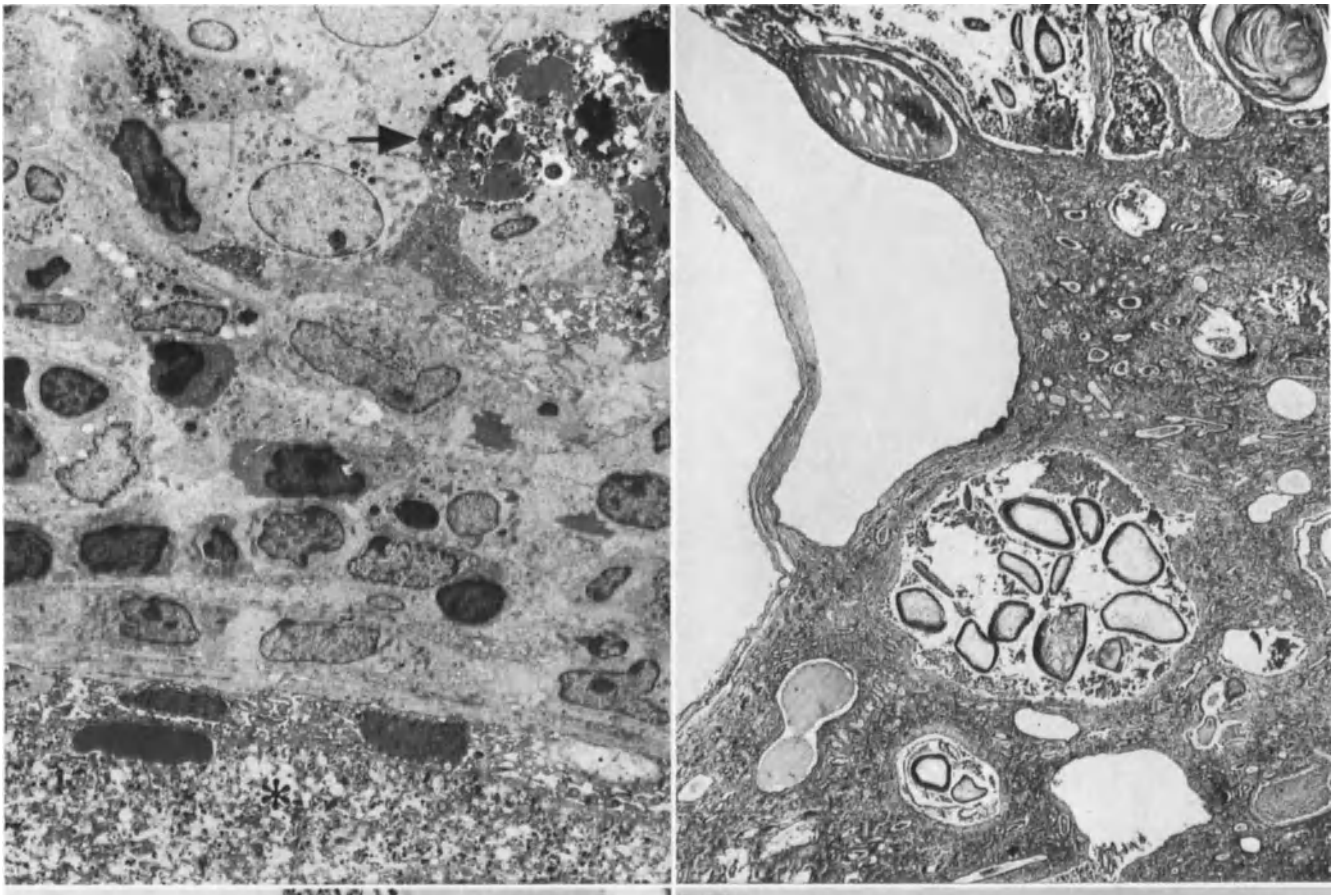

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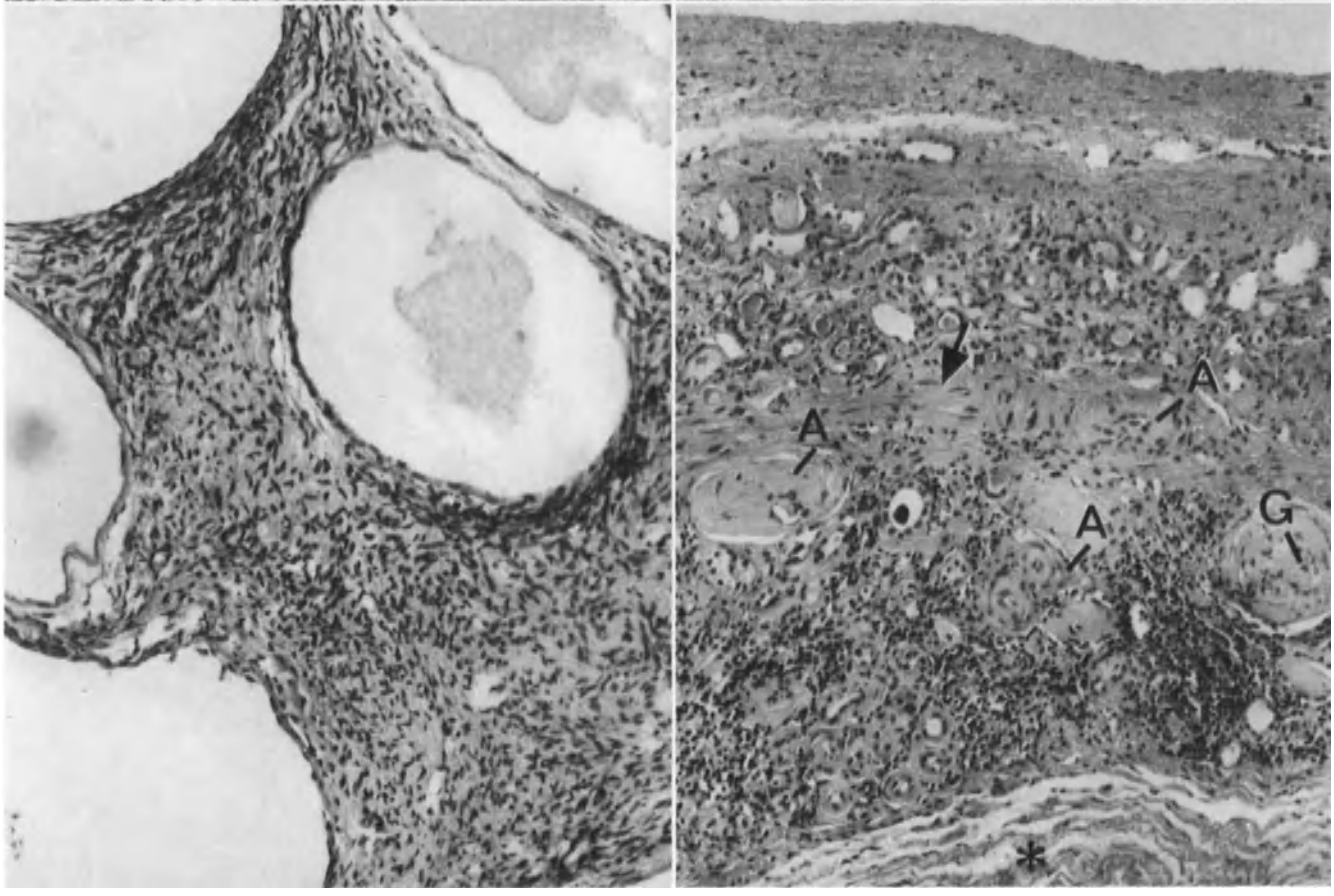


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### Microscopic Findings

A severe chronic pyelonephritis and pyonephrosis were present in only 1 out of 79 of our cases, whereas scattered, small pyelonephritic foci and chronic nondestructive interstitial nephritis of varying severity were a common finding. Acute renal failure, which was present in about one-sixth of our cases, was usually attributable to acute nondestructive interstitial nephritis (Fig. 28.6; [1791]). In some cases, post-traumatic bleeding in cystic kidneys can lead to acute renal insufficiency [655, 1791]. Bleeding into individual cysts may occur in the polycystic variety as well as in all other types of renal cysts. The breakdown of the blood masses leads to formation of cholesterol crystals, calcifications, and often to formation of a slight pad of granulation tissue (Fig. 28.7). This picture may cause unresolvable confusion with respect to dermoid cysts clothed with squamous epithelium, so-called cholesteatomas (Fig. 28.8). With EM, we always found secondary cysts (acquired during life) to be rich in debris (Fig. 28.9); which was always absent in primary cysts (congenital).

Lithiasis has been reported in 4% of bilateral cystic renal changes [655]. Concrements in individual cysts are, on the other hand, rarely encountered (Fig. 28.10; [1791]).

Malignancies do not appear to occur more frequently in kidneys with cystic disease than in those without [655, 1791]. In one case in our series of bilateral polycystic kidney disease, we saw cavitary tuberculosis associated with renal cell carcinoma.

### Differential Diagnosis

Diagnosis of dysplasia is possible due to the presence of poorly differentiated mesenchyma around the cystic spaces and the occurrence of undifferentiated epithelial cells (Fig. 28.11).

Severe atrophy of parenchyma surrounding large cysts is frequently encountered which occasionally cannot be differentiated from hydronephrotic atrophy in needle biopsy if cystic elements are absent. Demonstration of smooth muscle strands is not helpful since they may occur in both conditions (Fig. 28.12).

We feel that it is not possible to differentiate primary solitary cysts from those arising secondarily in severely contracted kidneys.

# 29. Kidney Tumors

[920a, 1791]

Although needle biopsy is hardly ever used in the presence of kidney tumors or when such tumors are strongly suspected, renal tumors nevertheless turn up now and again as a chance finding in renal biopsy material (0.25% of biopsies: Z).

*Nosology:* see Table 29.1.

## Mesenchymal Tumors

### 1. Benign and of Questionable Malignancy

#### Medullary Fibroma

This tumor is always benign and very sharply delimited. Due to its location in the papilla, it is hardly to be expected in needle biopsy material. This tumor is occasionally designated as renomedullary "interstitial cell tumor". Due to its content of lipid droplets, it is thought to arise from interstitial cells which secrete prostaglandin [942, 943], a substance suspected of reducing blood pressure [1583a].

#### Lymphangioma and Hemangioma

The morphology of these two tumors is the same in the kidney as in other organs and, accordingly, presents no diagnostic difficulties.

#### Hemangiopericytoma

This is a rare tumor [978] characterized by its richness in blood vessels and by the mantle-like, perivascular arrangement of small, polymorphic stellate cells.
It strongly tends to local recurrence and is, therefore, to be considered as a tumor of questionable malignancy [978]. Some investigators even consider this neoplasm as belonging to the sarcomas [465].
The clinical manifestation of hypoglycemia [978], which can lead to death in hypoglycemic coma [465], has been reported as a consequence of this tumor.

The absence of leiomyomatous cells and of lipocytes permits differentiation from periarterial hamartoma. Differential diagnosis with respect to the renin-secreting JGA-cell tumor is possible not only from the clinical picture, but also from the microscopic one by the absence of intracellular granules and mast cells as well as from the more pronouncedly developed cytoplasm and the stellate cell form evidenced in hemangiopericytoma.

#### Renin-Secreting JGA-Cell Tumor

This is an extremely rare tumor (7 cases in the literature: [203]) described in 13–37 year old subjects. It is accompanied by hypertension, increased sodium excretion, and decreased serum potassium [302].
In LM, the tumor cells appear compact and reminiscent of myocytes; in EM, they are seen to contain oval or rhomboid granules [302, 1265, 1346] in which renin can

Table 29.1

| | |
|---|---|
| *I.* | *Mesenchymal Tumors* |
| | a) Benign and of Questionable Malignancy |
| | Medullary Fibroma |
| | Lymphangioma, Hemangioma |
| | Hemangiopericytoma |
| | Renin-Secreting JGA Cell Tumor |
| | Para-arterial Corticomedullary Hamartoma (Leiomyoangiolipoma) |
| | b) Malignant Tumors (Sarcomas) |
| | Addendum: Renal Capsule Sarcoma |
| *II.* | *Epithelial Tumors* |
| | a) Benign and of Questionable Malignancy |
| | Adenoma |
| | Benign Grawitz Tumor |
| | Genuine Hypernephroma |
| | b) Malignant |
| | Carcinomas |
| | Addendum: Renal Pelvic Carcinoma |
| *III.* | *Mixed Tumors* |
| *IV.* | *Metastasis of the Kidney* |

be demonstrated with IF [302, 1346]. Marked infiltration of the tumor with mast cells is supposed to be a characteristic feature.
The tumor is not identical with hemangiopericytoma. The growth is benign and can, morphologically, be differentiated from other tumors such as oat-cell bronchial carcinoma with paraneoplastic renin secretion [669].

#### Para-Arterial Corticomedullary Hamartoma (Leiomyoangiolipoma)

This tumor may pose great diagnostic difficulties, even when dealing with material obtained from surgery. It cannot be fundamentally differentiated from leiomyoangiolipoma or from renal tumors associated with tuberous brain sclerosis [1049].
When even the smallest of these tumors are considered, they occur in about 5% of our autopsy material of which 80% are in women. It is difficult to estimate the associated incidence of tuberous brain sclerosis in these cases since it appears that even by careful clinical examination, only rudimentary signs of tuberous sclerosis may be present [788].
The tumors are usually solitary and unilateral, but may occur multiply and bilaterally [464]. As noticed in two of our own cases, the tumor may manifest itself clinically by acute, vigorous bleeding [26, 643, 1670].
Histologically, these tumors are characterized by spindle-shaped cells, arranged irregularly and sometimes in whorls, which often reveal the presence of more or less mature leiomyocytes. Furthermore, nests of mature lipocytes and extremely numerous capillaries and, above all, capillary buds (Fig. 29.1) are found.
In serial sections, the immediate vicinity of the tumor to arteries can almost always be demonstrated. The entire picture is relatively polymorphic. Nuclear polymorphism is clearly present; mitoses, however, are absent. Nor is there any perifocal inflammation even though the tumor tissue is not sharply demarcated.
Despite the rather alarming overall picture, the tumor is benign; malignant degeneration has been reported as extremely rare [920a] and may, in fact, be due to faulty interpretation (see also [1049]). However, there is no doubt that the tumor does demonstrate local infiltrative growth and a tendency to recurrence.

### 2. Malignant Tumors (Sarcomas)

Kidney sarcomas are extremely rare and constitute only 1.1% of all renal tumors [465]. The prognosis for all forms is very poor.
Liposarcoma can easily be distinguished from clear-cell renal carcinoma by its nonepithelial structure and by the presence of numerous lipoblasts with densely packed small lipid droplets (so-called morula cells).
The relatively frequent leiomyosarcoma is thought to originate from renal vessels or from the pelvic wall [98]. On the other hand, the extremely rare rhadomyosarcoma and the liposarcoma are suspected of being of dysontogenetic origin [465].
Locally originating malignant lymphomas are usually reticulum cell sarcomas [1443, 1506].
Plasmocytoma [462, 920a, 1260, 1791] is extremely rare.

### 3. Renal Capsule Sarcoma

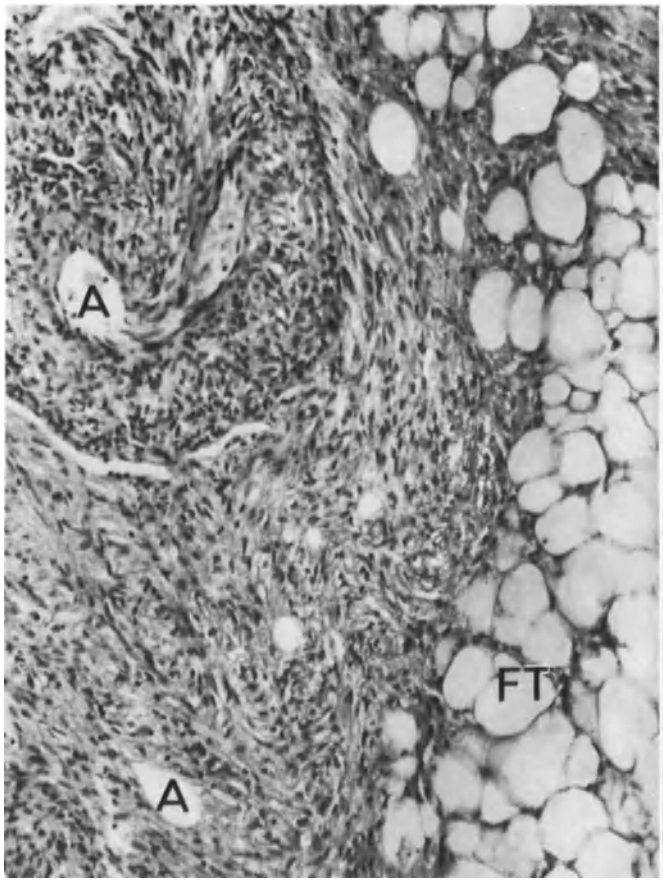
Since localization in needle biopsy is usually difficult, sarcomas of the renal capsule must also be considered in the presence of malignant mesenchymal tissue. Such tumors do not differ from other soft-tissue tumors [1791].

## Epithelial Tumors

### 1. Benign and of Questionable Malignancy

#### Adenoma

Adenoma is by far the most frequent in the group of benign epithelial tumors. Adenomas occur with increased incidence in the aged and chiefly in the region of scars. As demonstrated experimentally in the rat [1786a], this tumor arises from the tubules.
They show a papillary, cystoid (Fig. 29.2), tubular or trabecular structure. They usually consist of small cubic to low cylindrical cells (poor in cytoplasm) with uniform nuclei which are quite rich in chromatin (so-called basophilic adenoma; Figs. 29.2, 29.3). Entire tumors, parts thereof or individual tumor cells may evidence oncocytic differentiation, exhibiting a starkly granular and pronouncedly eosinophilic cytoplasm in LM (Fig. 29.4). In EM, their high content of very large mitochondria with plump matrix inclusions is typical [153, 310]. Impairment of phosphorilization is thought to be the cause of oncocytic transformation [153].
Adenoma cells tend to fatty degeneration, but actual tumor foam cells are rare; however, subepithelial clusters of histiocytic foam cells are frequently encountered. Epithelial cells are always surrounded by a BM which is absent around the histiocytic foam cells [310]. Occasionally the cells demonstrate considerable iron storage [1317].

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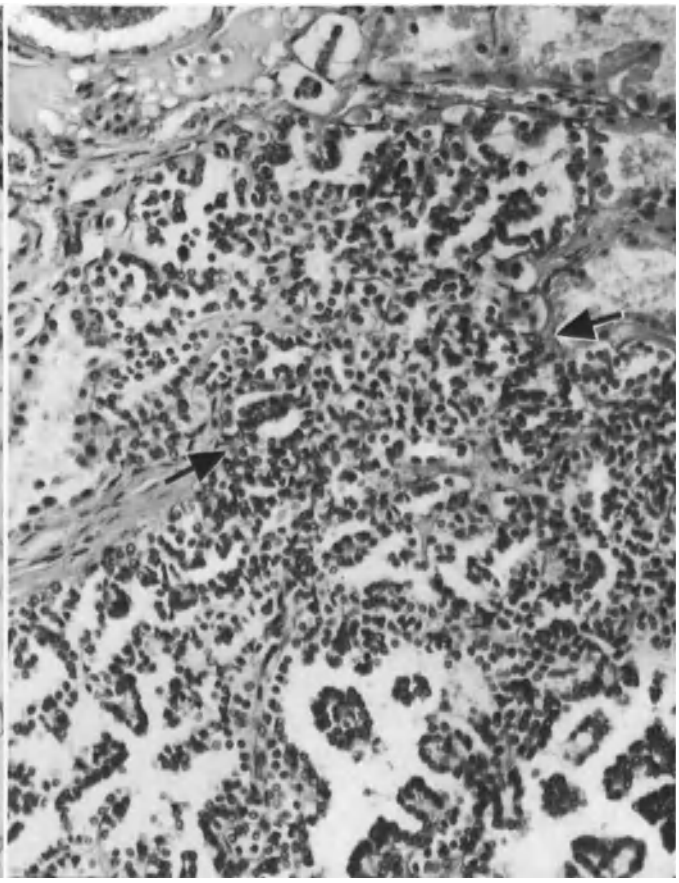

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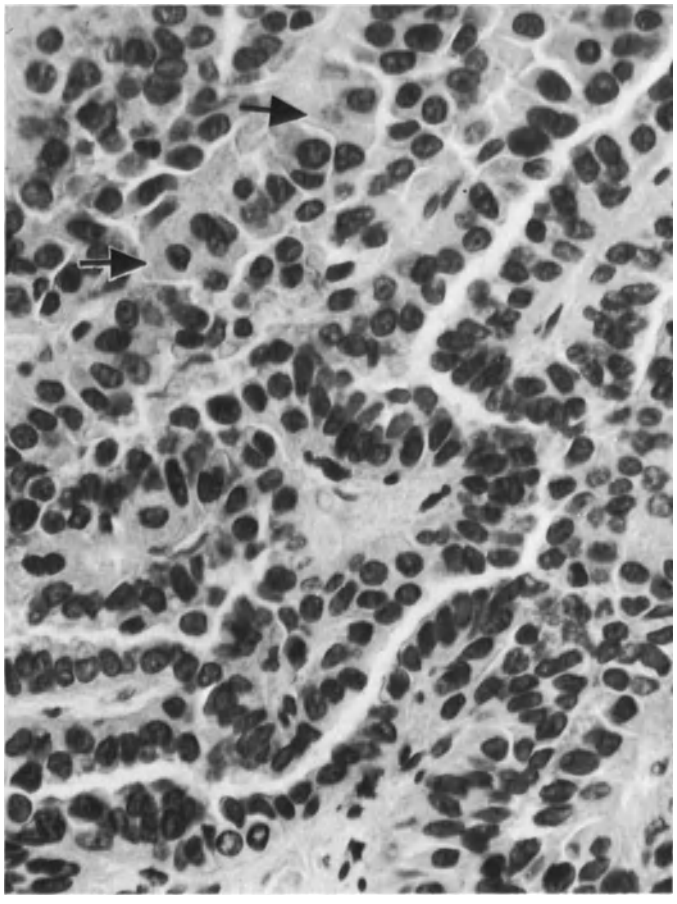

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**Fig. 29.1.** Para-arterial hamartoma in renal cortex. Spindly tumor cells are assembled around two arteries (*A*) whose walls they occasionally infiltrate. Fatty tissue (*FT*). HE (×100)

**Fig. 29.2.** Basophilic, partially papillary adenoma of renal cortex which has penetrated its own capsule (→←). Tumor-adjacent tubules are not destroyed, but only replaced. Nuclear polymorphism of tumor cells is not present. Male, 77 years. HE (×100)

**Fig. 29.3.** Part of a 16×13×13-cm-large papillary adenoma of renal cortex. Nuclei are, in general, uniform but do show slight variations in size. Isolated oncocytes (→) with abundant cytoplasm, are present. Female, 67 years. HE (×450)

In rare cases, adenomas become very large (head-sized) and cause clinical symptoms due to pressure [153]. In one patient with such a large tumor who was receiving anticoagulantia, we saw massive bleeding with rupture of the kidney and kidney capsule. Calcification and psammoma body formation only develop in very large adenomas.

The most important diagnostic problem of renal adenoma is related to its tendency to infiltrate into the surroundings (small tumors) without destruction of parenchyma and into the tumor capsule (large tumors: Fig. 29.2).

Since nuclear polymorphism – thought to be of degenerative character – is not rare, attention must be given to rule out malignant transformation. It is noted that the foam cells cited should not be confused with cells of a clear-cell renal carcinoma. Numerous mitoses (including pathologic types), multilayered cell clusters in tubular structured areas (possibly missed in flat sections) as well as destructive peripheral growth accompanied by perifocal inflammation are clearly indicative of malignant transformation (Fig. 29.5). In those cases in which the malignant or benign status of the tumor cannot be ascertained, we use the term "questionable benign adenoma" [920a].

Malignant transformation to granular cell renal carcinoma is rare despite the basically precancerous papillary structure which is more frequent in small than in large tumors. Classification of all adenomas as differentiated carcinomas [119] is not acceptable – nor is it for large adenomas – due to their biological behavior. We have never encountered transformation into genuine clear-cell renal carcinoma.

**Benign Grawitz Tumor (Clear Cell Adenoma)**

The so-called benign Grawitz tumor is not well known and, moreover, highly controversial. The tumor is 1–2 cm large and consists exclusively of clear cells containing much glycogen and lipid.

It is differentiated from clear-cell renal carcinoma by the uniformity of its tissue and cells, the intactness of its capsule, and the absence of perifocal inflammation. It is agreed that the benign Grawitz tumor is closely related to clear-cell renal carcinoma of which it appears to represent a precursor.

**Genuine Hypernephroma**

The genuine hypernephroma, which is very similar to the Grawitz tumor, is extremely rare. At autopsy, it is seen, now and again, that the tumor appears to originate from subscapsular embryonic adrenal tissue. Genuine hypernephroma may be benign or malignant [920a]. Hypercorticism (eventually associated with Cushing's syndrome) is typical and essential for the diagnosis. The clinical symptomatology can be confirmed by biological examination of the tumor for hormones [1032].

The differential diagnosis with respect to the benign Grawitz tumor and clear-cell renal carcinoma is only possible with EM in which the decisive features, as in adrenal tumors, are the presence of extensive smooth endoplasmic reticulum and of mitochondria with tubular cristae [1597] which are typical for steroid-producing cells.

## 2. Renal Cell Carcinoma

Cancer of the kidney is present in about 1% of all our autopsies (Z). It constitutes 4.2% of all cancers [496]. In about 25% of the patients, the survival time is 5 years [1307] and in 15–20%, 10 years [119].

Renal cancer is twice as frequent in males as it is in females. Individuals between 55 and 85 years are mainly afflicted, but this malignancy also attacks children and even infants [48].

Malignant epithelial tumors may rarely produce erythropoietin – leading to polycythemia – and possibly gonadotropin [578]. The tumor may also cause hyperpyrexia and amyloidosis and hypercalcemia. The leading symptom is hematuria.

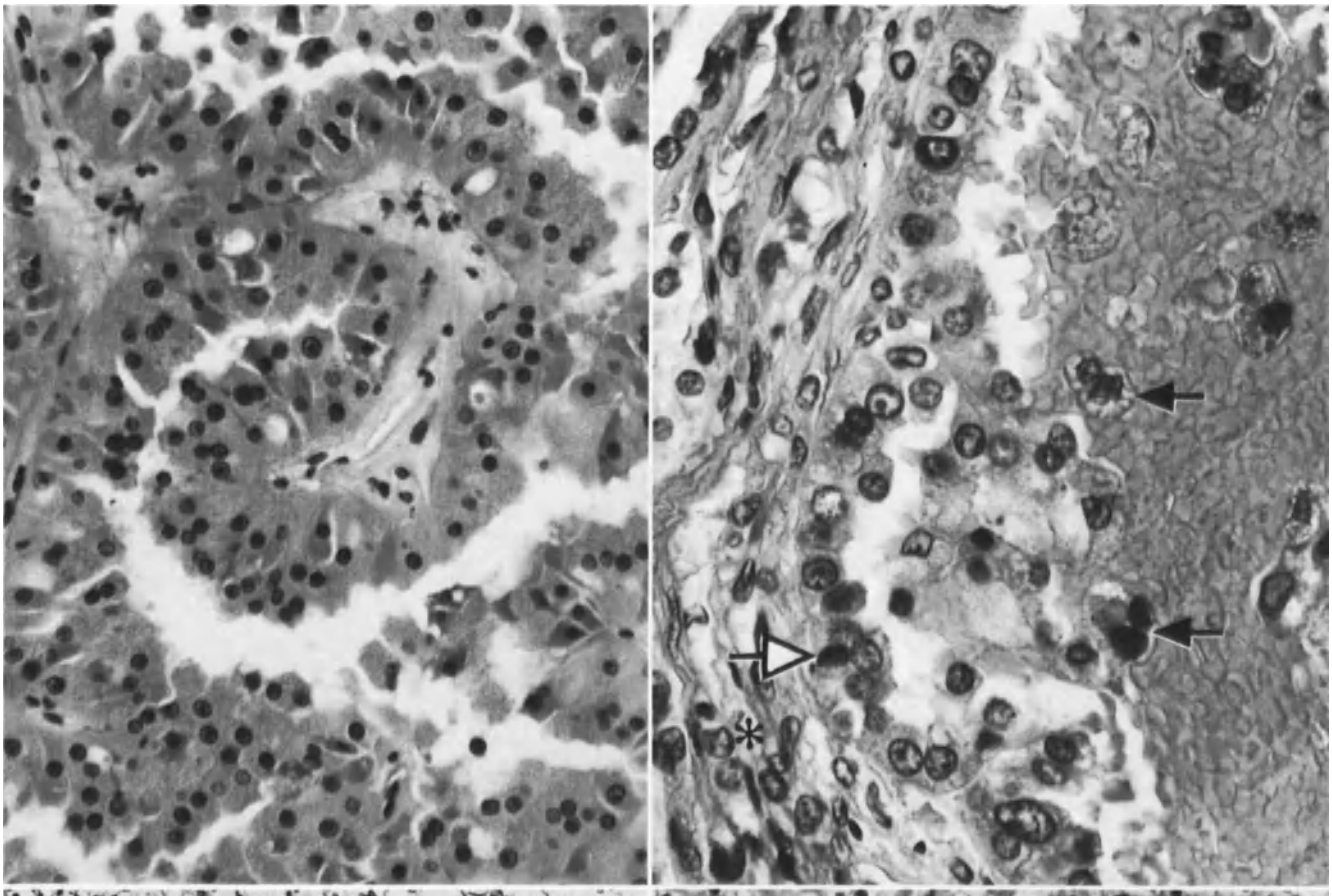
Secondary calcification of tumor necroses are of radiologic significance (4% of cases: [339]). Calcification is demonstrable histologically in 10–20% of cases [1153]. In 15 out of 15 cases, serum AB against fetorenal antigen was demonstrated [852a].

**Fig. 29.4.** Partly papillary oncocytoma of the renal cortex. Tumor ▷ cells have abundant, somewhat granular cytoplasm and are, like their nuclei, of uniform size. HE (×300)

**Fig. 29.5.** Periphery of a papilloma with malignant transformation of renal cortex in which cell and nuclear polymorphism are evident. Two multinuclear cells (→) are present in blood-containing tubular lumens. Note typical pycnomitosis (→▷) and perifocal inflammation (*). Female, 67 years. HE (×620)

**Fig. 29.6.** Part of a renal clear-cell carcinoma (*1*) showing completely uniform nuclei and trabecular arrangement of the cells. Another part of tumor (*2*) consists of polymorphic cells and nuclei with somewhat dense, granular cytoplasm. Both parts of tumor are richly supplied with capillaries. HE (×95)

**Fig. 29.7.** Part of a renal clear-cell carcinoma. Capillaries (→) are very clearly recognizable between trabecularly and tubularly arranged cells which evidence little polymorphism. Cytoplasm is mostly completely clear and cell membranes are very distinct. Nuclei are uniform in size and shape. There is practically no accompanying inflammation. Female, 20 years. HE (×220)



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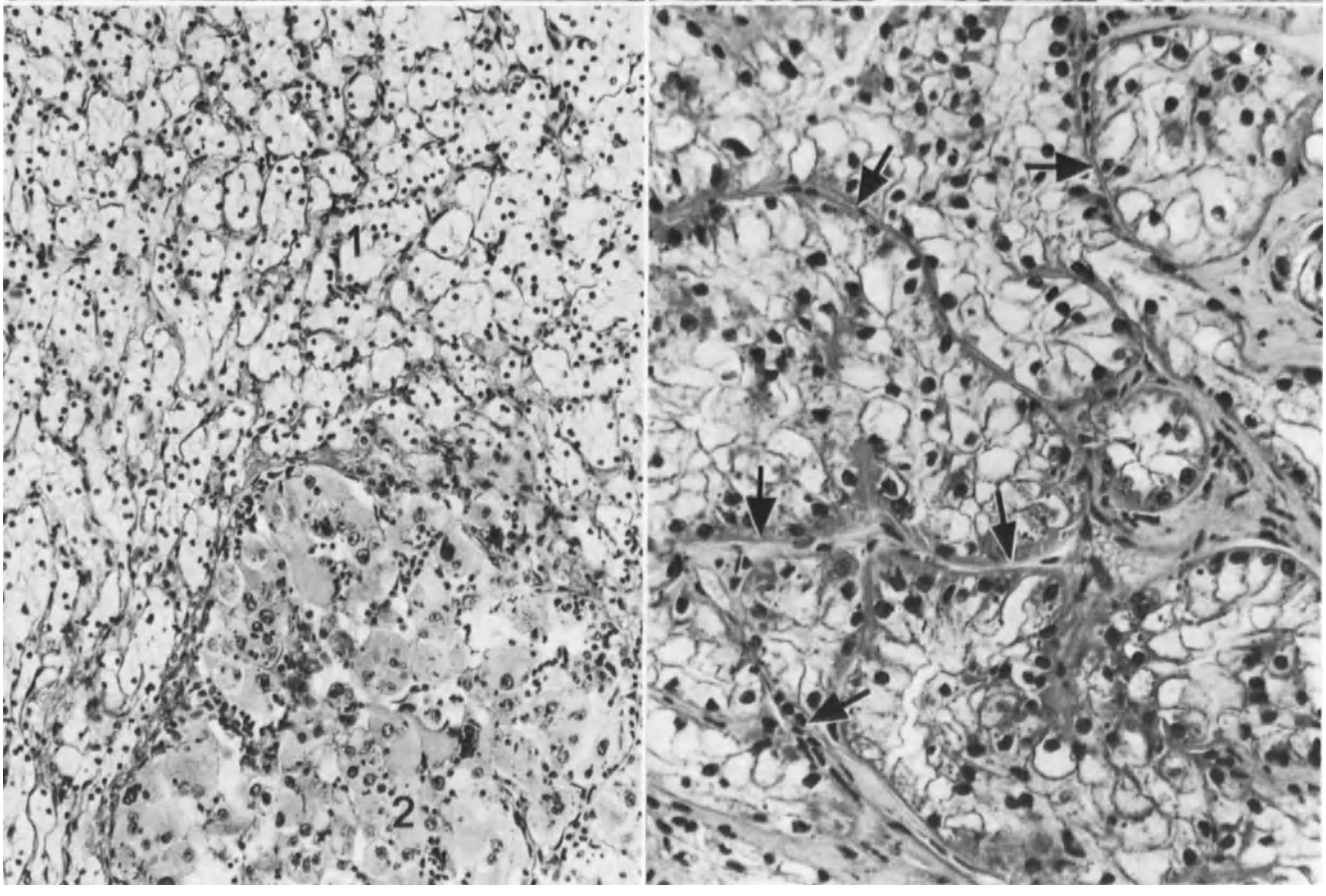


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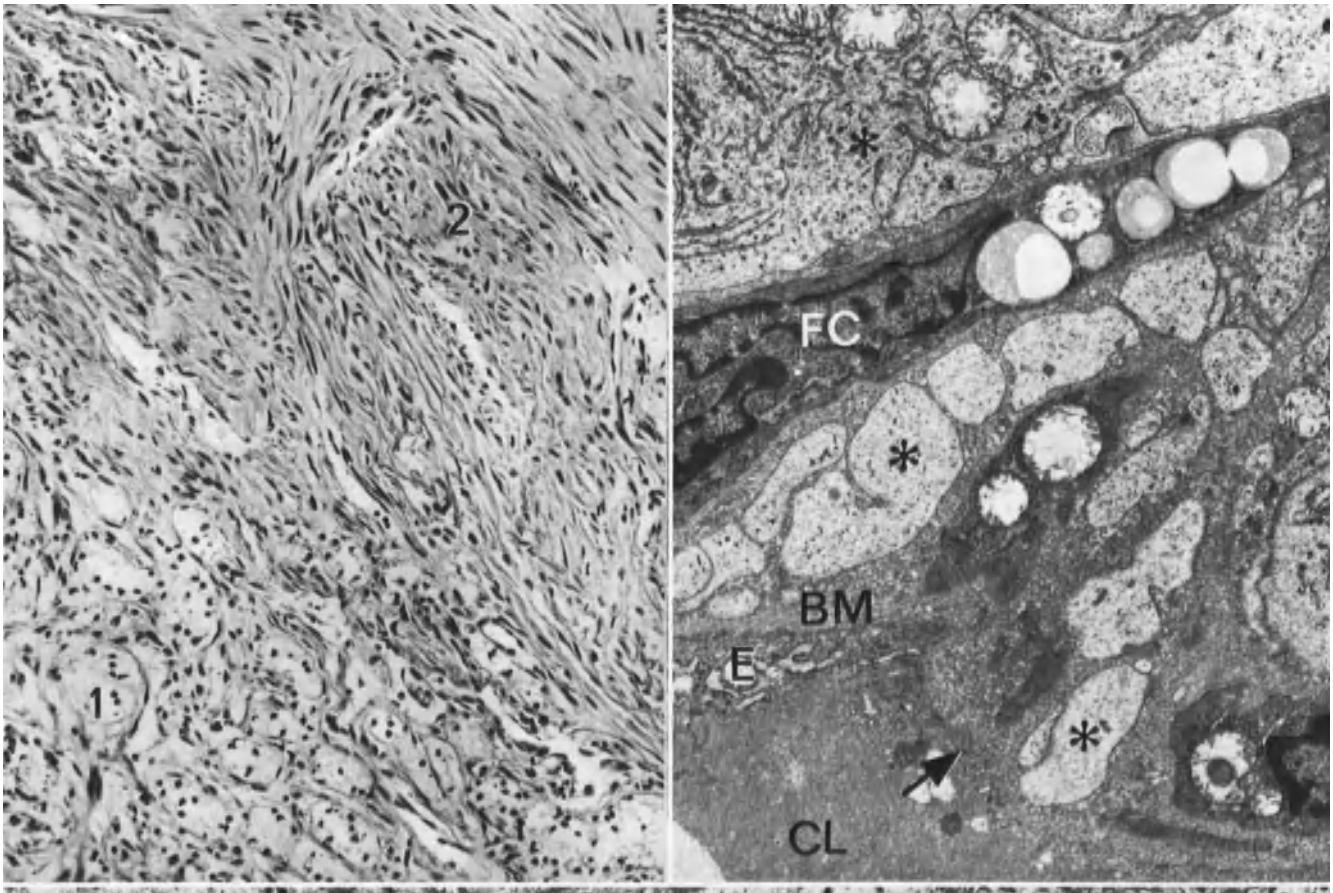


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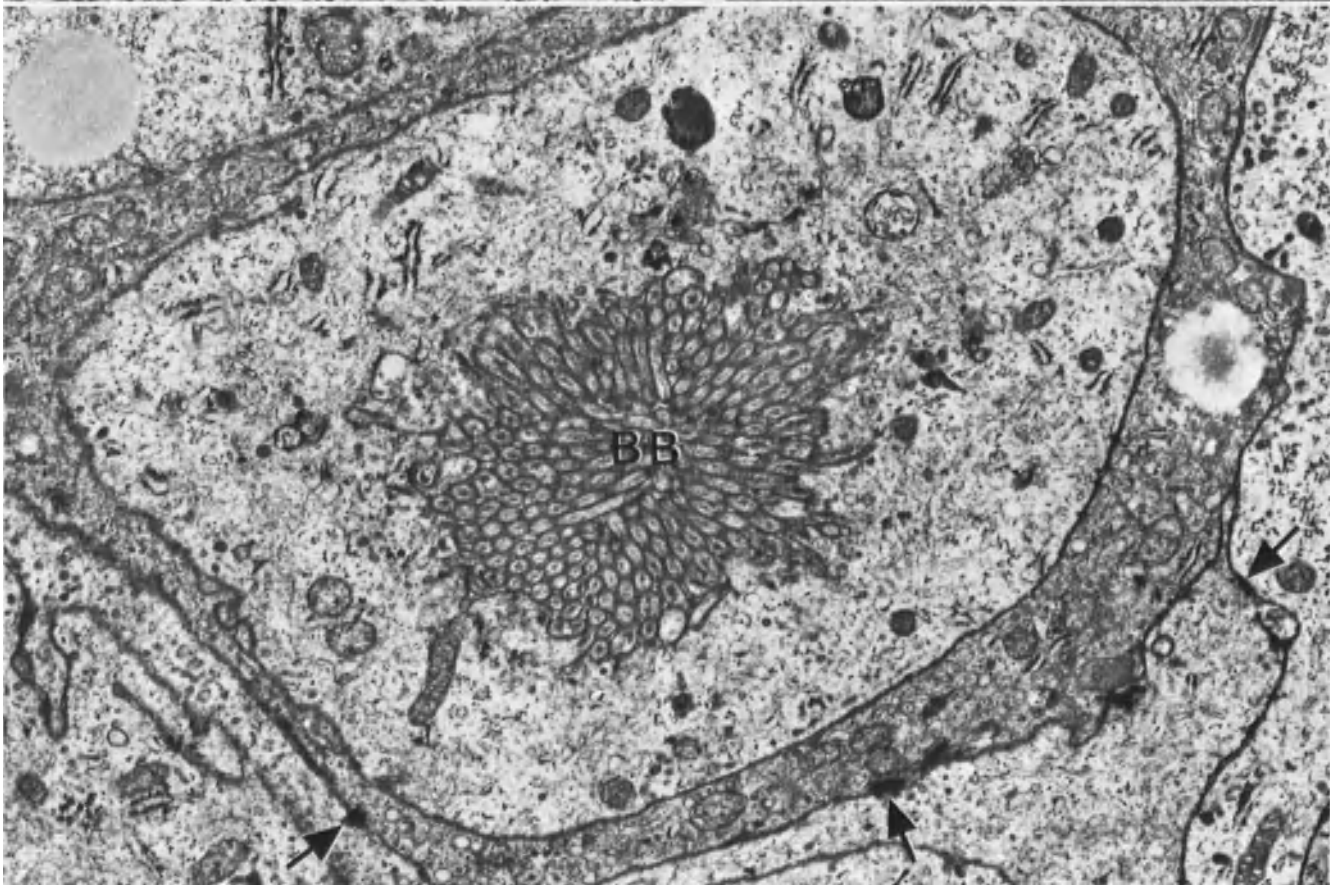


29.10

Clear-cell carcinoma (hypernephroid renal carcinoma) and granular cell carcinoma (tubular renal carcinoma) are no longer considered as different entities. The concomitant occurrence of clear cells and granular cells in the same tumor, and the absence of corresponding prestages of the tumor among the young, speak against the view of a dysontogenetic origin of the tumor as well as against differentiation between clear and granular cell types (the rare benign Grawitz tumor described occurs in older subjects). Today it is very clear that both forms demonstrate characteristics of renal tubules as seen in EM ([1597]; see below).

In LM, the cells of renal carcinoma appear solid, alveolar, trabecular (Fig. 29.6), tubular, cystic and, on occasion, slightly papillary. The cells themselves are usually cubic or polygonal and, in rare cases, cylindrical. The clear cells (Figs. 29.6, 29.7) are quite large, contain glycogen and lipids, and tend to multinucleate or mononucleate (Fig. 29.6) giant cell formation. The granular cells are strongly eosinophilic; they contain large amounts of mitochondria of various size and thereby correspond to the oncocytes occurring in adenomas (compare to Fig. 29.4).

Here and there, nests of small, polymorphic cells with scanty cytoplasm—which we consider to be dedifferentiated elements—can be recognized. They are closely related to so-called sarcomatoid, fusiform and polymorphic cells (Fig. 29.8; [463]) which we have found in 14% of our renal carcinomas [920a]. These sarcomatoid cell groups, when present in metastases or biopsy material exclusively, may present great diagnostic problems, since similar structures may be found in dedifferentiated renal pelvic carcinomas or sarcomas. Under EM, however, these sarcomatoid structures are seen to consist of epithelial elements only [1597].

All cell types may occur simultaneously. In EM, clear and granular cells evidence microvilli or remnants of brush border and glycogen granules and fat droplets (Figs. 29.10, 29.11). In clear cells, the particulate glycogen, in the form of granules measuring around 300 Å, is distributed in nests or diffusely (Fig. 29.12). Infoldings reminiscent of basal labyrinth are very typical while a high content of mitochondria is characteristic of granular cells [1331, 1597]. The ultrastructural findings by and large also confirm the proximal tubular origin of these tumors (for other opinions [1597]).

Renal cell carcinoma is very rich in vessels, and especially in capillaries. In LM, by careful search, intravascular (and especially intracapillary) tumor plugs can be found in almost every case (Fig. 29.9). The tumor tends to undergo central necrosis with extensive bleeding and secondary fibrosis or myxomatous degeneration. On occassion—and chiefly in sarcomatoid regions—osteoid formation is observed [463].

It has often been recommended that grading of renal cell carcinoma should include consideration of tubular and papillary formations (differentiation); the presence of clear and granular cells, the regularity, form and size of nuclei as well as of mitoses with the specific admonition that only the most malignant tissue should be considered [1331]. In common with other investigators [1153] we do not subscribe to these recommendations whose realization would require serial sections through the whole tumor. In biopsy and in its evaluation, the recommendations can hardly be applied. If needle biopsy reveals renal cell carcinoma, massive postbiopsy irradiation in the region of the biopsy canal is mandatory due to the possibility of having inoculated metastases.

◁ **Fig. 29.8.** Renal clear-cell carcinoma (*1*) with sarcomatoid transformation (*2*). Gradual transition from (*1*) to (*2*) is clearly evident. Male, 91 years. HE (×85)

**Fig. 29.9.** Infiltration (→) of a tumor cell (*) into a capillary lumen (*CL*). Endothelium (*E*), a probable fibrocyte (*FC*), basement membrane (*BM*). Male, 52 years. EM (×9000)

**Fig. 29.10.** Renal clear-cell carcinoma. Tumor cell depicted is reminiscent of a proximal tubular cell with its brush border (*BB*) (probably a bowl-shaped cell). Cell is free of lipids and contains only a small amount of extremely fine glycogen granules. Isolated desmosomes (→) are clearly recognizable. Male, 52 years. EM (×12,300)

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**Fig. 29.11.** Masses of lipid vacuoles in cells of a renal clear-cell carcinoma. Note newly formed BM (→). Female, 19 years. EM (×1660)

**Fig. 29.12.** Renal clear-cell carcinoma in which cells contain chiefly fine-granular glycogen in large amounts besides sparse lipid vacuoles. Note severe polymorphism and increase in size of nuclei. Female, 19 years. EM (×5100)

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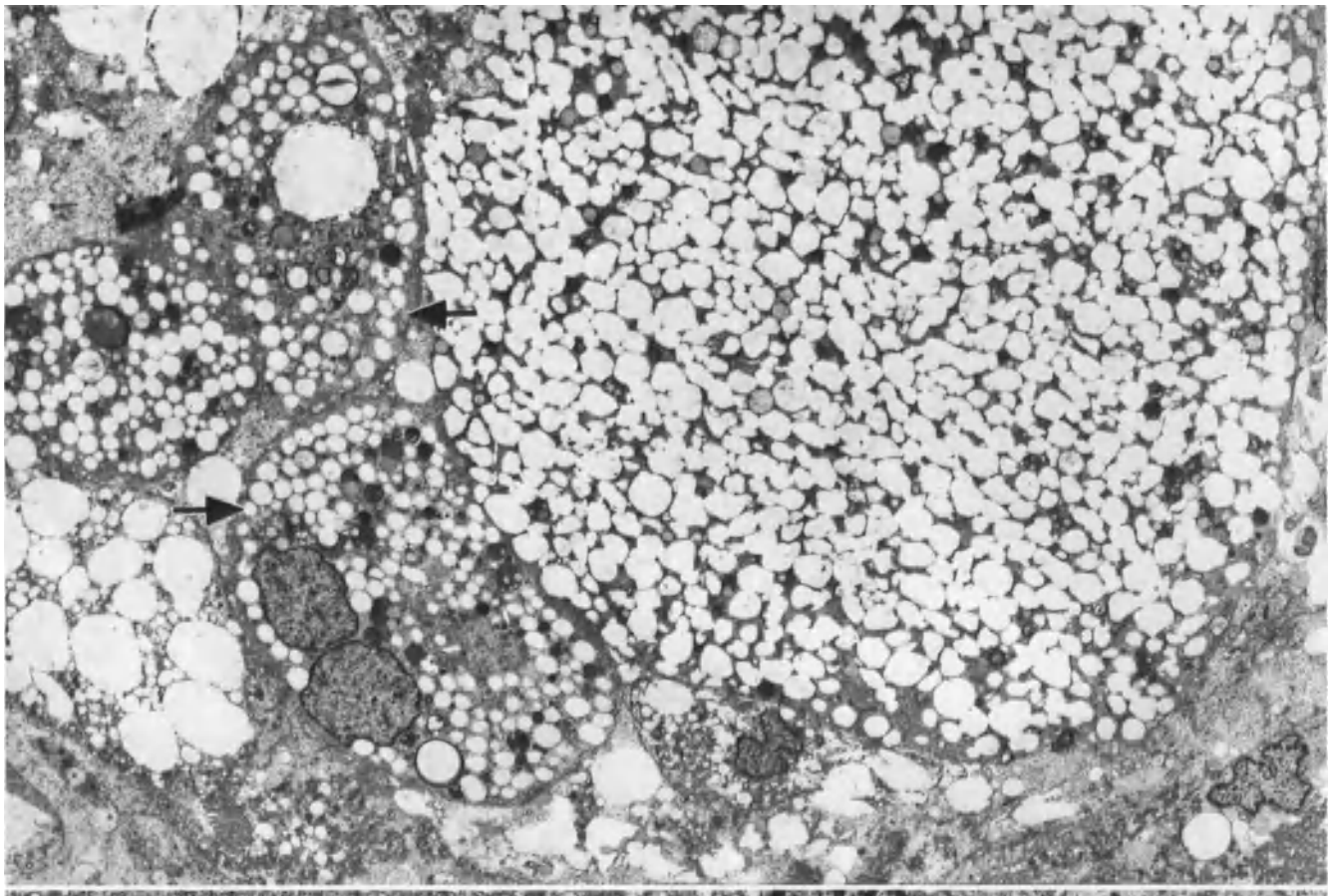
**Fig. 29.13.** Undifferentiated carcinoma of renal pelvis. Structures seen in this preparation are very reminiscent of sarcoma. There is a high degree of nuclear polymorphism and mitoses are abundant. Male, 65 years. HE (×210)

**Fig. 29.14.** Same tumor as in Figure 29.13 with typical perivascular epithelial arrangement of tumor cells. HE (×210)

**Fig. 29.15.** Same tumor as in Figure 29.13 with obvious urothelial differentiation in a peripheral tumor strand. HE (×210)

**Fig. 29.16.** Nephroblastoma. Two undifferentiated tubules are surrounded by a completely undifferentiated mesenchyma. Inset: a striated muscle fiber (a relatively rare finding). HE (×210); inset (×900)



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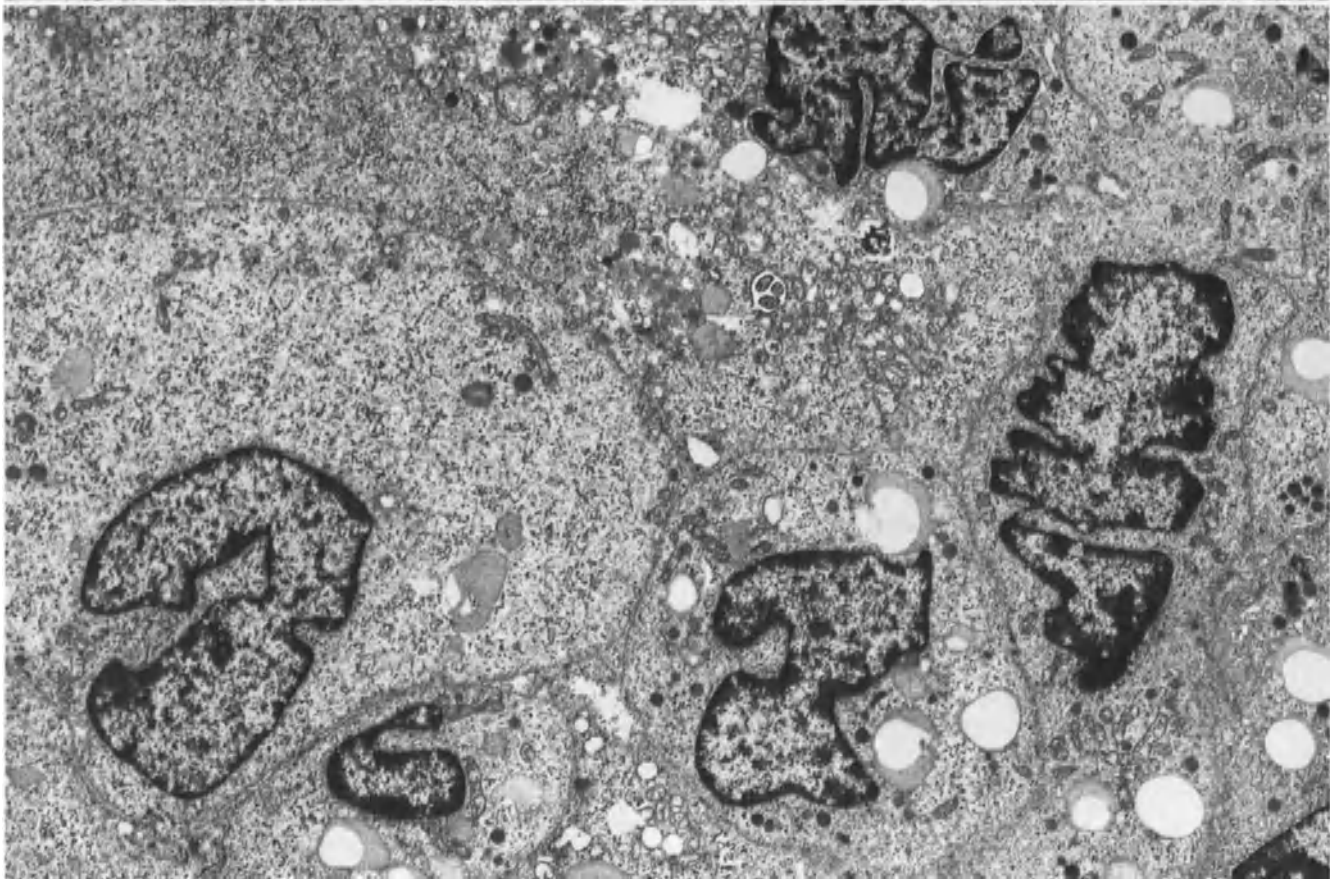

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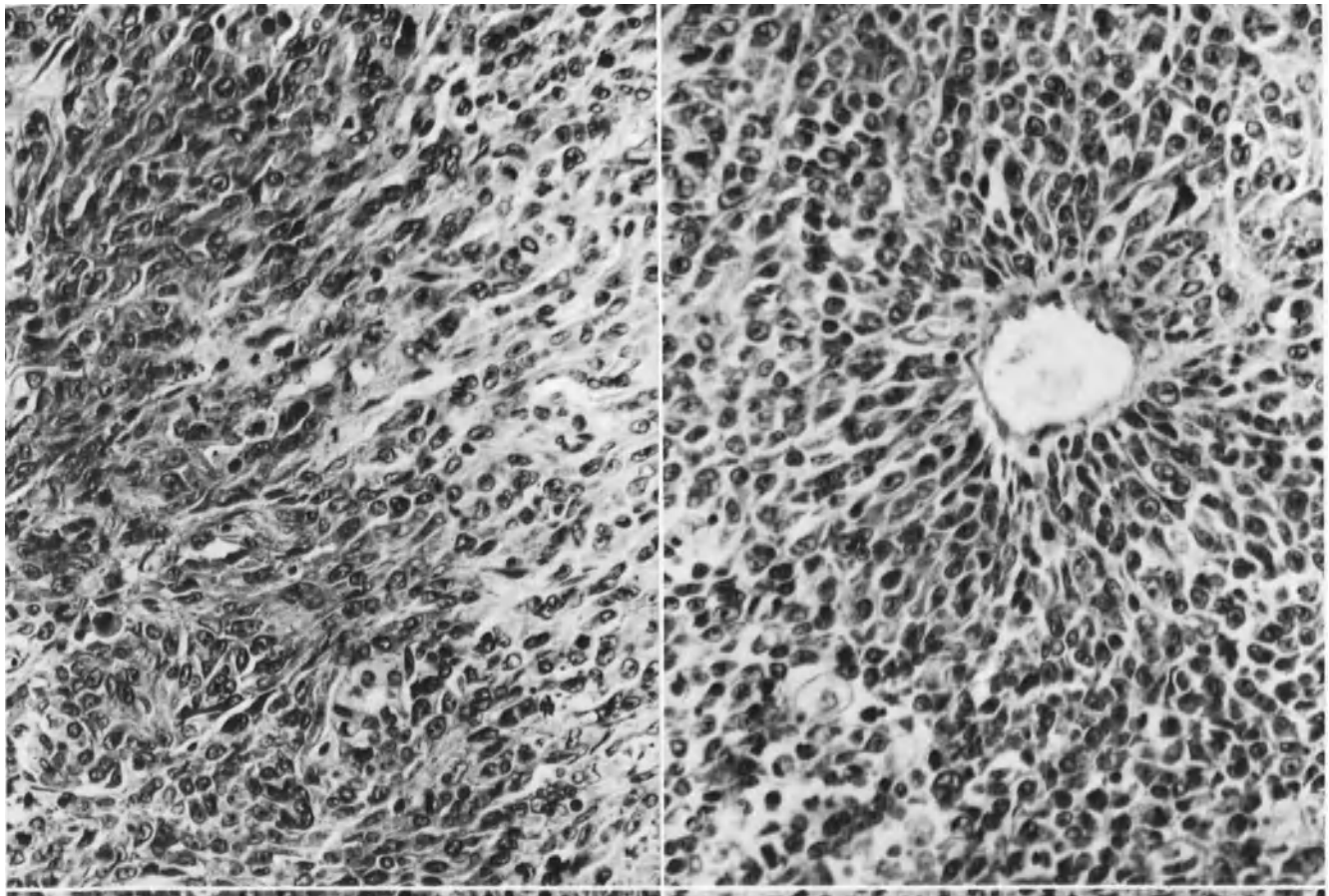

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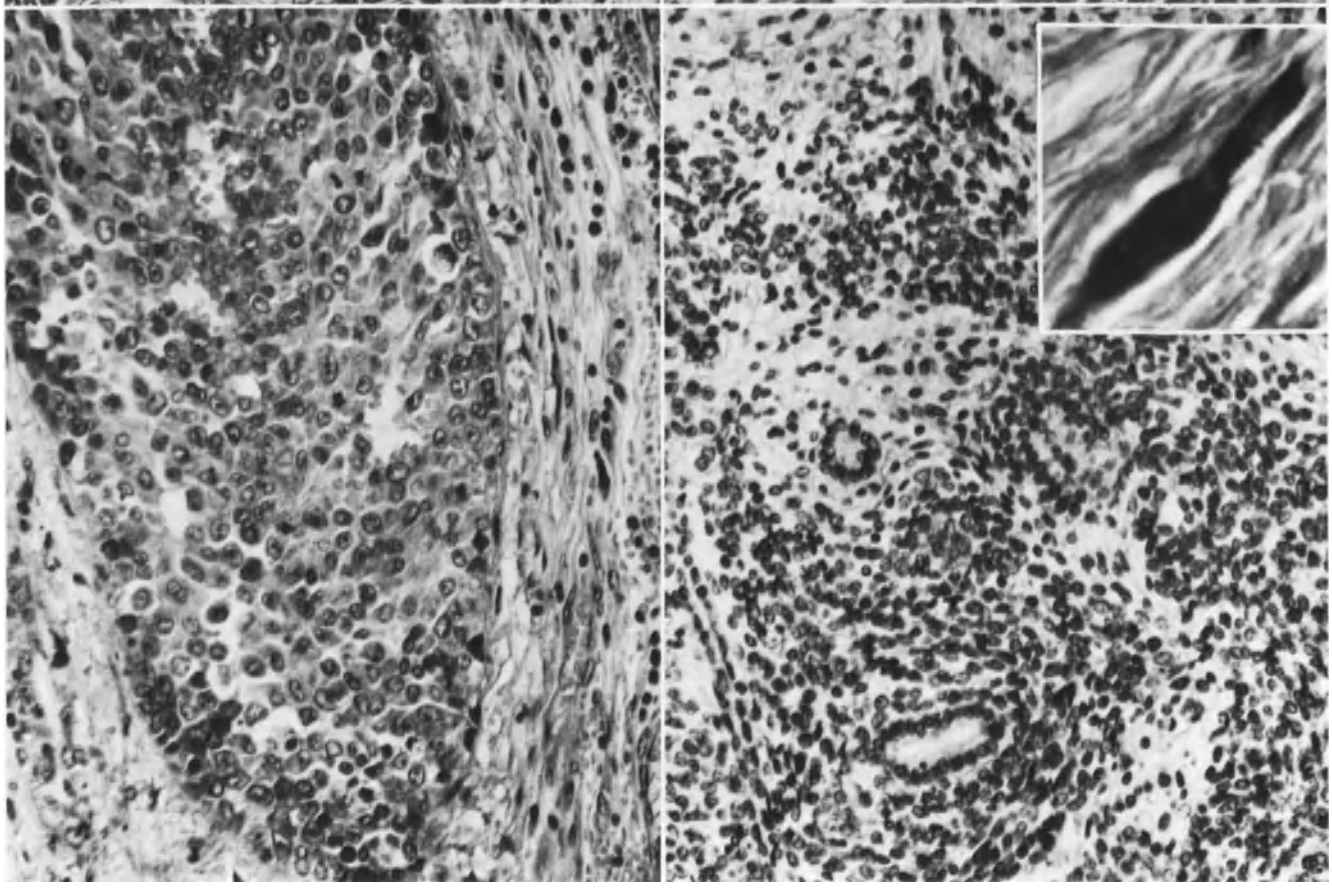

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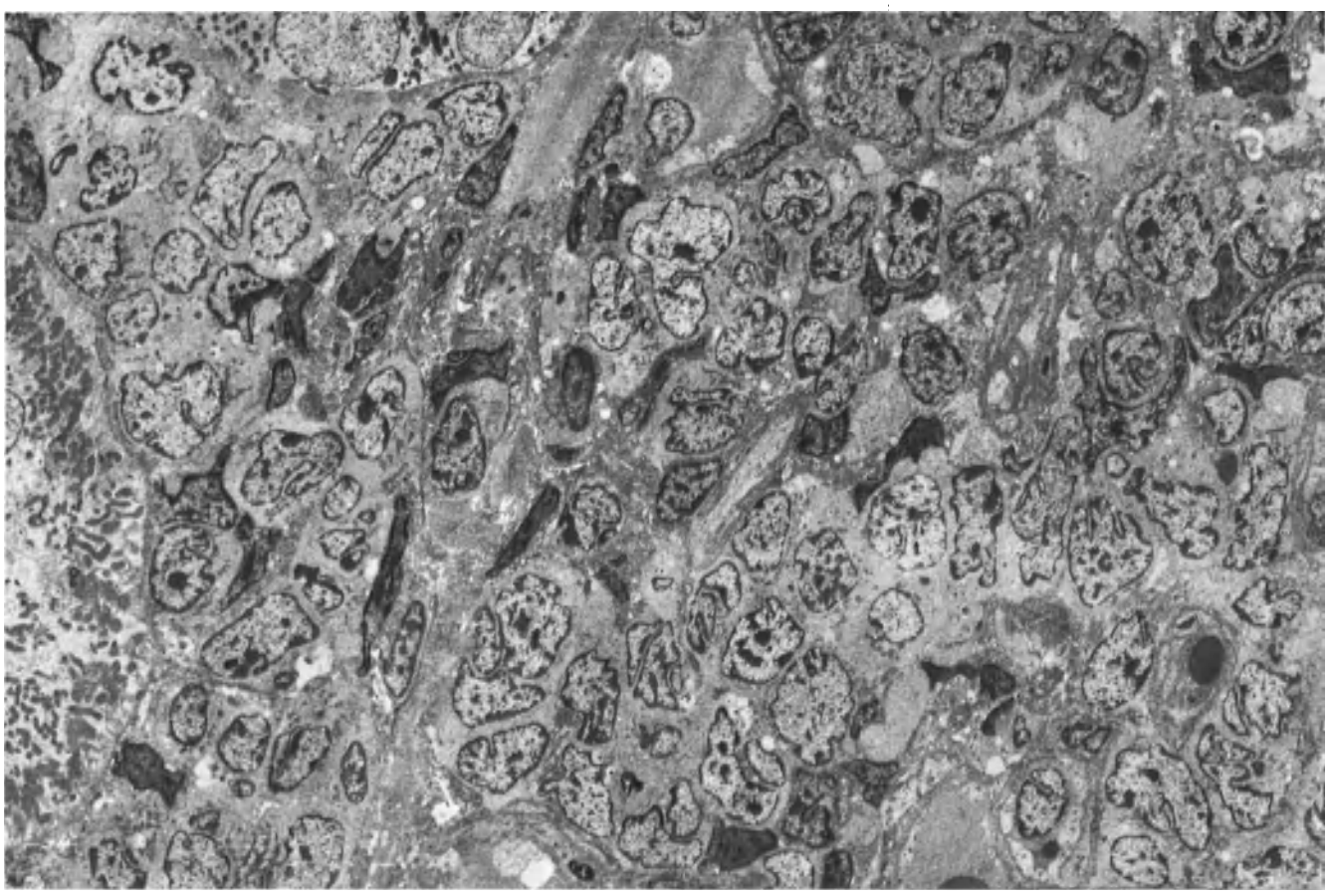

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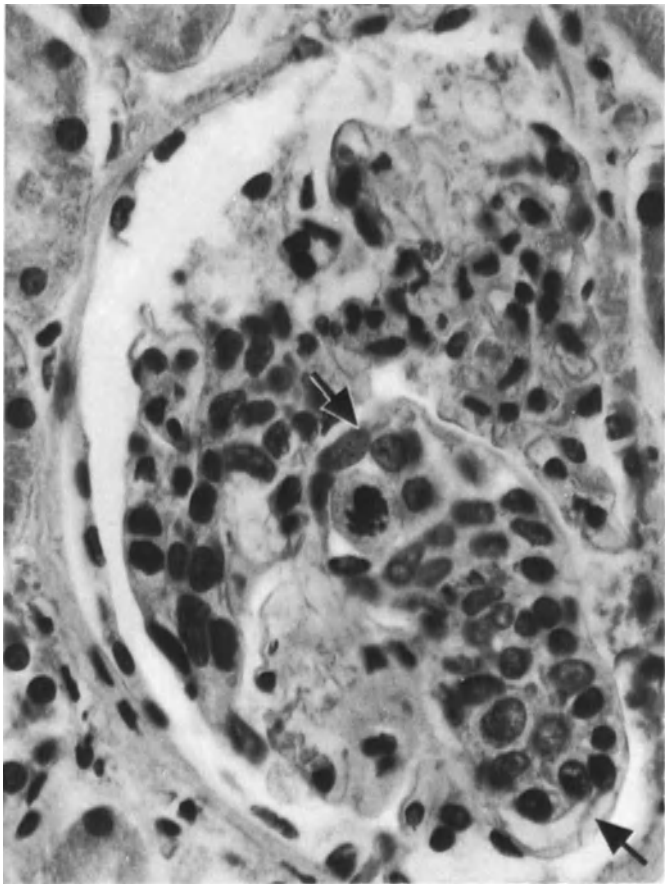

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**Fig. 29.17.** In this case, renal biopsy was done because of clinically unclear kidney disease in a 53-year-old woman. Histology revealed myeloid leukemia. In this EM preparation, masses of proliferated white blood cells are seen. These cells have little cytoplasm, enlarged nuclei and exhibit severe nuclear polymorphism. EM (×1620)

**Fig. 29.18.** Glomerular metastasis (→←) of an oat cell carcinoma of the right bronchus. Male, 63 years. HE (×700)

## 3. Renal Pelvic Carcinoma

Renal pelvic carcinoma must be mentioned here since, even in the early stage of its existence, the undifferentiated forms in particular (Fig. 29.13) may extensively infiltrate the renal parenchyma and thus become recognizable in biopsy.

The tumor has become far more frequent in women, a fact which is statistically shown to be related to the increase in long-term addiction to phenacetin [938]. In one-third of the cases with severe phenacetin addiction, urothelial tumors at different sites have been reported [776]. Renal pelvic carcinoma constitutes 6–14% of all malignancies of the kidney [920a].

The highly differentiated urothelial carcinomas usually demonstrate a papillary structure. They show weak infiltrative growth into the surrounding renal parenchyma. Squamous cell carcinomas, however, show marked infiltration; these tumors appear to arise very often by metaplasia and in association with nephrolithiasis [1791].

The purely mucous-forming adenocarcinoma is extremely rare, although isolated adenomatous structures may occur in squamous or urothelial cell carcinoma.

The entirely undifferentiated renal pelvic carcinoma consists of oval or spindle-shaped cells (Figs. 29.13, 29.14) and only careful scanning of entire sections permits identification of a few differentiated cellular strands (Fig. 29.15) or typical perivascular arrangement which are indicative of urothelial origin (Fig. 29.14). The prognosis of all forms is bad [776a]. For Thorotrast induced pelvic carcinomas, see: [1838, 1839].

## Mixed Tumor: Nephroblastoma

Nephroblastoma (Wilms-Birch-Hirschfeld tumor) is a very characteristic mixed tumor. It is the most frequently occurring kidney tumor in childhood, but is very rare in adults [463]. The congenital occurrence of this neoplasm has been described, but these tumors appear not only to have a structure different from the other nephroblastomas, i.e., presence of much smooth muscle, absence of striated muscle and fetal tubules, and occurrence of very cell-dense mesenchymal areas, but also to evidence a much better prognosis than those arising in later life [696]. Perhaps this congenital neoplasm is, indeed, a form different from nephroblastoma (fetal hamartoma: [1733]).

Nephroblastoma arises from the metanephros. It accounts for 6–8% of all malignant kidney tumors [718, 1331]. It consists of two tissue elements as also shown with EM (Fig. 29.16; [1385, 1597]). One tissue element is composed of more or less dense, undifferentiated small mesenchymal tumor cells with scanty cytoplasm, polymorphic nuclei, and numerous mitoses. The second tissue element consists of fetal tubules formed by tall cylindrical cells which are poor in cytoplasm and usually arranged in one layer. The tubular cell origin can be ascertained by EM [1597].

In the mesenchyma, there are many reticulin but few collagen fibers. In some but not all cases, fetal muscle fibers with cross-striations can also be identified (Fig. 29.16).

The tubular structures sometimes appear to arise within foci of extremely small-celled mesenchyma. The occurrence of squamous epithelium, mucous glands, and argentaffine cells is rare [718].

Glomeruloid structures repeatedly reported in the literature—which we cannot confirm in our cases (see also [1597])—are said to consist, under EM, only of BM material and podocytes with no endothelial or mesangial cells discernible [754, 1385].

Due to early diagnosis, extensive surgery, and combined radiation and cytostatic therapy, the prognosis has improved considerably.

## Metastases

Metastases may be found quite unexpectedly in renal biopsy tissue. In our own material, we found extensive infiltration of chronic myeloid leukemia in a 53-year-old female (Fig. 29.17) and of acute lymphatic leukemia in a 3.5-year-old girl. The infiltrates of lymphatic leukemia are considerably more sharply delimited and cellularly uniform than those of myeloid leukemia. The myeloid form may give rise to diagnostic difficulties with respect to pyelonephritis (see also [1471]).

Metastases to the kidney often occur in malignant lymphoma (50% of our cases) but only lead to renal insufficiency in extremely few cases [434, 1015, 1791].

Metastases of other primary tumors should present no difficulties if sufficient material is available for examination—which is rarely the case in renal biopsy.

Glomerular metastasis may be seen in renal needle biopsy, but such a finding is very rare (Fig. 29.18).

Parenthetically, it is noted that endometriosis has been seen in the kidney. The typical endometrial structure and evidence of recurrent bleeding, along with the age of the subject, should cause no difficulty in diagnosis in relation to nephroblastoma.

# 30. Kidney Transplantation

[27, 63, 189, 238, 315, 653, 698a, 733, 851, 1189a, 1264, 1266, 1287, 1309a, 1805]

The increase in renal transplantation has not only brought about an increase in renal biopsies for determining basic disease and, thereby, the indication for transplantation, but also an increase in transplant renal biopsies which are necessary for adequate therapeutic management.

Even the general pathologist is being called on more and more to interpret transplant biopsies which often exhibit a very complex picture of changes due to rejection as well as recurrence of the basic disease or to other complications. The following discussion is based on our own material from 76 transplant patients comprising 85 needle biopsies from allo-transplants, 16 surgical biopsies and 30 nephrectomies. The average age of our transplant recipients was 39. Since the time of working up our material, it has increased to 137 biopsies and 40 nephrectomies. To enhance the understanding of those who may not be too familiar with the terminology relating to immunogenetic principles underlying organ transplantation, a brief discussion of these topics is given below.

### Nosology

Four transplantation systems based on the genetic relationship between the donor and recipient are differentiated:

1. *Autologous transplant (Synonyms: Autogenic transplant, autograft).* The transplant donor and recipient are identical.
2. *Isologous transplant (Synonyms: Isogeneic or syngeneic transplant, isograft).* The transplant donor and recipient are different individuals with an identical genetic constitution, e.g., identical (monoval) twins.
3. *Homologous transplant (Synonyms: Allogeneic transplant, allografts resp. homografts).* Donor and recipient are of the same species but are genetically different individuals.
4. *Heterologous transplant (Synonyms: Xenogeneic transplant, heterograft or xenograft).* The donor is from a different species than the recipient.

No immunologically induced transplant rejection is to be expected with the auto- and isograft. However, since most kidney transplants are of the homologous (allogeneic) type, they bear the risk of histoincompatibility leading to transplant rejection.

## Immunogenetics

[1309a]

A specific chromosomal region consisting of a few directly neighbouring gene loci appears to be chiefly responsible for rejection in all species.

This entire chromosomal region (independent of species) is designated as the major histocompatibility complex (MHC). According to the latest knowledge, and in keeping with the newly agreed upon international nomenclature of 1975 [1189a], the entire human MHC is now termed the HLA (originally meaning human lymphocytic antigen). Currently, four different gene loci of the HLA are known:

***1. A-Locus.*** Genetically determines the presence of one of over 20 currently known antigens on the membranes of almost all body cells. These antigens may be tested in vitro by using sera of monospecific cytotoxic antibodies. The A-locus is identical to the earlier designation 1 (sub) locus of the LA-series.

***2. B-Locus.*** Genetically determines the presence of one or the other of a group of over 20 antigenes comparable to the A-locus. The B-locus is identical to the earlier designation 2 (sub) locus or FOUR series. These antigens can also be tested with monospecific cytotoxic antisera.

***3. C-Locus.*** The C-locus is identical to the long suspected and sought for 3 (sub)locus. Currently, only five antigens are known which are determined by the C-locus. Since monospecific cytotoxic sera for demonstration of these antigens are currently available to only a few laboratories for scientific investigations, the antigens of the C-locus cannot yet be routinely tested.

***4. D-Locus.*** Is identical with the so-called mixed lymphocytic response (MLR) or mixed lymphocytic culture (MLC) locus. At the present time, only six different D-antigens are known. As in the case of the C-locus, only a few laboratories have cytotoxic sera for testing the D-antigens. Thus, serologic testing of the D-locus antigens is not yet possible for routine clinical work.

Nevertheless, using the MLC reaction, in vitro studies can determine whether or not two different individuals have identical D-antigens.

Lymphocytes from both individuals exposed to each other in a culture, mutually stimulate themselves to transform into so-called immunoblasts in the case of different D-antigens (positive MLC test). In the case

of identity of D-antigens, no stimulation occurs (negative MLC test).

The term haplotype refers to the phenotype of the HLA constellation which is inherited from parental chromosomes. Since the chromosome pair is formed by one chromosome from the father and one from the mother, each individual possesses two haplotypes which, with the exception of crossing-over, are inherited as a gene block.

It is possible that other HLA loci will be discovered in the future. In man, a fifth locus may be present in the immediate neighbourhood of the D-locus. In this region, antigens are determined which are only demonstrable on B-lymphocytes. This region has long been known in the mouse as the Ia-Region (immune response region-associated antigens).

The HLA B-locus appears to predispose some individuals to specific diseases (e.g., Bechterew's disease from HLA-B-27). Other such predisposition in man appears to be determined by the supposed and little defined fifth locus (e.g., possibly multiple sclerosis, ragweed sensitivity, etc.).

The D-locus is probably the most important with respect to transplant rejection. The only two HLA loci which can be tested quickly today, the A and B locus, are of variable significance with respect to the survival prospects of a renal transplant.

Good compatibility of the A and B locus between donor and host appears to be especially important for a second transplant (following rejection of the first) and for recipients with preformed circulating anti-HLA-antibodies. If two siblings have identical A and B loci, there is a high probability (except in crossing-over) that all the other HLA-loci will also be identical. This is not patently true for two nonrelated individuals demonstrating identical A- and B-locus genes. This explains why the currently possible tests of A- and B-loci have chiefly shown an excellent correlation to survival probability of transplants between siblings and less so in the case of cadaver kidneys (see also [1850]).

ABO blood group antigens are present in almost all the somatic cells including the kidney. They are independent of the HLA antigens. ABO incompatibility leads to hyperacute transplant rejection [1510, 1559].

Pre-existing circulating cytotoxic recipient AB against donor HLA antigens are a hazard which can lead to hyperacute transplant rejection. Therefore, the so-called cross-match (recipient serum with donor lymphocytes in vitro) must be carried out to demonstrate the presence or absence of the above mentioned AB before transplantation. Cytotoxic AB may arise following multiple blood transfusions, previous transplantation, pregnancy, and probably after infections.

A positive cross-match test and ABO incompatibility are absolute contraindications for transplantation. Demonstration of cytotoxic AB giving a negative cross-match test (i.e., the circulating cytotoxic anti-HLA-antibodies have no specificity towards donor HLA antigens) is not a contraindication. Their presence, however, worsens the prognosis of transplants if the HLA-A and HLA-B donor/recipient compatibility is poor, as has been shown by experience.

Previously, HLA compatibility was evaluated by means of the A-F classification [933] or the Rank classification [1309a]. Today, evaluation is achieved simply by noting the number of compatible and incompatible antigens between donor and host (e.g., three identical antigens, one incompatible).

Since only two loci (A and B) can be routinely tested, and since both of these two loci may demonstrate a determination different on the paternal than on the maternal chromosome (heterozygote), maximally four antigens per individual are typified.

Despite great care in selection of allogeneic donor kidneys, antigen incompatibilities in cadaver kidney transplants can never be totally eliminated. Accordingly, immunopathologic changes must be expected to be present in every transplant since they cannot be totally suppressed by immunosuppression.

In the pathogenesis of transplantat rejection, cellular and humoral immune defense mechanismus play an important role (see p. 607).

## Indications for Biopsy

Biopsy is indicated in transplant patients [1100] under the following situations:

1. Postoperative anuria of longer than 2 weeks duration.
2. Following clinical rejection episodes which do not respond to increased immunosuppressive therapy.
3. Slowly deteriorating renal function.
4. Increase in proteinuria and/or hematuria.
5. Control following transplantation. This is done at most transplant centers [653] initially in 0.5–1 year intervals and later in 1 to several year intervals.

## Acutely Imminent Renal Injury (So-Called Conservation Injury)

Acutely imminent injury is practically limited to cadaver kidneys. Preservation of cadaver kidneys depends on a multiplicity of factors including the basic disease, cause of death of the donor, time elapsed between cardiorespiratory arrest and nephrectomy, as well as the duration of the warm and cold ischemic periods [653]. Renal biopsy is occasionally called for when, due to poor gen-

eral condition of the donor kidney, a lengthy postoperative anuric phase ensues.
In acutely imminent renal injury, morphologic changes are predominantly manifested by the tubules.

### LM Findings

The tubular cells are swollen. Necrobioses, necroses and, in later stages, signs of regeneration with mitoses are present. The tubular lumens are plugged up with a homogenous, PAS-positive material which is also occasionally found in the edematously widened interstitium. A few scattered polymorphonuclear leukocytes are present in the tubular lumen and in the interstitium.

### EM Findings

Pronounced lysosomal and mitochondrial swelling (Fig. 8.3), protein (hyaline) droplet storage and marked distention of the basal labyrinth (Fig. 30.1) are also found even in subsequently well-functioning transplants. Necrobiotic tubular cells are rarely observed (Fig. 8.3). All glomerular cells are edematous. The mesangial matrix in the early phases of the condition is occasionally loosened by edema. The larger blood vessels are usually unchanged but the arterioles may demonstrate considerable injury (Fig. 30.2).
Renal injury due to conservation must be differentiated from that attributable to prior disease present in the donor kidney which, by appropriate selection, should be very rare. The most frequent changes in donor kidneys are those attributable to shock.

### IF Findings

Granular deposits of IgM were present alone in 1 out of 3 and IgM and C3 in 2 out of 3 of our own cases biopsied a few minutes after revascularization and perfusion. In 2 out of 3 cases, IgM and C3 were present in the arterioles and also in 2 out of 3, fluorescence (severe and diffuse) was demonstrated interstitially for various immunoglobulins and once for fibrin(-ogen) as a result of interstitial edema.

## Peracute (Hyperacute) Transplant Rejection

This form of rejection usually already develops during surgery [238, 1557] and is reflected in biopsy by massive leukocytosis of the capillary loops. In a few instances, peracute rejection occurs after a few weeks. The presence of four or more leukocytes per glomerulus 0.5 h after transplantation is reported to be associated with a poor prognosis [844, 1100]. Additionally, platelet agglutination with fibrin formation resulting from reduction in fibrinolysis due to endothelial injury as well as the full-scale development of thrombosis [1690] are noted in the glomerular capillary loops and sometimes in arterioles and smaller arteries (Fig. 30.3; [655, 1491]). Arteriolonecroses are frequent [1386] and high-grade capillary loop widening with stasis of erythrocytes also develops (Fig. 20.27; see p. 423). In most cases, corresponding parenchymal necroses develop [159, 315, 1402] which are demonstrable after 24 h [655]. These necroses may coalesce and give rise to acute hemorrhagic cortical necroses.
A similar but possibly not unequivocally identical condition is triggered by diffuse intravasal coagulation [1556] in which, however, the leukocytic phase is missed. This complication develops somewhat tardily. No intravasal coagulation is usually observed in so-called second-set rejection ([1271]; contra: [1170]).

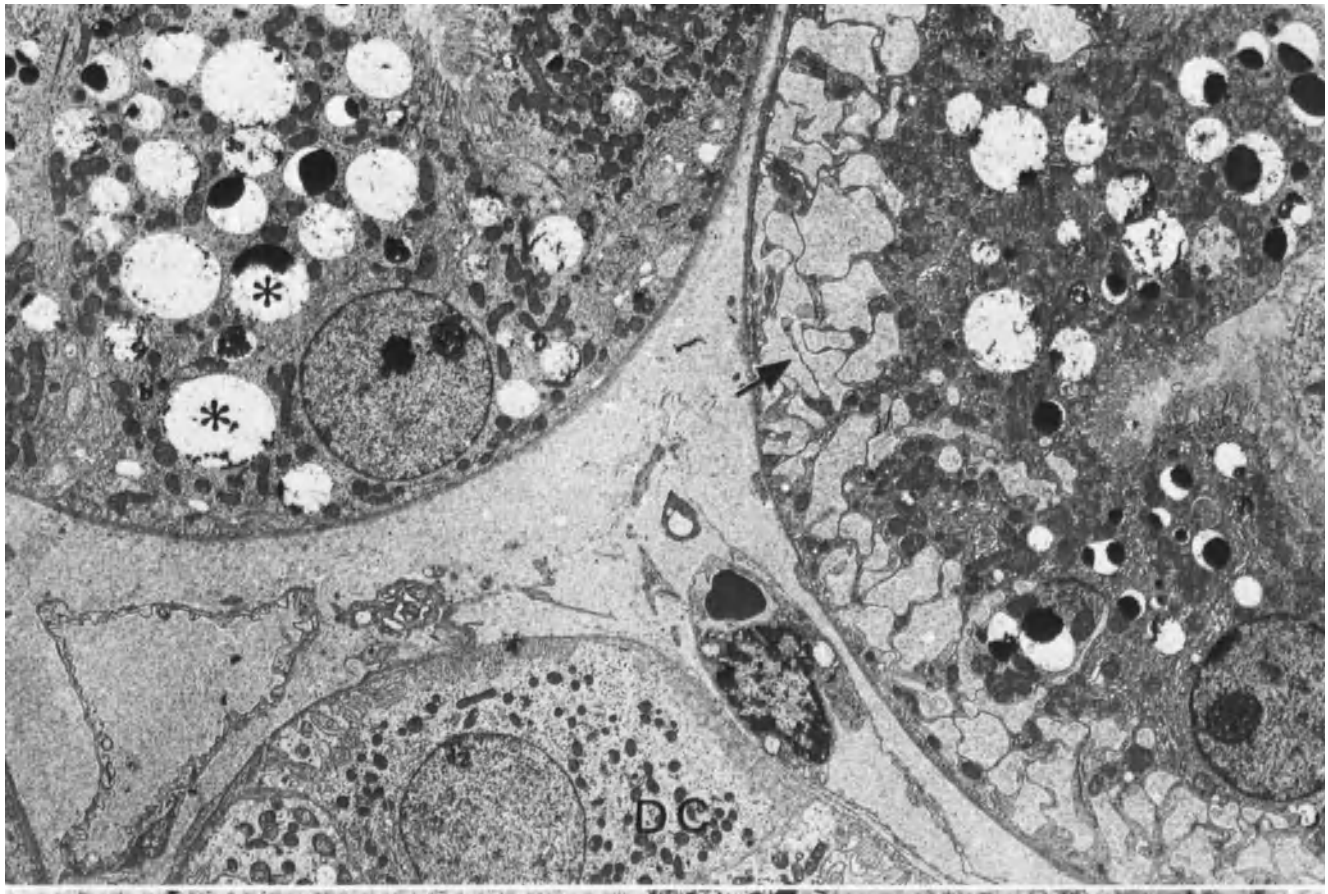
## Acute Transplant Rejection

### Incidence

Acute rejection was present in 26.7% of our 131 transplant biopsies. Clinical findings can appear as early as between the third and seventh, usually the fourth, post-transplant days [78] but may do so even weeks, months or years thereafter (Fig. 30.38).
In our material, 78% of all acute rejections occurred within the first 8 post-transplant weeks (Fig. 30.39). After the fourth post-transplant month, chronic transplant rejection is by far the most prominent form.

**Fig. 30.1.** Biopsy 1 h after transplantation. There are rather severe lesions caused by conservation of the proximal tubules including severe distention of the basal labyrinth (→) and masses of enlarged lysosomes some containing protein (*). Distal convoluted tubules (*DC*) are practically unchanged. Interstitium is slightly edematous. This transplant functioned well thereafter. EM (×3520) ▷

**Fig. 30.2.** A small renal artery after 20 min of homologous blood perfusion. There is a giant vacuole in the endothelium (→). A few erythrocytes (*) are present between the highly degeneratively changed myocytes of the media. EM (×4320)

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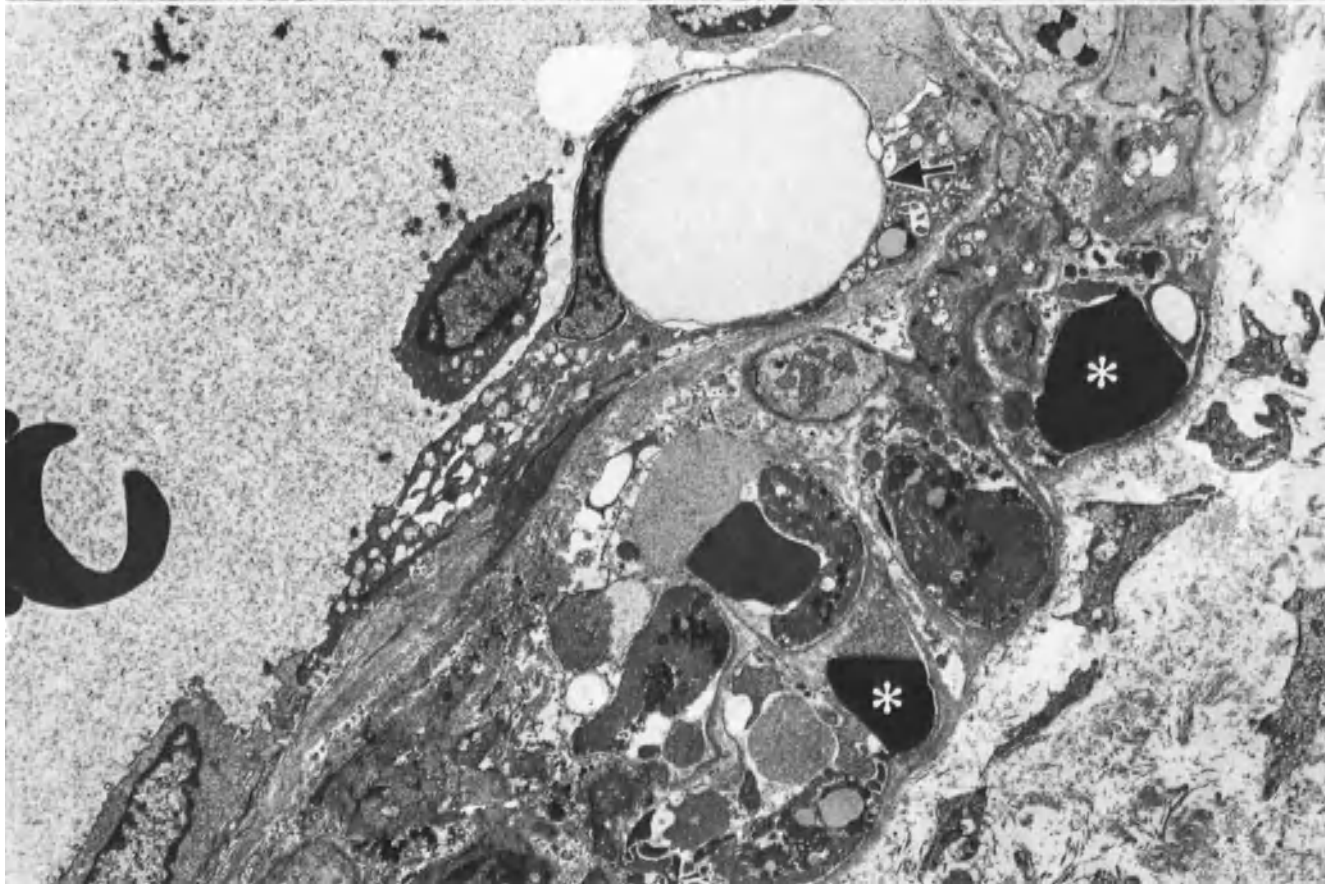

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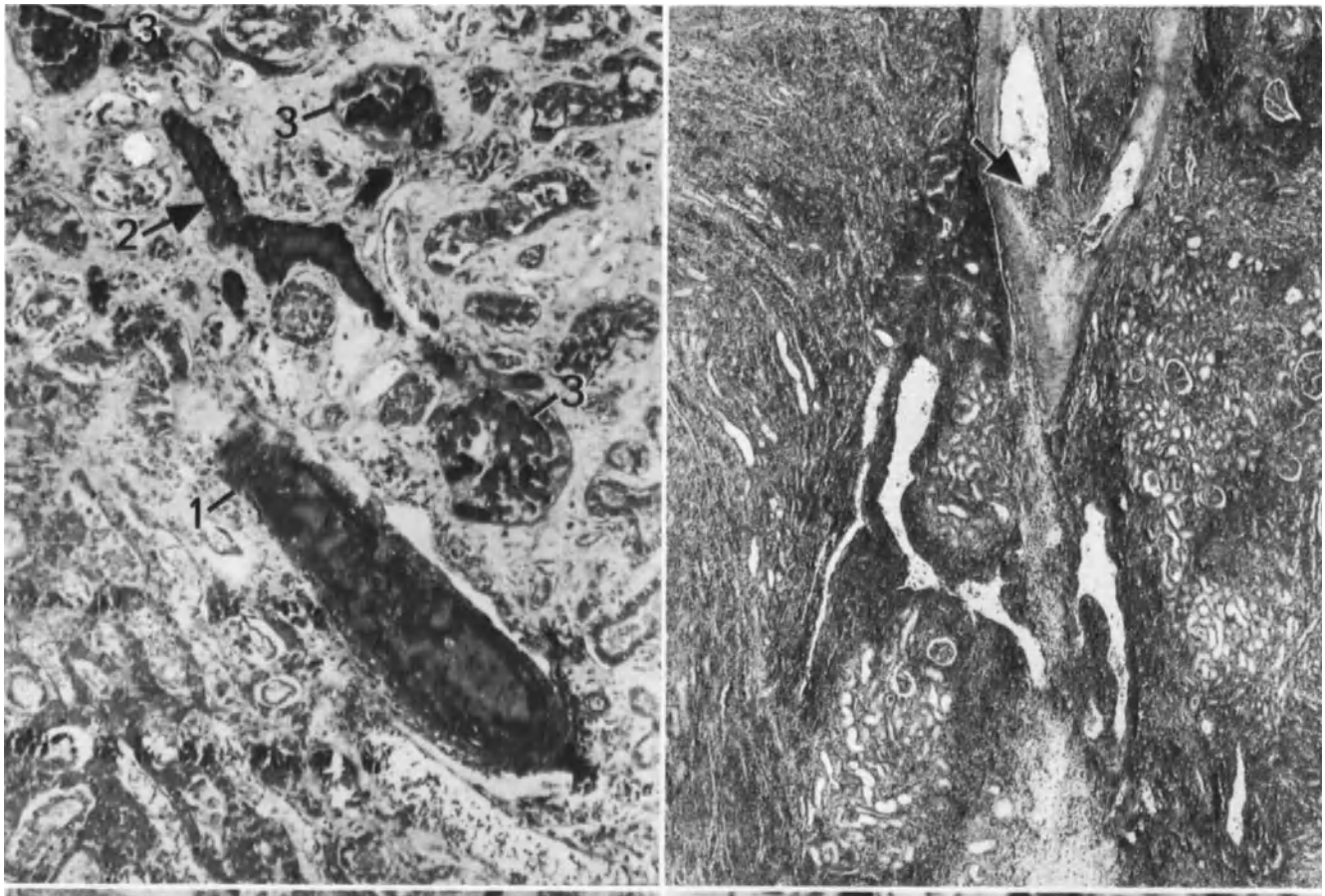


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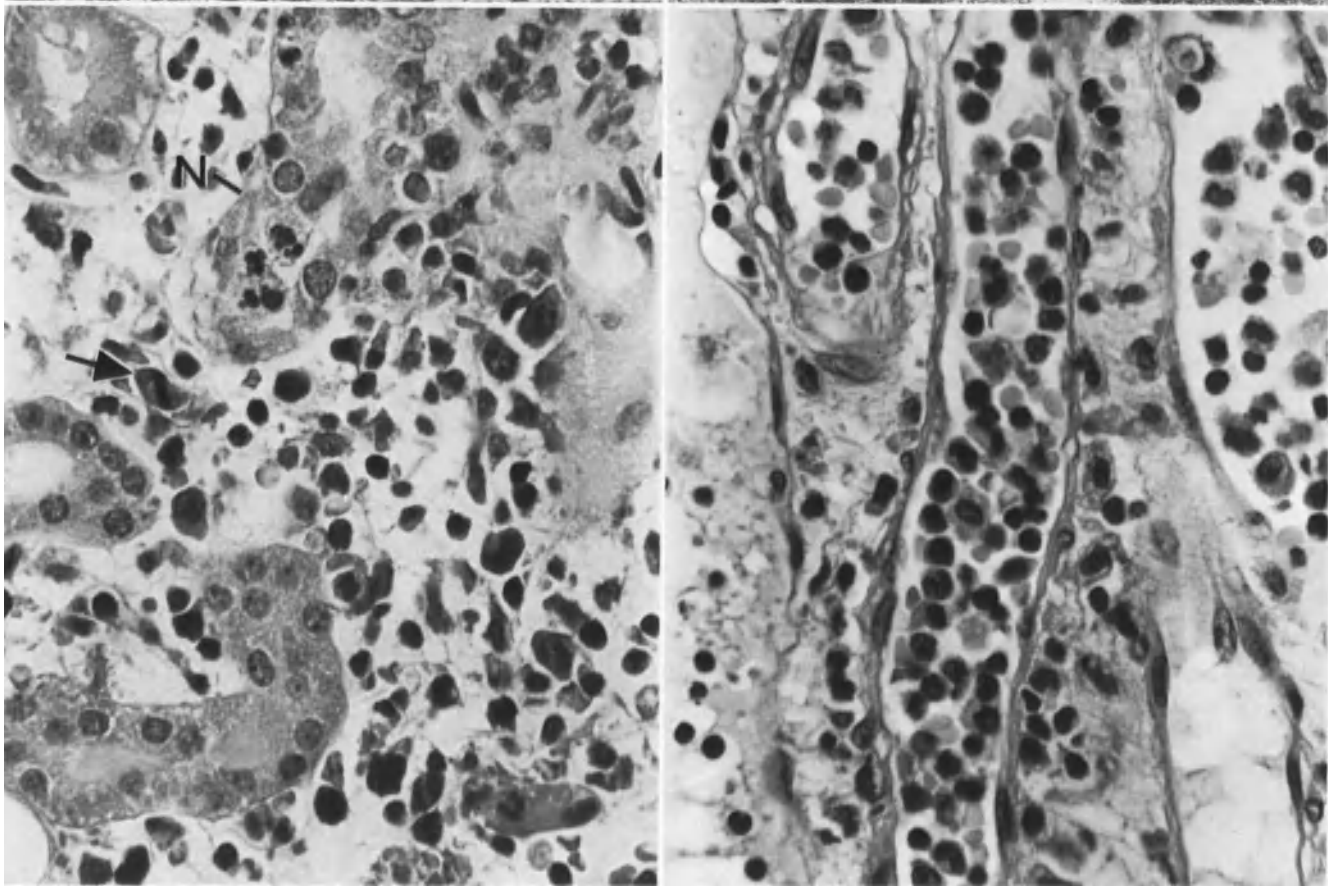


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### Clinical Findings

The following clinical symptoms singly or in combination are present: reduction of urine volume, reduction of sodium urine concentration, body weight and/or blood pressure increase, fever, impairment of renal function, sensation of pressure and tension at the site of renal transplant as well as palpable swelling and induration of the kidney, increase of small lymphocytes and pyroninophilic, activated lymphocytes in urine and increase in eosinophilic leukocytes in blood. Clinical symptoms do not allow reliable conclusions concerning the morphologic form of rejection. If impairment of renal function is accompanied by fever and thrombopenia, vascular rejection may be assumed. A kidney antibody independent of lymphocytotoxic antibody and HLA-antigen in a high titer in the serum is said to enable prediction of rejection with great accuracy [435a].

## 1. Acute Interstitial Transplant Rejection

Two forms of acute transplant rejection are differentiated, the acute interstitial and the vascular, of which the former will be presented first (Fig. 30.40).

◁ **Fig. 30.3.** Very acute transplant rejection on the 4th post-transplant day. Arteries (*1*), arterioles (*2*) and glomerular capillary loops (*3*) are filled with clumped erythrocytes, thrombocytes and fibrin. Nephrectomy. Masson's trichrome (× 140)

**Fig. 30.4.** Acute interstitial rejection with a slight vascular component (→) in a 35-day-old transplant. There are extensive inflammatory infiltrates in the surroundings of the dilated veins. HE (× 26)

**Fig. 30.5.** Interstitial infiltrate in acute interstitial transplant rejection on the 7th post-transplant day. Cells in infiltrate demonstrate mitoses (→). Note tubulonecrosis with nuclear disintegration (*N*). HE (× 520)

**Fig. 30.6.** Masses of predominantly immature white blood cells in the dilated intertubular capillaries in acute interstitial transplant rejection in which symptoms became manifest 7 days before biopsy. Three-months-old transplant. HE (× 500)

### LM Findings

The decisive changes in this type of rejection consist of a diffusely distributed, focally accentuated interstitial inflammatory infiltration (Fig. 30.4) with discrete hemorrhage and interstitial edema (see Table 30.1). Interstitial infiltration is initially predominant at the corticomedullary junction. The infiltrates consist of small and large lymphocytes, immunoblasts, plasma cells and histiocytes (Fig. 30.5). Mitoses are not infrequently observed (Fig. 30.5; [315, 1286]).

The cells constituting the interstitial infiltrate can be observed migrating from the congested intertubular capillaries (Fig. 30.6) into the interstitium. From the interstitium they move to a position underneath the tubular epithelium (Fig. 30.11) and may give rise there to patchy tubular cell necroses (see Fig. 8.4; [315, 1373, 1402]). The tubular cell necroses are usually not very extensive and are limited to individual tubules which are subsequently repaired by regeneration.

Glomerular changes may be absent in LM or only a slight mesangial enlargement due to cellular swelling may be present (glomerulonephrosis). Mesangial cell increase does not occur. A swelling of the wall of the capillary loops (Fig. 30.7) caused by endothelial and podocytic edema can be seen [1805]. The vascular changes are usually mild (see Table 30.1).

### EM Findings

Cells constituting interstitial infiltrates cannot be differentiated qualitatively from those in acute nondestructive interstitial nephritis (see Fig. 9.8, p. 144). These cells usually consist of activated lymphocytes with increased cytoplasm and of immunoblasts (Fig. 30.9) with massive numbers of ribosomes, a very pronounced Golgi apparatus but with a very small amount of rough endoplasmatic reticulum (Fig. 30.8). Mitoses are frequent (Fig. 30.10). Plasmoblasts and plasmocytes are also found (Fig. 30.8) and histiocytes and phagocytes (Fig. 30.8) are always present. Transformation of histiocytes into lipid-containing foam cells occurs from about the seventh post-transplant day onwards (Figs. 30.10, 30.11).

The intertubular capillaries, which are lined by a severely damaged endothelium, contain large numbers of activated lymphocytes which are rich in cytoplasm, as well as a few foam cells of probable monocytic origin (Fig. 30.11). Lymphocytes can be seen migrating from interstitial capillaries into interstitial tissue (Fig. 30.11). Sometimes these cells can be found between tubular epithelium and BM (Fig. 30.12), or inbetween epithelial cells. They do not necessarily cause epithelial damage [500].

**Fig. 30.7.** Acute interstitial rejection in a 3-month-old transplant. There is severe cellular swelling of the glomerular capillary loops with attendant complete occlusion of the lumens. Interstitium is edematous and evidences scanty infiltrates. HE ( × 280)

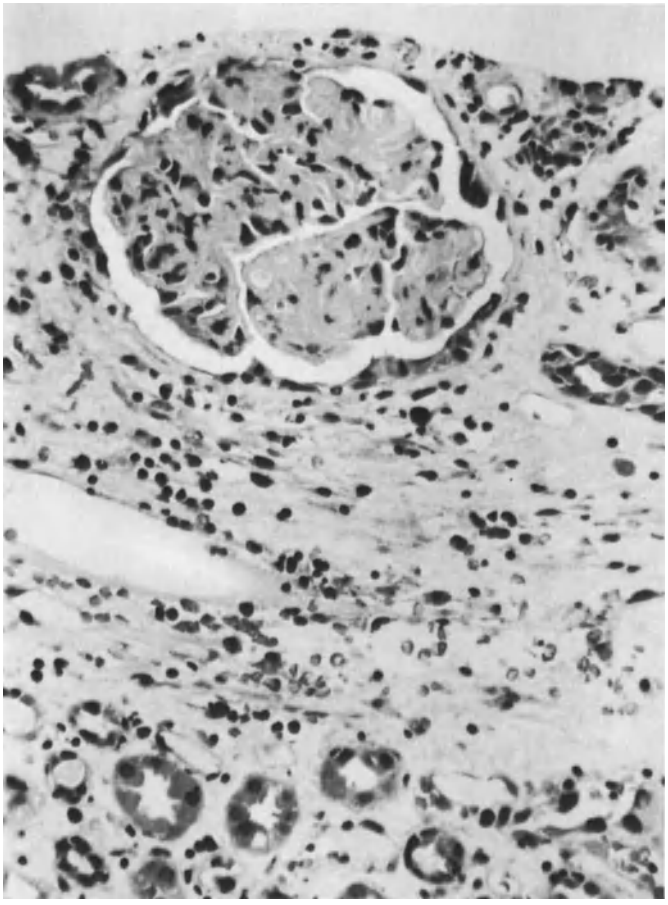

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**Fig. 30.8.** Interstitial infiltrate in acute transplant rejection on the 7th post-transplant day. Infiltrate in edematous interstitium consists of plasma cells (*PS*), plasmoblasts (*PB*) and phagocytes (*PH*) as well as scattered slightly activated lymphocytes (*AL*) and a few polymorphonuclear leukocytes (*PL*). EM ( × 3250)

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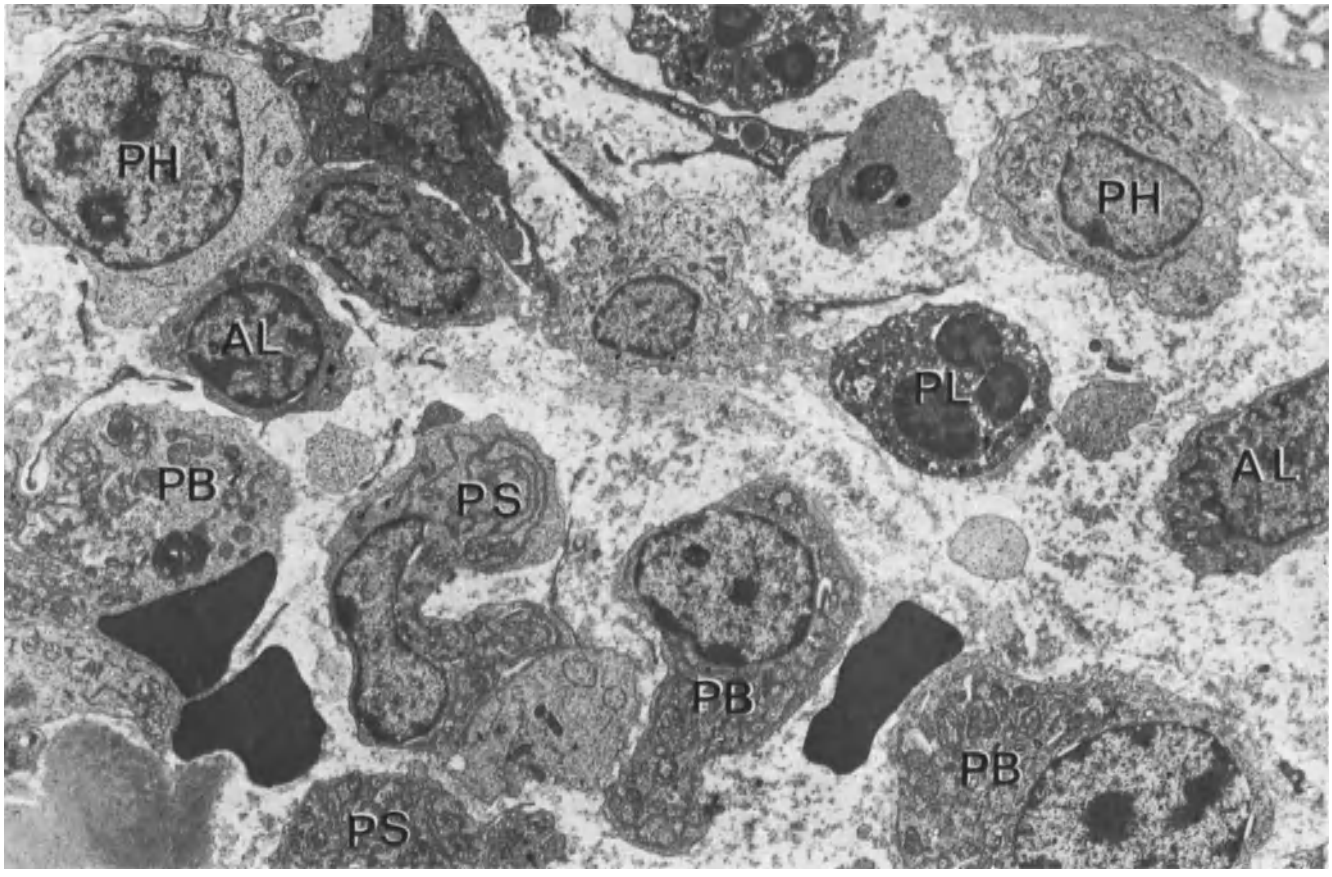
**Fig. 30.9.** Same case as in Fig. 30.8. Infiltrate consisting of numerous immunoblasts rich in polyribosomes and plasma cells (*PS*). EM ( × 7420)

**Fig. 30.10.** Interstitial transplant rejection on the 14th post-transplant day. Immunoblasts, a cell undergoing mitosis (→) and two lipid-containing phagocytes—foam cells (*F*)—are recognizable. EM ( × 5280)

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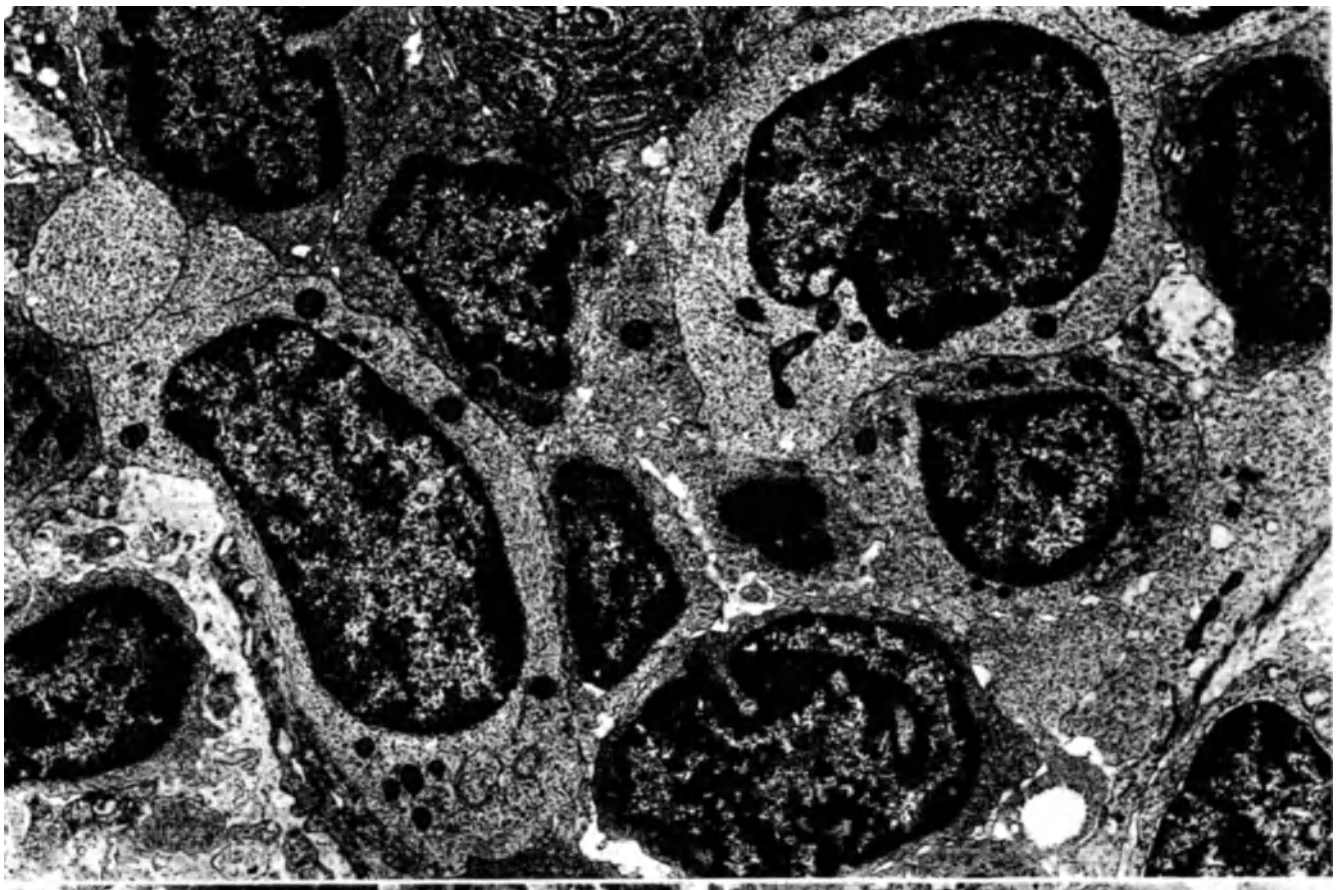

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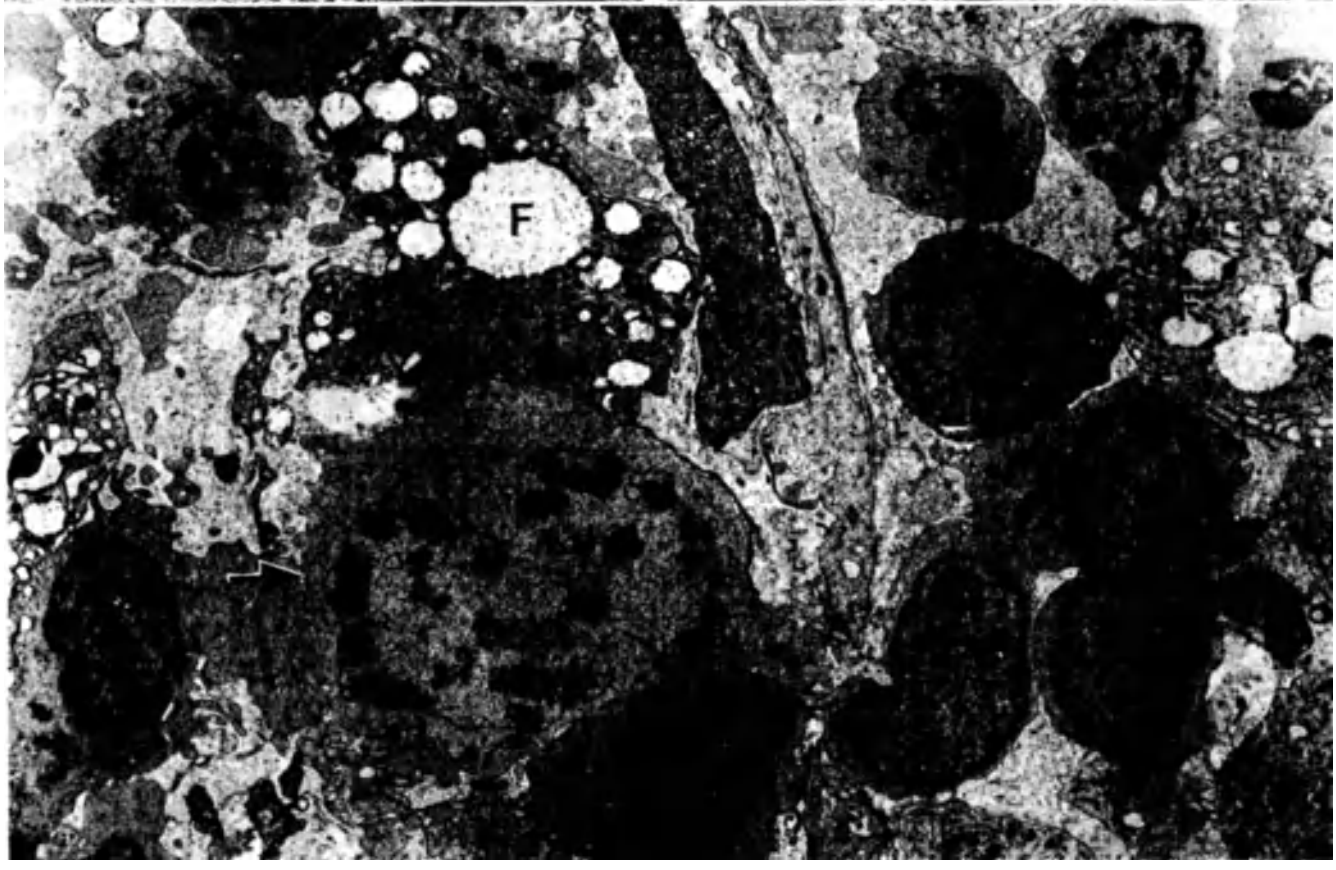


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Table 30.1. Differential diagnosis in acutely imminent transplant injury in peracute and acute transplant rejection

| Parameter | Acutely imminent transplant injury | Peracute transplant rejection | Acute transplant rejection | |
|---|---|---|---|---|
| | | | Interstitial type | Vascular type |
| Time interval between transplantation and biopsy | < 1 month | Minutes–hours | < 8 weeks, later rarer | > 14 days, later more frequent |
| Etiology/ pathogenesis | Conservation injury | Humoral immune reaction | Cellular immune reaction | Humoral/cellular immune reaction |
| Morphology | | | | |
| 1. Glomeruli | Edema of the mesangial matrix, mesangial cells, podocytes, endothelium | Leukocytosis of loops (+++)<br>Stasis of erythrocytes (+++)<br>Thrombocytes, fibrin and thrombi (+++)<br>Loop necroses (+−+++) | Edema of mesangial cells (+)<br>endothelium (+−++)<br>podocytes (+−++)<br>LM swelling of capillary loops (+−++)<br>Foot process fusion (+−++)<br>Loop leukocytosis (0−+)<br>Fibrin and thrombocyte thrombi (0−+) | As in interstitial type plus blood stasis (++−+++)<br>Glomerular necroses (+−+++) |
| 2. Tubules | Cellular swelling (+−+++)<br>Tubular necroses (+−++)<br>Tubular lumen contains homogenous PAS-positive material<br>Polymorphonuclear leukocytes (0−+)<br>Later appearing mitoses (+) | Focal→diffuse tubular necroses (++−+++)<br>Hemorrhage (+−++) | Tubular invasion by interstitial infiltrates (+−+++)<br>Tubular necroses (0−+)<br>Mitoses (0−+)<br>Shock tubules (rare) | Tubular necroses (+−+++)<br>Hemorrhage (+−+++)<br>"Shock tubules" (+−++) |
| 3. Vessels | ± Unchanged | Blood stasis (++−+++)<br>Leukocytes (++−+++)<br>Endothelial necroses (++−+++)<br>Arterial wall necroses (++−+++)<br>Leukocytic media wall infiltrates and fibrin (++−+++)<br>Dilatation and blood stasis (++−+++): especially arterioles, small arteries, veins, intratubular capillaries | Endothelial swelling (+−++)<br>Endothelial detachment and lymphoid infiltrates (0−+)<br>Endothelial proliferation (0−+) | Endothelial:<br>swelling (+−++)<br>detachment (++−+++)<br>Subendothelial proliferation (++−+++)<br>infiltrates (++−+++)<br>Media edema (+−+++)<br>necroses (0−++)<br>Parietal thrombi and fibrin insudation (0−+)<br>Subtotal arterial occlusion especially at points of branching<br>Dilatation and blood stasis (++−+++) in intertubular capillaries |

Table 30.1 (continued)

| Parameter | Acutely imminent transplant injury | Peracute transplant rejection | Acute transplant rejection | |
|---|---|---|---|---|
| | | | Interstitial type | Vascular type |
| 4. Interstitium | Focal diffuse edema (+ − + +)<br>Polymorphonuclear leukocytes (0 − +) | Hemorrhage, edema (+ − + + +)<br>Polymorphonuclear leukocytes (+ − + +) | Edema (+ − + + +)<br>Infiltrates (+ + − + + +)<br>Small lymphocytes, plasma cells, histiocytes and erythrocytes (0 − +) | Edema (+ − + +)<br>Bleeding (+ − + + +)<br>Lymphoidal infiltrates (0 − +) |
| Prognosis | Favorable | Hopeless | Therapeutically manageable | Poor |
| Miscellaneous | Overlapping with prior renal disease such as arteriolosclerosis, shock kidney glomerulonephrosis, glomerulosclerosis pyelonephritis | Overlapping with diffuse intravasal coagulation | In early cases, overlapping possible<br>In advanced cases, combination of acute and chronic rejection | |
| | | | Overlapping with pyelonephritis acute interstitial nephritis (sensu strictu) | In biopsy sometimes difficult to differentiate from thrombosis of renal artery (technical reason), ureteral obstruction, (genuine) shock |

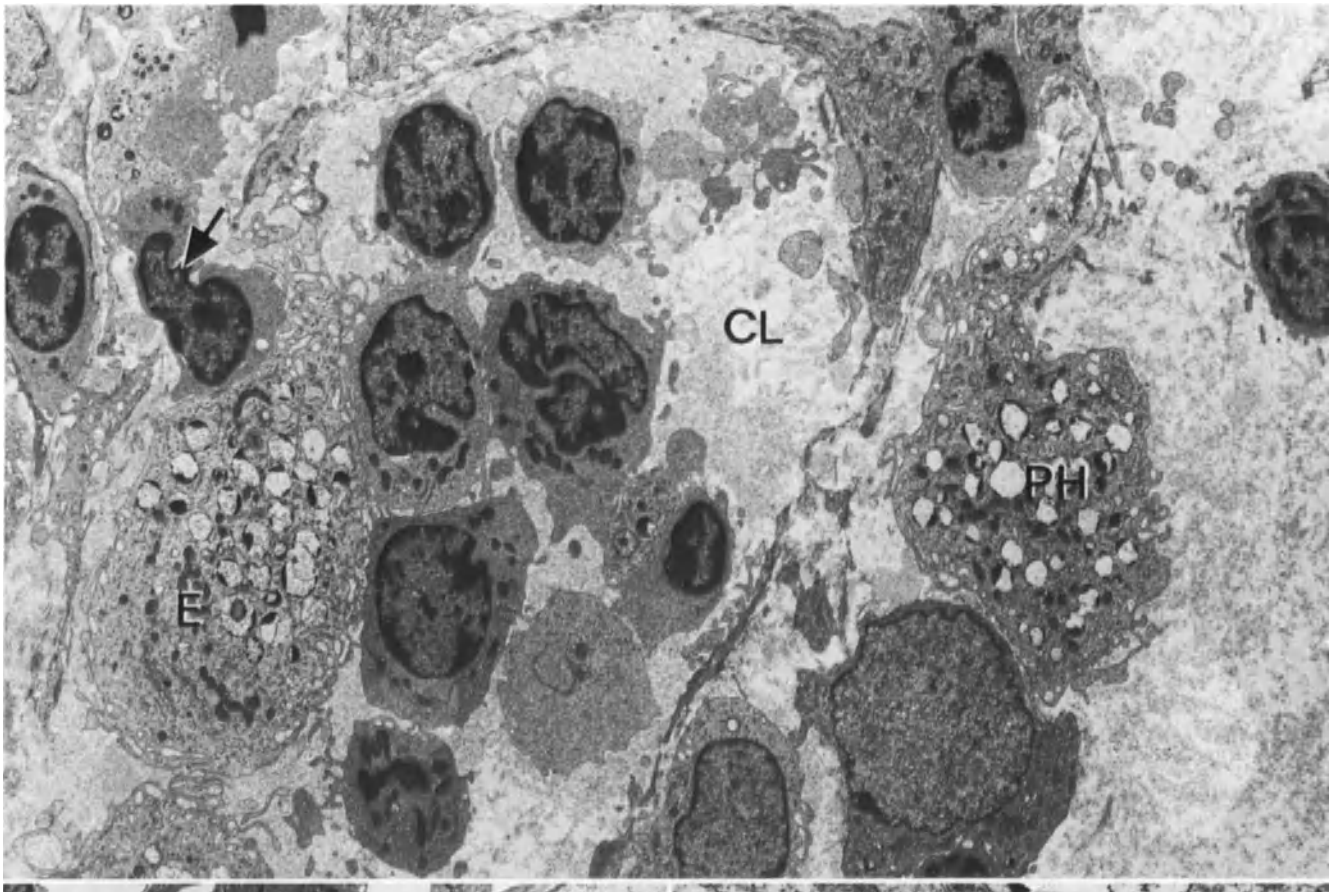
In glomeruli, an increase in thrombocytes (Fig. 30.13) and the presence of fibrin have repeatedly been reported [238, 838, 964]. We could confirm these findings in only 2 out of 36 cases of acute transplant rejection (Fig. 30.15). The glomerular endothelium is strongly edematous or hypertrophied (Fig. 30.16) and demonstrates arcade formation (Fig. 30.15). Occasionally, an increase in lysosomes (Fig. 30.16) – in addition to scattered foam cells, which sometimes contain thrombocytes (Fig. 30.14) – are encountered. Endothelial mitoses, genuine endothelial proliferation, and the presence of numerous monocytes in the lumen (Fig. 30.17) are very characteristic findings. The podocytes are very edematous or hypertrophied and demonstrate pronounced formation of microvilli (Fig. 30.17). (For glomerular findings compare also Figs. 6.9, 6.22, 6.34, 6.57, 6.64, 6.80, 6.88). The tubules evidence epithelial degeneration, and sometimes a few fibrin fibrils occur in their lumens (Fig. 30.18).

## 2. Acute Vascular Transplant Rejection

### LM Findings

Vascular changes are by far the most striking feature in this form of rejection (see Table 30.1). Endovasculitis, thrombi and arterio- and arteriolonecrosis are present in advanced stages, but we feel that endovasculitis is of primary significance (see also [1327]). Endovasculitis may be morphologically subdivided into two main phases: alterative-proliferative phase (acute transplant vasculopathy); and sclerosing phase (chronic vasculopathy). Since both main phases are often simultaneously present, subdivision is somewhat arbitrary. Initially, the endothelium of the small and middle-sized arteries is partly swollen and detached from the BM in an arcade-like fashion, but does not, as such seem significantly altered. The subendothelial space is soon filled with mononuclear cell infiltrates (Figs. 30.19, 30.20) composed of small and activated lymphocytes, monocytes, and, rarely, plasma cells, and the endothelium proliferates somewhat later (Fig. 30.22). Subendothelial foam cells, which are present in two-thirds of cases, may be seen as early as the twelfth day after transplantation (Fig. 30.23). Soon after subendothelial mononuclear cell infiltration, proliferation of (myo-)fibroblasts sets in. This proliferation is the most important factor in intimal thickening, and, consequently, in irreversible injury. In rare cases, veins, especially of greater size [78], show the same changes as seen in arteries in which endovasculitis is usually most pronounced at branching points. Subendothelial deposits discernible by LM are seen only in one-fourth of cases.

In less than 20% of cases, the media is also involved as recognized by fragmentation of the internal elastic lamina in the area of focal medial necrosis accompanied by polymorphonuclear leukocytic infiltrates. The media necroses rarely involve the entire thickness of the vessel wall, but if so, a pronounced perivascular mononuclear

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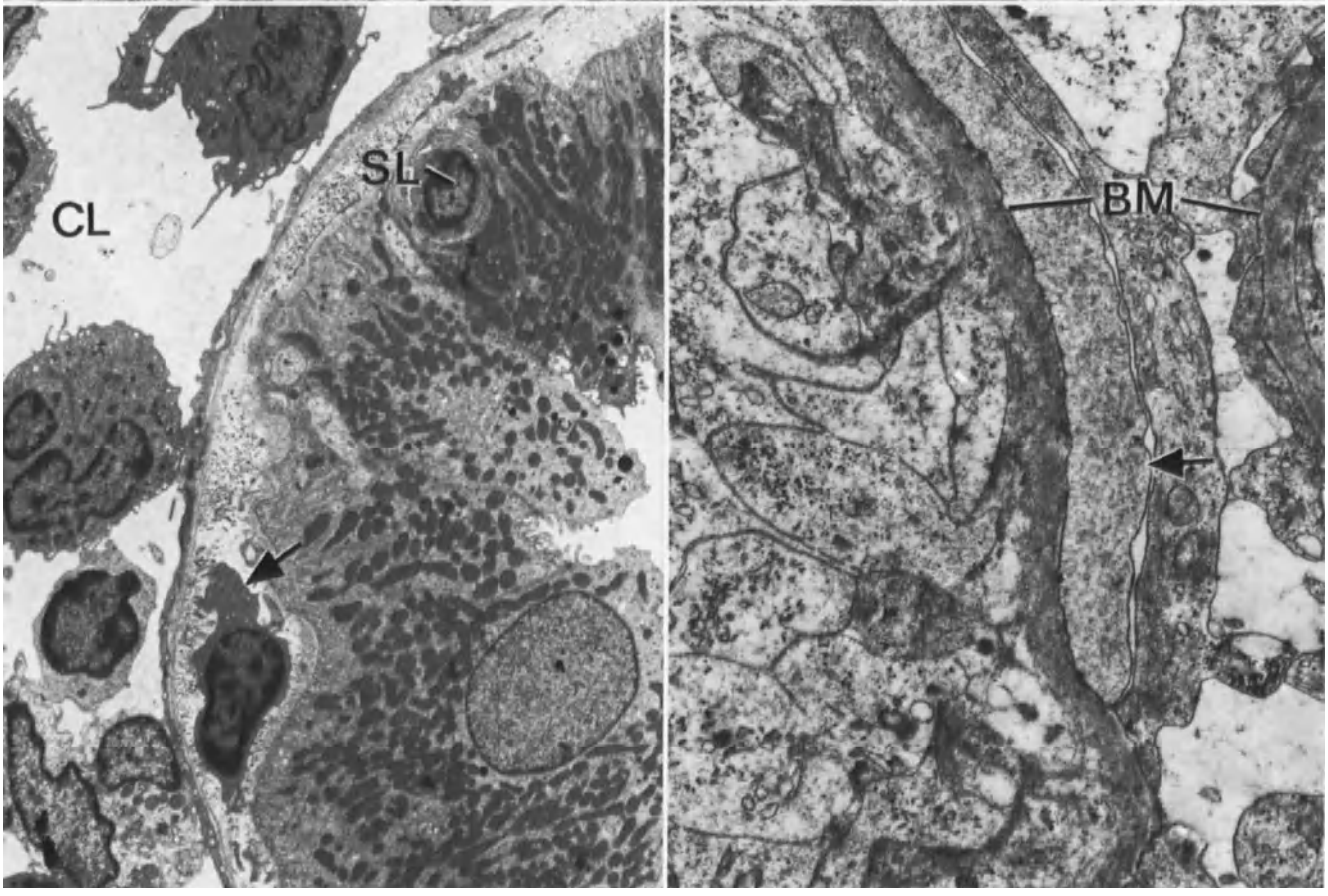


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infiltrate may be present which is usually limited to the inner third of the vessel wall.

As a consequence of endothelial and medial injury, we have seen secondary occluding thrombi in only 20% of cases in acute rejection. These were reported to be more frequent formerly but are now more rare with improved immunosuppression (33 out of 41: [238]; 4%: [1286, 838]).

Arteriolonecrosis, frequently mentioned in the literature and said to occur 3–4 weeks after acute rejection [337, 838, 964], was very rare in our cases of acute rejection (2 out of 38: Z; see p. 599).

It should be borne in mind that in early stages of acute vascular rejection, all vessels are by no means similarily affected, so that, especially in needle biopsies, the vascular changes may be missed (see p. 587).

Extensive parenchymal (tubular) necroses are the consequence of the severe vascular changes. The necrotic and/or dilated tubules (Figs. 30,24, 30.25) are sometimes extensively permeated by blood. In contrast to the interstitial type, extensive hemorrhage is also present in the interstitium loosened by edema. The interstitial capillaries are strongly dilated and evidence severe blood stasis (Fig. 30.24). Endothelium of the intertubular capillaries is not severely damaged. Immunoblasts are not all-too-rare in these capillaries, but the lymphoidal interstitial infiltrates are usually scanty.

In preserved parenchymal regions, the glomeruli show the same changes as are present in the interstitial type of rejection. At first, the glomerular cells are highly swollen (Figs. 30.26, 30.27). In some cases, the number of cells is strikingly increased (Fig. 30.80) simulating the picture of proliferative FGN. In later stages, the glomeruli show necroses – usually with severe loop dilatation and blood stasis (Fig. 30.28). In advanced stages, the glomeruli and vessels are filled with fibrin (Fig. 30.29).

◁ **Fig. 30.11.** Same case of interstitial transplant rejection as in Figure 30.10. Intertubular capillary (*CL*) contains numerous immunoblasts, one of which is seen passing through the capillary wall (→). Another cell, probably a monocytic or endothelial foam cell (*E*) in the lumen and a foam cell of histiocytic origin (*PH*) in the edematous interstitium are also shown. EM (×3420)

**Fig. 30.12.** Acute interstitial transplant rejection in a 2-year-old transplant. The lumen of a severely dilated intertubular capillary (*CL*) with immunoblasts is seen. An activated lymphocyte (→) is shown between proximal tubular epithelium and tubular BM. A small (non-activated) lymphocyte (*SL*) is present inbetween the tubular epithelial cells. EM (×3360)

**Fig. 30.13.** A glomerular capillary loop with numerous degranulated thrombocytes (*left*) in its lumen. Basement membrane (*BM*) of the loop. There is complete fusion of the foot processes (→). Acute interstitial rejection 6 weeks after transplantation. EM (×12,500)

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**Fig. 30.14.** A 4-month-old renal transplant. Endothelial foam cell in a glomerular capillary loop lumen with phagocytized thrombocytes. EM (×6100)

**Fig. 30.15.** A 66-day-old renal transplant. A leukocyte (*PL*) is seen in the lumen of a glomerular capillary loop as well as numerous fibrin strands (→). An endothelial cell (*E*) is hypertrophied. Endothelial lining of the BM is partly destroyed (*). There is minimal partial thickening of the lamina rara interna (→▷). BM is otherwise unaffected. Severe foot process fusion is present. EM (×9880)

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**Fig. 30.16.** An 11-day-old renal transplant with acute interstitial rejection. Numerous auto- and heterolysosomes (*) are present in the hypertrophied endothelium of a glomerular capillary loop. EM (×97,000)

**Fig. 30.17.** A 2.25-year-old renal transplant with acute interstitial rejection. Mitosis of an endothelial cell (*) in the distended glomerular capillary loop which also evidences numerous monocytoid cells (*MO*). Lamina rara interna is diffusely thickened (→). Podocytes demonstrate extensive microvilli formation (*VI*) and foot process fusion. EM (×4080)

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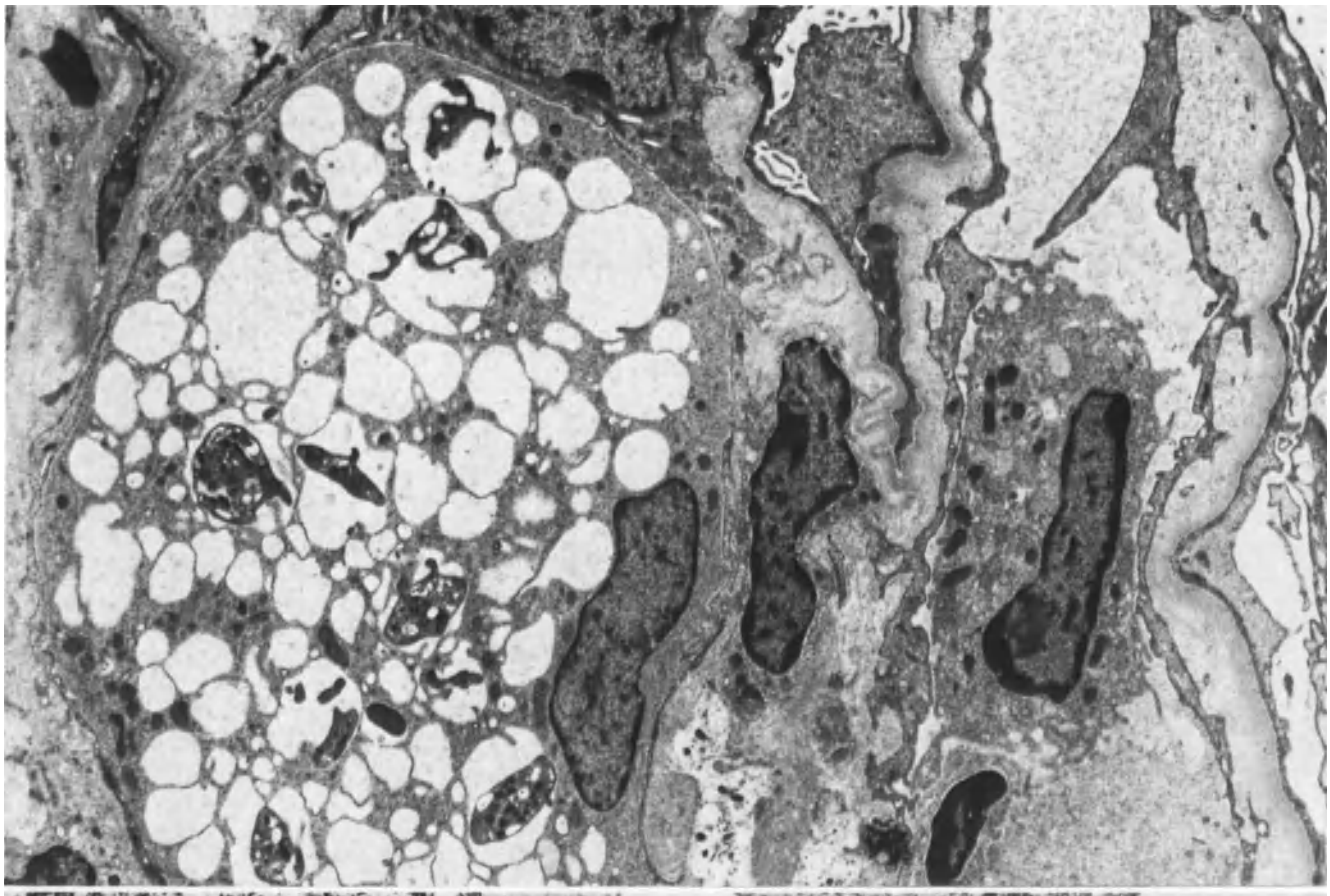
**Fig. 30.18.** A 4.66-year-old renal transplant with acute interstitial rejection. There are numerous fibrin strands in the tubular lumen. Note severe vacuolar transformation of endoplasmatic reticulum. BM is slightly thickened. EM (×2850)

**Fig. 30.19.** An 8-day-old renal transplant with predominantly vascular rejection. Arterial intima is detached by an extensive cellular infiltrate consisting mainly of immunoblasts. HE (×95)

**Fig. 30.20.** A 6.5-month-old renal transplant evidencing acute (alterative-proliferative) vascular rejection. Endothelium of a small artery (→) is extensively detached from the media by an infiltrate with abundant immunoblasts and a few activated lymphocytes. There are numerous immunoblasts also present in lumen. Perivascular infiltrate (*). HE (×140)

**Fig. 30.21.** An 8-day-old transplant evidencing acute vascular rejection. Wall of a vein shows an endothelium (*E*) which is highly detached from media by a dense infiltrate consisting of phagocytes, plasma cells and, above all, of activated lymphocytes. Semi-thin section. Giemsa (×700)



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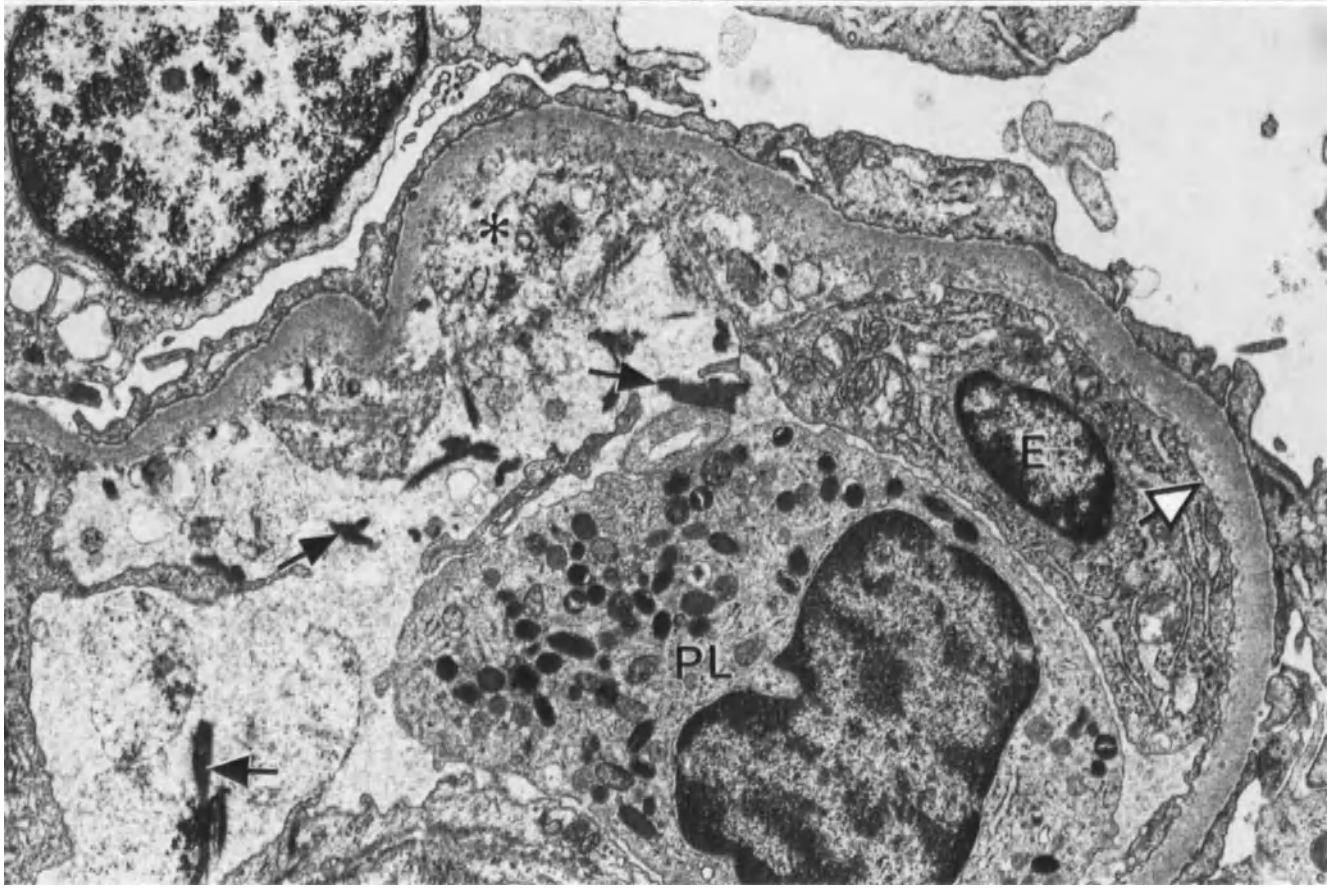


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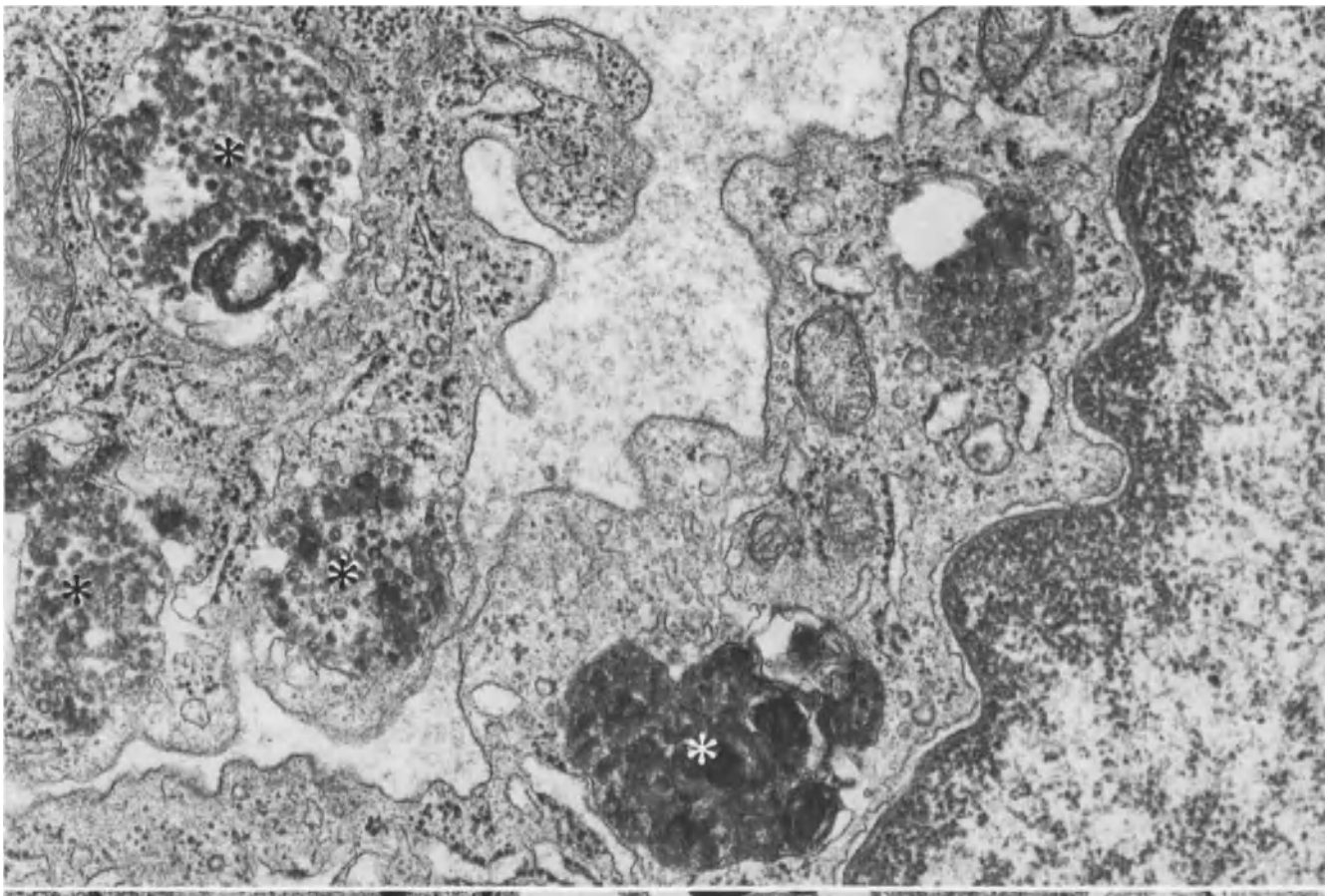

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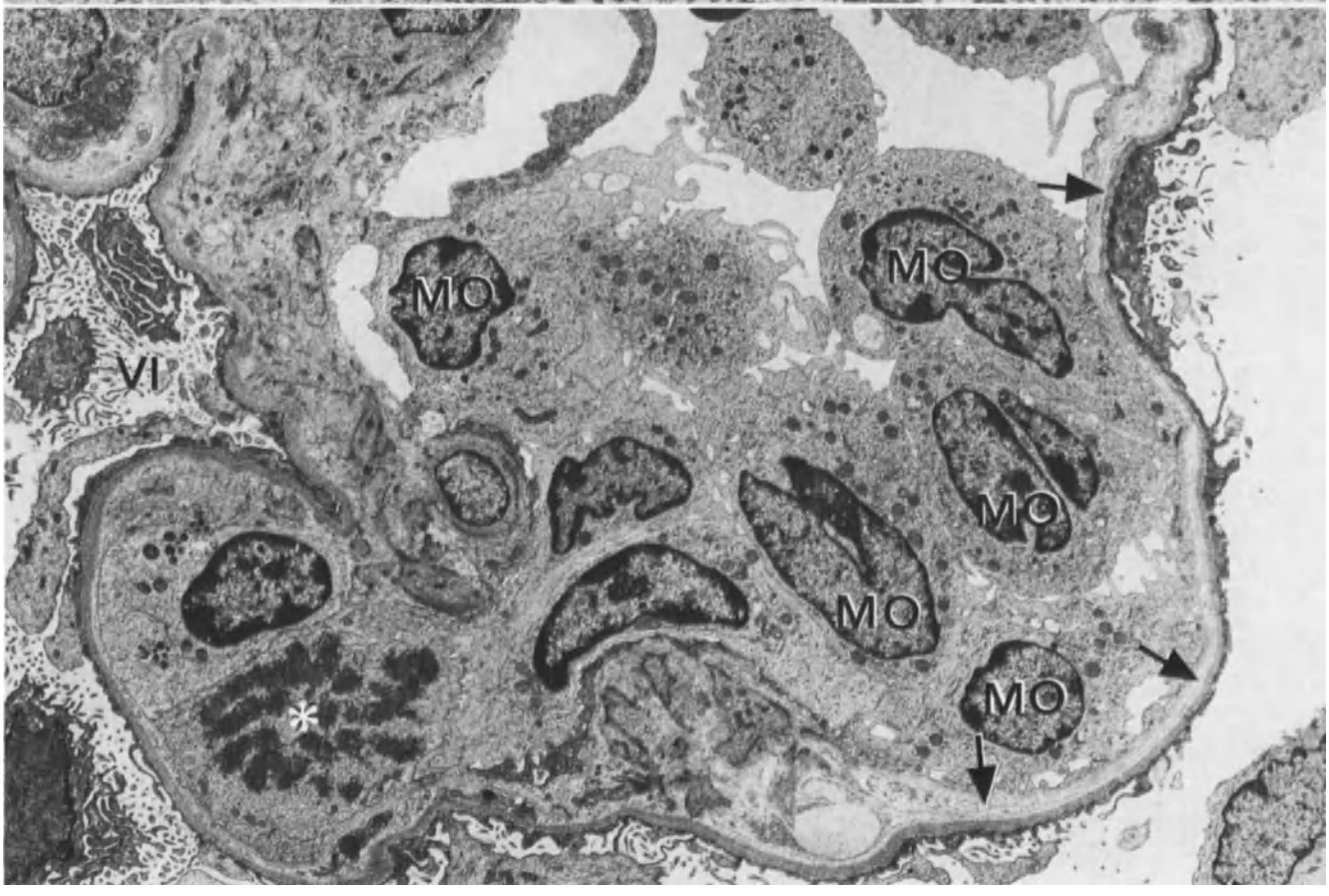


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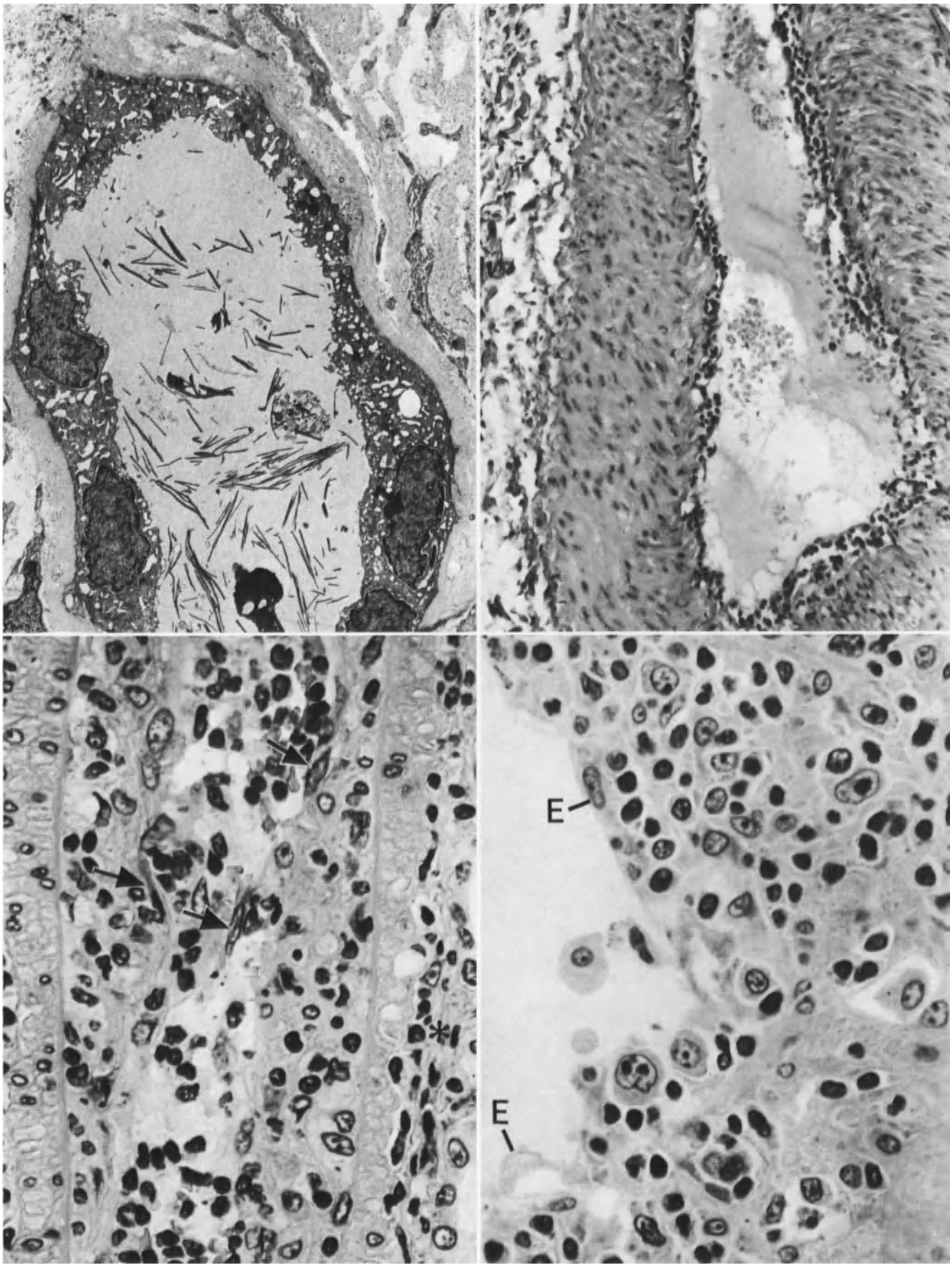


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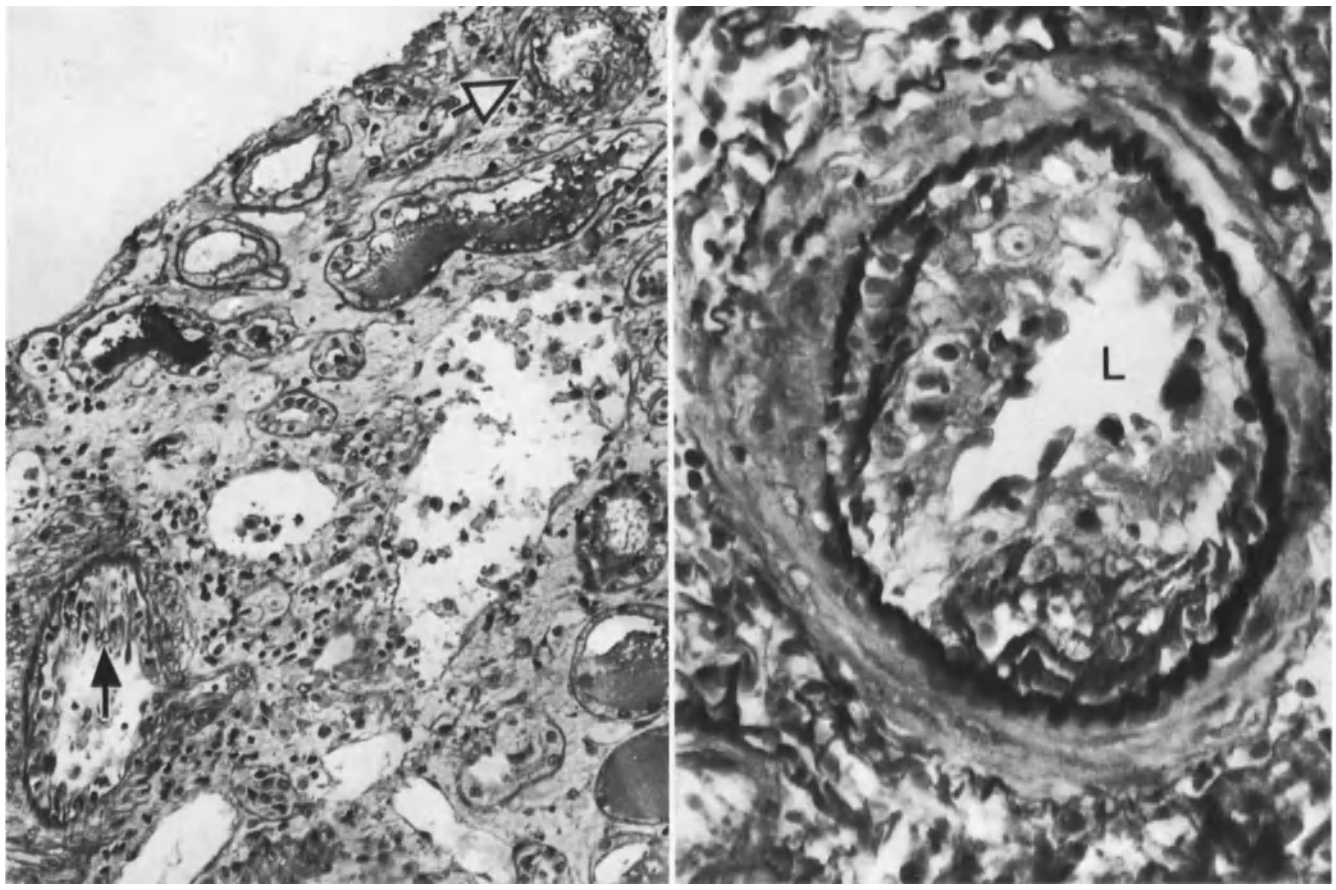


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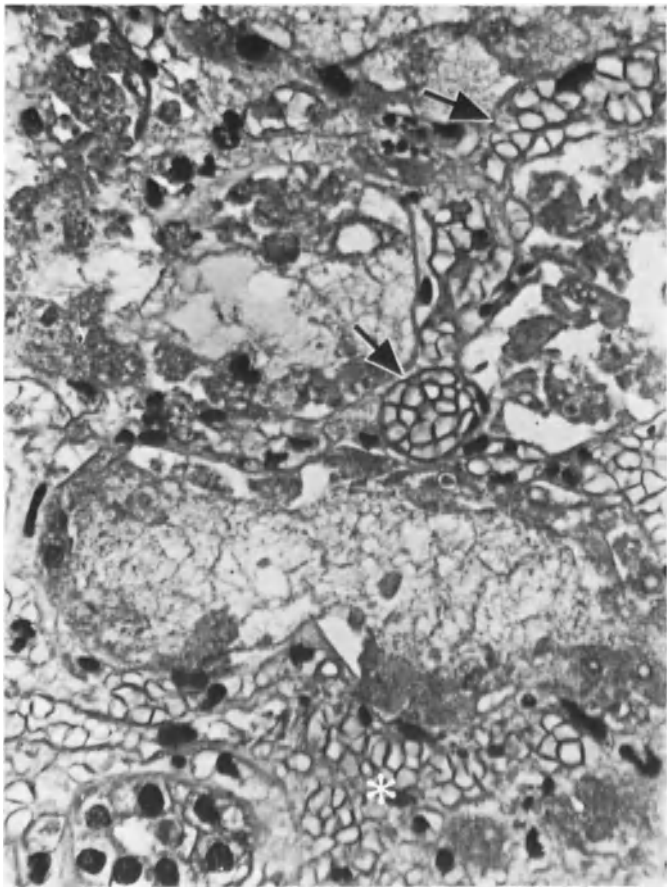
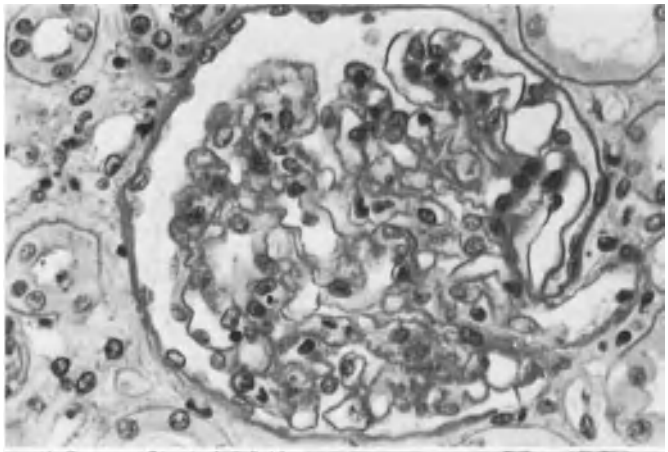
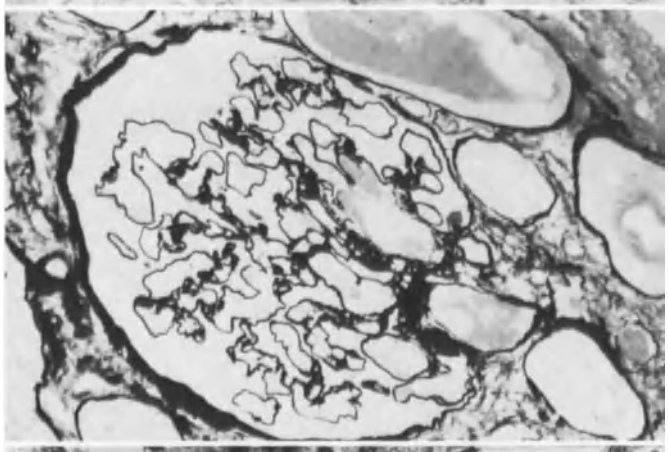
**Fig. 30.22.** A 12-day-old renal transplant evidencing a predominantly vascular acute rejection reaction. A cushion of proliferation is seen in a small artery (→). Lumen of one arteriole is highly narrowed by proliferative processes (↠). Only very scanty infiltrates are present in the edematous interstitium. There are numerous hyaline casts in the severely injured tubules. PAS (×200)

**Fig. 30.23.** Same case as in Figure 30.22. Subintimal pads severely narrowing the vessel lumen (*L*). Pads consist of proliferated (myo-)fibroblasts, foam cells and a few small lymphocytes. Lamina elastica is intact. Van Gieson-elastin (×320)

**Fig. 30.24.** A 13-day-old renal transplant with acute vascular rejection showing beginning infarction of the medulla. Some tubules are necrotic. Note extensive interstitial bleeding (→←). HE (×85)







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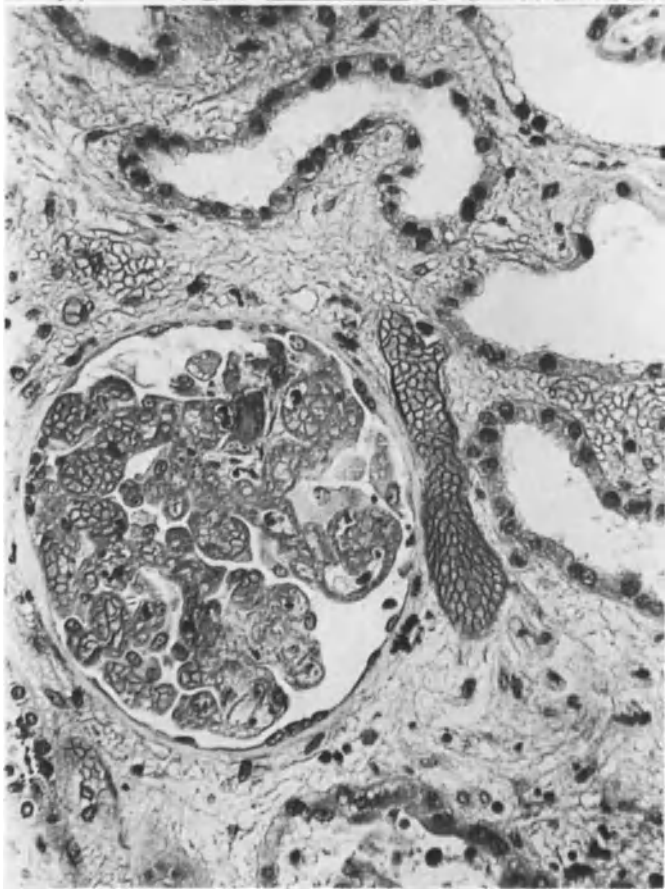

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**Fig. 30.25.** Same case as in Figure 30.24. Extensive necrosis of tubular epithelium with clumpy disintegration and detachment. Interstitial vessels are full of laked erythrocytes (→) which are also permeating the interstitium (*). HE (×400)

**Fig. 30.26.** Same renal transplant (with incipient infarction) as in Figure 30.24. Obvious swelling but no increase of glomerular cells with slight narrowing of the capillary loop lumens. PAS (×240)

**Fig. 30.27.** Same renal transplant as in Figure 30.24. In PASM stain the mesangium and BM are unchanged and not afflicted by swelling of glomerular cells depicted in Figure 30.26. (×240)

**Fig. 30.28.** A 7-week-old renal transplant with thrombosis of the renal artery. Severe blood stasis in glomerular capillary loops and intertubular capillaries. Glomerulus shows incipient necrosis. HE (×200)

## EM Findings

The severely injured endothelium of arteries as well as veins is usually detached from the BM (Fig. 30.33) and is occasionally necrobiotic. In other cases, severe swelling of endothelial cells results in almost total occlusion of the vascular lumen (Fig. 30.34). Rarely, activated lymphocytes in the vessel lumen are in immediate contact with the injured endothelium.

The subendothelial infiltrates are composed of small and activated lymphocytes, immunoblasts, plasmoblasts, and histiocytes (Fig. 30.33). Rarely, scanty polymorphonuclear leukocytes and erythrocytes are present. Foam cells may develop from monocytes from the blood stream as well as from myofibroblasts.

Depending on the severity of the lesion, the internal elastic lamina and media may be unchanged or severely damaged (see above and for further details p. 596).

Severe blood stasis with accumulation of thrombocytes is present in the intertubular capillaries (Fig. 30.35) as well as a few edematous cells which possibly represent lymphoid elements (Fig. 30.36).

In general, the tubules are severely but unspecifically damaged (Fig. 30.36). The tubular lumens contain fibrin strands which correlate with the excretion of fibrin-split products in urine (Fig. 30.18). Extravasation of blood into the interstitium and tubules is nearly always present.

The glomerular capillaries evidence blood stasis, which is severe, and contain edematously swollen lymphoid elements (Fig. 30.37). Stasis is followed by necrosis, which is accompanied by extensive fibrin deposition (Fig. 30.38) and thrombus formation (Figs. 30.38, 30.42). Glomeruli not exhibiting blood stasis consistently show endothelial swelling and degeneration (Fig. 30.41).

Recently, we have noted an inconstant glomerular change consisting of severe endothelial swelling together with an accumulation of monocytic elements (possibly immunoblasts) (Fig. 30.80; p. 608), which is sometimes present at the very beginning of acute vascular rejection. This change can easily be mistaken under LM for focal GN. We call this lesion *"pseudo-glomerulitis"*.

## IF Findings

In comparison to chronic rejection processes, the acute rejection crisis is said to be accompanied by very marked IF findings [470, 653]. From the seventh day on, the glomeruli, in 75% of the cases, contain granular deposits of IgG, IgM, complement and/or fibrin(-ogen). According to other investigators, granular deposits of IgG, IgM, and C3 were found in 50–70% of cases of acute and in 18% of chronic rejection [653]. In our own material, the IF findings were not very impressive. In 17 cases of acute rejection within the first two months after trans-

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**Fig. 30.29.** A 54-day-old renal transplant evidencing acute vascular rejection. Glomerular cells have almost completely vanished. There is severe thickening of glomerular BM by fibrin deposition. Artery and arteriole (*A*) are lined by coarse fibrin rings. Interstitium is edematous and demonstrates relatively scanty inflammatory infiltrates. Some of the tubular cells are necrotic and detached. PAS (×280)

**Fig. 30.30.** Segmental distribution of fibrin(-ogen) deposits along peripheral glomerular BM in a case of acute transplant rejection. IF (×400)

**Fig. 30.31.** Abundant fibrin(-ogen) is present in the capsular space and in proximal convoluted tubule (fibrinuria) in a case of acute transplant rejection. IF (×300)

**Fig. 30.32.** Diffuse permeation of a small artery with fibrin(-ogen) in late stage of acute vascular rejection. IF (×300)

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**Fig. 30.33.** Interstitial venule in a 66-day-old renal transplant with acute vascular rejection. Masses of fibrin strands and activated lymphocytes are present in the vessel's lumen. Endothelium is detached for a considerable distance by edema (→) or by subendothelial infiltrates (⇾⇽). Interstitial infiltrates composed of (*) histiocytes, small and activated lymphocytes are present, as is edema. EM (×1600)

**Fig. 30.34.** A 3.5-month-old renal transplant. Arteriole with severe swelling and proliferation of endothelium which is in intimate contact with an activated lymphocyte. This vascular change appears to be very acute. Myocytes (*MC*) are occasionally obviously contracted (so-called corkscrew nuclei). Lumen of vessel (*L*) is much narrowed. EM (×5440)

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**Fig. 30.35.** An 18-day-old renal transplant evidencing acute vascular rejection. Severe stasis of erythrocytes in intertubular capillaries (*) and extravasation of erythrocytes (→) in highly edematous interstitium. Plasma cell (*PS*) with distended rough endoplasmatic reticulum. In general, these findings are similar to those seen in Figure 30.25. EM (×3100)

**Fig. 30.36.** A 12-day-old renal transplant evidencing acute vascular rejection. There is severe cystoid degeneration of tubular epithelium (*). Interstitial edema with a few erythrocytes and severely edematous phagocytes (*PH*) is present. Monocytoid cells (*MO*) can be seen in the considerably dilated bloodless interstitial capillaries (*CL*). Cf. Figure 30.37. EM (×2260)

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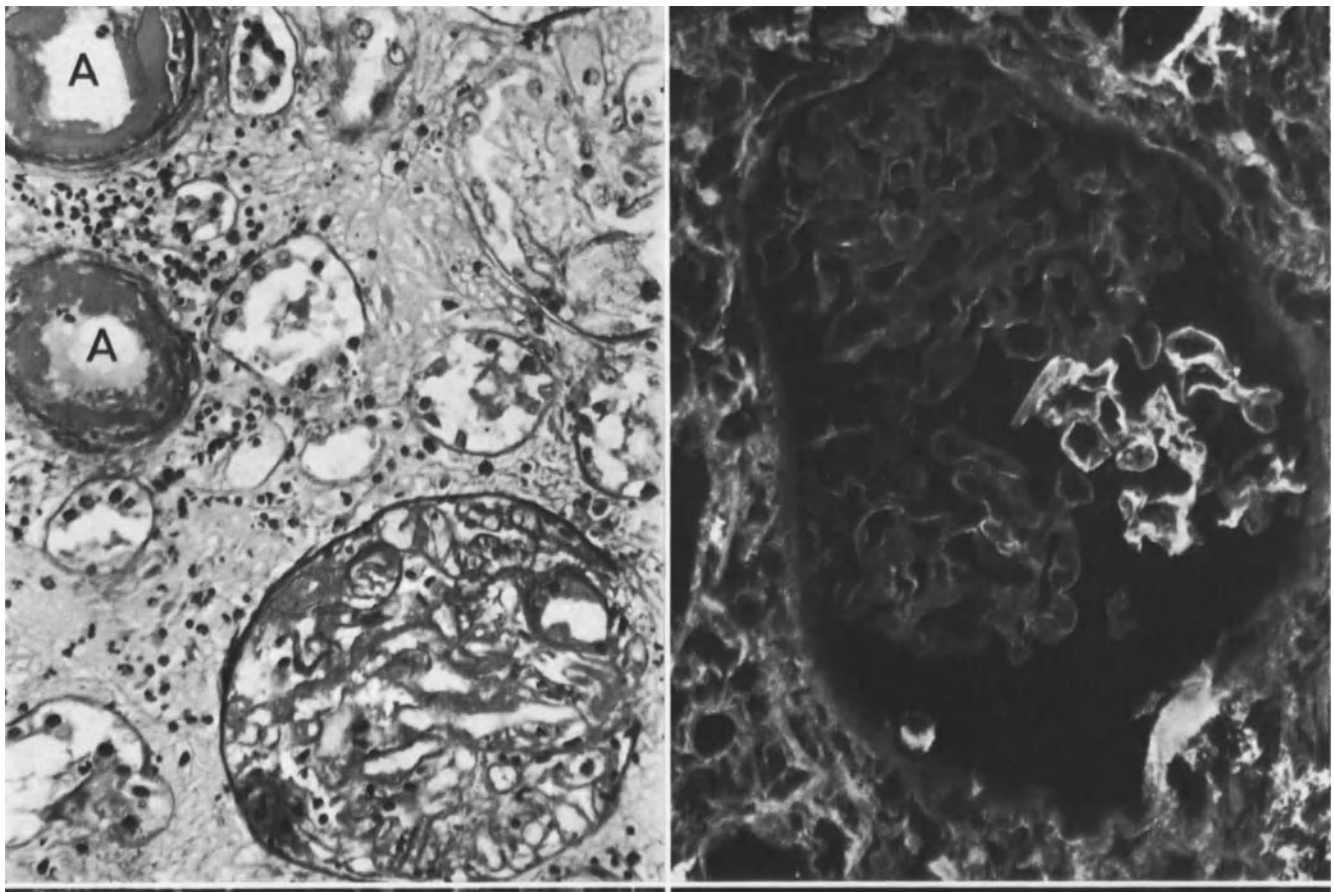
**Fig. 30.37.** Same case as in Figure 30.36. Severe blood stasis in glomerular capillary loops which also contain numerous monocytoid cells. Podocytes are highly edematous. EM (×1180)

**Fig. 30.38.** A 7-week-old transplant in which thrombotic occlusion of the renal artery at the site of suture occurred. There is severe anoxic injury of the glomeruli with complete endothelial necrosis. The glomerular capillary loops are distended and clearly evidence stasis of erythrocytes. Coarse fibrin clumps are present in the loop lumens (→) and are occasionally seen adhering to their walls. Note severely edematous podocytes with microvilli. EM (×3870)

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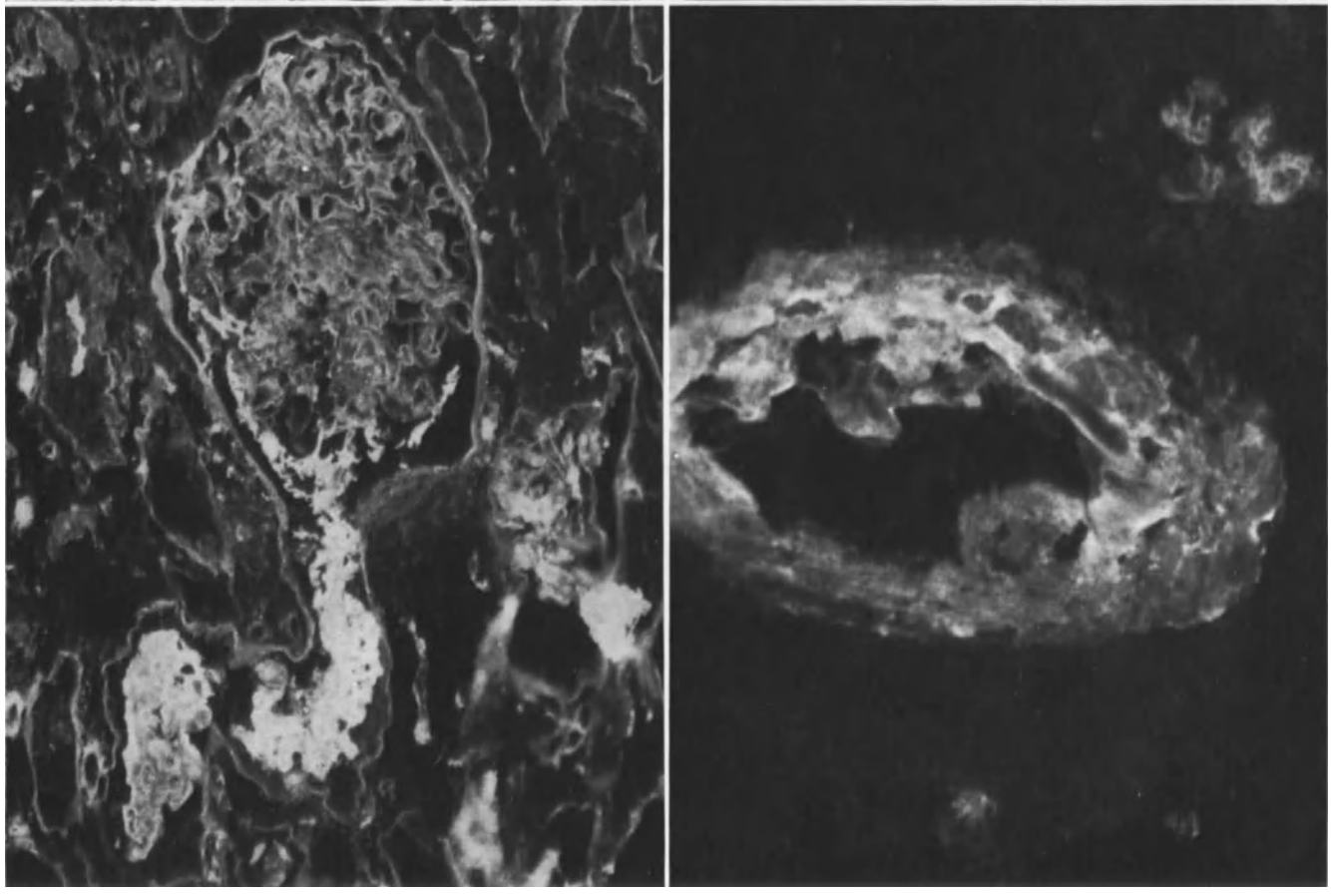

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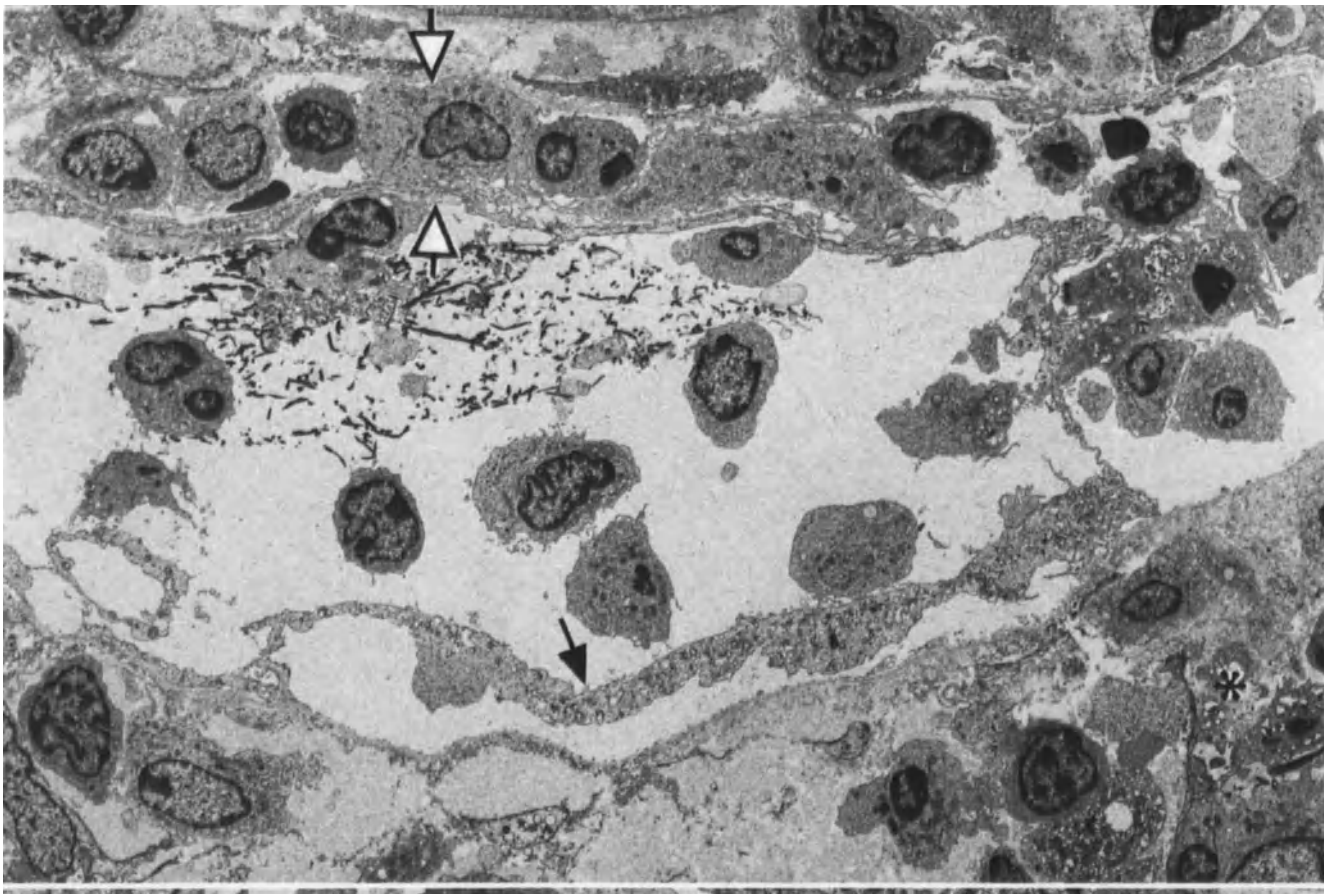

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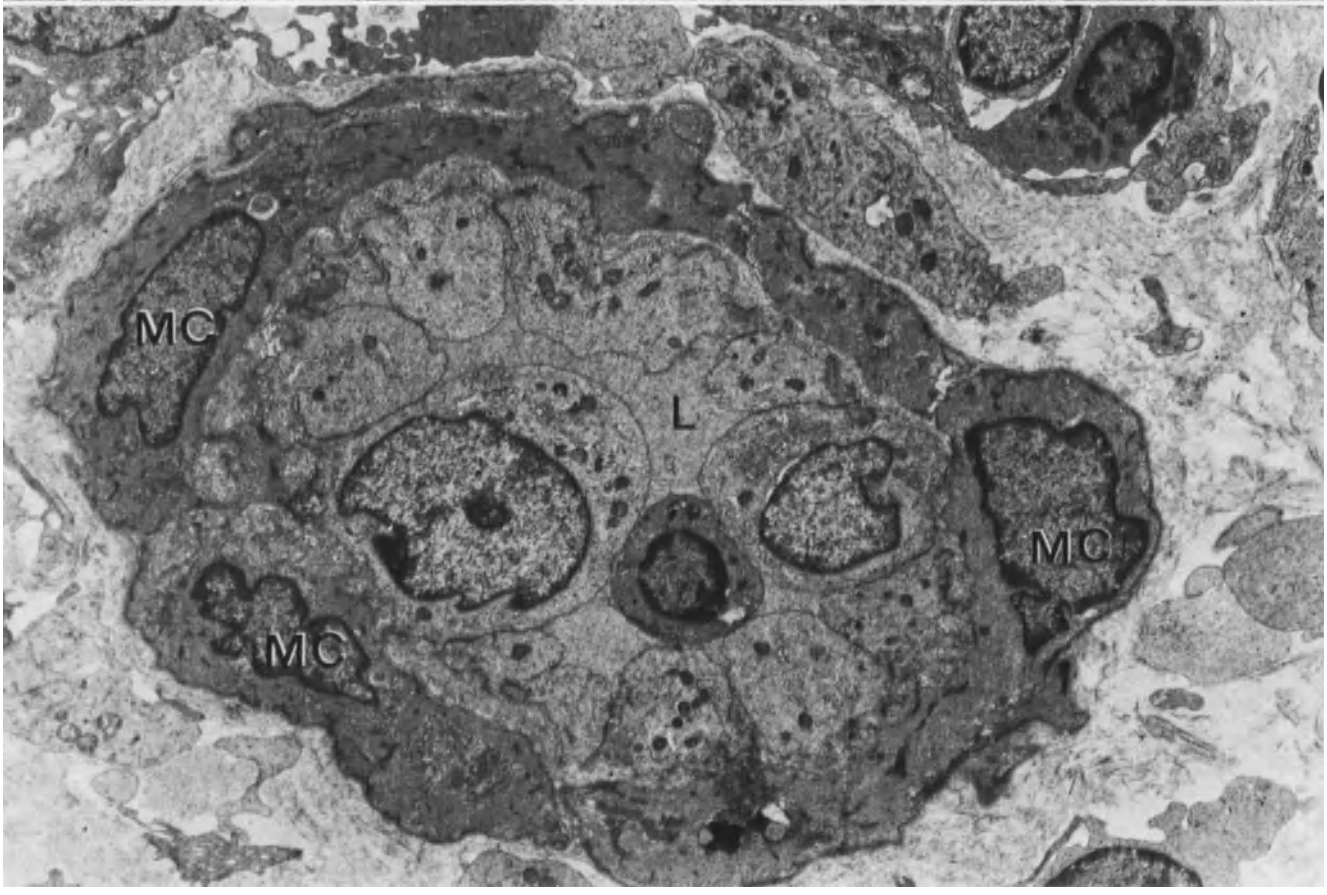


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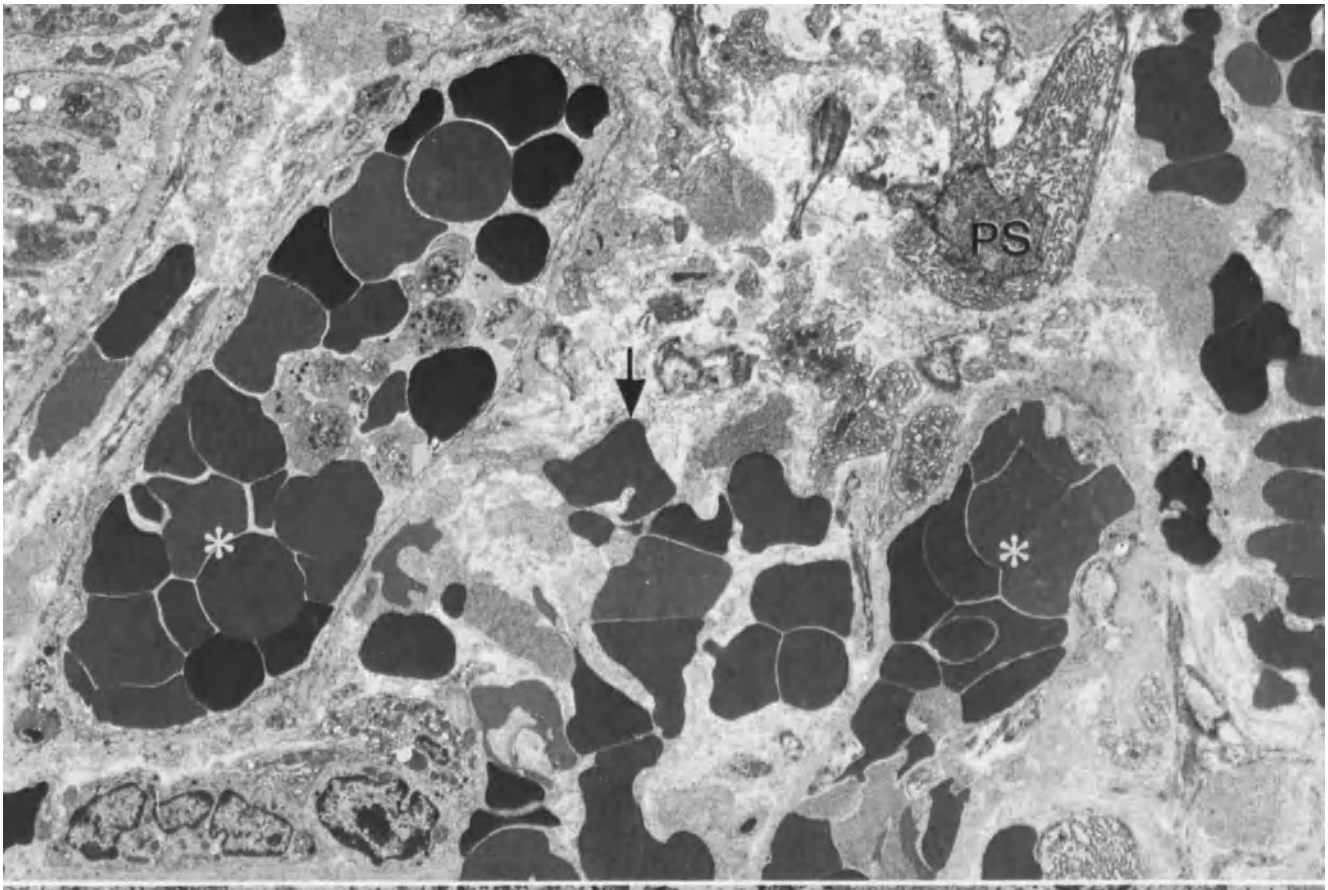


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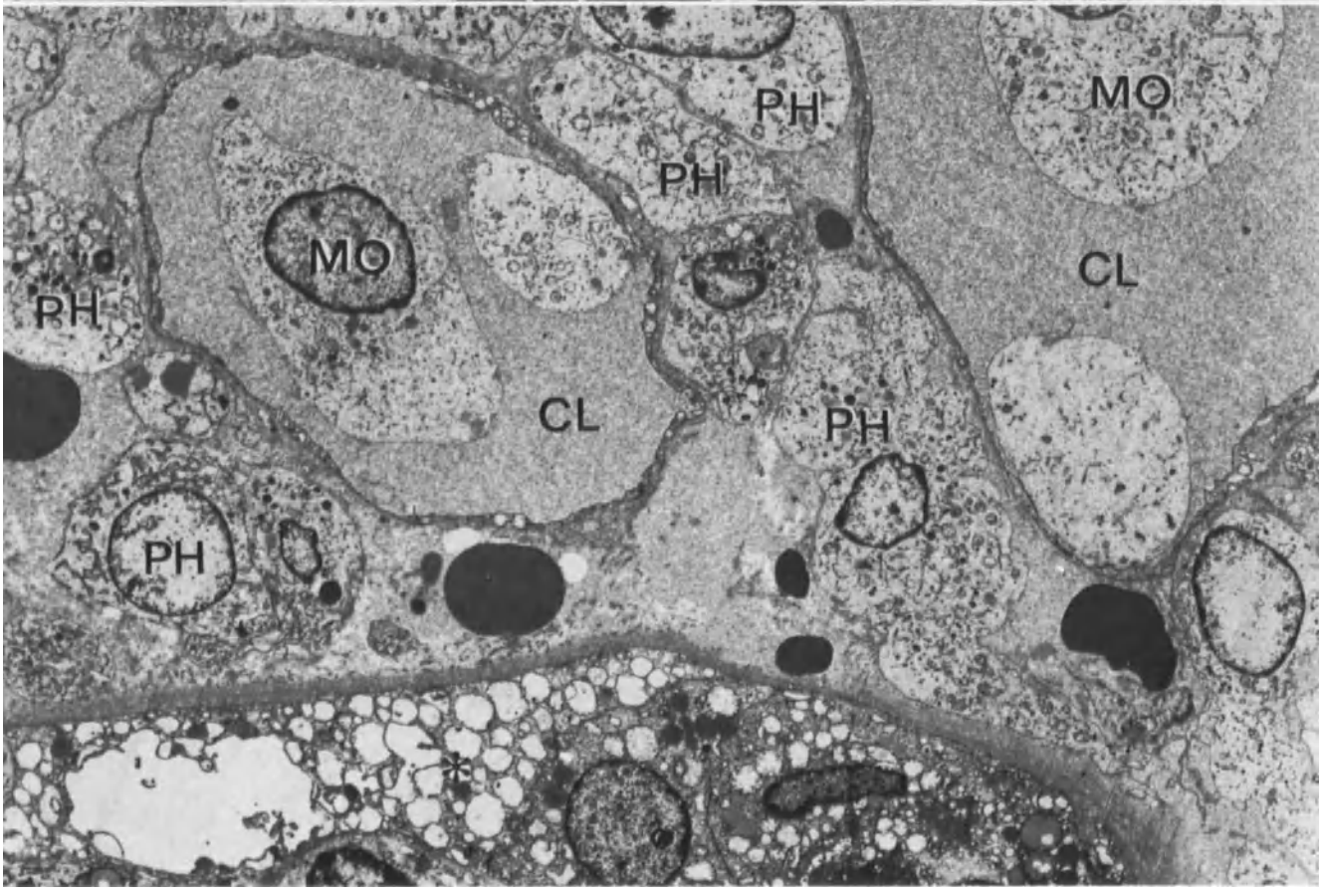


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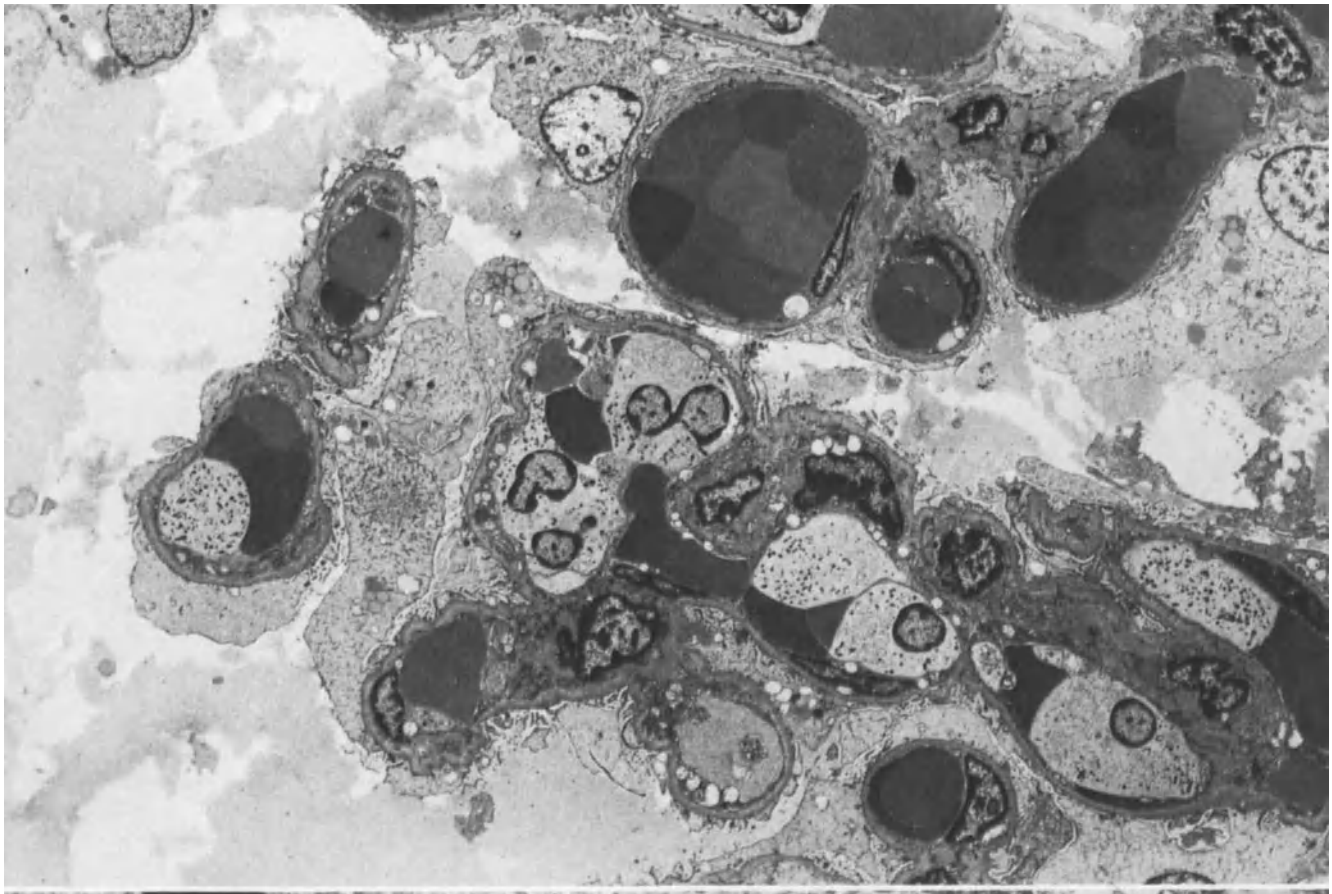

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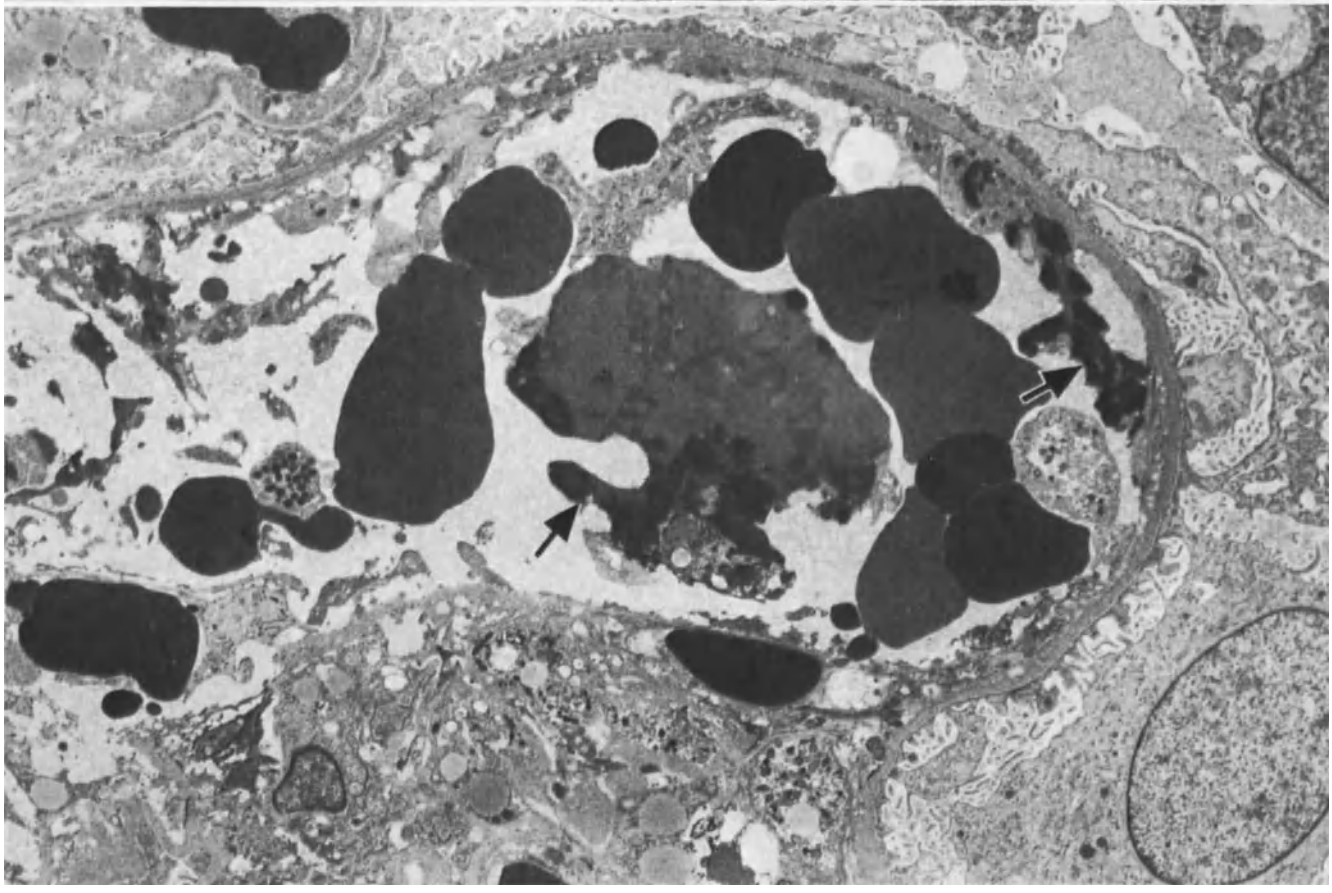


30.38

plantation in the absence of severe transplant glomerulopathy, the glomeruli were IF negative in 7 out of 17 cases, and 3 out of 10 cases showed granular deposits of IgM and C3, IgM alone, or fibrin alone (Fig. 30.30). In 7 out of 10 cases ultralinear deposits were present which stained positive for C3, IgG, IgM, IgA, and fibrin(-ogen) (compare Table 11.1). Re-biopsy of two patients 4–5 weeks after demonstration of the ultralinear IgG deposits revealed that the deposits were no longer present, a finding which we interpret as the expression of endothelial injury in the first biopsy.

IgG, fibrin and complement are frequently found in parenchymal necroses of vascular origin [238] and probably arise by secondary insudation.

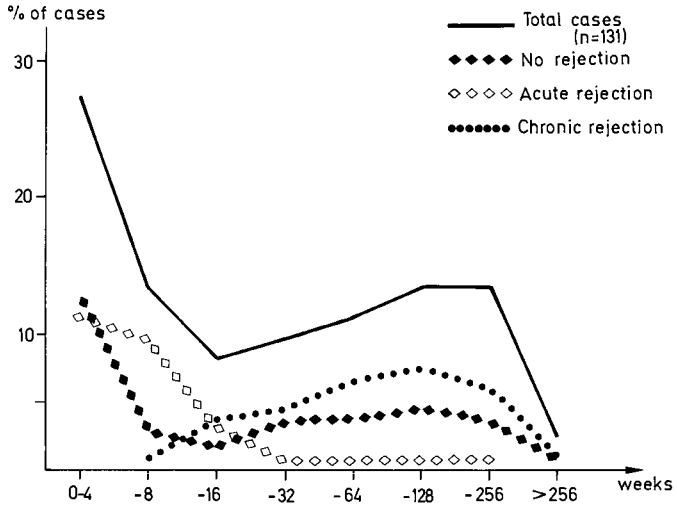



**Fig. 30.39.** Time elapsed between kidney transplantation and renal biopsy as related to rejection responses

Fibrin in vessels has been frequently reported to be present in acute rejection (Fig. 30.31). In our material, 9 out of 14 cases with small arteries in the biopsy were IF negative; in the other cases, IgM (Fig. 30.32) and C3 were present three times, and fibrin(-ogen) was always present. In 10 out of 13 of our cases, the interstitium was positive for fibrin(-ogen) deposits and in 6 out of 13 cases for other immunoglobulins.

The prognosis in acute rejection is not related to these IF findings [238].

## 3. Differential Diagnosis of Peracute and Acute Transplant Rejection

The essential findings for the differential diagnosis are summarized in Table 30.1 (compare also Figs. 30.39, 30.40).

Peracute rejection may be differentiated from acute intravascular coagulation by the presence of numerous intraglomerular polymorphonuclear leukocytes, extensive anoxic parenchymal injury and by the occasional interstitial hemorrhage occurring in peracute rejection. It is possible that cases considered as peracute rejection occurring relatively late after transplantation really represent acute intravasal coagulation.

The differentiation between acute interstitial transplant rejection and acute interstitial nondestructive nephritis is scarcely possible unless eosinophilic leukocytes predominate, a finding which indicates acute interstitial nephritis. Dense accumulation of infiltrates speaks rather

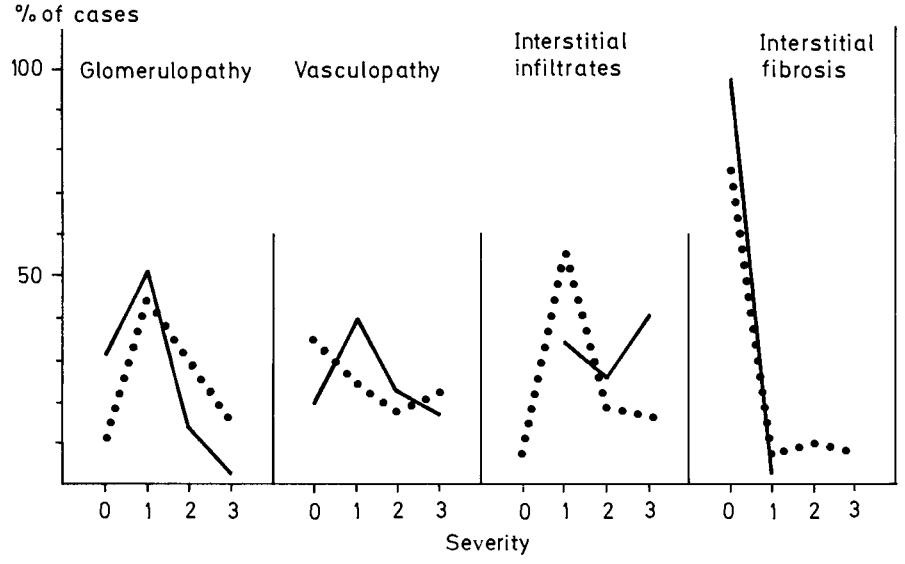



**Fig. 30.40.** Comparison of various semiquantitatively evaluated morphologic parameters in acute (——) and chronic (· · ·) renal transplant rejection. Numbers 0 to 3 on the abscissa refer to semiquantitative rating of the parameter

for transplant rejection; EM is not helpful in this differential diagnostic problem, nor is the quantitative differentiation of the infiltrate (see Fig. 9.2).

The vascular changes as such are so typical that they can hardly lead to differential diagnostic difficulties. At most, microangiopathy—which can also occur acutely after transplantation [994]—may prove troublesome.

In microangiopathy however, the intimal pads are—in the acute phase—rich in fibrin, while typical granulation tissue characterizes the chronic phase. The granulation tissue is more loosely structured than that of the inflammatory response and of the subsequently occurring scar tissue of transplant vasculopathy. We have encountered extensive arteriolonecrosis in humans (as opposed to experimental findings in the rat) only in the concomitant presence of hypertension.

The so-called pseudo-glomerulitis (p. 581), as occurs in acute vascular rejection, must not be falsely interpreted as genuine proliferative FGN.

Our main differential diagnostic problem encountered in 20 needle biopsies from patients with the clinical picture of acute transplant rejection from the first and second post-transplant weeks was that of so-called shock kidney characterized by greatly flattened proximal tubular epithelium and dilated proximal tubules. A retrospective study of the case histories of these patients has shown that in 4 patients, genuine circulatory/septic-toxic shock was etiologically responsible for the renal changes [1804]. Later biopsies—and occasionally nephrectomies—from the remaining 16 showed subtotal occluding arterial thrombosis at the suture twice (Fig. 30.43), a peripheral transplant vasculopathy mostly of severe degree, 6 times, and 3 instances of ureteral obstruction due to ureteral necroses. In 5 other transplants, function recovered completely, a finding which led us to consider "camouflaged" rejection as the cause of shock kidney. Relating to differential diagnosis, it is noted that the presence of a usually severe interstitial and, more rarely, glomerular blood stasis and marked tubular necrosis are in favour of vascular rejection or thrombosis of the renal artery. Lymph vessel casts, which were present in ureteral obstruction, were lacking in the other groups [1804].

From the above-instanced findings, it must be concluded that different etiologic factors, which cannot always be determined by morphologic investigations alone, can lead to a picture identical to that encountered in genuine circulatory shock. Pathogenetically, hypoperfusion may be the operative etiologic factor as it is in genuine shock [473, 1804]. The morphologic finding of so-called shock kidney in transplants must be considered as an indication for arteriography as well as pyelography. In a clinical study [1854], the following causes of oligo-anuria occurring within 10 days after transplantation were stated (in % of cadaver grafts/related living donor grafts): acute tubular necrosis 24%/0%; rejection 9%/3.2%; arterial thrombosis 0%/1.6%; venous thrombosis 4%/1.6%; ureteral obstruction 1.0%/3.2%; renal compression 2.1%/3.2%.

### Prognosis

In most cases, acute interstitial rejection can be clinically suppressed by increased immunosuppressive therapy. If no such therapy is introduced or, if it is started too late, the transplant will undergo irreversible injury from impairment of blood flow due to the severe vascular and/or interstitial changes. Acute vascular rejection appears to respond poorly to immunosuppressive therapy. The more severe the endothelial damage, the poorer the prognosis [1479]. It is noted that endothelial swelling alone apparently does not lead to functionally complete vascular occlusion for which vasoconstriction seems to be necessary [861a, 881, 1373, 1591c].

In our experience, subsequent to treated acute rejection, a certain degree of irreversible injury in vessels, glomeruli, and interstitium is present in every case studied. In all our biopsies with a history of acute rejection, we found, at least with EM, mild vasculo- and glomerulopathy or patchy interstitial sclerosis/fibrosis. There is probably a correlation between the severity and duration of the acute rejection to the severity of the residual changes. Therefore, each rejection episode worsens the prognosis of a transplant [983a].

## Chronic Transplant Rejection

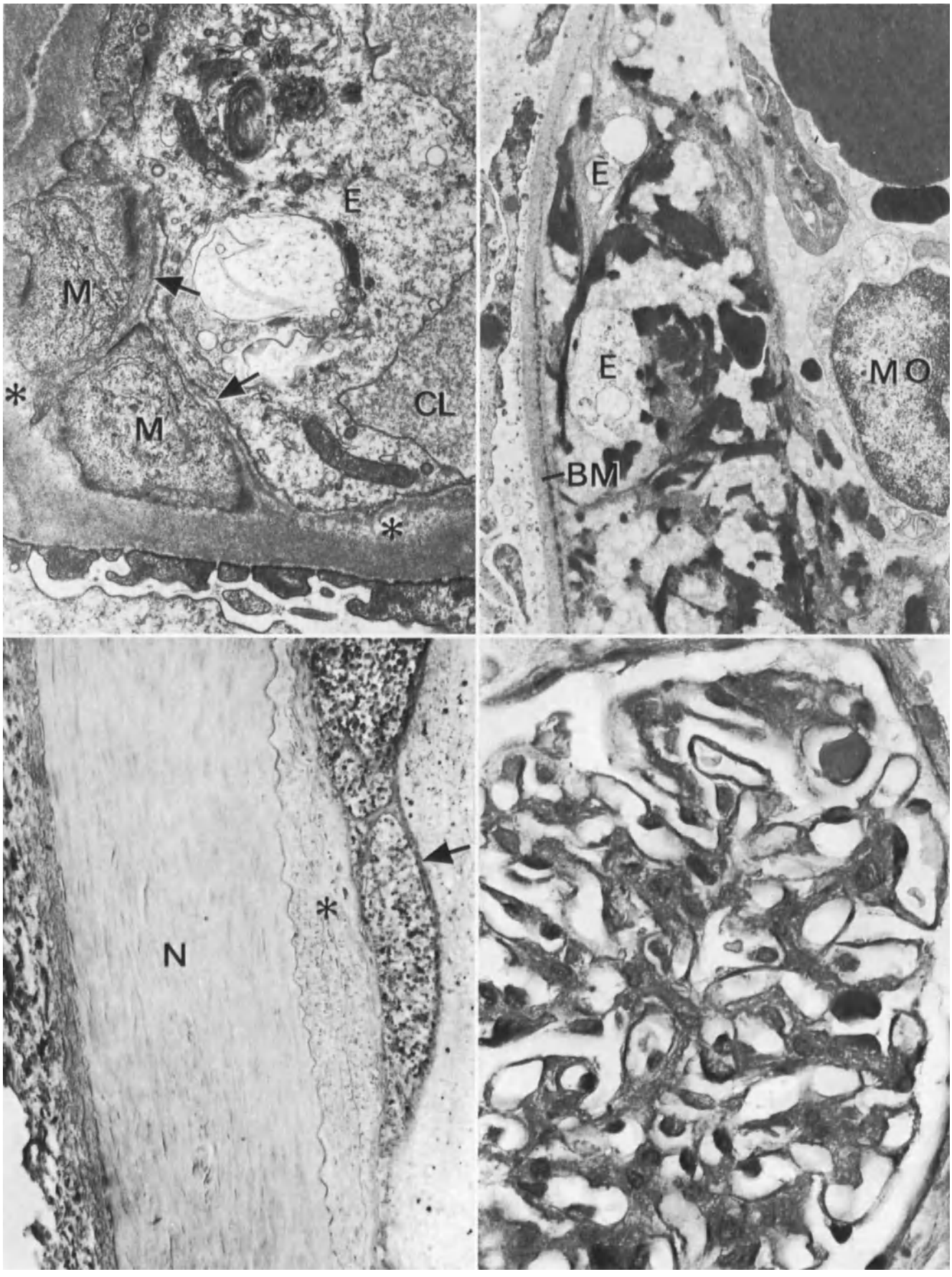
### Incidence

Of our renal transplants, 30% give evidence of a chronic transplant rejection which starts 2 months after transplantation to reach a maximum after 2.5 years (Figs. 30.39, 30.40).

### Clinical Findings

Chronic rejection usually does not cause subjective complaints, but it is characterized by a slowly progressive or stepwise deterioration in renal function. Often, in crease in proteinuria and blood pressure are present.

***Comparison of LM Findings in Chronic and Acute Rejection.*** In chronic changes, all four renal elements, i.e., glomeruli, vessels, tubules, and interstitium, may be changed to a varying extent. The comparison in Figure 30.40 shows that the glomerular changes are more pronounced in chronic than in acute transplant rejection.




30.41
30.42

30.43
30.44

In relation to vasculopathy, however, there are no significant quantitative differences, since vascular changes can be as extensive in acute as in chronic vascular transplant rejection. Narrowing of the lumen in acute vasculopathy is due to endovasculitis; in the chronic form, it is due to intimal fibrosis. Extensive interstitial inflammatory infiltrates are considerably less frequent in the chronic than in the acute form in which they are frequently quite dense. Interstitial fibrosis/sclerosis is not usually of great significance.

Table 30.2. Relationship between severity of glomerulopathy, and age of transplant

| Degree of glomerulopathy | No. of cases | | | | | | |
|---|---|---|---|---|---|---|---|
| III | – | 1 | 1 | 1 | 1 | 1 | 3 |
| II | – | 1 | 4 | 1 | 3 | 4 | 4 |
| I | 5 | 9 | 6 | 10 | 9 | 14 | 8 |
| 0 | 26 | 3 | – | – | – | – | – |
| weeks | −4 | −8 | −16 | −32 | −64 | −128 | 256 |

## 1. Chronic Transplant Glomerulopathy [1805]

### LM Findings

Mesangial thickening without increase in cells and a peculiar, blurred thickening of the peripheral capillary loop wall in the PAS stain (Fig. 30.44)—which at first can be confused with epimembranous GN—characterize chronic glomerulopathy.

The glomeruli are afflicted to varying degrees. In one of our needle biopsies, one glomerulus was severely changed, while nine others were more or less undamaged. In mild injury, the BM appears thickened in PASM stain; in moderate to severe injury it is doubled (!), and evidences optically empty interspaces (Fig. 30.45). In extremely severe damage, so-called pseudoaneurysms are present. The outer diameter of the afflicted loops is enlarged as much as ten times the normal value and the lumen appears to be empty (Figs. 30.46, 30.47)—with the exception of one to three nuclei which usually lie excentrically. Therein, scattered fibrin fibers are rarely seen in the fibrin stain, but a granular material is always present in which a few erythrocytes occur (Fig. 30.47). Centrally in the loop, a greatly narrowed lumen can occasionally be identified under high-power magnification, a finding which excludes true aneurysm. This is the result of a maximally thickened lamina rara interna, as made obvious in EM (see below). We believe the above-described change to be pathognomonic for transplant glomerulopathy.

Mesangial cell increase does not belong to the findings in transplant glomerulopathy but is always indicative of glomerulonephritis (see p. 173). Progression to obliteration of a few glomerular loops is rare but more frequent than total glomerular obsolescence. Although a severe glomerulopathy may be present as early as 40 days after transplantation, nevertheless, a significant correlation between the severity of the glomerulopathy and the age of the transplant is present (Figs. 30.39, 30.40). It is pointed out that transplant glomerulopathy does not always progress to the most severe stage (Table 30.2). Additonally, there is, in our material, a positive correlation between the degree of vasculopathy and of glomerulopathy [1097a].

### IF Findings

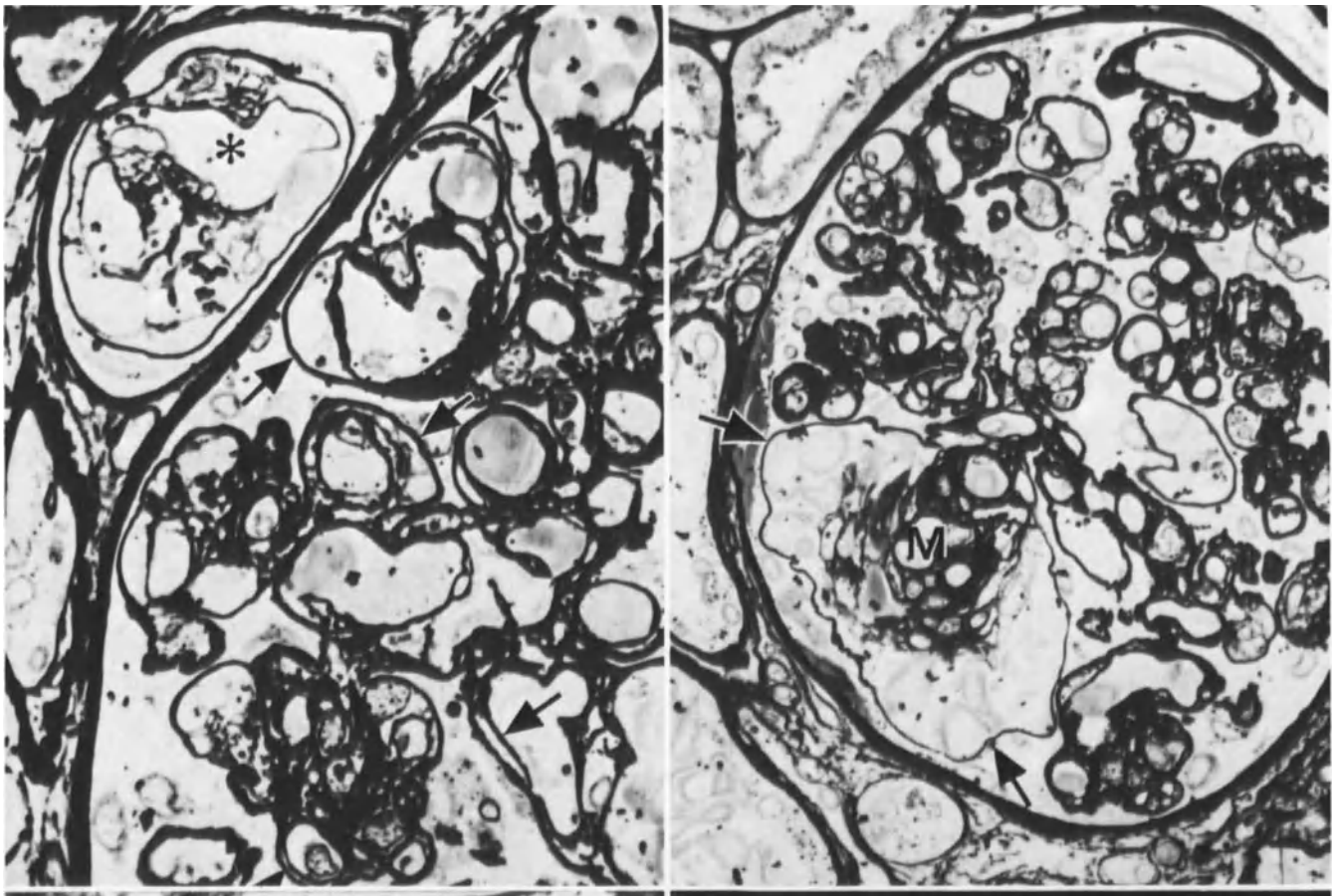
In analysing our findings, we differentiated between patients treated with antilymphocytic globulin (ALG) and those not treated with ALG.

◁ **Fig. 30.41.** An 8-month-old renal transplant evidencing acute vascular rejection. In a peripheral glomerular capillary loop there is an obvious interposition of a mesangial cell (*M*) with new formation of a thin, subendothelial BM (→). Note swollen endothelial cell (*E*) with signs of severe degeneration (lysosomes). Lamina rara interna is partially loosened and widened (*). Glomerular capillary loop lumen (*CL*). EM (×17,480)

**Fig. 30.42.** A 7-week-old renal transplant evidencing acute vascular rejection. Considerable destruction and detachment of podocytic foot processes in the peripheral glomerular capillary loop. Basement membrane (*BM*) appears unchanged, but subendothelially—and occasionally also between the endothelial cells (*E*)—numerous coarse fibrin clumps can be seen. Note monocytoid cell (*MO*) in the lumen. EM (×9960)

**Fig. 30.43.** A 14-day-old transplant. Preparation shows acute medial necrosis (*N*) of wall of renal artery at the site of suture. Intima shows proliferation (*) covered by a thrombus (→). HE (×70)

**Fig. 30.44.** A 19-month-old well-functioning transplant. Note peculiar swelling of mesangium without cell increase. PAS (×680)

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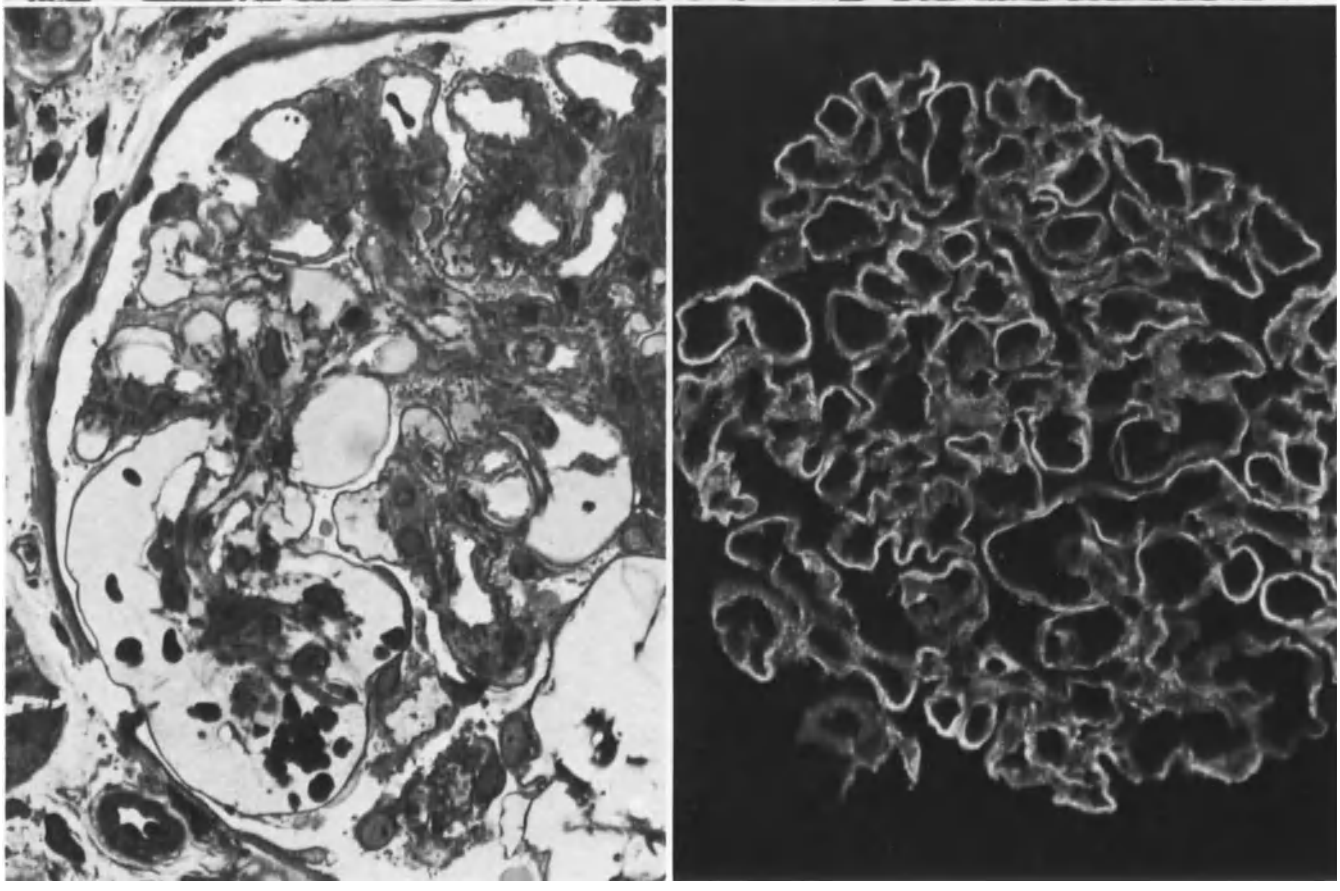

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30.48

Formerly, after ALG-therapy, linear deposition of horse gamma globulin was found (Figs. 30.48, 30.49) since the ALG, which is obtained from the horse, used to contain anti-BM-antibodies ([1805]; contra: [1158]). In the presence of immunosuppression, the IF findings usually correspond to a heterologous (Figs. 30.50, 30.51) or, exceptionally, to an autologous phase of anti-BM GN without corresponding structural LM or EM glomerular changes [1606]. In Rhesus monkeys without immunosuppression however, ALG induces severe extracapillary GN [1132]. No relationship exists between IF findings of ALG nephropathy and the severity of transplant glomerulopathy.

In patients without ALG-therapy, findings from 38 transplant biopsies are summarized in Table 30.3. In 34 out of 38 of these patients, a positive glomerular finding is present for which granular deposits of IgM and C3 are most frequent (see also [27, 1805]). In two-thirds of the cases, afflicted glomeruli in mild cases of transplant glomerulopathy evidence focal and segmental distribution for the cited immunoglobulins (Fig. 30.52) and in the other one-third a diffuse and global pattern. In moderately severe to severe forms, diffuse and global affliction of the glomeruli predominate in half the cases.

Table 30.3. IF findings (without ALG-therapy) in relation to the severity of glomerulopathy

| IF findings | Severity of transplant glomerulopathy | |
|---|---|---|
| | Mild | Moderate to severe |
| Case number | 24 | 14 |
| Number of positive cases | 22 | 12 |
| IgG[a] | 8/22 | 7/12 |
| IgM[a] | 20/24 | 9/14 |
| IgA[a] | 0/15 | 2/8 |
| C3[a] | 14/24 | 8/14 |
| Fibrin(-ogen)[a] | 5/24 | 3/14 |
| Immunoglobulin pattern: | | |
| IgM and/or C3 alone | 12/12 | 4/12 |
| Other Ig combinations | 10/12 | 8/12 |

[a] Number of cases positive/tested.

◁ **Fig. 30.45.** A 3-year-old renal transplant. There is a pronounced doubling of peripheral BM (→) in capillary loops with incipient narrowing of their lumens. Ladder configuration, which is typical for membranoproliferative GN is, however, absent. A similar BM change is present in the vas efferens (*). Semi-thin section. PASM (×840)

**Fig. 30.46.** Same case as in Figure 30.45. Inner layer of BM investing the mesangial plug (*M*) is no longer easily recognizable but the outer layer is clearly discernable (→). The abundantly present erythrocytes between the two BM layers may give rise to confusion with genuine aneurysm. BM thickening and doubling is also recognizable in neighboring glomerular capillary loops. Semi-thin section. PASM (×610)

**Fig. 30.47.** Same case as in Figure 30.45. Erythrocytes are now far more easily recognizable in the loop wall (pseudo-aneurysm). The supposed mesangial border is irregularly structured (cf. neighboring loops). Mesangium is rather severely enlarged without cell increase. Toluidine blue (×690)

**Fig. 30.48.** Linear deposition of horse gamma globulin (*ALG*) in the glomerulus after ALG therapy without LM indications of de novo glomerulonephritis. IF (×600)

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**Fig. 30.49.** Same patient as in Figure 36.48, but 41 months after the last administration of ALG. There is a delicate, linear deposition of horse gamma globulin (*ALG*) in the glomerular BM. Transplant is still functioning well. IF (×500)

**Fig. 30.50.** Granular deposits of horse gamma globulin (*ALG*) in the glomerular BM in a transplant without LM indications of de novo glomerulonephritis. IF (×400)

**Fig. 30.51.** Fine-granular, predominantly peripheral IgM deposits in transplant glomerulopathy. IF (×450)

**Fig. 30.52.** Moderately severe mesangial and peripheral fine-granular C3 deposits which are most pronounced in the vas afferens in a 3-year-old renal transplant. IF (×400)

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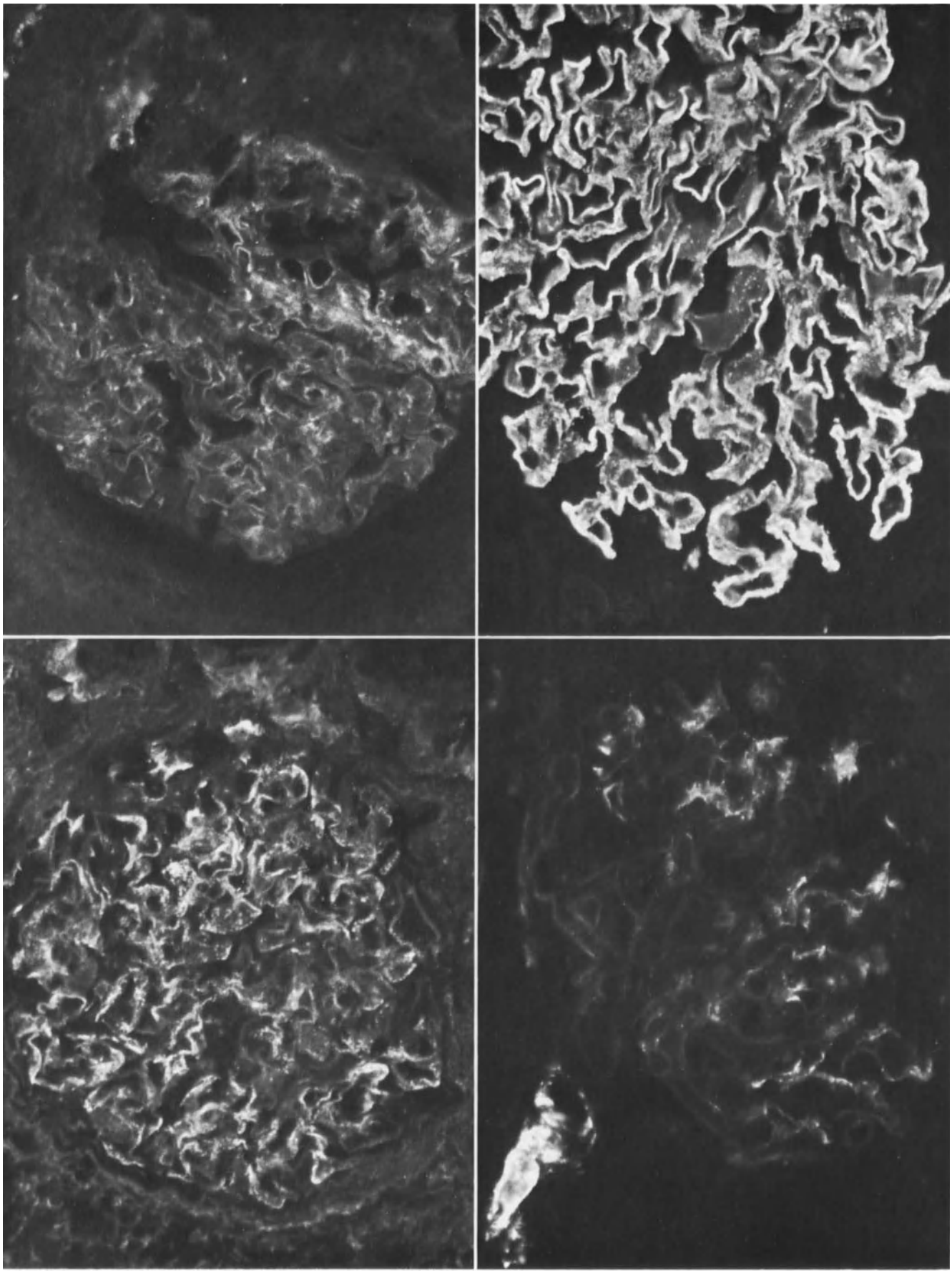
**Fig. 30.53.** A 15-month-old renal transplant evidencing moderately severe transplant glomerulopathy. There is massive thickening of the lamina rara interna (*) which contains numerous cell processes. Subendothelially, a newly formed thin lamina densa layer is present (→). Endothelium appears to be severely injured. Podocytic foot processes are pronouncedly fused. EM (×8790)

**Fig. 30.54.** Maximal glomerulopathy in a 1-year-old transplant. Highly thickened lamina rara interna (*) contains endothelial cell processes as well as several layers of newly formed densa lamellae. Lumen is considerably narrowed and there is a moderately severe fusion of foot processes. EM (×7700)



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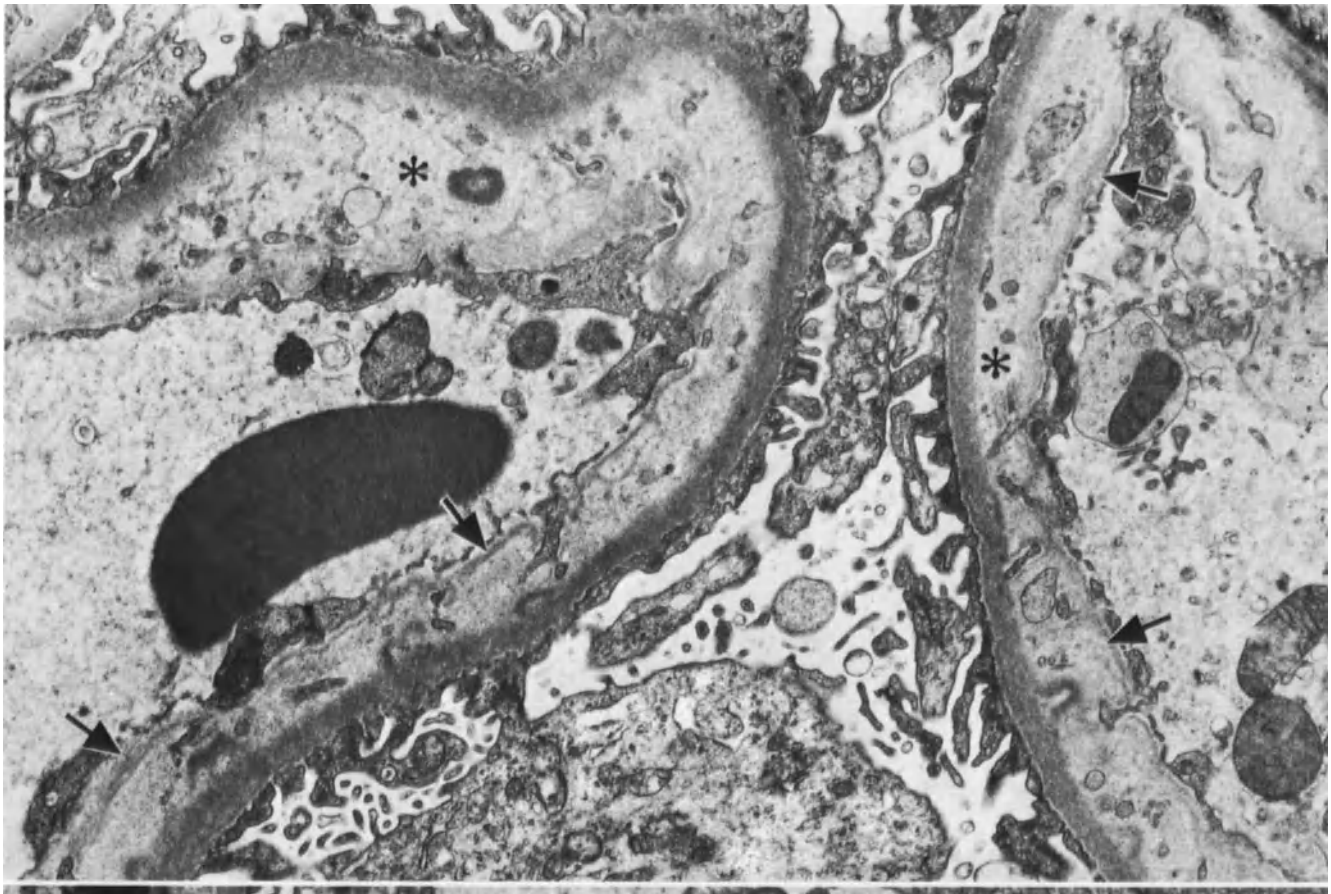

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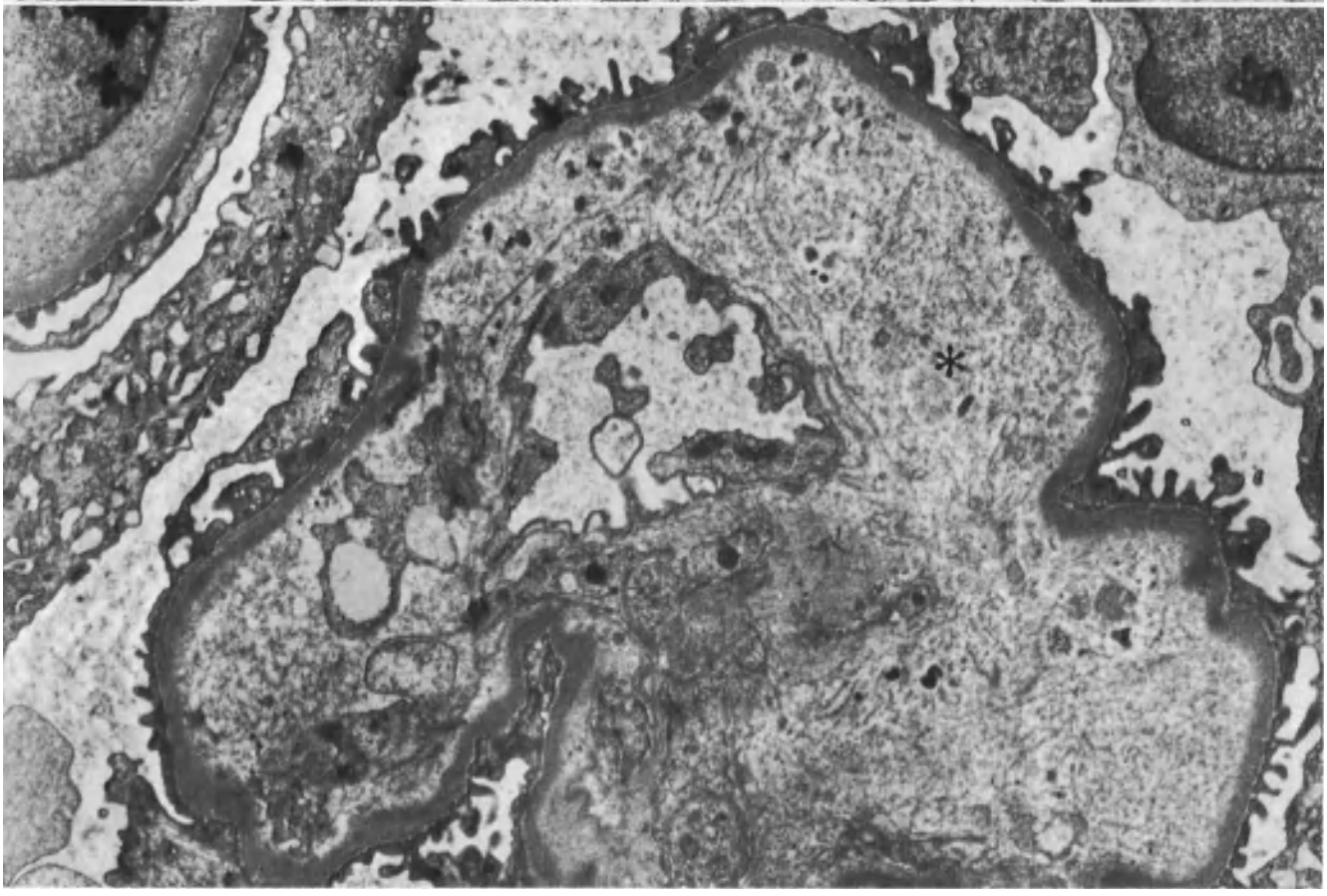

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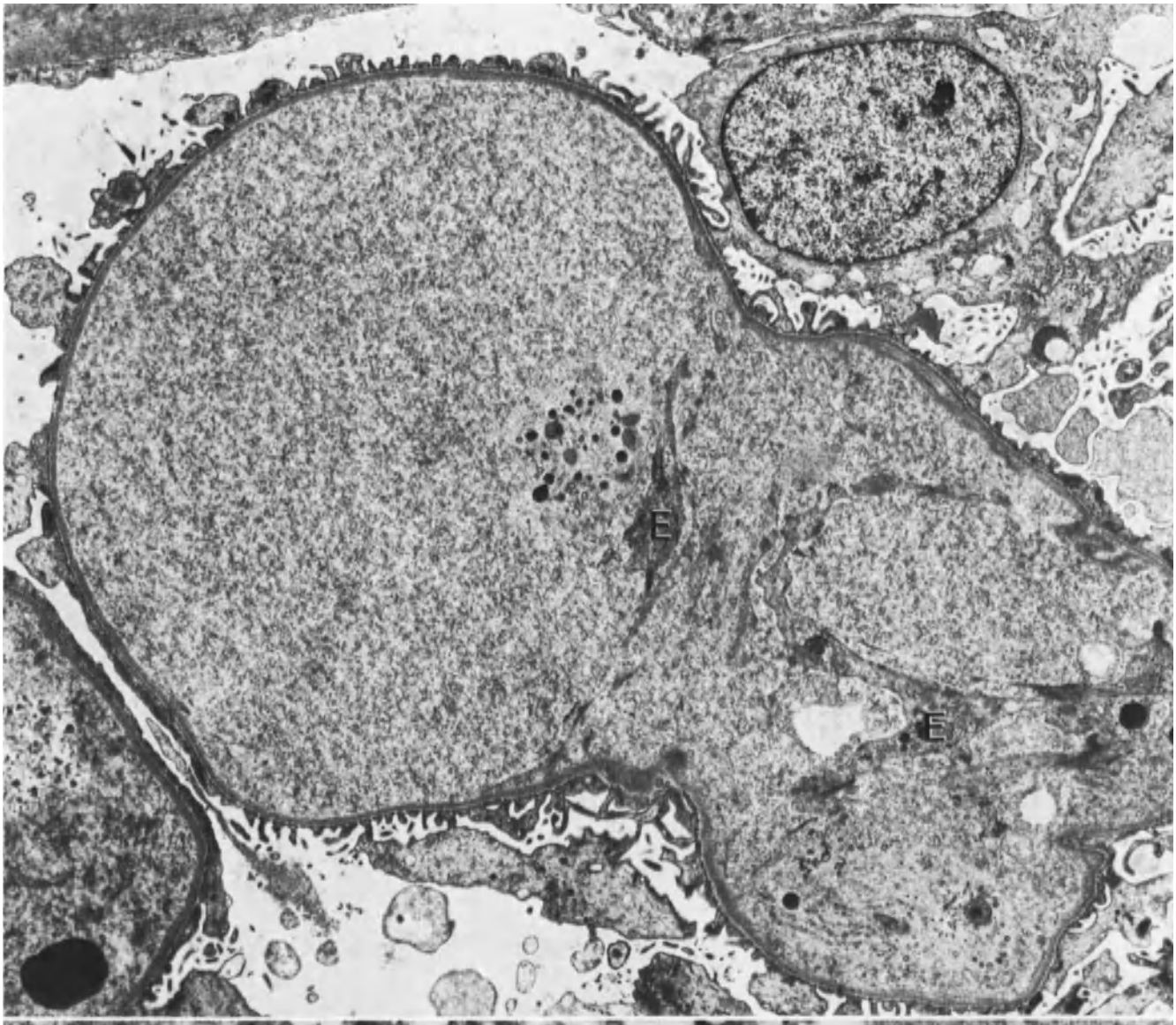


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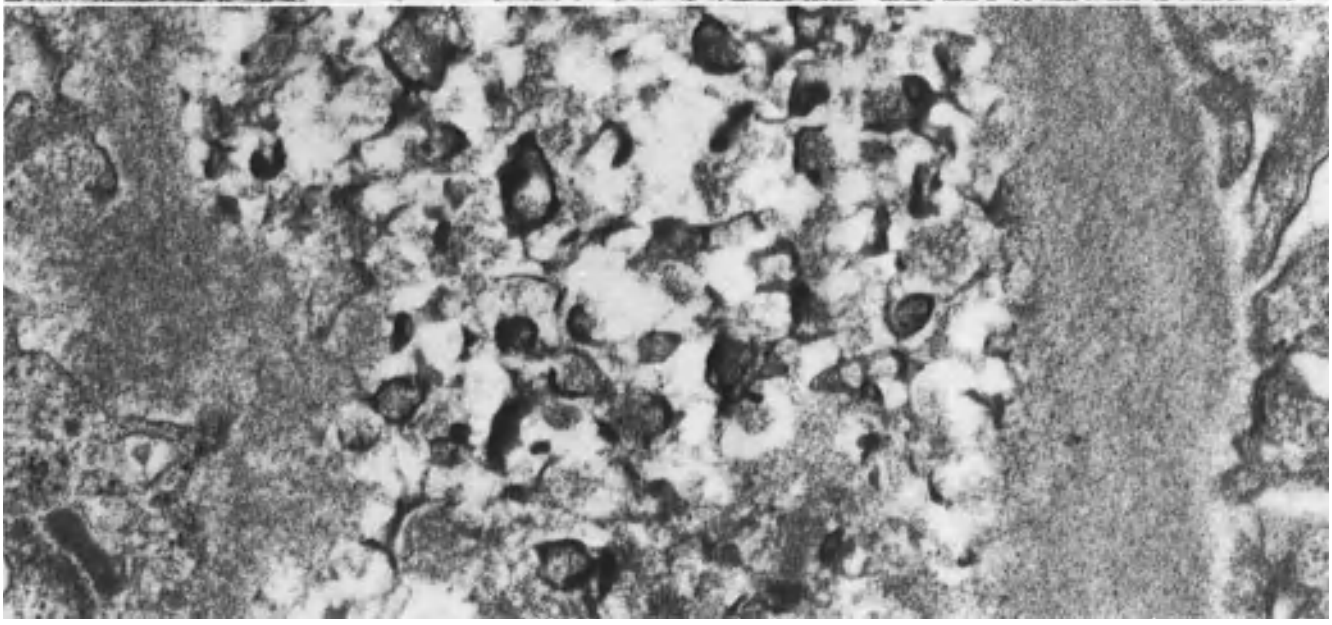

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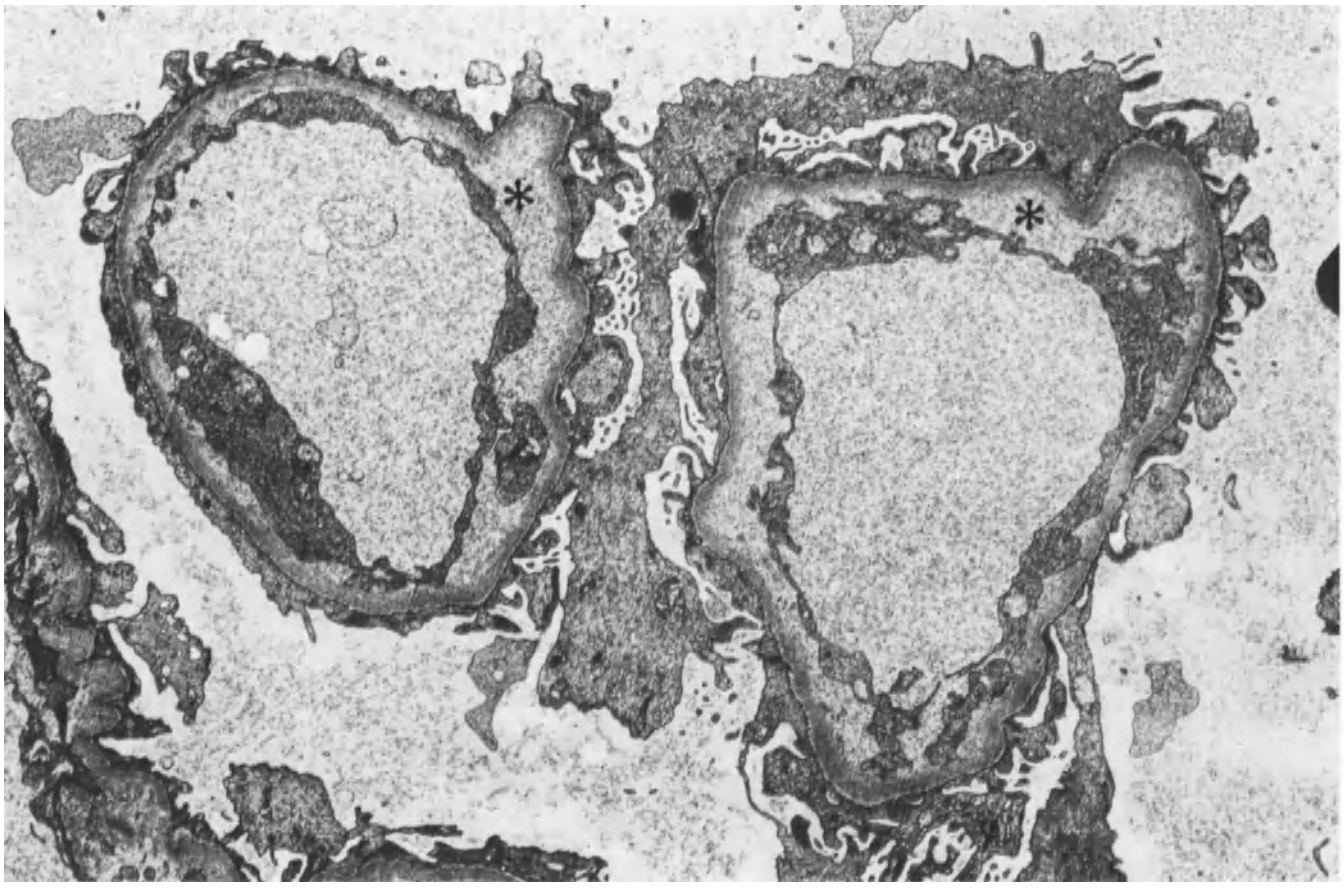


**Fig. 30.57.** A 19-day-old renal transplant evidencing acute vascular rejection. Because of anoxia, transplant glomerulopathy has been considerably accelerated. There is severe circular thickening of the lamina rara interna in the glomerular capillary loops (*) as well as hypertrophy and activation of the endothelium. Severe foot process fusion and podocytic hypertrophy are present. EM (×5100)

In mild cases, the immunoglobulins can be equally demonstrated either peripherally only, mesangially and peripherally or purely mesangially. In moderately severe to severe disease, simultaneous mesangial and peripheral involvement were dominant in two-thirds of the cases. Despite the differences cited, such as the somewhat more frequent occurrence of IgG and IgA in moderately severe to severe disease, there is no statistically significant correlation between the severity of glomerulopathy and IF findings.

◁ **Fig. 30.55.** Same case as in Figure 30.54. Thickening of the lamina rara interna has resulted in almost complete vascular occlusion. Residue of an endothelial cell (*E*). Original lamina densa is unchanged. There is obvious fusion of foot processes. EM (×4950)

**Fig. 30.56.** Peculiar shell-like osmiophilic structures in the thickened lamina rara interna in glomerulopathy from a 6-year-old transplant. EM (×42,730)

**EM Findings**

The earliest change noted in the glomerular BM is partial electron-translucent thickening of the lamina rara interna which contains very fine osmophilic granules [1805]. (For glomerular findings see also histograms Figs. 6.9, 6.22, 6.34, 6.57, 6.64, 6.80, 6.88.)

These thickened regions coalesce such that the periphery of the entire capillary loop becomes affected (Fig. 30.53). The lamina rara interna increases in thickness until pseudoaneurysms, described under LM, arise (Figs. 30.54–30.57). Thus, total BM reaches a maximal thickness of 80 μm. Finally, scattered cell organelles, cell fragments, and a few intact cells are found therein (Fig. 30.54).

Only in 5 out of 95 needle biopsies did we find a few coarse osmiophilic fibrils, presumably corresponding to changed fibrin fibrils. A delicate lamella of lamina densa material—but much thinner than the genuine lamina densa—is often encountered under the endothelium (Fig. 30.53). This lamina densa lamella is probably

formed by the endothelium and separated therefrom by a translucent lamina rara interna. A network of strands of lamina densa-like material is occasionally found in the thickened lamina rara interna (Fig. 30.54). In formalin-fixed material, the subendothelial electron-translucent masses of lamina rara interna often appear as coarse osmiophilic structures (Fig. 30.56). The lumen of the capillary loops ultimately disappears completely (Fig. 30.55).

The described changes of the BM are qualitatively very similar to lamina rara interna thickening in hypoxia. There is no doubt that transplant glomerulopathy is strongly accelerated in the presence of hypoxia in which it may be already extensively developed 40 days after transplantation (Fig. 30.57). The positive correlation which we found in our material between glomerulopathy and vasculopathy stresses the significance of hypoxia in the pathogenesis of transplant glomerulopathy [1097a].

The presence of virus particles is not a feature of this glomerulopathy. In studying four sequential biopsies obtained from one patient, we observed severe irregularity of the BM with the formation of a new subendothelial densa layer as well as membranoproliferative GN (Fig. 30.85; see p. 612). Nests of 200–300 Å (occasionally 600–1000 Å)-sized "vesicles", which sometimes demonstrated a central core, were found between the new densa layer and the original lamina densa (Fig. 6.75; see p. 94). These structures were also demonstrated in groups within the lamina densa and lamina rara interna. The larger elements were identified by IF as Epstein-Barr virus and the smaller as hepatitis B-antigen [1531]. Herpes capsides were described in 5 out of 18 cases by others [238].

In transplant glomerulopathy, very small osmiophilic deposits usually occur with moderate frequency (15 out of 95 cases) in the glomeruli: 11 out of 15 subendothelially, 8 out of 15 along the mesangial BM (Fig. 30.58) 1 out of 15 intramembranously (Fig. 30.59) and subepithelially, and 5 out of 55 in the capsular BM. Even though these deposits may represent immunocomplexes, there is no relationship to the basic disease or to ALG therapy [1805].

Endothelial cell hypertrophy with arcade formation is frequently seen in chronic transplant glomerulopathy. Foam cells of endothelial/mesangial origin are also occasionally observed (Fig. 30.60). The endothelial cells have been reported to evidence virus-like tubular structures in a high percentage of cases (33%: [85]); we have not been able to confirm this finding (0 out of 95 cases: Z; see p. 92).

Fusion of foot processes, usually only focal, is the most constant podocytic finding (Fig. 30.53) and it is generally accompanied by edema and microvillus formation. Lipid and protein droplets are found now and again in the podocytes.

The mesangial matrix is usually only slightly increased, whereas mesangial cell increase is absent (Fig. 6.79), while the presence of collagen fibrils is an exceptional finding (Fig. 6.82). Mesangial foam cells are a rarity, but mesangial hyaline droplets and degradation particles are quite common. The capsular BM may be thickened and capsular epithelium occasionally exhibits hyaline droplets but rarely myelin figures.

The presence of a few capillary loops undergoing obsolescence is not a rare finding, and foam cells are especially evident in this case.

## 2. Chronic Transplant Vasculopathy

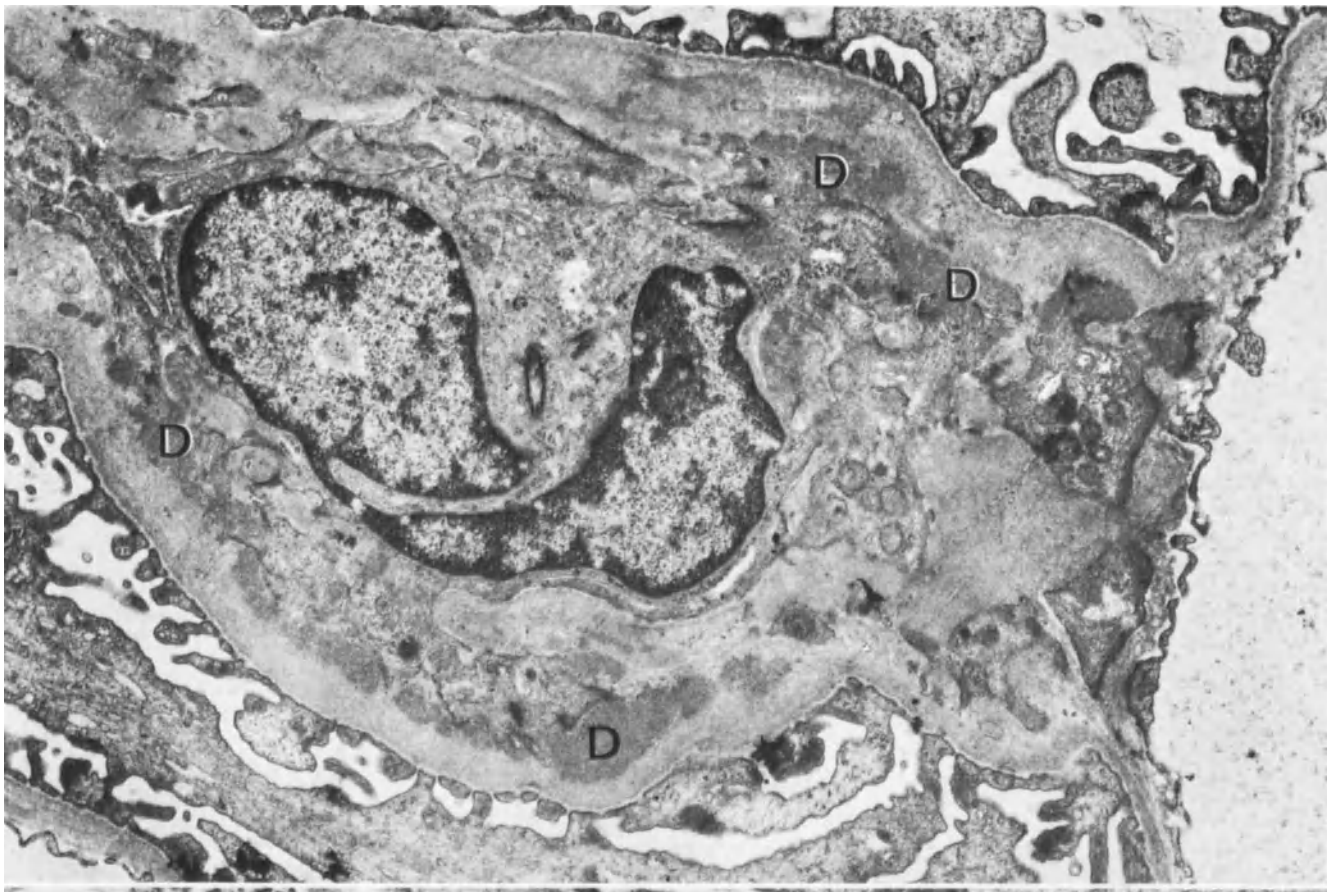
This lesion is of considerably greater importance for transplant survival than glomerulopathy; 16 out of 40 of our cases with total transplant failure suffered from severe vasculopathy (7 out of 18 cases: [238]). The extent of vasculopathy is highly variable, nevertheless, there is a significant relationship between its severity and the age of the transplant (Table 30.4). There is no clear-cut dividing line between acute and chronic vasculopathy and, quite frequently, acute changes are superimposed on chronic ones.

Table 30.4. Relationship between severity of vasculopathy and age of transplant

| Degree of vasculopathy | No. of cases | | | | | | |
|---|---|---|---|---|---|---|---|
| +++ | 0 | 3 | 2 | 2 | 2 | 3 | 3 |
| ++ | 2 | 0 | 4 | 2 | 4 | 0 | 2 |
| + | 3 | 5 | 0 | 2 | 4 | 5 | 5 |
| 0 | 20 | 6 | 5 | 6 | 4 | 10 | 7 |
| weeks | −4 | −8 | −16 | −32 | −64 | −128 | ≧256 |

**Fig. 30.58.** A 3.5-year-old renal transplant. Along the mesangial ▷ BM, there are extensive osmiophilic deposits (*D*). Mesangial cell is hypertrophied. EM (× 9600)

**Fig. 30.59.** A 3.66-year-old renal transplant. A small, loosely organized osmiophilic deposit (*D*), possibly in dissolution, is seen in the lamina rara interna along the mesangium. There is suggestive new formation of a second densa layer (→). In the BM, there are isolated cytoplasmic elements (*). Slight fusion of foot processes is present. EM (× 36,900)

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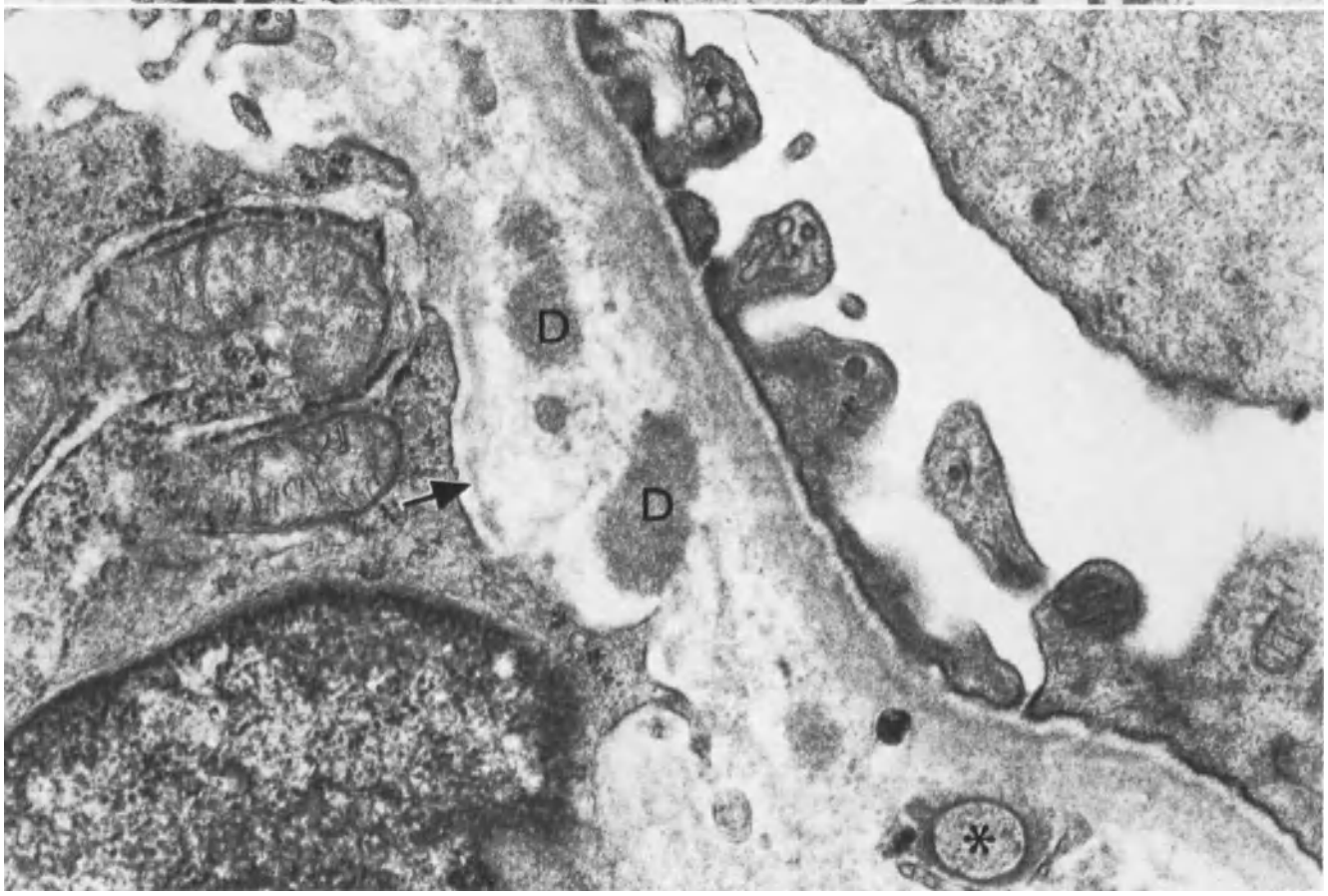


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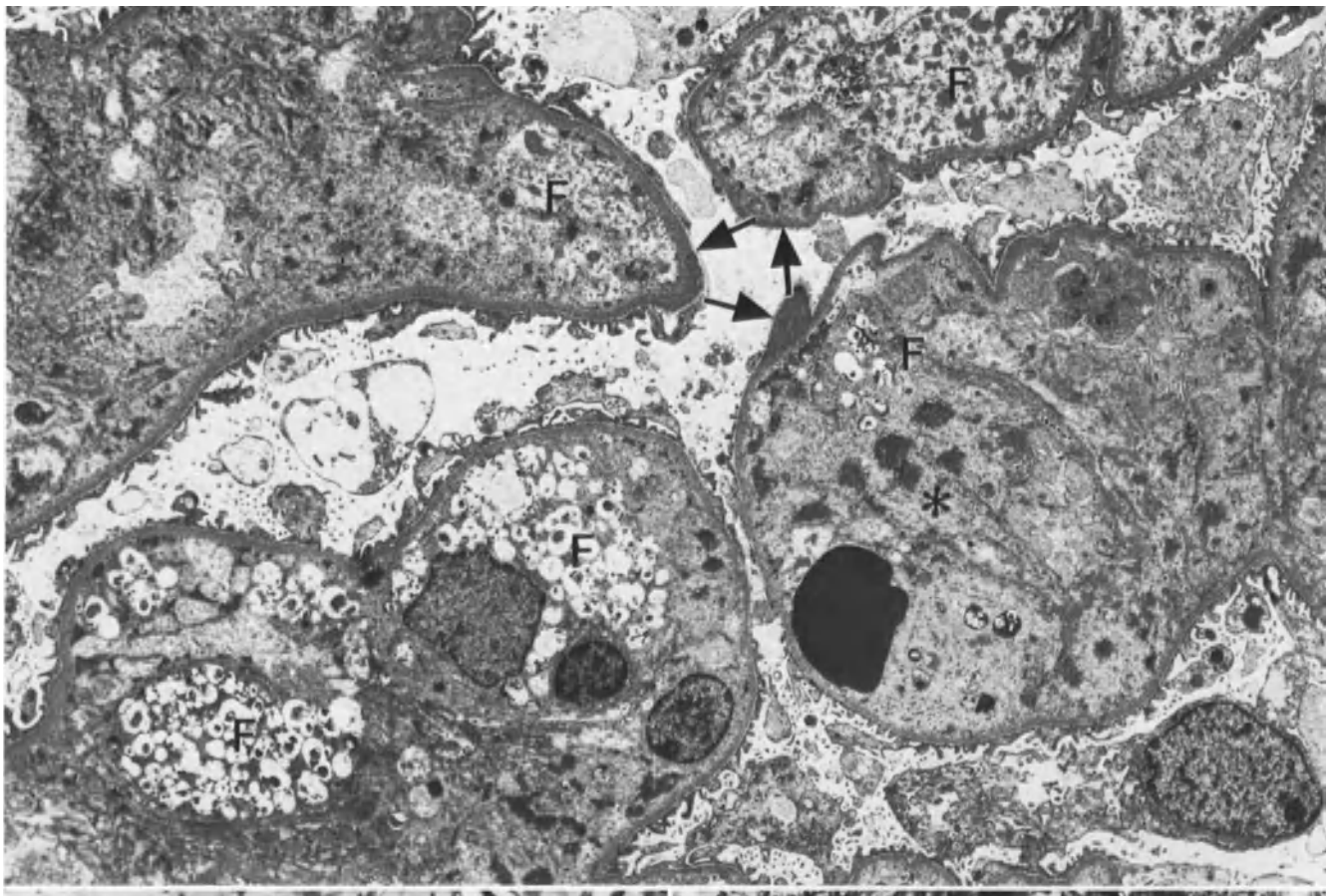


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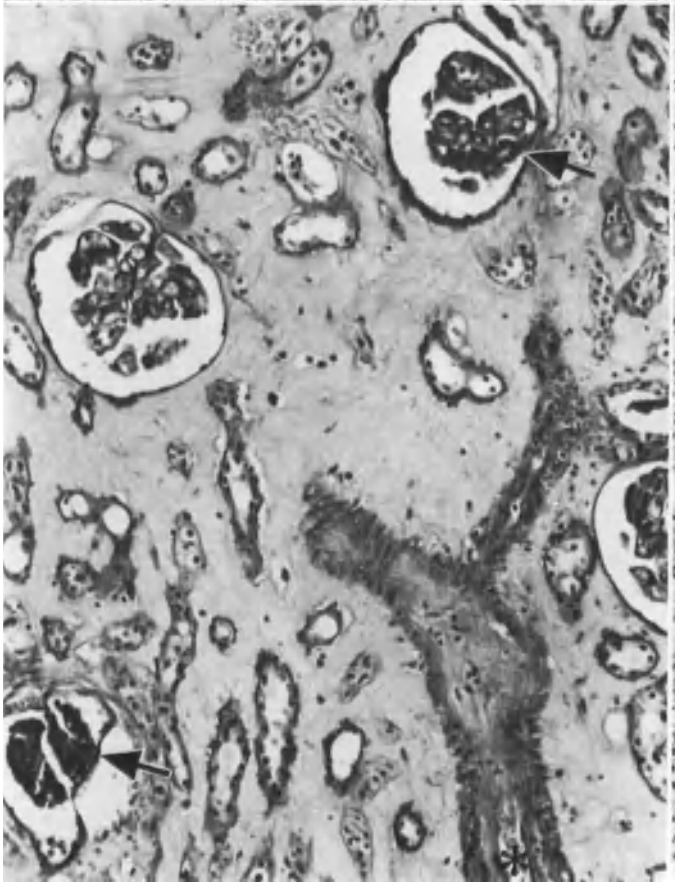

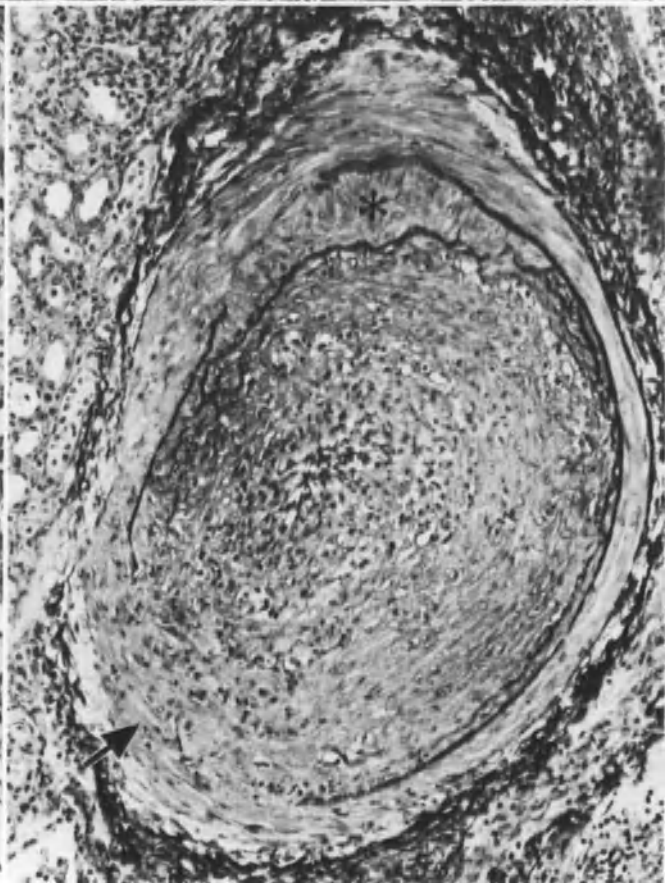


30.61
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### LM Findings

In the inactive sclerosing phase, the arteries often evidence an extremely thickened intima brought about by a fibrotic tissue, poor in cells, in which infiltrates are usually absent.

The media is occasionally atrophic and focally scarred and fibrosed (Fig. 30.61). The lamina elastica is frequently doubled or multilayered and sometimes interrupted (Fig. 30.62). The presence of extensive infiltrates and cellular proliferation indicate an acute attack (Fig. 30.63). The infiltrates are, as in the acute phase, composed of immunoblasts, plasma cells, and large as well as small lymphocytes. If small lymphocytes predominate, there is usually also a proliferation of (myo-)fibroblasts. The presence of large groups of lipid-containing foam cells (Fig. 30.65) is rare in chronic vasculopathy [652].

In contrast to acute vasculopathy, arterial changes in the chronic form show no predilection for certain segments of the vascular tree. Morphometric findings have shown renal vasculopathy to be as severely marked in the kidney as it is in the ureter; arteries of different diameter are also similarly afflicted [1097a]. Vasculopathy ceases almost abruptly at the point of anastomosis of the renal artery (Fig. 30.64).

In pre-existing arteriosclerosis, transplant vasculopathy develops between the endothelium and the arteriosclerotic patch. Old arterial changes, due to transplant vasculopathy, can still be differentiated from arteriosclerotic changes by the regular circular arrangement of delicate fibers in the thickened intima in the former [436].

According to our experience, secondary small arterial thrombi are rare. In 16 cases of chronic vasculopathy, we found thrombosis at the site of suture of renal artery 4 times; (4 out of 16 cases of transplant rejection: [1599]; see also [237]). Venous thrombosis without arterial occlusion is rare in transplants (5 out of 40: Z; [49]). Such venous thromboses do, however, occur with greater frequency in the ureter even without arterial occlusion. We did not find intramural aneurysms of the larger vessels as has been reported [1726].

Fibrosis is chiefly caused by inflammatory reaction of the intima (endovaculitis) in the acute phase, but it is not a simple organization of thrombi [238].

Changes in the region of the arterioles are much more difficult to interpret. Arteriolitis [652] is a chance finding. Scarified, obliterated arterioles are somewhat more frequent and may be the cause of solitary collapse glomeruli. We found arteriolonecroses in 6 out of 45 patients with transplants over 1 year old. All 6 patients were hypertensive, indicating secondary hypertensive vasculopathy to be the cause of the change.

### IF Findings

IgG, IgM, and C3 have been found in arteries and arterioles (Fig. 30.66) in one half of the cases [653].

We found positive IF results in arteries in 24% of 90 cases, in which IgM was present in 17%, complement in 14%, fibrinogen in 7% and IgG in 5%. Fibrin(-ogen) was found only in acute vascular transplant rejection, whereas IgG was present in chronic vasculopathy as well.

Arterioles evidenced positive IF findings in 60% of the cases, in which complement was present in 57%, IgM in 46%, IgG in 5%, and fibrin(-ogen)—during acute rejection episodes only—in 2%. The arteriolar IF transplant findings are practically the same as those occurring in GN and non-GN nephropathies, the arteries, however, are more frequently IF-positive than in GN (4%) and in non-GN (8%). With the exception of positive fibrin(-ogen) findings, there are no significant qualitative differences.

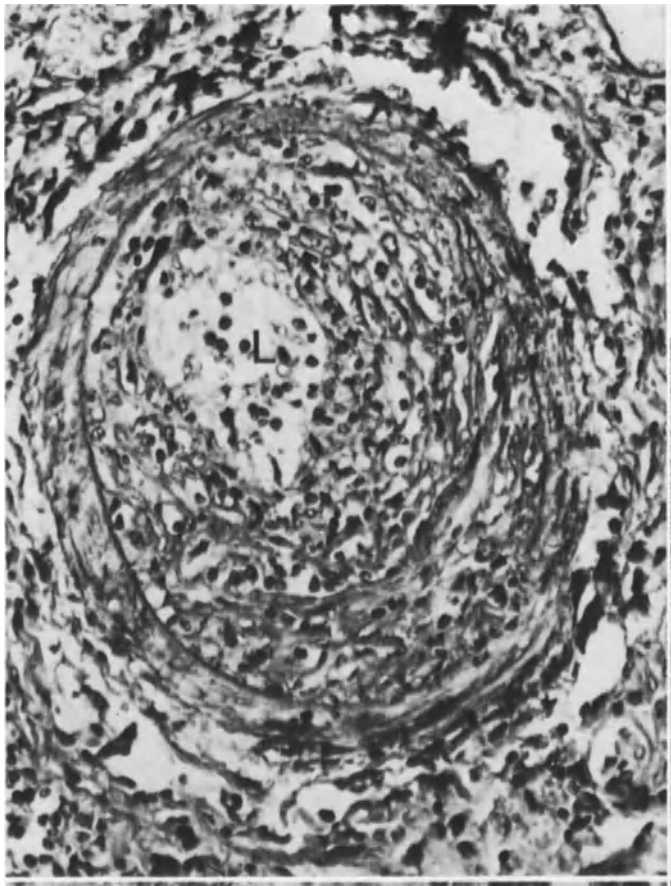
### EM Findings

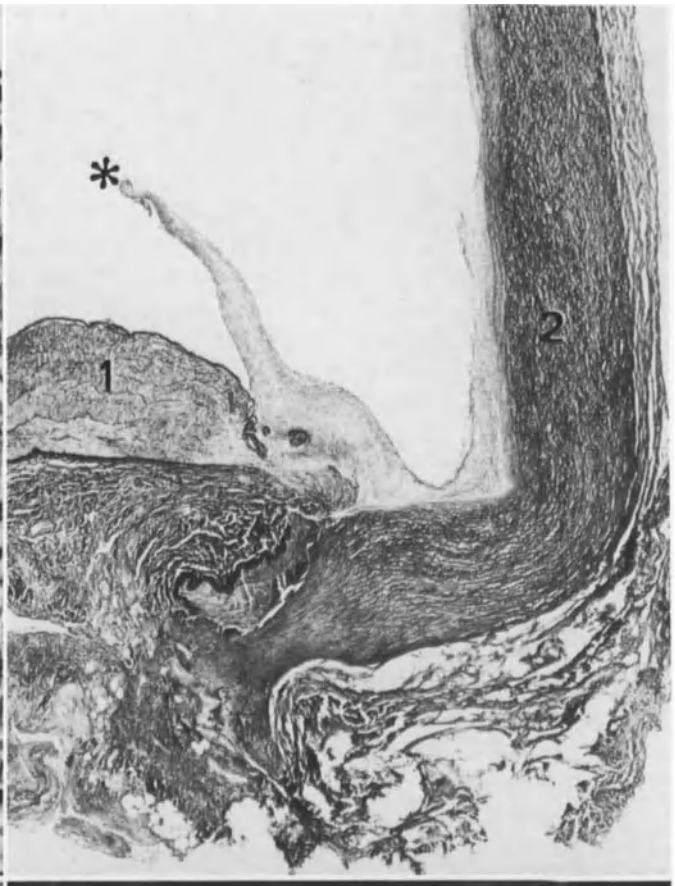
After the acute phase of the lesion with subendothelial infiltrates, the intima becomes much thickened, chiefly from proliferated (myo-)fibroblasts (Fig. 30.67), among which phagocytes as well as occasional activated lymphocytes are present. In this phase, the elastica interna and media are often unchanged (Fig. 30.67) but often the boundary between the elastica interna and media is blurred, and lumpy phagocytes appear at the juncture. The elastica interna is split, thickened, desintegrated,

◁ **Fig. 30.60.** A 40-day-old transplant undergoing subacute rejection evidencing extensive foam cell formation (*F*) in the glomerular capillary loops. It is thought that the foam cells are predominantly of mesangial origin. Mitotic figure (*). Podocytes are swollen and demonstrate isolated loss of foot processes (→). Masses of microvilli are present. EM (×3600)

**Fig. 30.61.** A 14-month-old transplant evidencing severe interstitial sclerosis after multiple acute rejection episodes. Moderate to severe sclerosing vasculopathy is also present (*). Two glomeruli (→) exhibit pronounced loop collapse. (×90)

**Fig. 30.62.** A 6.5-month-old renal transplant with slight interstitial rejection and massive chronic vascular rejection with an acute attack. The lamina elastica interna of the arcuate artery is partially split (*) and partially evidences complete destruction (→). Vascular lumen is totally occluded by a tissue which is sclerotic externally and which is very abundant in inflammatory cells internally. Weigert elastic fiber (×70)

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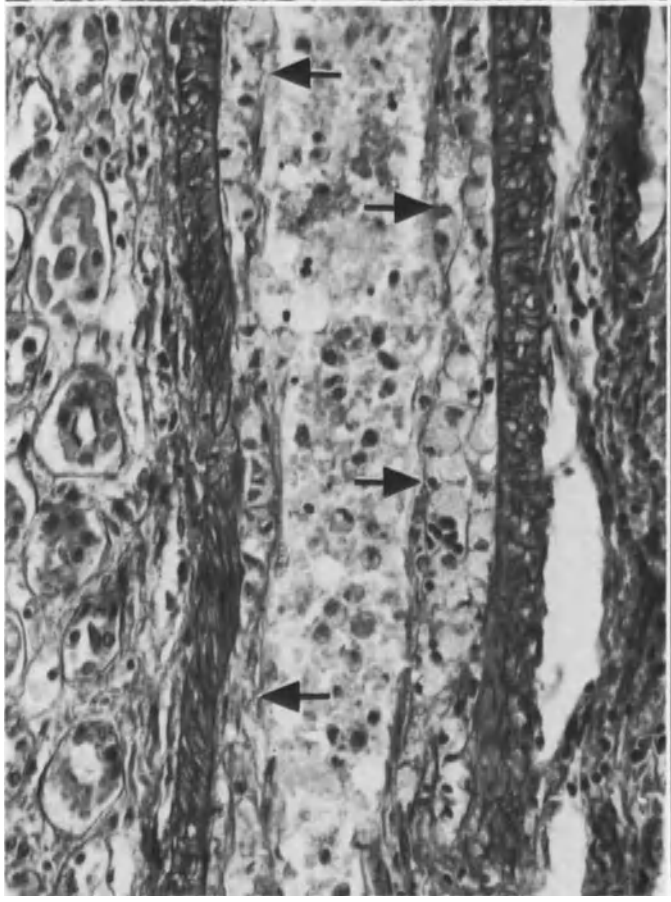

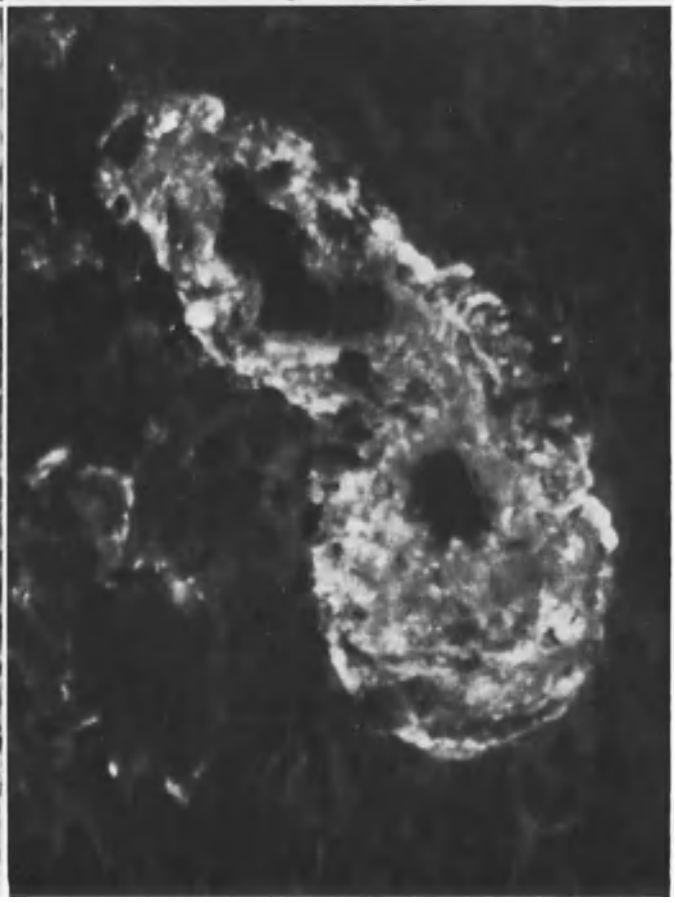

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and becomes doubled or multilayered. The endothelium may be completely unaffected, but is not infrequently damaged and may even show necrosis (Fig. 30.68), which predominates in the acute phase. As a consequence, the myocytes of the media respond vigorously in the form of stepwise transformation which finally results in myocytolysis (Fig. 30.68). This transformation corresponds to dedifferentiation in which myocytes assume a mesenchymal state and produce contractile proteins, mucopolysaccharides, collagen and elastin [65a, 861a, 1336]. The myocytes detach from their tissue organization and wander into the subendothelial space (Fig. 30.69) where they produce collagenous fibrils (Fig. 30.70).

The above descriptions, which are chiefly related to proliferative-sclerotic processes, correspond to findings occurring in reactions where defensive mechanisms predominate. However, when aggressive factors are dominant, severe destruction, possibly leading to total myolysis, may ensue (Fig. 30.71). Isolated myocytic necroses, accompanied by deposition of degradation products in the surroundings is viewed as an intermediate phase of the process (Fig. 30.72). Immunocomplexes have been supposed to be responsible for the necroses [1594a]. We believe, however, that the necroses arise via secondary insudation of plasma constituents subsequent to primary immunologic endothelial damage.

In transplant arteriopathy, intimal thickening is, therefore, a consequence of three factors: migration of phagocytes, proliferation of in situ fibroblasts, and migration of myocytes (see also [8a, 65a, 666a, 791b, 1594a]). Immunohistochemical and EM study have proven that the majority of the proliferating cells in the thickened intima are vascular myocytes [861a] besides host-cell infiltrates.

◁ **Fig. 30.63.** A 6.5-month-old renal transplant evidencing relapsing severe transplant vasculopathy. Vascular lumen (*L*) is severely narrowed by a tissue rich in proliferated (myo-)fibroblasts and lymphoid cells. In the outer zone, there is incipient sclerosis. Media appears to be mostly intact except for a small necrotic area (*right*). Numerous lymphoid cells in the lumen. PAS (×110)

**Fig. 30.64.** Site of suture of the artery in a 51-day-old renal transplant. Renal artery of the donor kidney (*1*), iliac artery of the recipient (*2*). A cushion of connective tissue has developed in the donor artery which is artificially detached (*), and is seen to be very slightly extending to the recipient artery. Van Gieson-elastin (×20)

**Fig. 30.65.** A 2-months-old renal transplant. Endothelium of a small artery (→) has been detached from media by a massive collection of foam cells. Media is unchanged. PAS (×150)

**Fig. 30.66.** Coarse, clumpy IgM deposits in a small renal artery in chronic transplant vasculopathy. IF (×310)

Page 602

**Fig. 30.67.** Part of a small artery in a 1-year-old renal transplant with subacute transplant vasculopathy. Severe cellular proliferation is occurring in the intima. (Myo-)fibroblasts (*FC*), phagocytes (*PH*), activated lymphocytes (*AL*). Medial myocytes (*MC*), fibrous tissue (*AD*) in the adventitia. EM (×2900)

**Fig. 30.68.** Chronic transplant vasculopathy in a 1-year-old renal transplant. Note isolated necrotic endothelial cells (*N*). There is rather pronounced lamellar thickening and doubling of elastica interna and BM (→←). Subendothelial space is widened and myocytes are degeneratively changed as indicated by their rounding off, loss of myofibrils and occasional disintegration (*). EM (×3640)

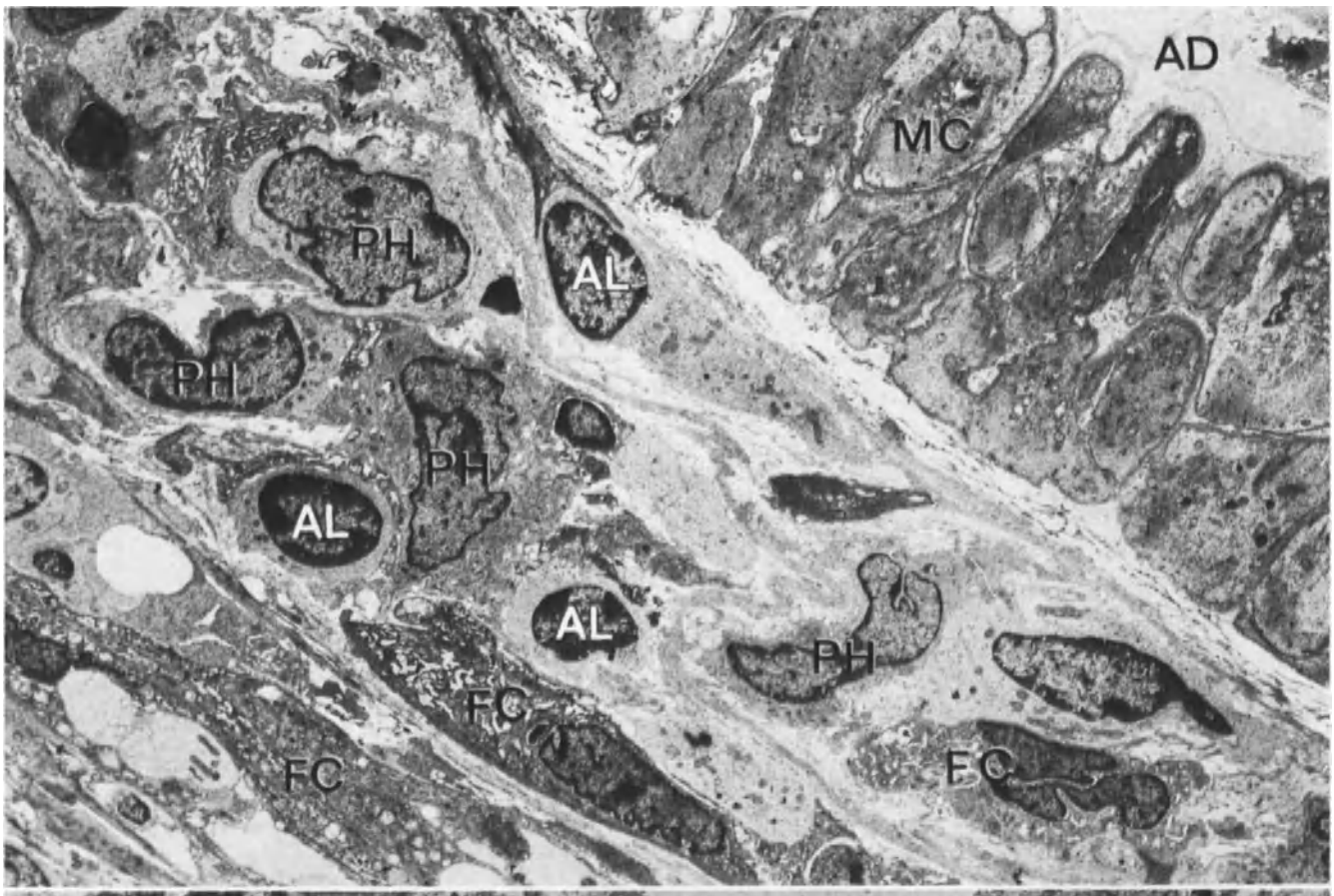
Page 603

**Fig. 30.69.** Slight vasculopathy in a 3-month-old renal transplant. Endothelium evidences a mushroom-like evagination into the lumen (*) due to cellular swelling. BM shows irregular lamellar thickening. Three transformed (myo-)fibroblasts (*MC*) are present in the subendothelial space. Medial myocytes are irregularly shaped and show spike-like projections (→) and a caterpillar-like nucleus. EM (×2700)

**Fig. 30.70.** Progressive transformation of myocytes (myofibrocytes). An artery from a 37-day-old renal transplant. Peculiar-shaped cell bodies and nuclei, massive increase of basement membrane-like material and fibrils are present. EM (×3300)

**Fig. 30.71.** Severe transplant arteriopathy in a 4-year-old renal transplant. Endothelium (*E*) is intensely swollen and activated. Elastica interna and BM show severe lamellar thickening (*BM*). Extensive wall necrosis (*N*) is present. Only one intact myocyte (*MC*) is recognizable. This preparation illustrates the most severe degree of medial involvement in transplant vasculopathy. Lumen (*L*). EM (×2640)

**Fig. 30.72.** A 3-year-old renal transplant evidencing severe transplant vasculopathy showing the boundary between the media and a highly lamellated BM (BM). Transformed, rounded-off, damaged myocyte ($MC_1$) which appears to be producing ground substance (→). A necrobiotic myocyte ($MC_2$) with shrunken osmiophilic cytoplasm. Cellular detritus (*). EM (×8400)

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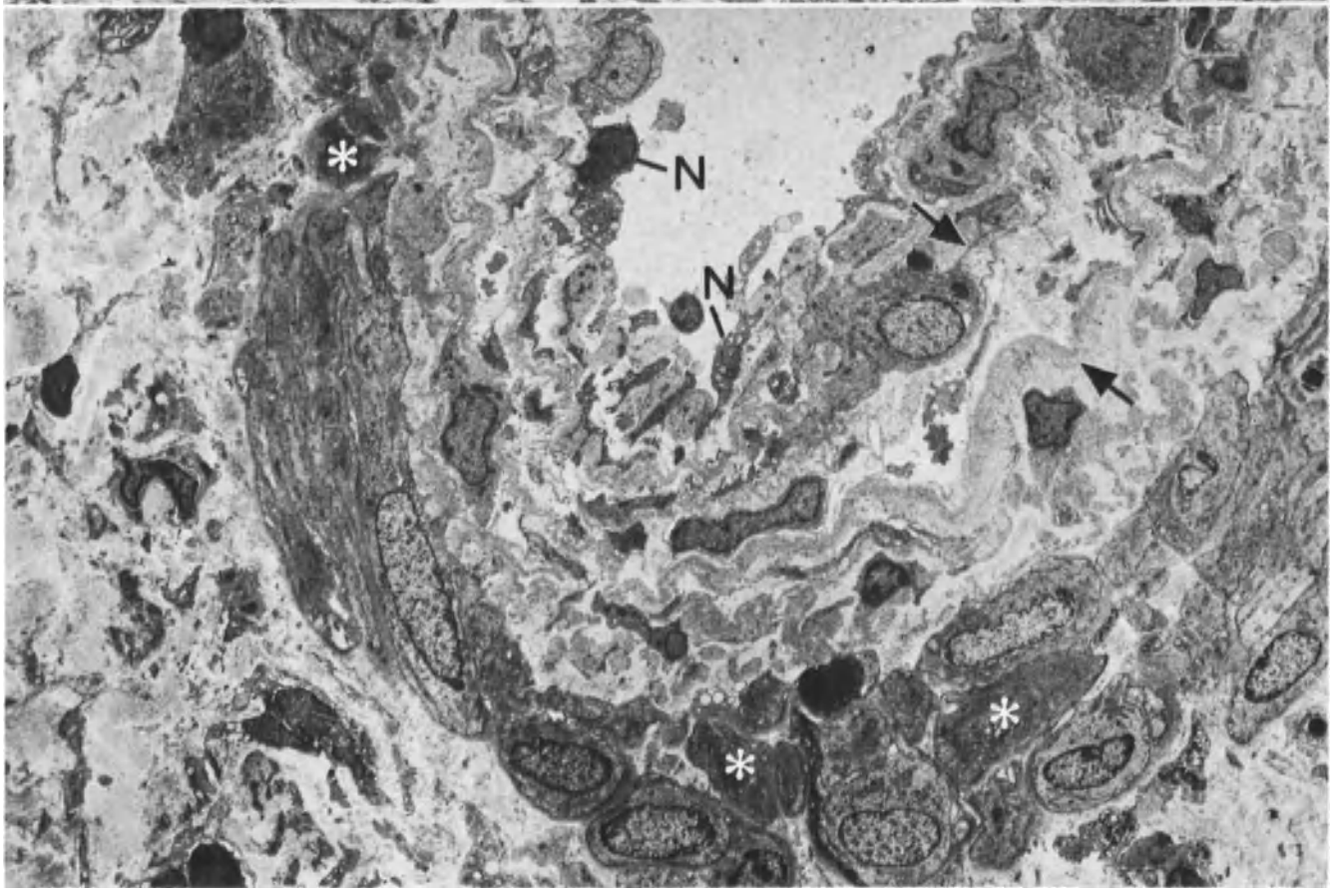


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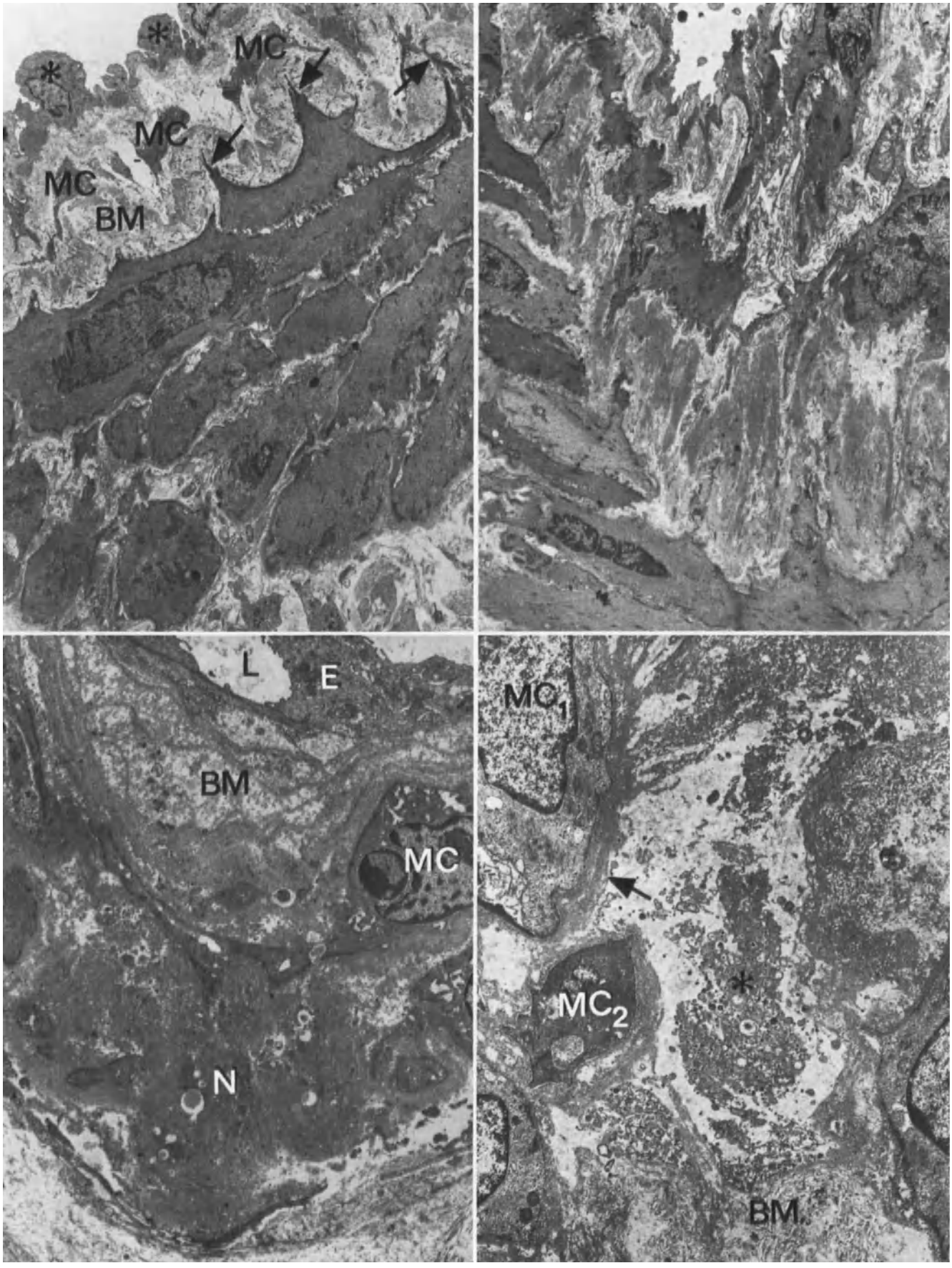


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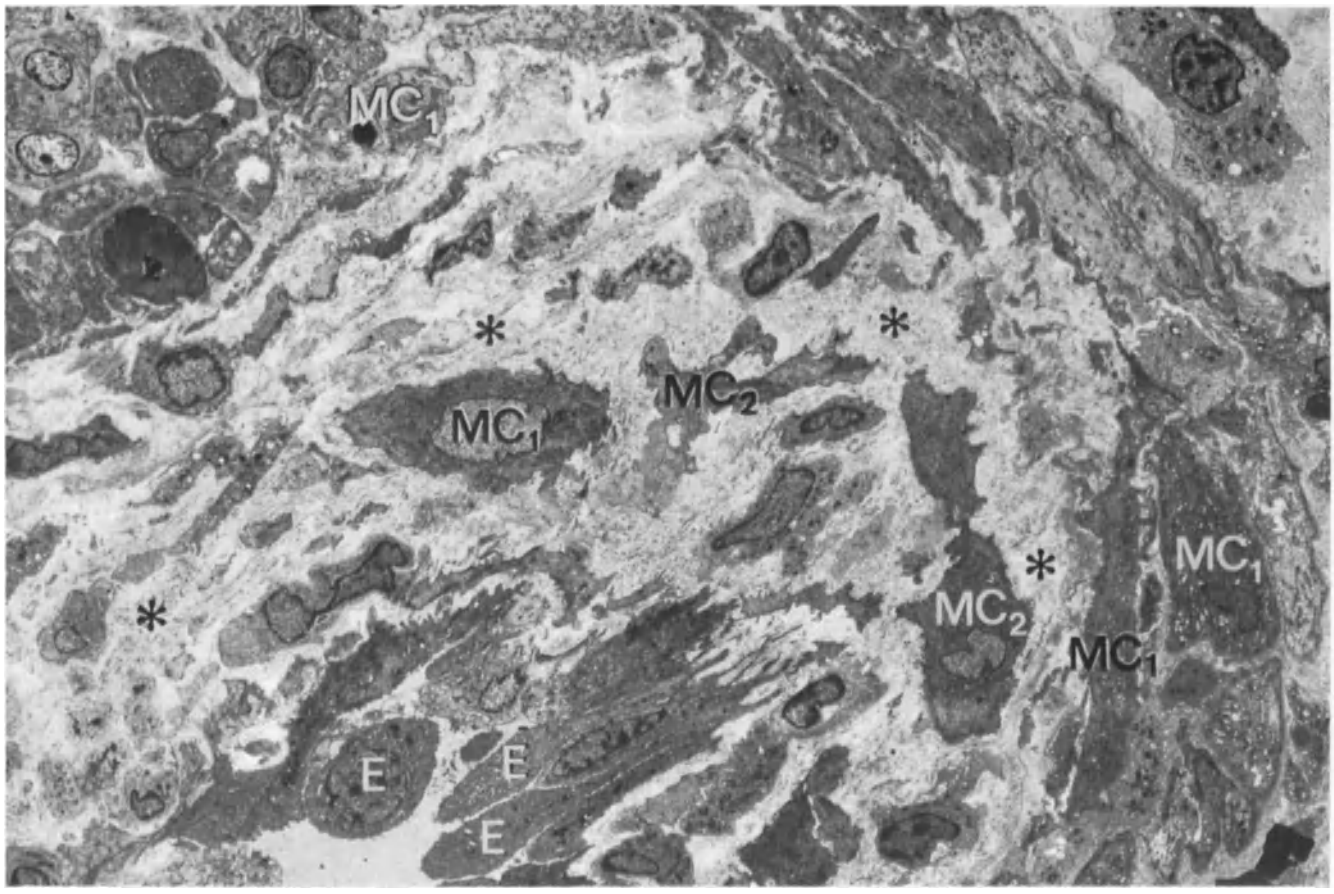



**Fig. 30.73.** A 3-year-old renal transplant evidencing chronic transplant vasculopathy. Myocytes of the media ($MC_1$) are loosely arranged and show fine vacuoles. There are numerous transformed myofibrocytes with multiple extensions ($MC_2$) present in the subendothelial space. There is severe subendothelial sclerosis (*). Endothelial cells (*E*) are clearly swollen. Tangential section. EM (× 1470)

The resulting terminal picture of chronic transplant vasculopathy corresponds to severe intimal thickening caused by deposition of coarse collagenous bundles, between which a few transformed myocytes and some phagocytes are always present (Fig. 30.73).

The intertubular capillaries in old transplants—with the exception of mild splitting and thickening of the BM—are often unchanged. However, in a few cases, endothelial vacuoles, abnormally dense cytoplasm, swelling of organelles and/or detachment of a few cytoplasmic processes can be observed (Fig. 30.33; experimental data: [514]). Scattered endothelial mitoses indicate the regenerative capability of the endothelium. Very rarely, subendothelial loosening, which structurally corresponds to the glomerular lamina rara interna change, is found. Monocytes and lymphocytes are frequently present in the lumen, even in those cases without acute rejection. The migration of lymphoid and monocytic elements from the intertubular vessels into the tubules, which is seen with LM, can also be confirmed with EM (Figs. 30.11, 30.33).

## 3. Interstitial and Tubular Changes

In periods following rejection episodes, the interstitium is either unchanged or sclerosed to varying degrees (Fig. 30.61). There is no significant correlation between the extent of interstitial changes and the age of the transplant. In LM, the interstitium is strikingly dense, hyalinized and usually very poor in cells (Fig. 30.61). The fibers are coarse and an increase in ground substance is present.

The overall picture corresponds to that of inveterated edema, i.e., to sclerosis as in nondestructive, chronic IN and not to that of a scar as in PN. When no transplant rejection occurs, a few small lymphocytes and histiocytes are the most that is found in the interstitium whereas during chronic rejection, small and large lymphocytes, immunoblasts, plasma cells, and histiocytes occur in about the same frequency. An acute rejection episode, on the other hand, is characterized by the obvious predominance of immunoblasts and large lymphocytes over

small lymphocytes and plasma cells. Interstitial foam cells are rarely seen during inactive phases.
Tubular changes are unspecific. Those tubules associated with severe collapse glomeruli are atrophic and their BM is thickened. Multinucleated proximal tubular giant cells indicate regeneration after previous damage (Fig. 30.75). Individual or groups of tubular cell necroses, which arise as a consequence of anoxia even in the absence of acute rejection processes, are sometimes encountered (Fig. 30.76).
We have never observed papillary necroses in our total of 40 nephrectomies (10 out of 12 cases: [519]). In transplant biopsies, the JGA is often found to be enlarged (Fig. 30.74)—usually only slightly—and especially in cases with chronic vasculopathy, renal artery stenosis or hypertension. JGA enlargement in cases without hypertension is possibly a reaction to excessive sodium loss.

**IF Findings**

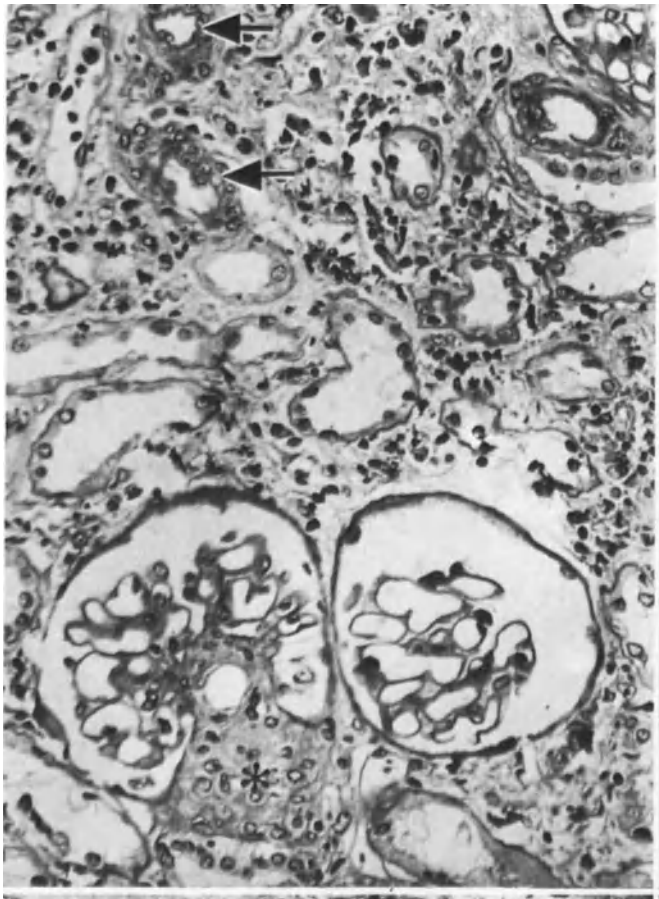
The interstitium of transplants demonstrates positive findings in 40% of cases. This is considerably more frequent than in other nephropathies (13%). In 17%, interstitial immunoglobulin-containing plasma cells are found; in 16% there is diffuse staining of the interstitium for immunoglobulins, and in 22% for fibrin(-ogen). Fibrin(-ogen) is twice as frequent in acute as in chronic rejection.
Tubular BM is IF positive in 38% of the cases. In 30% complement (usually in short linear form), in 22% IgM, and in 3% IgG, are demonstrable along the tubular BM.
We could not find a correlation between positive tubular IF findings and the extent of interstitial fibroses, inflammatory infiltrates, and tubular atrophy in our material. Tubular BM deposits are probably the consequence of relapsing acute interstitial rejection episodes.

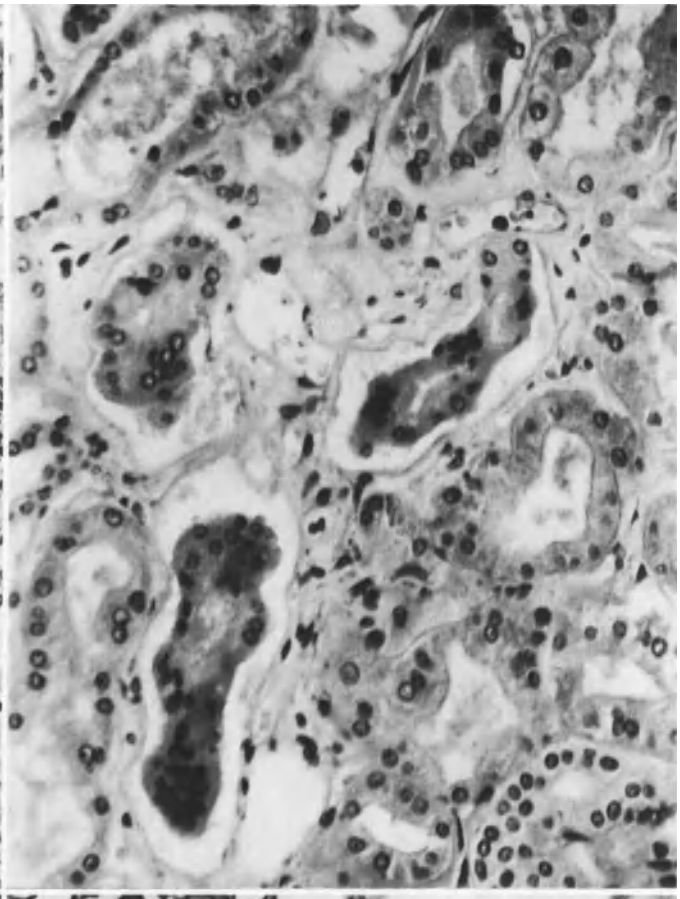
**Prognosis**

Glomerulopathy does not appear to influence the prognosis. Vasculopathy, however, is decisive as it can lead to parenchymal damage, renal hypertension and, finally, to transplant failure. Accordingly, in severe vasculopathy the prognosis is poor. Following withdrawal of immunosuppressive therapy, the course of vasculopathy is rapidly progressive [238]; it can, however, in rare cases, remain stationary for years. It is thought that interstitial sclerosis is of lesser prognostic significance.
Forty nephrectomies from 38 patients, of whom 17 subsequently died, demonstrated transplant insufficiency due to acute interstitial rejection in 4, to acute vascular rejection in 3, and to chronic vascular rejection in 16 cases; from the latter, 4 had thrombosis and 1 necrosis of the renal artery. Thrombosis at the site of suture of the renal artery was present 5 times, twice associated with renal artery necrosis. Isolated venous thrombosis was encountered 5 times and resulted in spontaneous rupture of the transplant once. Circulatory or septic-toxic shock was the cause for transplant failure 5 times, once due to massive hemorrhage from the renal pelvis. Severe acute pyelonephritis was the cause for nephrectomy once.

## 4. Differential Diagnosis of Chronic Transplant Rejection

Differential diagnostic problems in chronic transplant rejection are minor. Mild chronic transplant glomerulopathy cannot be distinguished from unspecific glomerulonephrosis in LM or even in EM except in the presence of a very pronounced lamina rara interna thickening. Severe transplant glomerulopathy can be differentiated from epimembranous GN due to the absence of spikes and deposits and the presence of membrane doubling as demonstrated with PASM in the former. Differentiation of transplant glomerulopathy from membranoproliferative GN is achieved by demonstrating with LM, and even more clearly with EM, the presence of BM doubling due to interposition of mesangial cells, a condition which hardly ever occurs in transplant glomerulopathy. For differentiation of the severe form of transplant glomerulopathy from genuine loop aneurysm see p. 56. Pure glomerular ischemia may lead to collapse glomeruli which are frequently found in transplants, but never to changes similar in extent to those in transplant glomerulopathy.
In chronic transplant vasculopathy with typical concentrically layered intimal fibrosis, scarring of defects of the lamina elastica interna as well as of the media, the presence of foam cells and absence of cholesterol crystals easily allow differentiation from arteriosclerosis.
Healed periarteritis nodosa can be excluded since it demonstrates typical transmural scarring. Scleroderma and malignant nephrosclerosis can be eliminated due to the occurrence of onion-bulb splitting of the vascular wall which does not occur in chronic transplant vasculopathy.
In adaptive intimal fibrosis (see p. 151), the connective tissue is much more loosely arranged and richer in amorphic intercellular substance, and there are no medial defects.
Interstitial sclerosis in transplants demonstrates an extreme paucity of nuclei and a basically preserved parenchymal structure, and as such is differentiable from scars arising from destructive inflammation. Such striking interstitial sclerosis, almost devoid of inflammatory infiltrates, is not observed in nondestructive chronic interstitial nephritis.





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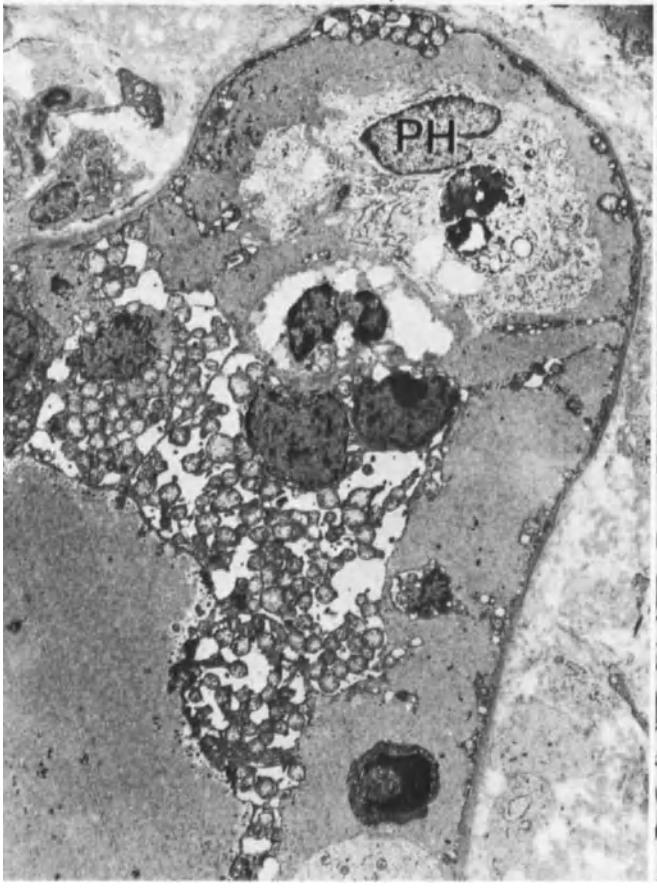


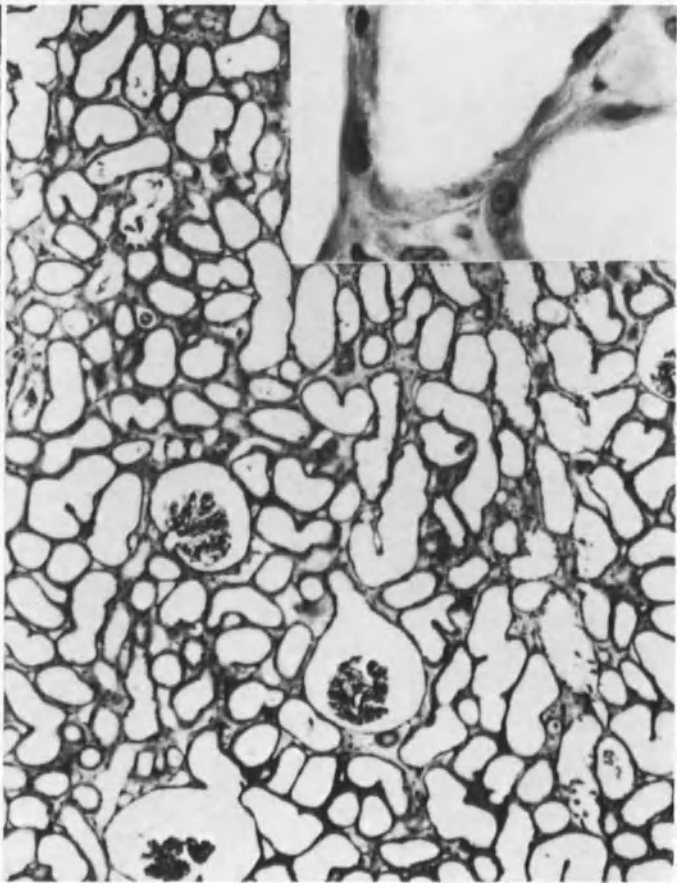

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## Pathogenesis of Transplant Rejection

[238, 733, 964, 732, 768, 653, 1601a, 1805, 1287, 1386a]

In the pathogenesis of transplant rejection, cellular and humoral immune-defence mechanisms play an important role. In the absence of antigenetic identity (probably of the HLA-D antigens), specific recognition of the foreign antigen is realized by the T-lymphocytes of the recipient (recognition phase). Stimulation of these antigen-reacting T-lymphocytes sets off a series of effector mechanisms of the T and B cell systems which can lead to destruction of the transplant (effector phase).

Via stimulation of T-lymphocytes, so-called killer lymphocytes are formed which can destroy transplant cells by direct contact and, possibly, by means of a hypothetic lymphotoxin. Although initially stimulated by HLA-D-incompatibility, it appears that the killer lymphocytes attack only cells with HLA-A and HLA-B (possibly HLA-C) incompatibility.

Attraction and activation of macrophages also occur via T-lymphocytic factors. The macrophages become cytotoxic for transplant cells.

B-cells, which are probably activated by T-helper cells, can influence rejection by direct contact or by release of antibody. The humoral immune response (circulating AB) is mediated by activated T-lymphocytes in the regional lymph-nodes. Antibody production in these lymph-nodes can be detected as early as 48 h after transplantation. The antibodies are directed against donor lymphocytes as well as kidney cells. The antibodies may lead to either transplant rejection or to its enhancement.

◁ **Fig. 30.74.** A 20-month-old renal transplant with moderate subacute to chonic, predominantly interstitial rejection. Juxtaglomerular apparatus is enlarged (*). Interstitial infiltrates, tubular atrophy, and slight arteriolopathy (→) are present. PAS (×400)

**Fig. 30.75.** The numerous tubular multinuclear giant cells in this 11-month-old renal transplant are signs of regeneration. HE (×110)

**Fig. 30.76.** Chronic vascular transplant rejection in an 8-month-old transplant. There is a high degree of vacuolar change in the tubular epithelium, the mitochondria of which are severely swollen. For the most part, epithelium has been detached from BM. Phagocyte with heterolysosomes (*PH*). EM (×2560)

**Fig. 30.77.** A 50-day-old renal transplant with acute functional impairment but no clinical evidence of shock. Typical picture of so-called shock kidney. Tubular lumens distended due to severe atrophy of tubular epithelium (see also inset). Endothelial-like appearence of flattened epithelium is especially conspicuous in the inset. PAS (×80); inset (×350)

Preexisting antibodies directed towards ABO or HLA antigens, are of special importance since they may result in cases of positive cross-match (see p. 564) in peracute transplant rejection. In our material, we found a positive correlation between the degree of vasculopathy and the presence of preexisting cytotoxic AB (negative cross-match).

In the various *morphologic rejection forms*, either the humoral or cellular immune-defence mechanism consistently plays the dominant role.

Peracute transplant rejection is, as mentioned above, brought about by preexisting AB directed against ABO or HLA antigens which bind directly on renal tissue cells.

Acute interstitial rejection arises by cell-mediated immune responses. Vascular and glomerular rejection is said to result from humoral immune responses [732, 768, 1287]. But, in addition to the predominantly cell-mediated immune response in acute interstitial rejection, the presence of plasma cells, especially in the late stage, indicates participation of a humoral immune response as well. Vice versa, in acute vascular transplant rejection, the dense lymphocytic infiltration of the vascular wall as well as the loose interstitial lymphocytic infiltration point, in our opinion, to a participation of cell-mediated defence mechanisms. The cellular reaction in vascular rejection is, we feel, of importance for the progression of the vascular lesion. In chronic rejection, which can procede subclinically, i.e., without acute rejection episodes, humoral and cellular immune responses are operating of which the humoral may be predominant.

The *target structure* for the immunologic reaction in the different morphological rejection forms is probably the endothelium. In peracute rejection, binding of antibodies on the endothelium results in its injury, in aggregation and degranulation of thrombocytes, in intravascular coagulation and, by activation of the complement cascade, in leukocytosis. The end result is a hemorrhagic kidney necrosis [99, 364, 1059, 1690].

In interstitial rejection, the endothelial lesion of the intertubular capillaries is prominent and brought about by direct action of lymphocytes. This lesion allows migration of immunoblasts and effusion of plasma into the interstitium. Interstitial sclerosis can, in part, be viewed as a response to relapsing interstitial edema which occurs in multiple acute rejection episodes of slight intensity.

In glomerulopathy, endothelial injury due to circulating antibodies leads to insudation of various plasma components (IgM > IgG > IgA and C3, see p. 591) which come to rest in the region of the lamina rara interna. Fibrin is certainly also present as a consequence of decreased fibrinolysis and increased coagulation due to endothelial injury [1059, 1690]. A few investigators [841] even maintain that fibrin plays the decisive role in this condition. Changes analogous to those in transplants, however, occur in Weil's disease and in radiation kidney,

in both of which glomerular changes are due to a primary endothelial lesion [1805].

In vasculopathy, the arterial endothelial lesion is brought about by circulating antibodies followed by severe invasion of the vascular wall by host immunoblasts [159], insudation of plasma proteins (IgM > IgG and C3 see p. 591) and by deposition of fibrin which result in endarteritis [1097a]. Although intimal fibrosis in vasculopathy can be reduced by heparinization, and even possibly prevented on occasion [289], morphological findings strongly suggest that there is no significant participation—at least at onset—of thrombotic processes with secondary organization (contra: [238]).

Local vasospasms accompanying acute rejection are a further factor which plays a significant role [159, 1323, 1264, 365, 710]. Thus, we found 20 cases of so-called shock kidney with severely flattened tubular epithelium, interstitial edema, lympho-plasmocytic infiltrates (10 out of 55 cases: [937]; Fig. 30.77; see also p. 586) and interstitial blood stasis. Among the etiological factors in these cases, we found camouflaged rejection as well as genuine circulatory shock and peripheral transplant vasculopathy (missed in the biopsy), partial renal artery thrombosis (Fig. 30.78) and ureteral obstruction. The significance of local vasospasm is especially marked in cases of camouflaged rejection in which hypoperfusion, as in other etiological groups, probably assumes the major role.

Even if the discussion above indicates the importance of cellular and humoral immunodefense mechanisms, the prognosis of the transplant—especially in cadaver grafts—depends not only on the aggressive immunological factors but also on the effectiveness of immuno suppression. Accordingly, the morphological end result is the same for favorable histocompatibility and inadequate immunosuppression as it is for poor histocompatibility and very effective immunosuppression.

## Complications

Basically, seven groups of complications can be recognized:

**1. Glomerulonephritis** [734, 1065b, 1805, 1853]

Recurrence of host GN is especially frequent in isotransplants without immunosuppression (11 out 17 cases: [1082, 560]).

In allografts, GN relapses also occur and predominantly so in anti-BM-type GN, membranoproliferative (Fig. 30.79) and intramembranous GN (see Table 30.5). The frequency of recurrent GN reported in the literature varies between 5–18% [1065b].

Formerly, we believed that we were dealing with a peculiar case of an acute attack of FGN in a donor kidney which showed old glomerular lesions surely present before transplantation. Upon reappraisal, however, this case proved to be one of transplant pseudoglomerulitis (see p. 587; Fig. 30.80).

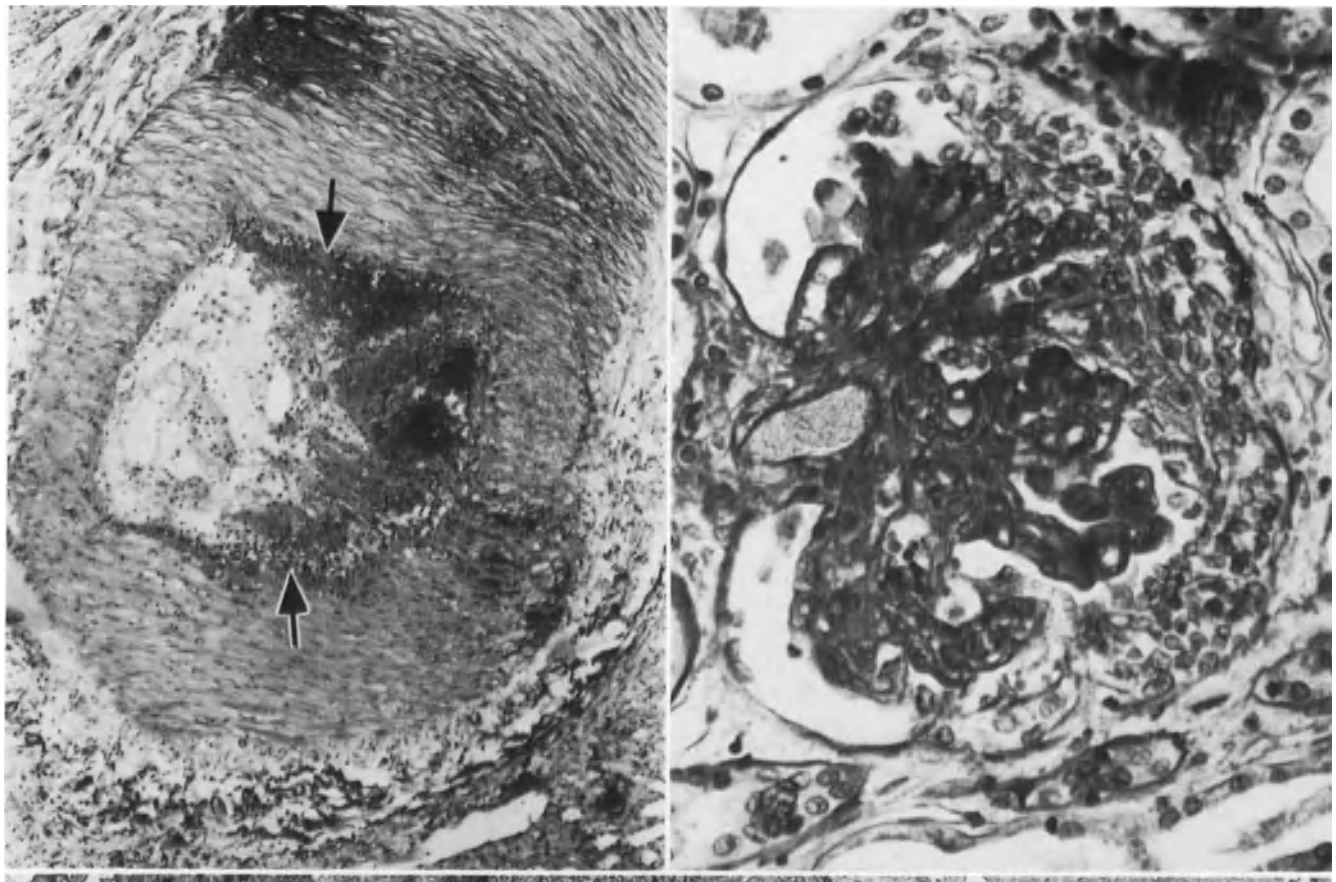
In two of our cases, in which needle biopsy was performed 1 h after transplantation, glomeruli showed slight mesangial enlargement and cell proliferation, a finding suggestive of GN. Nevertheless, progressive renal disease did not develop and the lesion was stationary in subsequent biopsies 4.5 months and 1 year after transplantation (compare: [209a]).

In addition to the two above-mentioned possibilities—relapse of host disease or progression of preexisting donor disease—we have observed de novo occurrence of membranoproliferative GN or proliferative FGN in 4 out of 76 of our cases (Figs. 30.81–30.83). One of these cases was very probably caused by virus (Figs. 30.84, 30.85, 6.75; see p. 94); de novo disease was reported in 1 out of 109 cases in another series [1020].

**Fig. 30.78.** A 21-day-old renal transplant which required removal ▷ because of numerous infarcts. There are very fresh thrombi in small and large arteries, the lumens of which are considerably narrowed by the thrombotic masses which are separated from the media by a fringe of inflammatory cells (→). Thus, thrombosis is due to acute vascular rejection. In renal biopsy done previously, the picture of so-called shock-kidney was present. HE (×50)

**Fig. 30.79.** Relapse of a membranoproliferative GN with severe extracapillary involvement in a 2.5-year-old renal transplant. (×250)

**Fig. 30.80.** So-called pseudoglomerulitis in a 27-day-old renal transplant. Lumens of the glomerular capillary loops are practically completely occluded by the severre swelling and activation of endothelial and mesangial cells. In a residual lumen (*CL*) an erythrocyte can be recognized. Large, swollen cells which appear to be lying freely in the lumen are probably monocytes (*below left*). There is podocytic hypertrophy. BM is more or less unchanged. Osmiophilic deposits were not demonstrable. EM (×2760)



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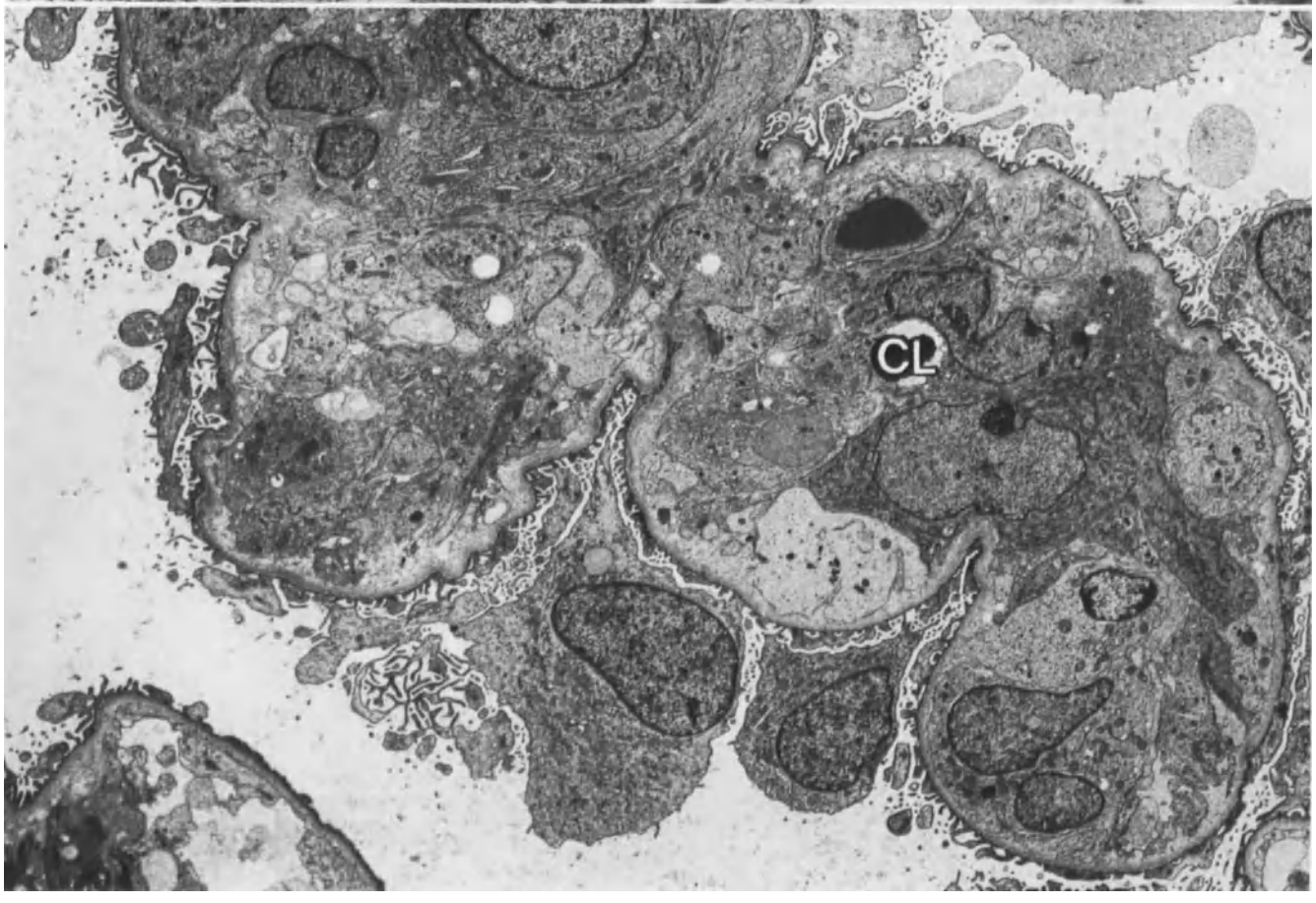



30.80

## 2. Recurrence of Renal Damage in Metabolic Disease

Recurrence of metabolic disease is an unusual finding (Table 30.5), except in primary oxalosis, where it is always present, and in cystinosis in which cystine crystals may appear, which, however, do not lead to functional impairment of the transplant. The kidney from a patient with idiopathic hypercalciuria [484] or those from patients with hepatic glomerulosclerosis [878] are of special interest since, after their transplantation, they showed no functional defect.

Table 30.5. Recurrence of host renal disease in transplants

| Disease | No. of recurrence/ patients/ transplants [*from 1750] | Further literature |
|---|---|---|
| Alport's syndrome | 0/73/83* | [268] |
| Amyloidosis | 1/21/22* | [296, 784a] |
| Cystinosis | 1/24/27* | [649, 930, 977, 1000] |
| Diabetes mellitus | 0/104/114* | [854] |
| Fabry's disease | 0/9/11* | [217, 284a 604, 1261, 1650a] |
| Familial nephritis | 0/55/66* | |
| Gout | 0/19/20* | |
| Medullary cystic disease = nephronophthisis | 0/70/84* | [691] |
| Nail-patella syndrome | – | [421] |
| Primary oxalosis | 10/10/14* | [366, 481, 647, 1420] |
| Scleroderma | – | [1836] |
| Glomerulonephritis | Recurrence | [734, 1065b, 1805, 1853] |
| – endotheliomesangial | extremely rare | [1478a] |
| – extracapillary accentuated | frequent | [323, 385, 1209, 1330, 1574] |
| – membranoproliferative | frequent | [481, 804, 1063, 1461, 1484, 1761, 1778] |
| – intramembranous | probably always | [99a, 126, 231, 245, 523, 524, 651, 1652] |
| – epimembranous | rare | [332, 1290] |
| – segmental-focal sclerosing | moderately frequent | [321, 720, 1020, 1659] |
| – IgA | moderately frequent | [651, 1020] |
| – systemic diseases and special forms | rare | [422, 466, 719, 1197, 1293, 1505, 1750] |
| Glomerular minimal change | rare | [651] |

## 3. Spontaneous Transplant Rupture

The pathogenesis of this condition is not completely understood [495, 547]. We have observed one case of spontaneous rupture due to renal vein thrombosis (6 out of 100 cases: [1104]); the overall frequency is reported as 3–6% [25a].

It is possible, at least in some cases, that anticoagulation may play a role [980]. It appears to us that the concomitant occurrence of kidney swelling, increased bleeding tendency, and parenchymal necroses are decisive with respect to pathogenesis. Our point of view is supported by the fact that spontaneous kidney rupture following anticoagulation also occurs in nontransplanted kidneys, but only if there is preexisting parenchymal damage [1716]. Thus, in 35 cases from the literature, transplant rejection was present in 17. Other causative factors are ischemia or acute tubular necroses as well as abnormal flexion of the body [25a]. Concomitant ureteral insufficiency as a possible etiologic factor has also been discussed [495]. Suturing may be successful in saving spontaneously ruptured kidneys [1104].

## 4. Changes of Renal Artery Anastomosis

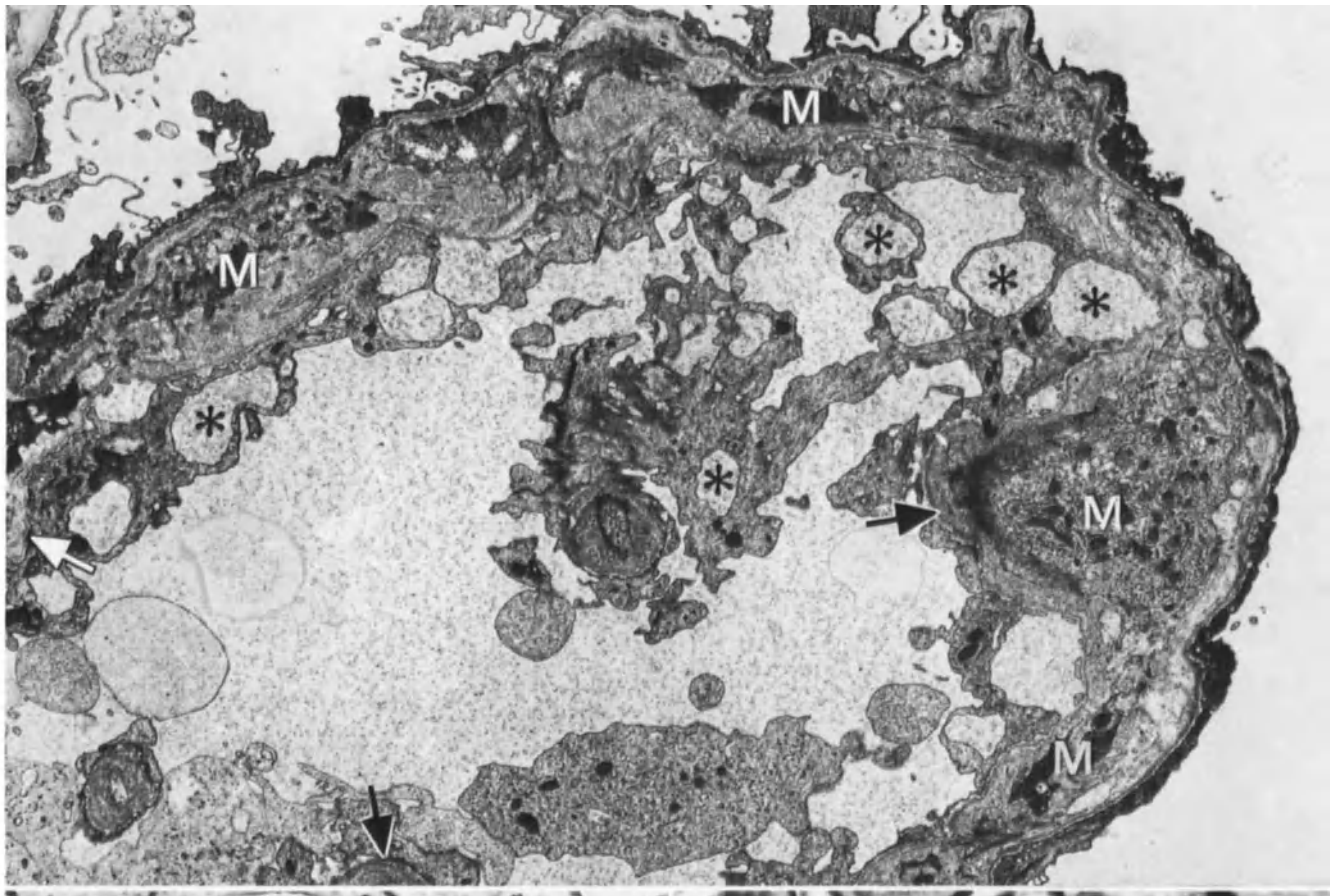
Changes at the site of renal artery anastomosis can lead not only to transplant insufficiency and necrosis but also to considerable difficulties in interpreting biopsies since, in the absence of transplant vasculopathy in biopsy material, the cause of pre-infarct or infarct, which may be present, cannot be determined.

**Fig. 30.81.** De novo proliferative FGN in a 2.25-year-old renal transplant. Circumferential interposition of mesangial cells (*M*) with new formation of a second subendothelial densa layer (→) are present in the periphery of the glomerular capillary loop. Vacuolized (*) endothelial cells are irregularly shaped and exhibit numerous processes projecting into the lumen. There is complete fusion of foot processes. EM (×5620) ▷

**Fig. 30.82.** Proliferative FGN (→←) in a 3.5-year-old renal transplant. Masson's trichrome (×450)

**Fig. 30.83.** Same glomerulus as in Figure 30.82. Slight increase of the mesangial matrix is obvious in the afflicted glomerular capillary loop convolute (→←). PASM (×450)

**Fig. 30.84.** Relapse of membranoproliferative GN in a 3.5-year-old renal transplant. Epstein-Barr and hepatitis-B virus were identified by EM and IF (cf. Fig. 30.85). (Case published [1531]). PAS (×500)

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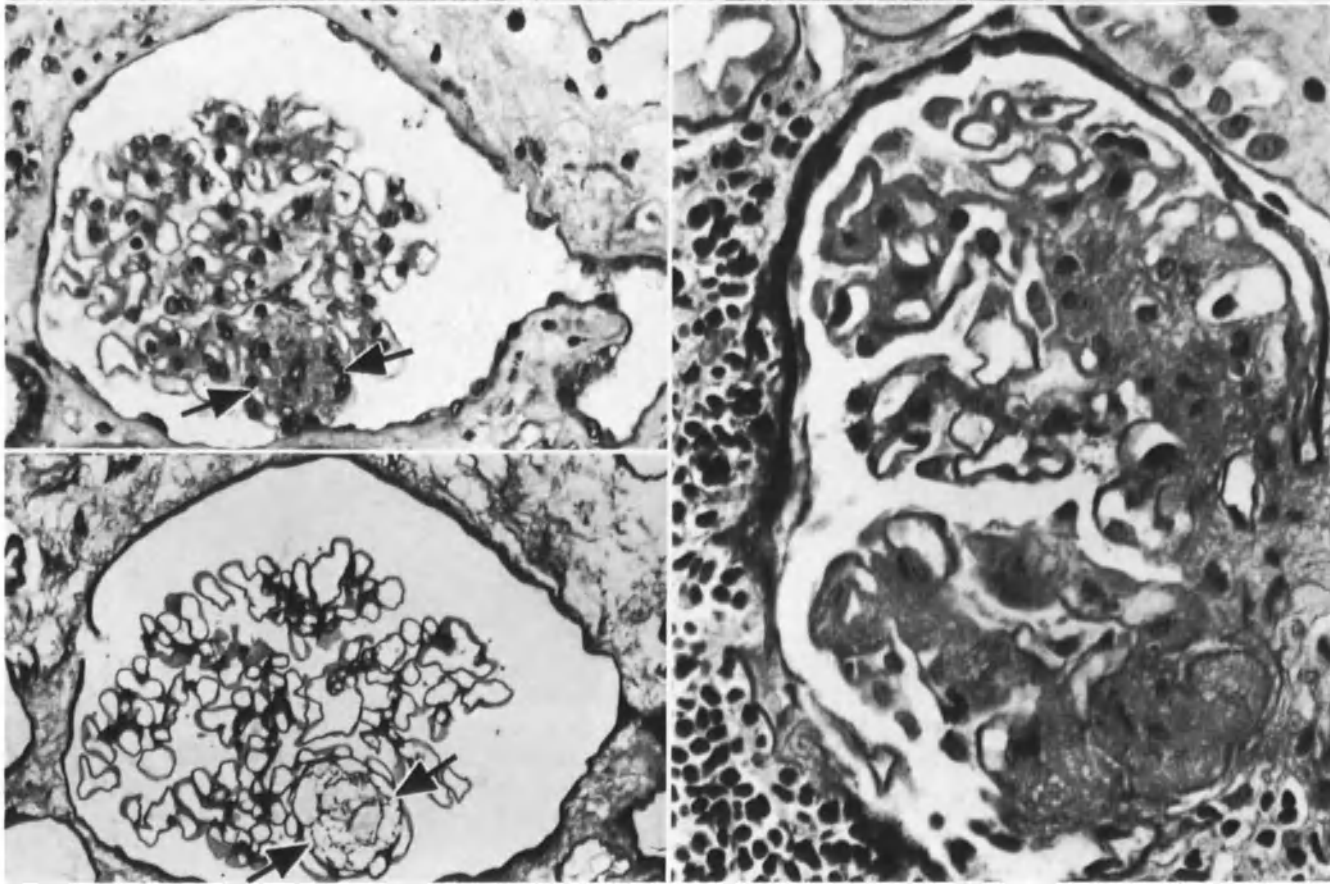

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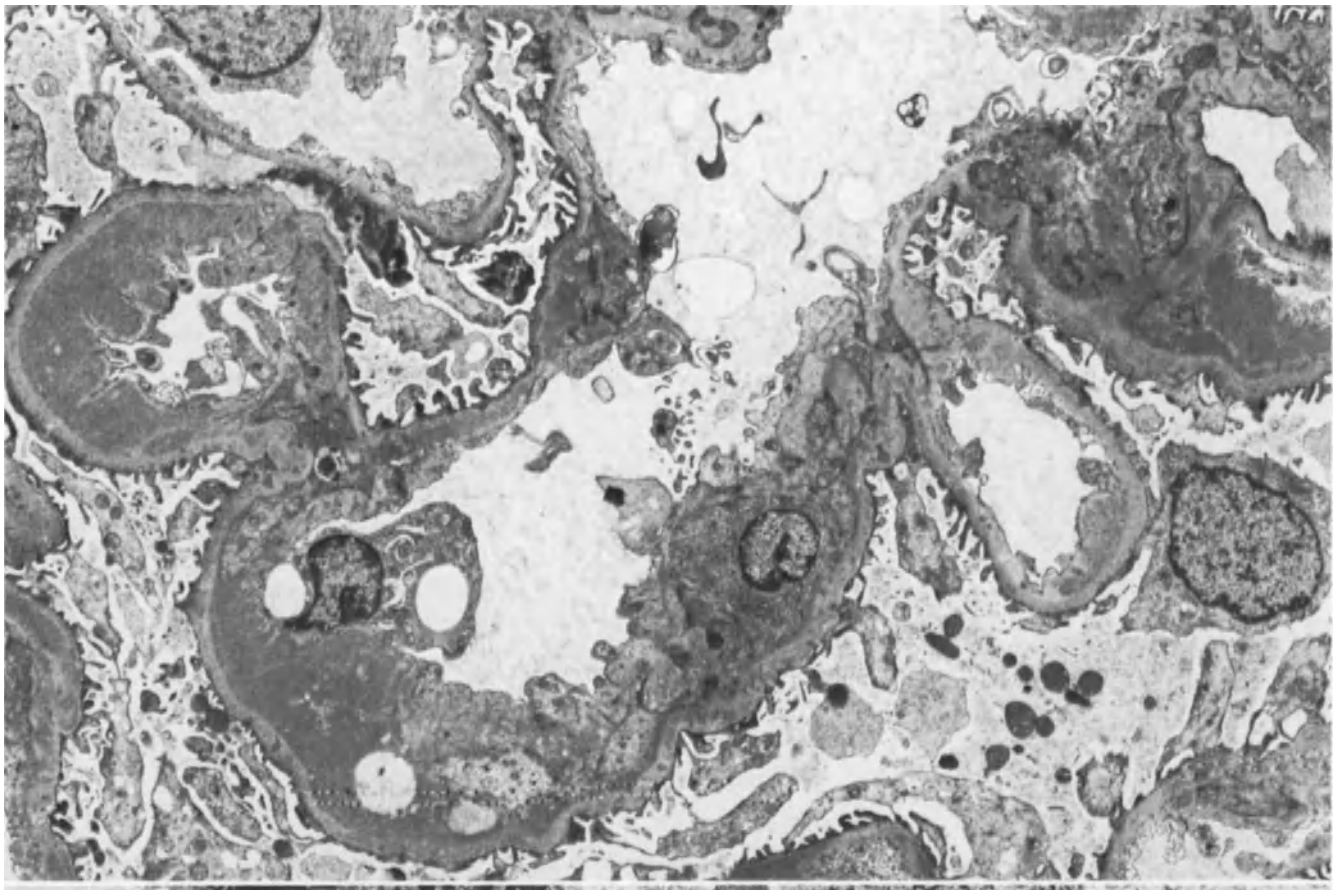

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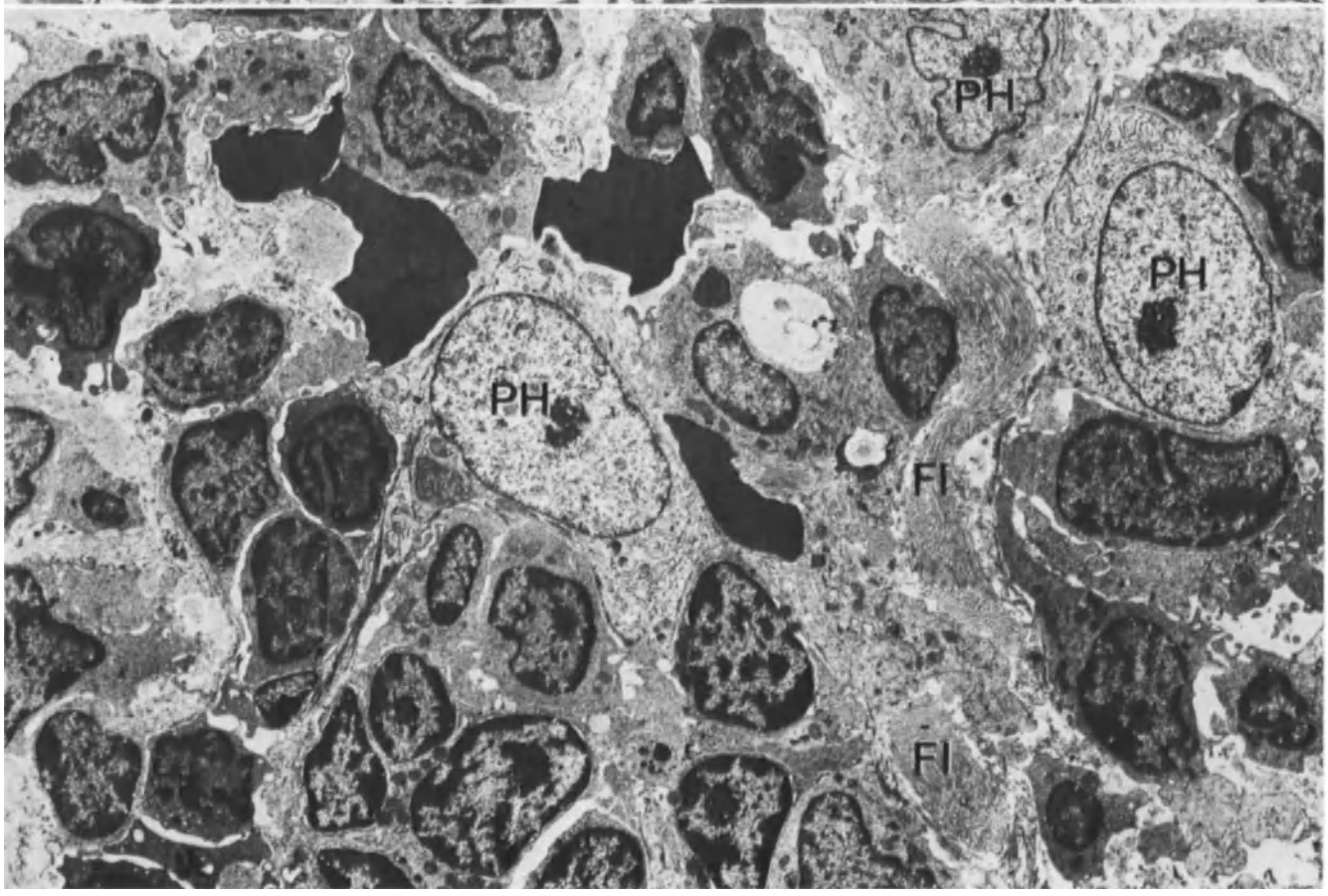


30.86

Altogether, we have observed five cases of arterial thrombosis between post-transplant days 7 and 21. In one of our cases, there was total kidney infarct subsequent to thrombosis of the renal artery at the site of the anastomosis. In three cases, there was transmural necrosis of the donor renal artery at the site of anastomosis.

Stenosis of the donor renal artery 1–1.5 cm distal to the anastomosis may be caused by scar tissue. It appears 5–6 months after operation and leads to hypertension. It may be due to intraoperative arterial injury occurring during removal of the donor kidney [1743]. In another series, 8 out of 50 cases developed renal artery stenosis due to arterial trauma during nephrectomy or transplant preservation [1429a]. Slowly increasing hypertension may also be engendered by especially severe transplant vasculopathy at the site of the anastomosis; we have also observed this in one case (see also [63a]).

### 5. Nephrocalcinosis

In old transplants, nephrocalcinosis with calcification of the vessels along with severe clinical hypercalcemia is encountered. This condition is thought to be caused by incomplete functional normalization of hyperplastic parathyroid glands [1017, 1467].

### 6. Infection

Infections are the consequence of immunosuppressive therapy and must frequently be considered as the result of the weakening of defense mechanisms and of gastrointestinal injury which may serve as their portal of entry.

◁ **Fig. 30.85.** Same case as in Figure 30.84. Membranoproliferative GN in a 3.5-year-old renal transplant in which Epstein-Barr and hepatitis-B virus were identified (see Fig. 6.75, p. 94). There are extensive subendothelial osmiophilic deposits which have severely narrowed the glomerular capillary loop lumen. Moderately severe foot process fusion and edema of podocytes are present. EM (×2960)

**Fig. 30.86.** Interstitial infiltrate in a 5-month-old renal transplant with chronic pyelonephritis. Infiltrate consists predominantly of small, nonactivated lymphocytes, phagocytes (*PH*), and scanty polymorphonuclear leukocytes. Interstitial fibrosis is present (*FI*). Note the few deformed extravasated erythrocytes. EM (×3470)

On must be on the alert for changes in biopsy brought about by gram-negative bacteria or by fungi, as in pyemia [1339, 1599], by protozoa (Pneumocystis carinii; 3 out of 9 cases: [1599]) as well as by viruses (125 out of 610 cases: [1162]). In another series of cases, 87% of isolated viruses belonged to the herpes group of which 77% were cytomegalovirus [969]. These infections may lead to rejection. Particles of 300–600 Å in size are frequently encountered in transplant biopsies, but it is not known whether they represent virus, degradation products, protein deposits, or cellular remnants. Most particles 700–2000 Å in size are interpreted as arising from desintegrated tissue [1210]. We have indicated previously that particles of various size groups could be virus as has, on occasion, been proven [1531] (see p. 94).

According to our experience, cytomegalovirus must be diligently sought for in transplant nephrectomy and autopsy material, while it is demonstrated with ease in the newborn. In any event, it is exceedingly rare in needle biopsy (1 out of 33 cases: [1338]) whereas serologic evidence of cytomegalovirus infection is frequently found (73% of cases: [327]; 91%: [25]). In 1 out of 3 of our cases evidencing positive urinary findings for cytomegalovirus, we were able to demonstrate affliction of the tubular epithelium with LM. Recently, more attention has been directed to demonstrating hepatitis B-AG in transplants [1601a; see p. 92).

Pyelonephritis plays a surprisingly insignificant role in transplants although urinary tract infection is quite frequent (females: 83%; males 43%: [655a]). In 131 transplant biopsies, including nephrectomies, we observed pyelonephritis only twice: 1 case with hematogenous medullary foci of unknown origin and 1 case of ascending infection due to ureteral necrosis (Figs. 30.86, 8.38); for malakoplakia, see: [1851]). The cause of death (Fig. 30.87) in 34 transplant patients was due to infections 21 times: acute and chronic viral hepatitis, abscesses (abdominal wall with pertonitis, upper leg), miliary tuberculosis, pneumonia, and 9 instances of septicemia. The causes of death in the remaining 13 patients were hypertensive cardiac failure in five cases, hemorrhage in four (pancytopenia twice, anticoagulation twice) and acute gastroduodenal ulceration in four. Infections not related to death were frequent: acute and chronic viral hepatitis B six times and cytomegalovirus infection eight times.

### 7. Malignant Tumors

The development of usually undifferentiated malignant tumors in various organs [1018a, 1255, 1699, 1852] as well as proliferation of donor tumor cells in graft from patients suffering from malignant tumors is due to immunosuppressive therapy [1316]. Antilymphocytic serum leads to increased tumor development in experimental

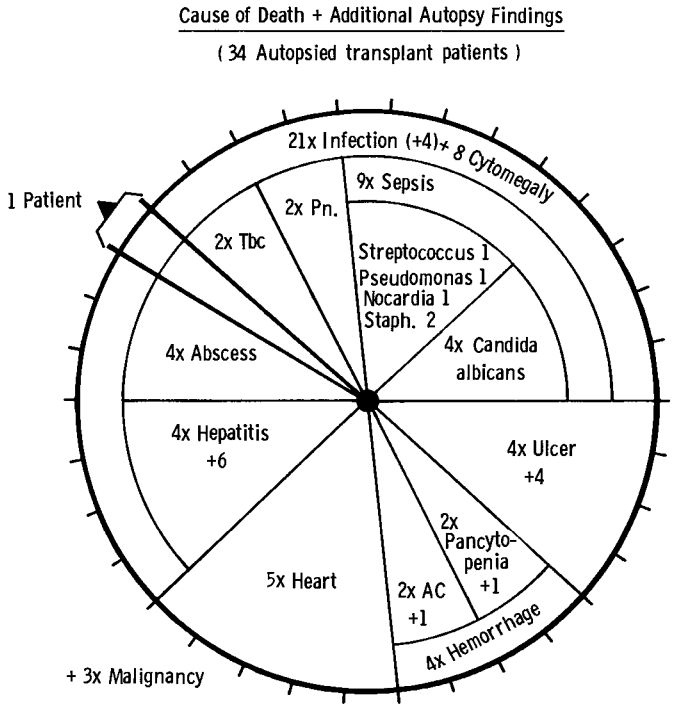


**Fig. 30.87.** Cause of death and additional autopsy findings in 34 autopsied transplant recipients. Anticoagulation (*AC*), pneumonia (*Pn*). For details, see text

animals [33, 235]. "Reticulum cell sarcoma" of the brain, which is otherwise extremely rare, is relatively common [1441]; recent studies indicate that the tumor is more probably a B-lymphocytoma (immunoblastoma) [1564]. In immunosuppressed transplant patients, malignant lymphoma was 35 times and "reticulum cell sarcoma" 350 times more frequent than in nontransplant patients [712, 1018a].

Kaposi sarcoma—interpreted by some investigators as a "reticulum cell tumor"—has been reported 5 times [1570].

We have encountered undifferentiated liver cell carcinoma, "reticulum cell sarcoma" of the brain, and an adenocarcinoma in colitis once each.

Complete disruption or severe impairment of the immunologic defense system against mutations in the host's somatic cells has been suggested as the cause for the increased occurrence of malignancies in these patients. Chronic stimulation of the immune system, on the other hand, could lead to a pathologic reaction which may be implicated in cerebral "reticulum cell sarcoma" [1018a].

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