The Renal Biopsy

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● ***Context.*—The first renal biopsy was carried out more than a century ago, but its widespread introduction into clinical use, beginning in the 1950s, helped develop nephrology into the powerful subspecialty of internal medicine that it is today. In the past 25 years, the use of the spring-loaded biopsy gun, in combination with newer visualization techniques, including ultrasound and computed axial tomography scanning, has led to greater tissue yield and to a much lower risk of complication. During this same time, our understanding of renal pathology has increased many fold. Correct fixation and processing of renal biopsy tissue is critical, and the laboratory must be skilled with renal biopsy light microscopy, immunohistochemistry, and transmission electron microscopy preparation.**

***Objectives.*—To provide an overview of the renal biopsy, including the techniques and its complications, and to summarize proper laboratory methods for processing renal biopsy tissue.**

***Data Sources.*—This article is based on a review of the literature and on the experience of the author.**

***Conclusions.*—The experienced nephropathologist, knowledgeable in both renal medicine and pathology and thus able to correlate subtle tissue-derived information with appropriate clinical data, remains the most important key to the development of an accurate clinicopathologic diagnosis.**

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The first renal biopsy was likely performed in 1901 in New York City, NY, as part of a renal decapsulation procedure for the treatment of Bright disease.[1] Similar material was obtained soon after in Toronto,[2] Liverpool,[3] and Glasgow.[4] Although the tissues were examined and, in some instances, the histologic information was used to modify treatment, these open renal biopsy materials were secondary to the main purpose of the procedure. Castleman and Smithwick[5] (and later Heptinstall[6]) examined a large series of open renal biopsies taken at the time of dorsolumbar sympathectomy, a procedure used to treat hypertension. The reports provided insight not only on the renal vascular pathology associated with hypertension but also on the reliability of the biopsy material by comparing samples taken from both kidneys.

RENAL BIOPSIES

The Aspiration Technique

The percutaneous aspiration needle biopsy had been successfully used to acquire liver material as early as 1895 (reviewed in Iversen and Brun[7]), but it was not until 1939 that Paul Iversen and Kaj Roholm published the first large, systematic series of liver biopsies.[8] Other organs, not as large and as easily accessible as the more superficial liver, were thought to be poor candidates for this procedure. However, in 1944, Nils Alwall began using the aspiration technique to biopsy the kidney after first localizing it using an x-ray. He collected tissue successfully in 10 (77%) of 13 patients but did not publish his results until 1952.[9] It was the publication in 1951 of the results of 133 aspiration biopsies of the kidney by Poul Iverson and Claus Brun, one of the first nephrologists, that led to the keen interest in diagnostic renal biopsies that quickly followed[10] (commentary in Iversen and Brun[7]). Interestingly, only 50% (67/133) of the biopsies in this first series had sufficient renal tissue for evaluation.

The Needle Biopsy

The use of the Vim-Silverman cutting needle, with the patient prone, was described by several investigators (reviewed in Cameron and Hicks[11]), but the information did not become widespread until Kark and Muehrcke published their series in the *Lancet* in 1954.[12] They demonstrated a marked improvement in tissue yield (48 [96%] of 50 samples had diagnostic tissue) and that the procedure was safe. This report[12] led numerous nephrologists to learn this technique and eventually resulted in the influential CIBA Symposium on Renal Biopsy, Clinical and Pathological Significance, held in London, England, in March of 1961.[13] The renal biopsy rapidly became a key part of renal evaluation, so much so that only 2 years after the CIBA symposium, Roland and Dimond[14(p140)] remarked on the critical contributions of the renal biopsy to the ''diagnosis, treatment, and management of patients ill with renal disorders. It has illuminated the anatomy, pathology, and biochemistry of the kidney in health and disease.'' Today, the renal biopsy is recognized to have played a critical role in the development of nephrology as a subspecialty.[11]

Current Practices

A spring-loaded, automated, cutting-needle biopsy ''gun'' was developed in the early 1980s.[15] It was quickly adopted for renal biopsies because of its ease of use, decreased risk of renal laceration, and lessened pain report-

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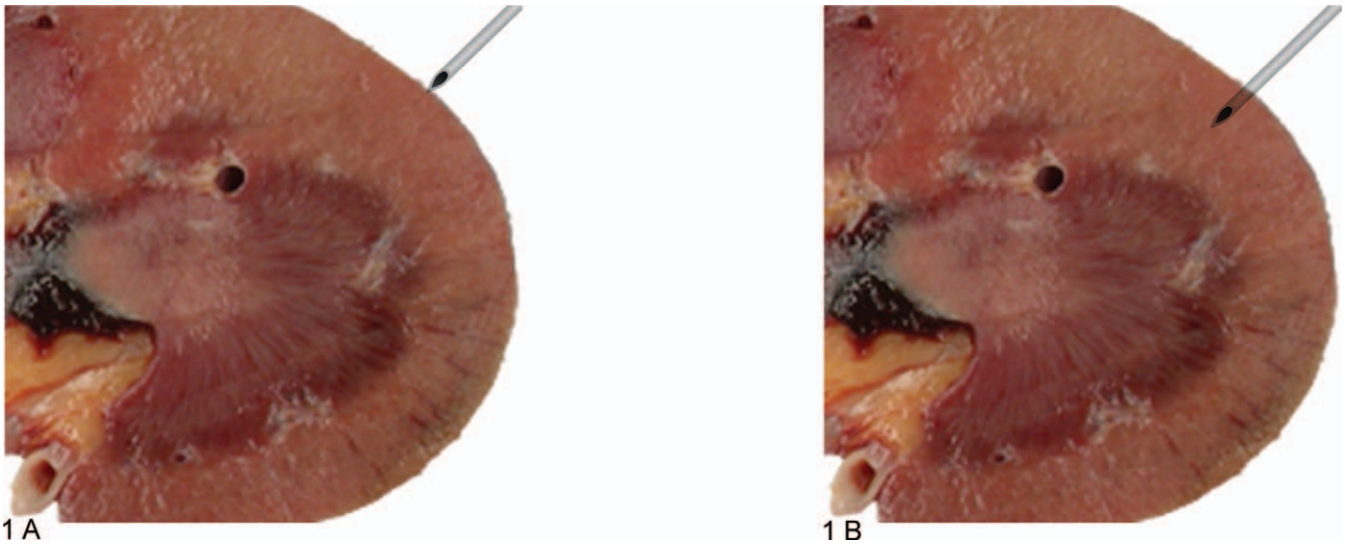

Figure 1. *A, Gross appearance of a kidney showing the lower pole with the biopsy needle correctly positioned. B, Pushing the needle through the capsule can result in the needle starting in midcortex as shown. Note the large vessel in the center of sample that could easily be reached by the needle if it were displaced only slightly. Photographs courtesy of Stephen M. Bonsib, MD.*

ed by patients (reviewed in Burstein et al[16]). The use of the biopsy gun, in combination with advanced imaging techniques, primarily ultrasound (reviewed in Geddes and Baxter[17]) has led to an increase in safety and yield.[16,18–23] The impression among renal pathologists is that there has also been an increase in the number of renal biopsies (oral communications), but there is no published data to verify this conclusion.

Native kidney biopsies are performed with the patient prone and transplant kidney biopsies with the patient supine. In general, a prebiopsy ultrasound scan is used to localize the optimal biopsy site.[22] The lower pole of the native left kidney and the most visible or easily accessed pole of the transplant kidney are the usual targets. Following local anesthesia, the skin is lanced and the biopsy needle inserted. Using real-time ultrasound guidance, the needle is advanced to the kidney, and the biopsy gun is activated.

The number of biopsy attempts varies widely. The questions of how much kidney is enough or how many attempts to obtain good tissue are sufficient have a very unsatisfying answer—''It depends!'' Sometimes one pass is all that is required for adequate material. Usually 2 or 3 attempts produce the desired result, with some operators limiting themselves to no more than 5 tries.[19,20,22–24] It does seem that fewer passes are required today with the combination of the biopsy gun and the newer ultrasound equipment.[23]

Sample Size and Needle Gauge

A renal biopsy that yields inadequate tissue is obviously a very unpleasant result, and all care should be exercised to avoid this situation. Not only is there no tissue for diagnosis but also the complication rate is the same or possibly greater if the biopsy is too deep because of the presence of larger vessels in the medullary region.

Real-time imaging allows an accurate approach to the kidney. The tendency is to reach the outer cortex (Figure 1, A), and then, to go just a little deeper ''to be sure.'' The normal adult renal cortex is only 10 mm. Thus, that last push ends with the needle well into the cortex (Figure 1, B). Because the needle extends slightly before beginning to cut, the resulting sample may have little or no cortex. An assistant (eg, pathologist, technician, nurse) trained in the use of a dissecting microscope can usually quickly determine whether a sample is adequate (see below).

The biopsy gun is supplied with various needle gauges, but practically, only the 14- through 18-gauge needles should be considered. The internal diameter of the 18-gauge needle is 300 to 400 μm, the 16-gauge needle is 600 to 700 μm, and the 14-gauge needle is 900 to 1000 μm.[25] The average diameter of a normal glomerulus from a newborn is about 100 μm. Glomeruli reach the normal adult size of 200 to 250 μm by about 8 years of age. So, the internal diameter of the 18-gauge needle is only slightly larger than the average glomerulus in an adult. More problematic is the volume of tissue available with the smaller needles. Not only is there less tissue per section (Figure 2, A and B), there are fewer sections. Finally, 18-gauge needles produce a significantly greater percentage of fragmented or lost glomeruli (Figure 2, C).[25] It is thus apparent that 14- or 16-gauge needles are ideal in adults, whereas 16- or 18-gauge needles are more appropriate in children younger than 8 years.

Biopsy Complications

Renal biopsy using the spring-loaded biopsy gun with ultrasound guidance appears to be a safe procedure.[20,23,26] Following a biopsy, hematuria is present in about 35% of patients, but gross hematuria is seen in less than 0.5% of patients. A perirenal hematoma is found in as many as 65% of patients, depending upon the diligence of the search, because most are silent. Transfusion is required in less than 1% of biopsies, renal loss in less than 0.1% of cases, and loss of life is extremely rare.[21,26–30]

Other Renal Biopsy Techniques

Most renal biopsies can be done percutaneously. Still, this approach may be contraindicated, such as, for example, in patients with bleeding diatheses.[31–35] A transjugular retrograde approach to the kidney can be attempted with a small biopsy instrument introduced by catheter.[34,35] With

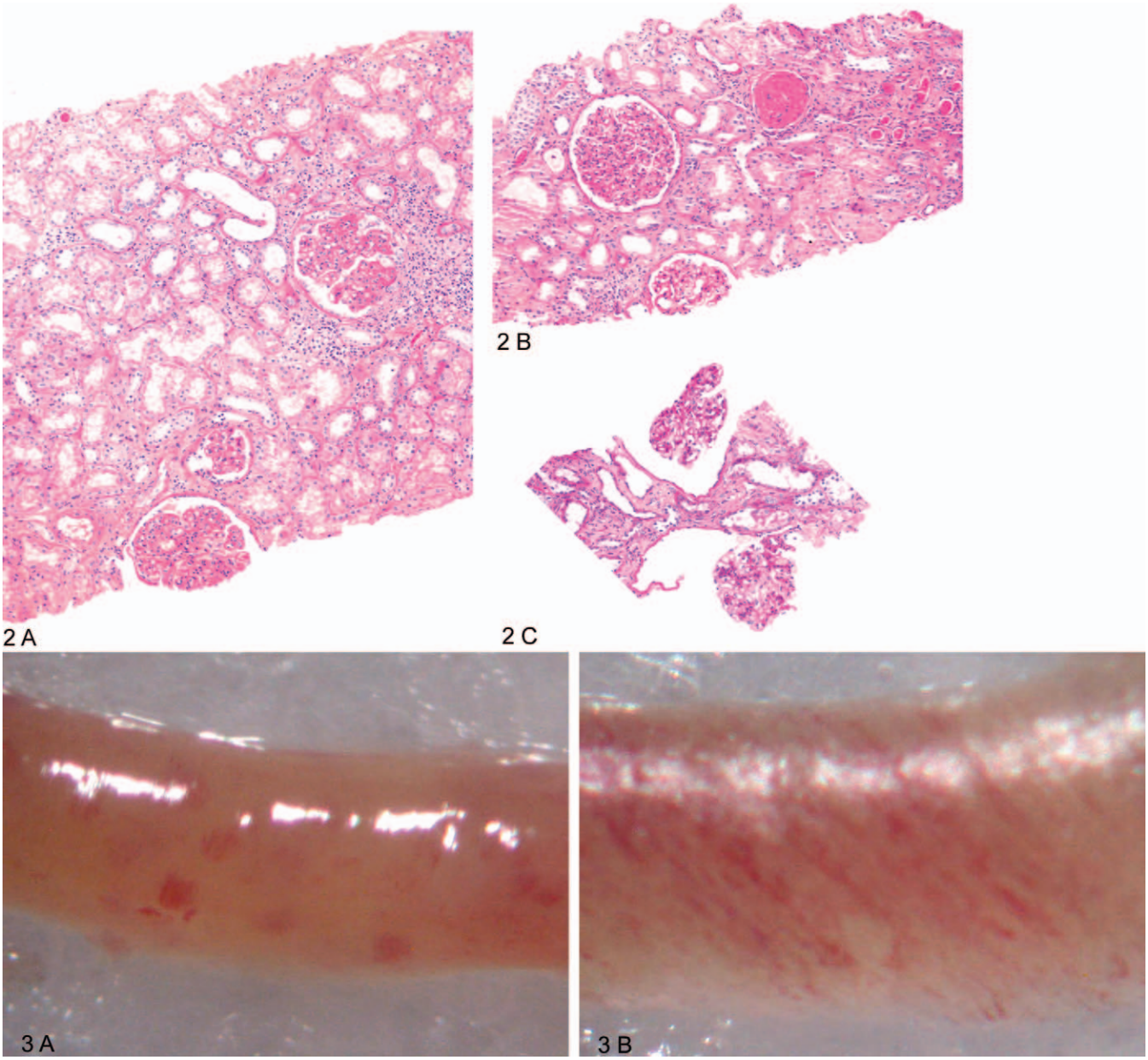

Figure 2. *A, Section of renal biopsy from a 16-gauge needle. B and C, Sections of a renal biopsy from an 18-gauge needle. There is much less overall volume in the 18-gauge samples. Fragmentation and potential glomerular loss are also shown (periodic acid–Schiff, original magnifications ×100).*

Figure 3. *A, Gross appearance of renal cortex showing reddish, circular structures, typical of glomeruli. B, Gross appearance of renal medulla, showing reddish streaks and lacking typical glomerular structures (original magnifications ×10 [A] and ×20 [B]). Photographs courtesy of Alexis Harris, MD, and Myra Zucker.*

this technique, any bleeding that may occur does so into the circulation and is, therefore, of no consequence, per se. Alternatively, a laparoscopic technique can be used.[36–38] Here, a posterior approach, with introduction of a laparoscope, is used. The biopsy is then performed under direct visualization, followed by hemostasis, before closing the wound.

RENAL BIOPSY SAMPLE PREPARATION

Intraoperative Sample Preparation

To provide an accurate diagnosis, the renal pathologist needs to evaluate a renal biopsy with immunohistochemical techniques, light microscopy, and transmission electron microscopy (EM). Separation of biopsy material for each of these techniques occurs optimally at the time of the biopsy, which is best accomplished using a dissecting microscope. A trained observer can recognize glomeruli, allowing sufficient material to be placed quickly in the appropriate media for all 3 modalities (Figure 3, A and B).

Lacking a dissecting microscope or training in its use, the operator may elect to section each biopsy sample into halves for immunohistochemical and light microscopy after removing small sections of each for EM (Figure 4). Some centers still mistakenly attempt longitudinal sectioning. This was appropriate when the needle aspiration tech-

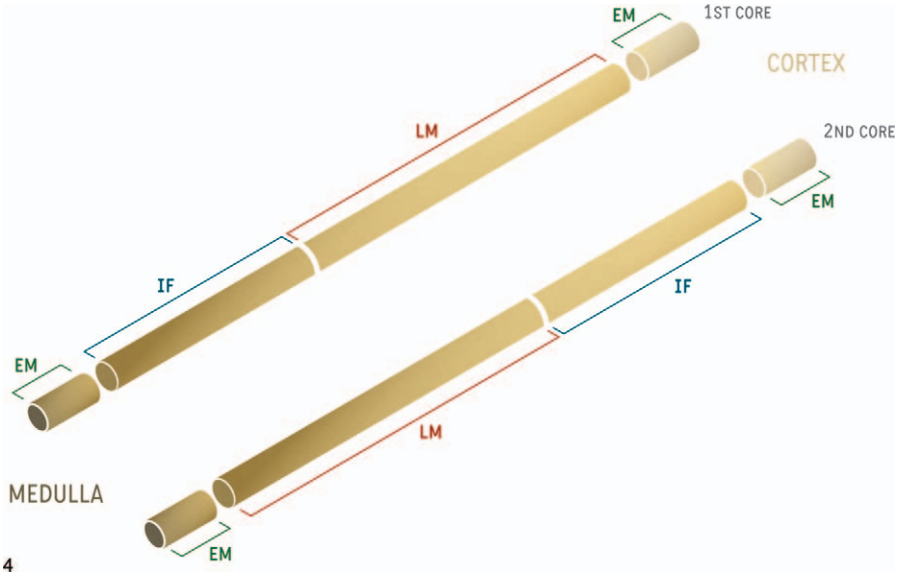

Figure 4. *Schematic of renal biopsy cores demonstrating a sectioning scheme designed to maximize the chance of having glomeruli available for light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM).*

nique was in use in the 1950s because the core diameter of the aspiration needle was 1900 μm, as opposed to the core diameter of a typical needle in use today of 600 μm.[8,25] Longitudinal sectioning should not be done on tissue obtained with biopsy needles currently in use.

The sample should be removed from the biopsy needle with gentleness, taking care not to stretch or crush the tissue. Forceps should be avoided. An 18-gauge needle or a thin, wooden stick, such as a toothpick, is a good alternative. The sample should not be placed on dry gauze because that leads to desiccation and/or to stretch artifacts.[39] Freezing the entire sample distorts the delicate detail required for accurate light microscopic and electron microscopic examination. Ideally, the carefully and gently removed biopsy tissue is quickly examined with a dissecting microscope. A scalpel or single-edged blade (clean and not exposed to fixative) is used to section pieces containing glomeruli. A cutting protocol can be used as shown in Figure 4.[39] Samples for immunofluorescent microscopy are placed in transport solution. The remainder is quickly placed in fixative for light microscopy and EM. Rapid tissue fixation, with minimal delay from time of biopsy to entry into fixative, is required for quality light microscopy and EM morphology.

Most North American renal pathology laboratories use immunofluorescence techniques for immunohistochemical examination. Europe and other parts of the world rely on formalin-fixed, paraffin-embedded immunohistochemical methods. Tissue handling is simplified in these areas because the samples need only be divided into light microscopy and EM fixatives.

Fixatives and Transport Media

Historically, several fixatives for light microscopy have been used, and some are favored today because of their ability to preserve certain morphologic features of interest. The utility as well as the difficulties associated with these various fixatives have recently been reviewed.[39] High-quality, 10% buffered-aqueous formaldehyde (formalin) is the most common method of tissue fixation for light microscopy. Buffered formalin penetrates and fixes tissue rapidly; it is an excellent transport fluid in that it is stable at room temperature (has a long shelf life and does not require refrigeration or freezing), and tissues do not degrade during shipping. If handled properly, formalin-fixed tissues do not lose significant antigenic sites and can be used for immunohistochemistry. Molecular studies can also be performed on formalin-fixed samples. Formalin-fixed, paraffin-embedded tissue can be used for immunohistochemistry or EM if adequate tissue was not available for either or both. Although the reprocessing delays the final results, neither formalin fixation nor paraffin embedding significantly impedes the interpretation of electron photomicrographs.

Immunofluorescence Transport Media.—If the renal pathology laboratory is close to the biopsy site, the tissue can be transported on saline-soaked gauze. A technician must be available to quickly freeze the tissue. Otherwise, the tissue can be stabilized in Michel transport media.[40] Antigens of interest in the renal biopsy are protected for as long as a week in this media, and the sample is stable at room temperature. This allows transport of renal biopsy samples to renal pathology laboratories by air express service if a local laboratory is unavailable. A sample in Michel transport media must be washed before freezing.

EM Fixatives.—Many renal pathology laboratories use ice-cold, 1% to 3% glutaraldehyde as an EM fixative. Others prefer 1% to 4% paraformaldehyde. Glutaraldehyde is excellent when the fixative is kept cold and the tissue is removed after several hours to prevent the tissue from becoming brittle. However, glutaraldehyde does not penetrate quickly, must be refrigerated, and has a short shelf life. Paraformaldehyde is an excellent fixative, but it must be made up, fresh, right before use, and again, the tissue must be removed after a few hours of fixation. Formalin provides good fixation, does not require refrigeration, has a long shelf life, and the tissues are stable for long periods while in the fixative. Formalin does cause shrinkage artifacts, and measurements of such things as glomerular basement membrane thickness must be calibrated to account for this.[41] Whatever fixative is chosen, the key to ultrastructural preservation is rapid placement of the tissue into the fixative.

Mercury-based fixatives, such as Zenker fluid or B-5, cannot be used for EM without heroic effort. Tissue in

Michel transport media is not fixed, and as such, ultrastructural detail is very poor. Still, even with the poor fixation and the freezing artifact, certain diagnostic features, such as immune deposits, are usually still visible.

Light Microscopy Samples

Tissue Processing.—The small, thin core of renal biopsy tissue requires special handling to prevent artifacts and, worse yet, loss, during processing. The tissue should be enclosed in lens paper or other appropriate materials developed for this purpose. This prevents loss through the cassette holes during processing. Netted bags and sponges should not be used because they almost inevitably lead to pressure-induced, mechanical artifacts.

Automated tissue processors have small-sample cycles, and renal biopsy tissue should be processed with other biopsies using this protocol. Some laboratories use a same-day processing system designed specifically for small samples.[42–44]

Sectioning and Staining.—Serial sectioning at 2 to 3 μm is critical for accurate evaluation of renal biopsy material. A ribbon with 2 to 4 sections should be placed on each slide. Great care must be taken to avoid chatter, folds, or tearing. Various schemes are used involving 10 to 15 slides stained with alternating hematoxylin-eosin, periodic acid–Schiff, Jones silver, and trichrome techniques.

Immunofluorescent Microscopy

Processing and Sectioning.—Tissue for immunofluorescent microscopy is snap-frozen, not fixed, and sectioned in a cryostat. Cryostat sections of 2 to 4 μm thick are placed on clean, air-dried slides that are prelabeled with the name of the antigen used.

Antigen Reaction.—The routine diagnostic kidney biopsy should be examined for the presence of immunoglobulins (IgG, IgM, and IgA), complement components (C3, C1q, C4), fibrin, and κ and λ light chains. Certain medical conditions may require more specialized studies, such as the α chains of type IV collagen in hereditary nephritis, C4d in renal transplant biopsies, among others.

Appropriate controls include a negative control (without antibody) and a known positive control (albumin can serve this purpose, although it has other uses as well). There are various internal positive controls, such as C3 in blood vessels, C4d in mesangial areas, IgG in protein droplets, among others. Appropriate dilution should be determined with known positive material each time a new vial of antibody is opened.

Tissue Examination.—A microscope fitted with a high-power epifluorescent attachment and appropriate filters is required. A skilled and experienced observer can evaluate the intensity and localization of immunoreactants while recognizing the normal background and internal positive controls for each antigen tested. Overinterpretation and underinterpretation plague the beginner and the irregular reader.

Immunohistochemistry

Processing, Sectioning, and Immunoreaction.—Tissue for immunohistochemistry is taken from the block also used for light microscopy. No special fixation or freezing is required. Microtome sections, cut at 2 to 3 μm, are placed on coated slides before any of several antigen retrieval steps.[45–47] Certain antigen protocols require overnight processing for optimal results, whereas other techniques can be detected in 3 to 5 hours (SV40, AA amyloid, among others).

Tissue Examination.—The presence of a positive reaction can be subtle and again requires a skilled and experienced observer. Use of ×40 objective magnification or even ×100 oil objective magnification may be required to recognize certain subtle patterns in various glomerular diseases. The possible presence of such a small amount of reaction product requires excellent color titration and quality control of nonspecific background staining.

Immunofluorescence Versus Immunohistochemistry

The choice between these immunofluorescent and immunohistochemistry techniques is highly specific to the renal pathologist. Familiarity with the variables associated with each of these methods, as well as the resources and experience of the pathologists and the renal pathology laboratory, will determine the best choice. In the right hands, either method can provide important diagnostic information, and in many laboratories, the strengths of each procedure are used, as appropriate, to produce the most accurate diagnosis.

Transmission EM

Tissue Processing and Sectioning.—Tissue for transmission EM is processed into plastic, then trimmed, and a 1-μm section is cut and stained, usually with toluidine blue. This section is reviewed to select an appropriate glomerulus and other structures for ultrastructural examination. These so-called thick sections may also yield diagnostic information not present on the light microscopy sections. Examples of this information include the lone atherosclerotic embolus or focal segmental glomerulosclerosis lesion. The ultramicrotome is then used to prepare the very thin sections required. The tissue is collected on a copper grid and usually stained with lead citrate and uranyl acetate.

Ultrastructural Examination.—One or 2 glomeruli are examined. A series of low, medium, and high magnification photomicrographs are prepared that include representative capillary loops and mesangial regions. Tubulointerstitial areas and vascular structures are also examined, and photomicrographs are taken that demonstrate any findings of pathologic abnormalities.

RENAL BIOPSY INTERPRETATION AND THE RENAL BIOPSY REPORT

Determining the correct renal biopsy diagnosis requires recognition and interpretation of findings present on a variety of light microscopy stains, immunohistochemistry materials, and EM photomicrographs. Integration of the pathology material with detailed and sometimes subtle clinical information presupposes a thorough understanding of renal disease. Finally, detailed communication with the nephrologist or other clinician caring for the patient leads to an accurate clinicopathologic correlation and the correct diagnosis.

The pathology report should include a glomerular count with a statement regarding the number of obsolescent glomeruli. In the case of crescentic glomerulonephritis, the number of glomeruli with crescents, and of those, the number that are, for example, cellular, fibrocellular, and fibrous should be documented. A description of the changes seen in the glomerular capillaries and the mesangium should be given, including information on alter-

nations in the glomerular basement membranes, hypercellularity, leukocyte infiltration, matrix expansion, and the presence of deposits or thrombotic changes, among others. The other renal compartments should be described as well, including descriptions of the tubules, the interstitium, and the blood vessels. Each slide is another page in the story, and the diagnostic lesion may only be present in one section. Occasionally, the only slide containing the pathologic feature of interest is the toluidine blue–stained, thick section, produced for EM, which emphasizes the importance of a careful examination of all available material.

Dark-field immunofluorescent microscopy is usually graded using a semiquantitative scale, such as 0, trace, 1+, 2+, and 3+. Some laboratories divide a positive reaction into 0 to 4+. It has long been accepted that such semiquantitative analysis is both accurate and reproducible.[48] The report should include the name of the antigen, its location, intensity, and characteristics. Although the glomerulus is the usual site of interest, the tubulointerstitium and the vessels may also react with various antibodies, and a description of these changes is also required. An experienced observer will be familiar with background fluorescence and the positive control area for each immunoreactant. Awareness of these changes is important, but they may or may not be included in the microscopic description, depending on the preference of the renal pathologist.

Immunohistochemical staining, most often using diaminobenzidine to reveal the reactive products, should also be graded and described fully. Variability of the stain from antigen to antigen and from day to day requires an experienced renal pathologist to provide correct interpretation. Immunohistochemistry techniques have several variables that affect reactive outcomes and these must be understood. These include antigen retrieval, background elimination, and development of the reaction signal. Even with widespread availability of automated staining devices, these techniques are time-consuming, include multiple steps, and the results can be misinterpreted in inexperienced hands.

Electron microscopy, the tool of promise in the 1960s and 1970s, has little diagnostic utility in the daily practice of anatomic pathology, having been almost completely replaced by diagnostic immunohistochemical examination of pathologic tissues. Paradoxically, the electron microscope remains critical in renal pathology. Electron microscopy reveals the major diagnostic characteristic or provides important refinements and/or additional diagnostic features in about half of all native kidney biopsies.[49–51] This percentage has not changed since EM was first shown to be required for accurate biopsy diagnosis in the middle of the previous century.[49] The EM report should include a description of the glomerular basement membranes, including thickness, presence or absence of deposits or infiltrative processes, the status of the foot processes, and changes in the endothelium. A description of deposits should contain information on location, density, granularity or fibrillarity, size, and frequency. Abnormalities of the glomerular basement membranes, such as wrinkling, folding, collapse, sclerosis, or duplication, should be described. Hypercellularity should be documented, including degree, location, and cell type, if possible. Changes noted in the tubules, the interstitium, or the blood vessels should also be described.

The report is completed with a list of diagnoses derived from all of the pathologic materials examined, interpreted in light of the patient's clinical information, including discussions with the clinician caring for the patient. Many reports will include a comment explaining the rationale for the diagnosis and suggesting the implications of the results.

THE RENAL TRANSPLANT BIOPSY

Donor Transplant Biopsy

A biopsy may be used to determine suitability of a kidney from a deceased donor, especially in extended-use situations, such as with an older donor. The frozen section is most often used, but the utility of that method is linked to the quality of the section produced. In general, the percentage of sclerosed glomeruli, the presence of major glomerular lesions (crescents and diffuse proliferation, among others), significant tubulointerstitial inflammation, and/or vasculitis are identifiable. The degree of global sclerosis correlates well with outcome, but a minimum of 25 glomeruli is required in the donor biopsy.[52] Detection of subtle glomerulonephritis, evaluation of the degree of acute tubular injury, and quantification of interstitial fibrosis are not practical with frozen-section techniques.

Allograft Biopsy

Clinical and laboratory information is insufficient to explain renal allograft dysfunction, necessitating a biopsy of the transplant for correct diagnosis. In general, a minimum of 2 cores should be submitted for light microscopy. The sensitivity for transplant rejection with one core is 90%, but rises to 99% with the addition of a second core.[53] A third core submitted for immunofluorescence can be used for rapid determination of humoral rejection, as shown by deposition of the complement component C4d along peritubular capillaries.[54–56] Immunohistochemical techniques for C4d can be used, but these methods usually require significantly more time.[57,58]

The recognition of recurrent or de novo glomerular disease requires light microscopy, immunohistochemical tests, and electron microscopy examination similar to a native kidney biopsy. This full workup is recommended after the first 6 months of transplantation or in the presence of clinical or laboratory evidence of glomerulonephritis.

Transplant Protocol Biopsy

In spite of a marked decline in acute transplant rejection and early graft loss during the past 15 years, the incidence of late graft loss has changed little (reviewed in Mengel et al[59]). Protocol biopsy screening is designed to detect subclinical pathologic events, which are thought to play a role in long-term outcome. Ideally, the use of regular biopsy in a clinically normal transplant would reveal any pathologic process early in its course, allowing time for effective therapeutic intervention. The utility of the protocol biopsy has been debated,[60–62] but recent studies strongly suggest that protocol biopsies reveal a significant percentage of subclinical rejection at every time point examined (Table; reviewed by Nankivell and Chapman[63]). The finding of subclinical rejection has been associated with decreased graft survival at 10 years, and there is evidence that treatment of subclinical rejection improves long-term results (reviewed by Wilkinson[62]). Based on the above data, protocol biopsies have become standard in many transplant centers.

Protocol Biopsies Demonstrating Rejection*		
Time Posttransplant	Percentage With Banff IA, Mean (Range)	Percentage With Banff Borderline, Mean (Range)
1–2 wk	17 (13–25)	24 (12–38)
1–2 mo	29 (11–43)	23 (21–27)
2–3 mo	17 (3–31)	23 (11–41)
12 mo	18 (4–50)	17 (7–44)

* Data were compiled from multiple studies. Permission was granted by Wiley-Blackwell Publishing (Hoboken, NJ) to present the data in the Table, previously published in the *American Journal of Transplantation* (Nankivell BJ, Chapman JR. The significance of subclinical rejection and the value of protocol biopsies. *Am J Transplant.* 2006;6:2006–2012).[63]

CONCLUSION

As other analytical techniques have emerged (genomics, proteomics, and metabolomics, among others), many physicians have predicted the disappearance of anatomic pathology in general and renal biopsies specifically. However, similar to Mark Twain, who upon reading a premature obituary remarked, ''The report of my death was an exaggeration,'' so too, for the disappearance of the renal biopsy. The very complex nature of the nephron and the difficulty of teasing out complex molecular events using whole organ fragments or, harder still, using urine, or even blood, suggests an exciting future for renal pathology. The interplay of classic morphologic analysis, with as yet undeveloped microchemical methods, will hopefully allow greater insight into the various medical renal diseases that are at the heart of modern nephropathology.

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