Kidney International, Vol. 44 (1993), pp. 411–422

International standardization of criteria for the histologic diagnosis of renal allograft rejection: The Banff working classification of kidney transplant pathology

KIM SOLEZ (Edmonton), ROY A. AXELSEN (Brisbane), HALLGRIMUR BENEDIKTSSON (Calgary), JAMES F. BURDICK (Baltimore), ARTHUR H. COHEN (Los Angeles), ROBERT B. COLVIN (Boston), BYRON P. CROKER (Gainesville), DOMINIQUE DROZ (Paris), MICHAEL S. DUNNILL (Oxford), PHILIP F. HALLORAN (Edmonton), PEKKA HÄYRY (Helsinki), J. CHARLES JENNETTE (Chapel Hill), PAUL A. KEOWN (Vancouver), NIELS MARCUSSEN (Aarhus), MICHAEL J. MIHATSCH (Basel), KUNIO MOROZUMI (Nagoya), BRYAN D. MYERS (Stanford), CYNTHIA C. NAST (Los Angeles), STEEN OLSEN (Aarhus), LORRAINE C. RACUSEN (Baltimore), ELEANOR L. RAMOS (Gainesville), SEYMOUR ROSEN (Boston), DAVID H. SACHS (Charlestown), DANIEL R. SALOMON (Bethesda), FRED SANFILIPPO (Baltimore), REGINA VERANI (Houston), EEVA VON WILLEBRAND (Helsinki), and YUTAKA YAMAGUCHI (Tokyo)[1]

International standardization of criteria for the histologic diagnosis of renal allograft rejection: The Banff working classification of kidney transplant pathology. A group of renal pathologists, nephrologists, and transplant surgeons met in Banff, Canada on August 2–4, 1991 to develop a schema for international standardization of nomenclature and criteria for the histologic diagnosis of renal allograft rejection. Development continued after the meeting and the schema was validated by the circulation of sets of slides for scoring by participant pathologists. In this schema intimal arteritis and tubulitis are the principal lesions indicative of acute rejection. Glomerular, interstitial, tubular, and vascular lesions of acute rejection and "chronic rejection" are defined and scored 0 to 3+, to produce an acute and/or chronic numerical coding for each biopsy. Arteriolar hyalinosis (an indication of cyclosporine toxicity) is also scored. Principal diagnostic categories, which can be used with or without the quantitative coding, are: (1) normal, (2) hyperacute rejection, (3) borderline changes, (4) acute rejection (grade I to III), (5) chronic allograft nephropathy ("chronic rejection") (grade I to III), and (6) other. The goal is to devise a schema in which a given biopsy grading would imply a prognosis for a therapeutic response or long-term function. While the clinical implications must be proven through further studies, the development of a standardized schema is a critical first step. This standardized classification should promote international uniformity in reporting of renal allograft pathology, facilitate the performance of multicenter trials of new therapies in renal transplantation, and ultimately lead to improvement in the management and care of renal transplant recipients.

[1] All authors made an intellectual contribution to the writing of this paper. The blinded reviews of panel slides for assessment of reproducibility were conducted by Drs. Benediktsson, Jennette, Marcussen, Olsen, Racusen, and Solez.

Received for publication September 1, 1992
and in revised form February 8, 1993
Accepted for publication March 10, 1993

© 1993 by the International Society of Nephrology

Standardization of allograft biopsy interpretation is necessary to guide therapy in transplant patients and to help establish an objective rejection end point in clinical trials. Stimulated by standardization efforts in heart and lung transplantation [1, 2], and sponsored by the International Society of Nephrology Commission on Acute Renal Failure, a group of renal pathologists, nephrologists, and transplant surgeons met in Banff, Canada from August 2 to 4, 1991 to construct a schema for nomenclature and classification of renal allograft pathology. The schema underwent considerable evolution over the next year through follow-up meetings, correspondence, and the circulation of panel sets of biopsy slides for assessment using schema criteria. The resulting formulation, previously reported in abstract form [3], is described in this paper.

In the Banff schema tubulitis and intimal arteritis are regarded as the principal lesions indicative of acute rejection. Although the most obvious lesion in cases of renal transplant rejection is often interstitial infiltration by mononuclear inflammatory cells, five different studies in which stable kidney transplants were biopsied have shown that focal or mild diffuse infiltrates occur commonly in well functioning grafts [4–8]. The presence of interstitial infiltration has a negligible effect on graft survival [9–12]. The index patient with a biopsy heavily infiltrated by lymphocytes illustrated in the 1984 study of Burdick et al [6] still has normal graft function ten years later and has never had a clinical rejection episode. D'Ardenne et al [4] found interstitial infiltration in 80% of stable grafts on cyclosporine therapy with diffuse infiltrates in 42%. Clearly, if interstitial infiltration is seen in a significant proportion of well functioning grafts, it cannot be used alone as a specific sign of rejection. It is only when interstitial inflammation is accompanied by tubular invasion (tubulitis) that it has any degree of specificity.

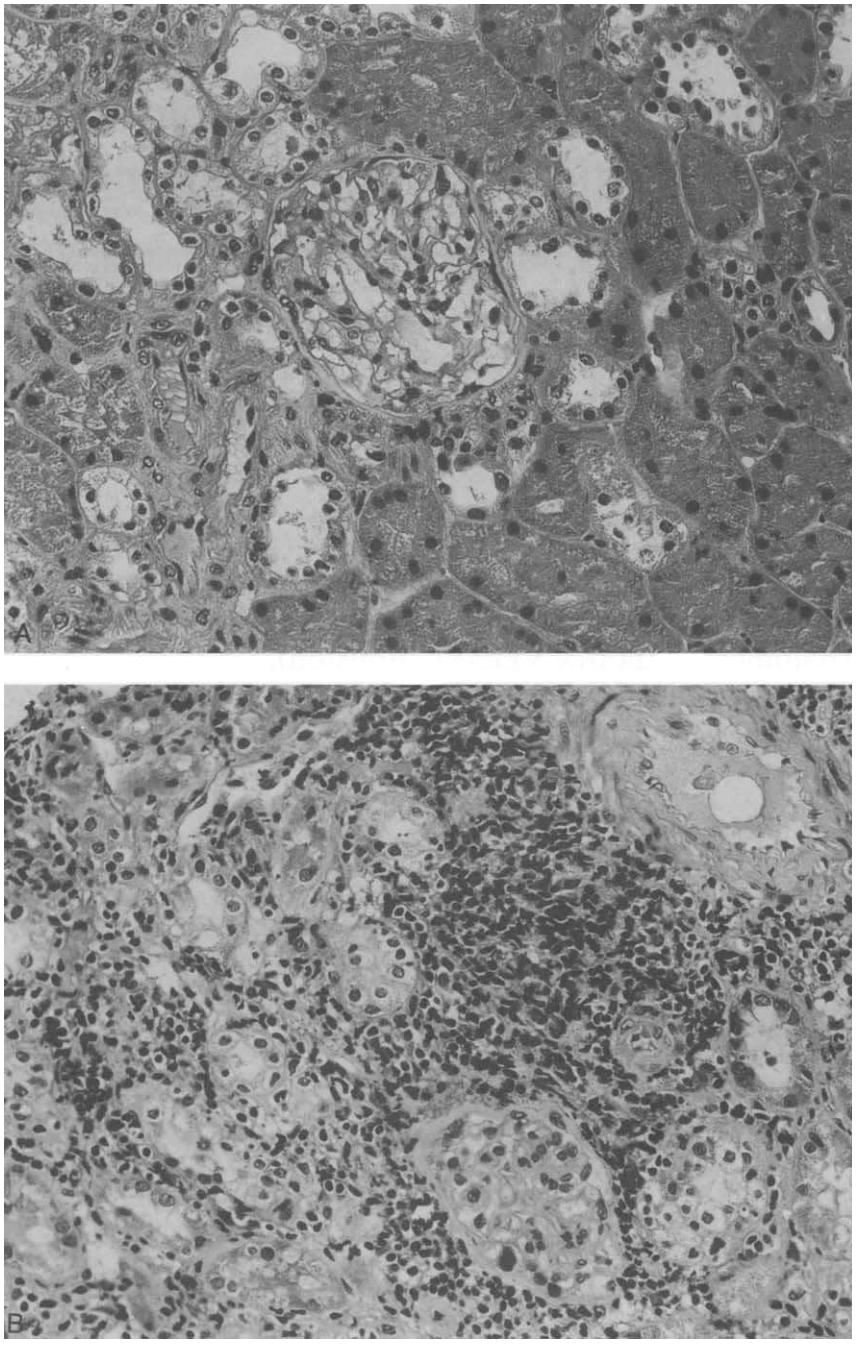


Fig. 1. A. *Representative field from one core of a biopsy from a patient with clinically-typical acute rejection.* The core was histologically normal and no interstitial infiltrate was found (H&E, × 190). **B.** Representative field from second core from same biopsy. There is a heavy interstitial infiltrate of mononuclear inflammatory cells (H&E, × 190).

Although it is not specific for rejection, interstitial inflammation is a typical finding in that condition, and various authors have suggested grading severity of rejection by the extent of the interstitial infiltrate. The objection to use of severity of interstitial inflammation seen on biopsy to grade rejection relates to sampling error. Rejection in the kidney, as in the heart [1], begins as a patchy process. By analogy with animal models, if one examined a cross section of the entire kidney it is likely that there would be a good correlation between extent and intensity of inflammation and severity of rejection [13]. However random sampling by a single core needle biopsy may eliminate this correlation and interstitial infiltrates can be seen in patients without rejection as mentioned above. Also rare cases of moderate-to-severe rejection may be sampled in such a way that an entire biopsy core may appear normal (Fig. 1a and b). The degree of infiltration has no correlation with response to therapy [5, 11, 12], probably due, at least in part, to sampling error.

Methods

Description of the schema

The formal classification is presented in Tables 1 to 4. It includes hyperacute rejection, borderline changes, three grades

Table 1. Diagnostic categories for renal allograft biopsies

1. Normal
2. Hyperacute rejection (see **Definitions**)
3. Borderline changes ("very mild acute rejection")
   This category is used when no intimal arteritis is present, but only mild or moderate focal mononuclear cell infiltration with foci of mild tubulitis (1 to 4 mononuclear cells/tubular cross section).
4. Acute rejection

   Grade I, mild acute rejection
   Cases with significant interstitial infiltration (> 25% of parenchyma affected) and foci of moderate tubulitis (> 4 mononuclear cells/tubular cross section or group of 10 tubular cells).

   Grade II, moderate acute rejection
   Cases with (A) significant interstitial infiltration and foci of severe tubulitis (> 10 mononuclear cells/tubular cross section) and/or (B) mild or moderate intimal arteritis.

   Grade III, severe acute rejection
   Cases with severe intimal arteritis and/or "transmural" arteritis with fibrinoid change and necrosis of medial smooth muscle cells. Recent focal infarction and interstitial hemorrhage without other obvious cause are also regarded as evidence for Grade III rejection.
5. Chronic allograft nephropathy
   (Glomerular and vascular lesions help define type of chronic nephropathy; new-onset arterial fibrous intimal thickening suggests the presence of chronic rejection.)

   Grade I — Mild, chronic transplant nephropathy
   Mild interstitial fibrosis and tubular atrophy

   Grade II — Moderate chronic transplant nephropathy
   Moderate interstitial fibrosis and tubular atrophy

   Grade III — Severe chronic transplant nephropathy
   Severe interstitial fibrosis and tubular atrophy and tubular loss
6. Other (changes not considered to be due to rejection, see **Table 3**)

The recommended format of report is a descriptive narrative signout followed by numerical codes in parentheses (see **Table 2**). Categorization should in the first instance be based solely on pathologic changes, then integrated with clinical data as a second step. More than one diagnostic category may be used if appropriate.

Table 2. Numerical codes, specimen adequacy, and minimum sampling standards

Qualify diagnostic categories 3, 4, and 6 from Table 1 by g, i, t, v, and ah coding			
g	0, 1, 2, 3	—	no, mild, moderate, severe glomerulitis (g3 = mononuclear cells in capillaries of all or nearly all glomeruli with endothelial enlargement and luminal occlusion)
i	0, 1, 2, 3	—	no, mild, moderate, severe interstitial mononuclear cell infiltration (In rejection edema and lymphocyte activation usually accompany mononuclear cell infiltration; i3 = > 50% of parenchyma inflamed)
t	0, 1, 2, 3	—	no, mild, moderate, severe tubulitis (t3 = > 10 mononuclear cells per tubule or per 10 tubular cells in several tubules)
v	0, 1, 2, 3	—	no, mild, moderate, severe intimal arteritis (v3 = severe intimal arteritis and/or transmural arteritis and/or hemorrhage and recent infarction)
ah	0, 1, 2, 3	—	no, mild, moderate, severe nodular hyaline afferent arteriolar thickening suggestive of cyclosporine toxicity (ah3 = severe PAS-positive thickening in many arterioles)
Qualify diagnostic category 5 from Table 1 by cg, ci, ct, and cv with different definitions			
cg	0, 1, 2, 3	—	no, mild, moderate, severe chronic transplant glomerulopathy
ci	0, 1, 2, 3	—	no, mild, moderate, severe interstitial fibrosis, often with mononuclear cell inflammation
ct	0, 1, 2, 3	—	no, mild, moderate, severe tubular atrophy and loss
cv	0, 1, 2, 3	—	no, mild, moderate, severe fibrous intimal thickening often with elastica fragmentation (cv3 indicates complete occlusion); (cg and cv lesions suggest the presence of chronic rejection)
Both acute and chronic codes can be used together if the situation warrants			
Specimen adequacy (state number of glomeruli in report)			
Unsatisfactory		—	No glomeruli or arteries
Marginal		—	1–6 glomeruli with artery
Adequate		—	7 or more glomeruli with artery
Minimum sampling		—	7 slides with 3 H & E, 3 PAS and 1 trichrome

Table 3. Differential diagnosis: Entities in "other" category of Table 1, Changes not considered to be due to rejection

1. Post-transplant lymphoproliferative disorder—Diffuse interstitial infiltration by plasmacytoid cells (usually atypical) with no signs of rejection in tubules, vessels, or glomeruli (usually g0,i3,t0,v0)
2. Nonspecific changes
   - Focal interstitial inflammation without tubulitis (may be difficult to distinguish from borderline changes)
     - nodular infiltrates
     - perivascular infiltrates
   - Vascular changes
     - endothelial reactive changes
     - vacuolization
     - venulitis
3. Acute tubular necrosis
   - Cell loss, non-replacement
   - Cell necrosis
   - Regenerative changes
   - Interstitial edema, mild infiltrate
   - Nucleated cells in the vasa recta
4. Acute interstitial nephritis (may at times be impossible to distinguish from rejection)
   - Neutrophilic
   - Eosinophilic/allergic
   - Mononuclear cells
5. Cyclosporine associated changes, acute or chronic
   - *Tubular* — isometric vacuolization, eosinophilic inclusions, microcalcification
   - *Vascular* — nodular hyaline afferent arteriolar deposits, thrombotic microangiopathy, occlusive arteriolar change, medial degeneration
   - *Interstitial* — striped or patchy fibrosis
   - *Glomerular* — sclerosis or ischemic collapse, juxtaglomerular apparatus hyperplasia
6. Subcapsular injury (surgical)
7. Pretransplant acute endothelial injury
8. Papillary necrosis
9. *De novo* glomerulonephritis
10. Recurrent disease
    - Immune complex glomerulonephritis
    - Focal sclerosis
    - Diabetes
    - Hemolytic-uremic syndrome
    - Other
11. Pre-existing disease
    - Nephrosclerosis, glomerular disease
12. Other
    - Arterial or venous thrombosis
    - Viral infection, CMV
    - Obstruction and reflux, lymphocele, urine leak

of acute rejection, chronic allograft nephropathy, and "other" changes not thought to represent rejection. This classification is very likely to change as our knowledge grows concerning significance of pathologic changes observed. At present, for instance, the classification does not incorporate glomerulitis (Fig. 2) as a defining feature, since its significance as evidence of rejection is uncertain although its presence in the first few months post-transplant has been reported to shorten graft survival time [14–20]. Glomerulitis as described in Table 4 is included in the scoring system for individual pathologic features, however (see below). The classification also groups together under the term "chronic allograft nephropathy" at least four entities that at present cannot always be distinguished by biopsy (chronic rejection, chronic cyclosporine toxicity, hypertensive vascular disease, and chronic infection and/or reflux). New-onset fibrous intimal thickening (Fig. 3) is suggestive of chronic rejection [21] if recipient hypertension can be excluded as a cause.

In comparison with the summary classification of diagnostic categories and grades, which may undergo evolutionary changes, the numerical scoring system (Table 2) is less likely to be altered with time. The scoring codes which are used to establish rejection grades but also have independent usefulness are designated g, i, t, v, ah, for glomerular, interstitial, tubular, or vascular changes, and arteriolar hyalinosis, respectively, in the acute setting. Chronic changes are scored cg, ci, ct and cv, respectively. It would be possible to apply relative weightings and calculate overall severity scores using this coding system.

Table 4. Definitions

Arteritis, intimal (synonymous with endothelialitis). Intimal thickening with inflammation of arterial subendothelial space ranging from rare intimal inflammatory cells to necrosis of endothelium with deposition of fibrin, platelets and inflammatory cells. The cellular infiltrate is composed of lymphocytes and monocytes. Severity is determined by the number of vessels affected as well as by intensity of individual lesions. Mild degrees of intimal arteritis can be extremely focal.

Arteritis, transmural. Injury and inflammation of the whole arterial wall including the media, necrosis of medial smooth muscle cells, fibrin insudation and cellular infiltration with mononuclear as well as polymorphonuclear leukocytes.

Borderline changes. Changes which might be considered suggestive of rejection but which are nondiagnostic (such as a moderate interstitial mononuclear cell infiltrate with very mild tubulitis).

***De novo* glomerulonephritis.** Glomerulonephritis in the allograft morphologically dissimilar to the original disease and distinct from transplant glomerulopathy or transplant glomerulitis. Presumed to be due to etiologies similar to those responsible for native kidney glomerulonephritis.

Hyperacute rejection. Rejection presumed to be due to preformed antibody, usually characterized by polymorph accumulation in glomerular and peritubular capillaries at one hour post-transplant with subsequent endothelial damage and capillary thrombosis.

Ischemic glomerulopathy. A. *Acute*: glomerular capillary engorgement and glomerular necrosis. May occur in hyperacute and in severe acute rejection. B. *Late*: Thickening, wrinkling and collapse of glomerular capillary walls associated with extracapillary fibrotic material. May be a sequel to diffuse arterial occlusion in chronic vascular rejection.

Recurrence. Lesions in the graft morphologically similar to the original disease, and presumed to be due to persistence of pathogenetic mechanism leading to end stage disease in the native kidney, such as, diabetic glomerulopathy, recurrent glomerulonephritis, and amyloidosis.

Transmission. Persistence of lesions which were present in the transplanted kidney before transplantation, such as, glomerulonephritis. This should not be mistaken for recurrence.

Transplant glomerulopathy. Immunologic glomerular damage due to transplant antigens. A. *Early* form (glomerulitis): Endocapillary accumulation of lymphocytes and monocytes with endothelial cell swelling. B. *Late* form (syn. chronic transplant glomerulopathy): Mesangial cell proliferation, peripheral mesangial interposition and sometimes cellular crescents. The late form is usually associated with marked proteinuria, often in the nephrotic range. Should be distinguished from ischemic glomerular change, recurrent glomerulonephritis and transmitted glomerulonephritis.

Tubulitis. Infiltration of tubular epithelium by leukocytes, usually lymphocytes.

The scoring codes can also be used without the classification system or vice versa if that is the wish of individual centers.

The classification in Table 1 combined with the differential diagnoses ("other" categories) in Table 3 and the definitions in Table 4 will provide a reproducible system which maximizes the clinical utility of the biopsy. The utilization of this schema in studies of therapeutic modalities to minimize rejection will be an important assessment of its validity. The schema is designed so that the false positive rate in diagnosis of rejection should be very low. Standards for adequacy and minimum sampling and stains are provided in Table 2. If these standards are not followed severity of lesions may be underestimated. Owing to the patchiness of early rejection there may be a substantial false negative rate if only a single core of tissue containing a small amount of cortex is examined. This diminishes considerably if two or three cores are obtained or if there is a substantial amount of cortex represented in a single large core.

The portion of the schema which evaluates new-onset arteriolar hyaline thickening (Fig. 4) as a sign of cyclosporine nephrotoxicity assumes the presence of a baseline (implantation) biopsy or other prior negative biopsy for comparison. Although on occasion a destructive hyalinosis characteristic of cyclosporine toxicity may be recognized [22], arteriolar hyaline thickening is usually of little diagnostic value in the absence of a prior biopsy lacking this change, as it could have been present in the donor kidney as a result of hypertension or age. This change, which is potentially reversible [23], may also develop independent of cyclosporine toxicity as a consequence of diabetes or hypertension in the recipient. Similarly, some chronic changes, such as fibrous intimal thickening and interstitial fibrosis may pre-exist in kidneys from older donors [24]. The concepts of "acute" and "chronic" entities in the transplanted kidney may require further modification in the future. Neither the lesions observed themselves nor the time post-transplant are sufficient to completely define these terms. Acute rejection may occur many years after transplantation if immunosuppression is stopped. Similarly, "chronic" lesions may be observed in an implantation or early post-transplant biopsy if the donor has age-related vascular disease. Such lesions are a definite indication of chronic processes in the recipient only if they were not present in the donor.

Table 5, which contains a simplified description of the schema, was developed recently for participants who wanted a single page summary which would include possible clinical response to various biopsy appearances and grades. The "possible clinical approach" column is meant only as a general guide; it should not be taken as a recommendation for specific therapies or approaches. Clearly individual centers will develop their own clinical strategies for dealing with various biopsy findings.

Despite the fact that there will be individual variations in therapeutic approach, it is necessary to have a general understanding of the defining characteristics and significance of the three grades of acute rejection.

Grade I (mild) acute rejection differs from the borderline changes category in that it has tubulitis quantitatively more severe than that observed in kidneys with normal function or in ATN [5]. Tubulitis severity is most easily assessed in PAS-stained sections by examining the number of lymphocytes present in the most inflamed tubule in an area after observing the overall severity of interstitial inflammation and degree of tubulitis in less affected tubules. The use of thin well stained sections is a necessary prerequisite for this assessment to be reliable. Quantitative criteria for tubulitis scoring are discussed further in the section below.

In Grade II (moderate) rejection the diagnosis of rejection is more secure because the lesions on which the diagnosis depends, foci of tubulitis with >10 lymphocytes per most inflamed tubular cross section (Fig. 5) or intimal arteritis (Fig. 6), are highly specific for rejection. Cases with this grade of rejection are likely to behave more aggressively than those in Grade I.

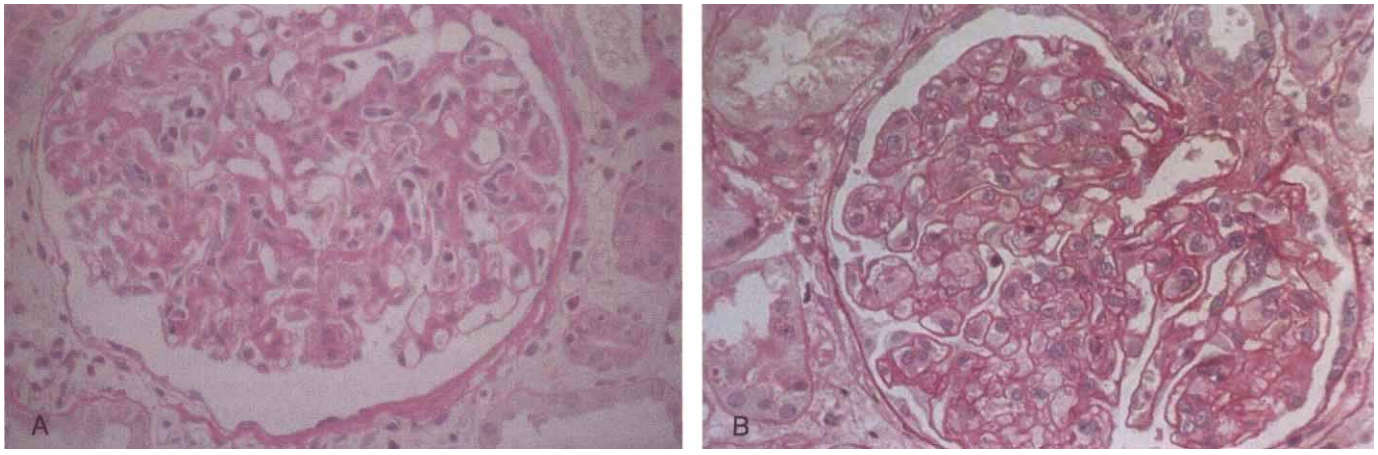


Fig. 2. A. *Example of glomerulitis showing accumulation of mononuclear inflammatory cells in glomerular capillaries.* Tubulitis is also seen at lower right (PAS, × 120). **B.** Another example of glomerulitis showing extensive capillary occlusion by endothelial swelling and accumulation of monocytes (PAS, × 120).

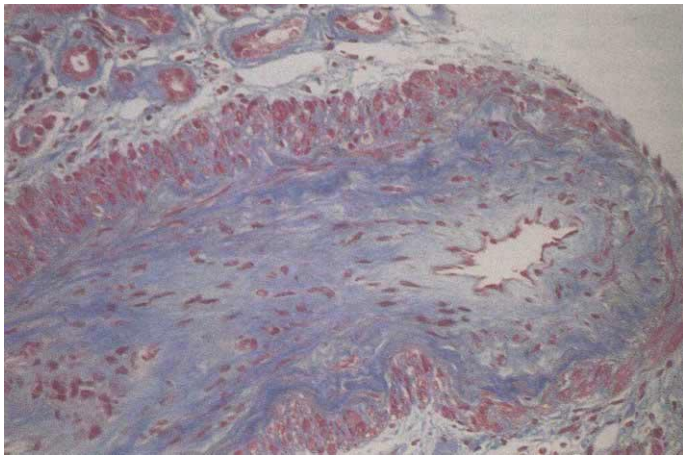


Fig. 3. *Fibrous intimal thickening in a patient with chronic rejection (Masson trichrome stain, × 57).*

In Grade III (severe) rejection the process is so aggressive that highly potent antirejection therapies need to be considered, as well as the possibility that the rejection process may not be reversible. Necrotizing vascular changes (Fig. 6C) suggest irreversible rejection, and are most commonly observed only in nephrectomy specimens.

Quantitative criteria for lesion severity

Preliminary results assessing panel slides with the use of the Banff schema indicate an 82% agreement on diagnosis of rejection [25]. The panel slide assessments, which will be reported separately, led to the development of quantitative criteria for lesion severity (Tables 6 to 10). These criteria represent a compromise between a formal morphometric assessment of these lesions and a fully qualitative approach. Our experience with the panel slides also resulted in the recommendation that PAS stains be used to assess tubulitis, glomerulitis, and arteriolar hyaline thickening.

In the tubulitis scoring (Table 6) it is important to differentiate lymphocytes from apoptotic tubular cells (Fig. 7). Lymphocytes between or beneath tubular cells are often surrounded by a clear space and have an appearance similar to lymphocytes seen in the surrounding interstitium. The t 1 designation is used for the very mild tubulitis, below the threshold for diagnosis of rejection, which can be observed in the normally functioning kidney or ATN [5]. The manner in which tubulitis and intimal arteritis are used to establish a diagnosis of rejection of various severities is shown in Tables 1 and 5: mild (t 1) tubulitis = borderline changes, moderate (t 2) tubulitis = mild (grade I) rejection, and severe (t 3) tubulitis = moderate (grade II) rejection, mild to moderate (v 1 or 2) intimal arteritis = moderate rejection, and severe (v 3) intimal arteritis = severe

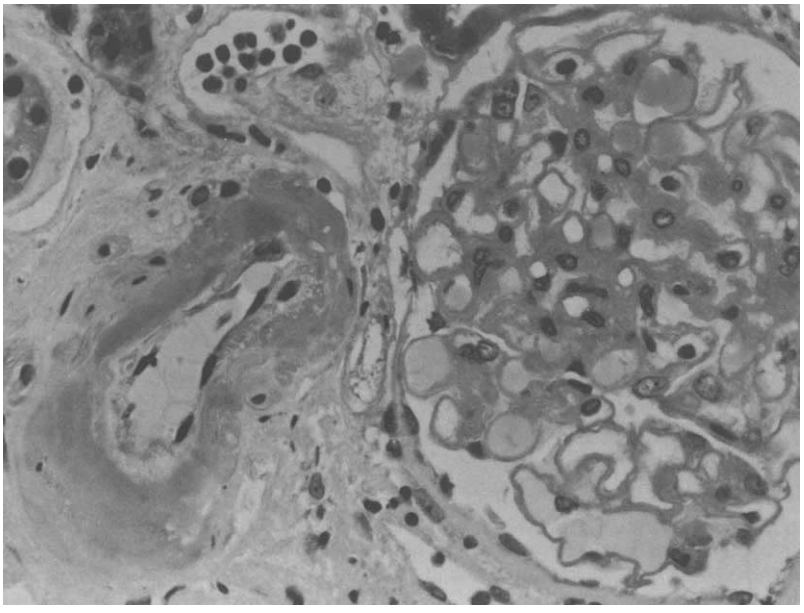


Fig. 4. *Nodular hyaline arteriolar thickening (PAS, × 550).*

Table 5. The Banff schema simplified

Biopsy findings	Banff classification	Possible clinical approach
Normal, minor changes, or infiltrates *without* tubular invasion	Normal or "other" (non-specific changes)	No treatment, or treat other entity
Mild lymphocytic invasion of tubules (tubulitis)	Borderline changes	No treatment, or treat other entity
Widespread interstitial infiltrate with moderate invasion of tubules	Mild acute rejection (Grade I)	Treat for rejection if there are clinical signs
(A) Widespread interstitial infiltrate with severe invasion of tubules and/or (B) mild or moderate intimal arteritis	Moderate acute rejection (Grade II)	Treat for rejection, consider ALG/OKT3 if refractory to steroids
Severe intimal arteritis and/or "transmural" arteritis, fibrinoid change, and medial smooth muscle cell necrosis often with patchy infarction and interstitial hemorrhage	Severe acute rejection (Grade III)	Treat for rejection unless clinical course suggests rejection cannot be reversed in which case consider abandoning the graft
Hyaline arteriolar thickening (new onset, not present in implantation biopsy), and/or extensive isometric vacuolization of tubules, smooth muscle degeneration, thrombotic microangiopathy.	"Other", cyclosporine toxicity	Reduce cyclosporine therapy
Tubular cell loss and necrosis, regenerative changes	"Other", acute tubular necrosis	Await recovery
Interstitial fibrosis, tubular atrophy (new onset arterial fibrous intimal thickening suggests chronic rejection)	Chronic transplant nephropathy	Temporize

The detailed version of the Banff Schema outlined in Tables 1 to 4 and described in the text is designed to address all circumstances that might be encountered. However, the simplified schema above will suffice for many common biopsy appearances.

rejection. The interstitial inflammation scoring (Table 7) evaluates extent of parenchymal infiltration rather than intensity (which is to some extent indirectly evaluated in the tubulitis scoring).

Discussion

Unlike the heart transplant formulation [1, 26], the schema for the kidney employs the term "rejection" only for those

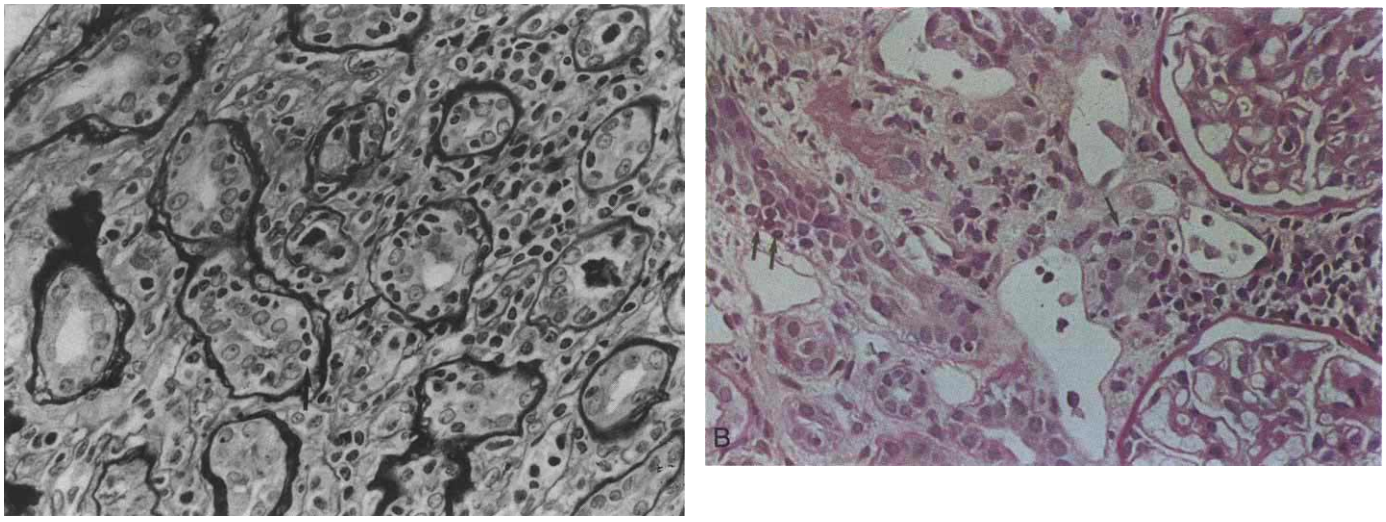


Fig. 5. A. *Tubulitis*. Note the clear spaces that usually separate lymphocyte nuclei (arrows) from adjacent tubular cells (PAS, × 281). There is a tubule (center) in which the number of infiltrating lymphocytes exceeds ten consistent with severe tubulitis (T 3). **B.** Another example of severe tubulitis. The tubule to the left (double arrow) can be used for grading, but the one on the right (single arrow) which has lost its basement membrane, cannot (PAS, × 170).

Table 6. Quantitative criteria for tubulitis ("t") score (0–3+) (assumes that minimum sampling standards in Table 2 are adhered to.)

0 = No mononuclear cells in tubules
1 = Foci with 1 to 4 cells/tubular cross section or 10 tubular cells
2 = Foci with 5 to 10 cells/tubular cross section
3 = Foci with >10 cells/tubular cross section

Table 7. Quantitative criteria for mononuclear cell interstitial inflammation ("i") (0 to 3+)

0 = No or trivial interstitial inflammation
1 = up to 25% of parenchyma inflamed
2 = 26 to 50% of parenchyma inflamed
3 = >50% of parenchyma inflamed

Table 8. Quantitative criteria for the early type of allograft glomerulitis ("g") (0 to 3+)

Accumulation of monocytes and lymphocytes in glomerular capillaries with endothelial swelling
0 = No glomerulitis
1 = Glomerulitis in a minority of glomeruli
2 = Segmental or global glomerulitis in about 25 to 75% of glomeruli
3 = Glomerulitis (mostly global) in all or almost all glomeruli

Table 9. Quantitative criteria for arteriolar hyaline thickening ("ah") (0 to 3+)

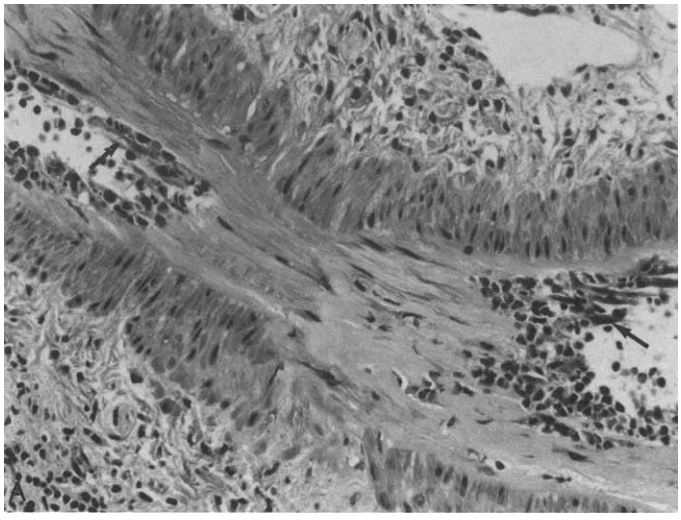
0 = No PAS-positive hyaline thickening
1 = Mild-to-moderate PAS-positive hyaline thickening in at least one arteriole
2 = Moderate-to-severe PAS-positive hyaline thickening in more than one arteriole
3 = Severe PAS-positive hyaline thickening in many arterioles

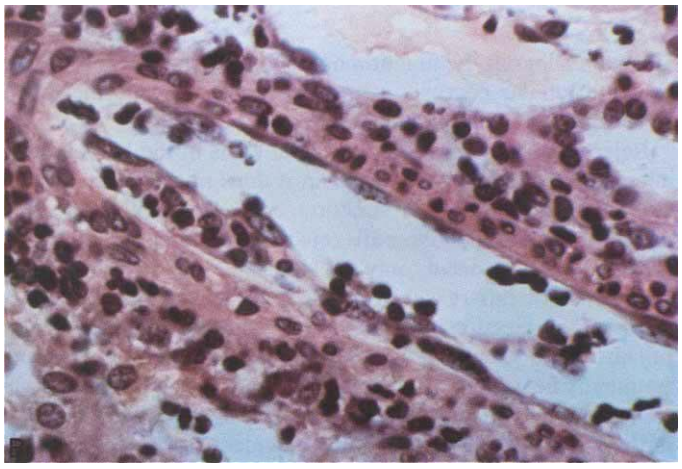
Table 10. Quantitative criteria for intimal arteritis ("v") (0 to 3+)

0 = No arteritis
1 = Mild-to-moderate intimal arteritis in at least one arterial cross section
2 = Moderate-to-severe intimal arteritis in more than one arterial cross section
3 = Severe intimal arteritis in many arterial cross sections and/or "transmural" arteritis, fibrinoid change and medial smooth muscle necrosis, often with patchy infarction and interstitial hemorrhage

conditions likely to be treated with increased immunosuppression. Thus "grade 1 rejection" in the heart schema, which would not be treated, would correspond to the "borderline changes" category in the Banff formulation. Clearly, the differentiation of borderline changes from mild rejection is a crucial part of the Banff schema, since it may mean the difference between not treating and treating an episode of reduced renal function with increased immunosuppression. It is important to factor in considerations relating to sampling error, time from onset of rejection to biopsy, and the effect of anti-rejection treatment in the final evaluation of biopsy appearances. It is possible that eventually immunophenotyping of lymphocytes [such as CD57 (Leu 7) staining of intratubular lymphocytes] and especially immunophenotyping of activated lymphocytes by activation markers (IL2R, perforin, granzyme B, and class II HLA antigen staining) will be used to fine-tune the distinction between borderline changes and rejection [27–37].

In most centers patients will not be treated for rejection unless they have clinical signs (allograft dysfunction) suggesting this diagnosis, regardless of the biopsy findings observed. Patients with persisting allograft failure from time of transplantation (delayed graft function) will, however, have to be diagnosed and treated largely on the basis of biopsy appearance,





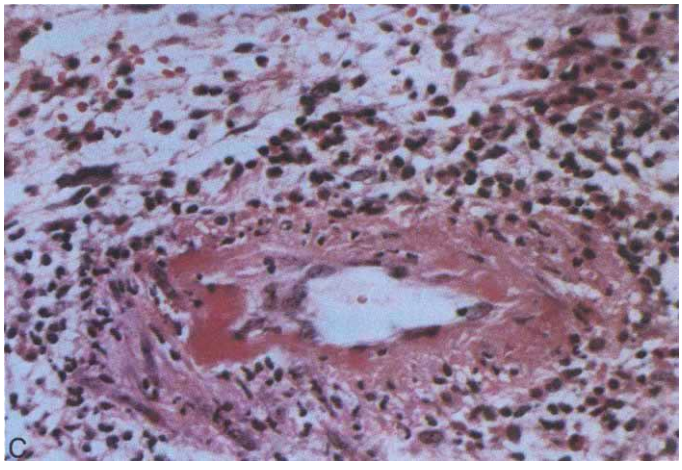


Fig. 6. A. *Intimal arteritis typical of acute rejection sectioned in transverse section.* Endothelial cells (arrows) can be seen overlying the lymphocytic mass in the thickened intima (H&E, × 201). **B.** Severe intimal arteritis in cross section showing lymphocytes under the endothelium and focally penetrating the media (H&E, × 360). **C.** Severe transmural arteritis with fibrinoid change (H&E, × 170).

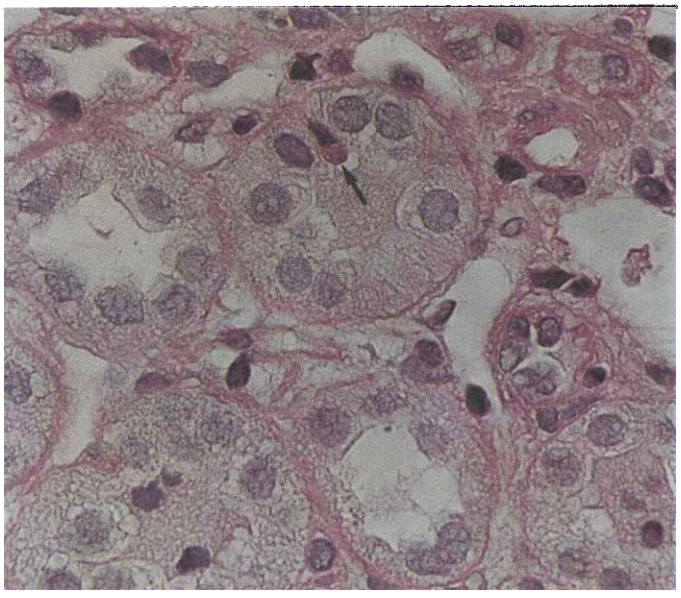


Fig. 7. *Tear drop-shaped apoptotic tubular cell (arrow) in the process of being extruded into the lumen between two normal cells in a renal allograft biopsy.* The cell has condensed, granular, PAS-positive cytoplasm. The apparent bare nuclei seen in the lumen of other tubules may represent a later stage of apoptosis. Extensive apoptosis is sometimes observed by electron microscopy in transplant biopsies [53]. Apoptosis is unlikely to be confused with tubulitis as long as one insists that tubulitis lymphocytes be located beneath or between tubular cells and have an appearance similar to lymphocytes in the interstitium (PAS, × 554).

since the allograft dysfunction observed clinically could be due to acute tubular necrosis, acute rejection, cyclosporine nephrotoxicity, or a combination of these.

Rejection has more reliable clinical signs in the kidney once allograft function commences than it does in the heart. In this setting changes in renal function are a relatively sensitive indicator of kidney allograft rejection, whereas changes in cardiac function occur only in late stages of heart allograft rejection. For this reason it may not be reasonable to make a diagnosis of rejection in the functioning kidney transplant solely on histologic grounds, whereas biopsy evidence alone must frequently be used in the heart and other functioning solid organ transplants in which rejection is often clinically silent. Reports in the heart of persistent histologic evidence of rejection without evidence of graft dysfunction [38] underscore the great advantage of working with an organ like the kidney in which both functional and structural data can be used together in many instances to make a secure diagnosis of rejection. On the other hand, elevation of serum creatinine may prove to be too insensitive an indicator of rejection. Future studies may show that prolongation of graft survival results if the "subclinical" rejection represented by the borderline changes category in the present classification is treated with increased immunosuppression.

The Banff schema is based on the concept that the degree of lymphocytic invasion of tubules (tubulitis) is a better measure of severity of rejection than the intensity or extent of interstitial lymphocytic infiltration (**Introduction**). Tubulitis is a typical feature of acute rejection [39–41]. Analysis of protocol biopsies from patients with stable function or acute tubular necrosis [5] shows that very mild tubulitis may occur in these settings (up to 4 lymphocytes per most affected tubule). However, more intensive tubulitis is relatively specific for rejection (unpublished observations). Immunophenotyping of lymphocytes invading tubules may provide even greater specificity [27–37].

Intimal arteritis is the pathognomonic lesion of acute rejection, as first noted by Dammin [42]. The biologic and diagnostic significance of this lesion in acute cell mediated rejection is well established [6, 9, 43–46].

Most biopsies contain only two or three arterial cross sections so it is easy for all observers to concentrate on exactly the same fields in their assessment of intimal arteritis in an individual case. In contrast a single biopsy section may contain several hundred tubular cross sections. If the biopsy is diffusely infiltrated it becomes a matter of chance whether two observers concentrate on the same microscopic fields in assessment of tubulitis. Devising a more accurate and reproducible method for assessing tubulitis which is still practical and time-efficient remains one of our goals for the future.

An interstitial infiltrate of polymorphonuclear leukocytes as a feature of acute rejection has not been dealt with specifically in the present schema. Polymorphs and eosinophils are sometimes present in the interstitial infiltrate of acute rejection. Pure polymorph infiltrates occur at the periphery of recent infarcts and may therefore be seen in cases with arteritis and infarction. They may also be observed in cases of antibody-mediated rejection [47, 48] and are particularly likely to be seen in ABO-incompatible grafts.

Concerns about inaccuracy due to sampling error led Rapaport, Converse and Billingham to state in 1977 that "percutaneous renal biopsy of renal transplants has been generally abandoned because rejection injury is not distributed uniformly throughout the transplanted kidney" [49]. Although the demise of the renal allograft biopsy did not occur, the sampling error considerations noted by Rapaport are still important today. As Sanfilippo has emphasized, "healing in" of the graft may lead to a subcapsular infiltrate unrelated to rejection [50]. Substantial interstitial infiltrates may also be found in non-rejecting grafts in the mid-to-deep cortex [4–8]. Although experimental studies [51, 52] have indicated that serious sampling error with percutaneous biopsies is likely to be infrequent, such error nevertheless occurs and must be taken into account in biopsy interpretation.

In conclusion, we have presented a formulation for the evaluation of rejection and other conditions in renal allograft biopsies. We feel that it can be applied reliably to diagnose and grade rejection as long as criteria of minimum sampling and specimen adequacy are met. The schema presented is an important step in the design of effective multicenter trials and in the study of the clinical significance of lesions observed on biopsy. This classification has already been adopted for international multicenter trials of four new immunosuppressive agents (RS61443, Cyclosporin G, brequinar, and anti-CD45), and should lead to international uniformity in evaluation of biopsy findings in many centers currently performing renal transplantation. The numerical coding of specific biopsy features, in particular, should contribute in a major way to objective data assessment and statistical analysis. The ultimate hope is that such a classification will lead to major improvements in patient care and management.

Acknowledgements

We are grateful to Ortho Biotech (Don Mills, Ontario) for support of the original Banff meeting and of the color illustration publication costs. The authors thank Irene Freeman, Lynda Harrison, and Susan Todd for typing the manuscript and for managing the extensive correspondence which contributed to its finalization.

Reprint requests to Dr. Kim Solez, Department of Laboratory Medicine and Pathology, University of Alberta, 5B4.02 Walter Mackenzie Centre, Edmonton, Alberta, Canada T6G 2R7.

References

1. The International Society for Heart Transplantation: Billingham ME, Cary NRB, Hammond ME, Kemnitz J, Marboe C, McCallister HA, Snover DC, Winters GL, Zerbe A: A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart rejection study group. *J Heart Transplant* 9:587–593, 1990
2. The International Society for Heart Transplantation: Yousem SA, Berry GJ, Brunt EM, Chamberlain D, Hruban RH, Sibley RK, Stewart S, Tazelaar HD: A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Lung rejection study group. *J Heart Transplant* 9:593–601, 1990
3. The International Society of Nephrology Commission on Acute Renal Failure: Solez K, Benediktsson H, Burdick JF, Cohen AH, Colvin RB, Croker BP, Halloran PF, Hayry P, Keown PA, Myers BD, Nast CC, Olsen S, Racusen RC, Ramos EL, Rosen S, von Willebrand E: Banff international classification of renal allograft pathology. (abstract) *Lab Invest* 66:103A, 1992
4. d'Ardenne AJ, Dunnill MS, Thompson JF, McWhinnie D, Wood RFM, Morris PJ: Cyclosporine and renal graft histology. *J Clin Pathol* 39:145–151, 1986
5. Solez K, Racusen LC, Marcussen N, Slatnik I, Keown P, Burdick JF, Olsen S: Morphology of ischemic acute renal failure,

function, and cyclosporine toxicity in cyclosporine-treated renal allograft recipients. *Kidney Int* 43:1058–1067, 1993
6. BURDICK JF, BESCHORNER WE, SMITH WJ, MCGRAW DJ, BENDER WL, WILLIAMS GM, SOLEZ K: Characteristics of early routine renal allograft biopsies. *Transplantation* 38:679–684, 1984
7. NEILD GH, TAUBE DH, HARTLEY RB, BIGNARDI L, CAMERON JS, WILLIAMS DG, OGG CS, RUDGE CJ: Morphological differentiation between rejection and cyclosporine nephrotoxicity in renal allografts. *J Clin Pathol* 39:152–159, 1986
8. MATAS AJ, SIBLEY R, MAUER SM, KIM Y, SUTHERLAND DER, SIMMONS RL, NAJARIAN JS: Pre-discharge, post-transplant kidney biopsy does not predict rejection. *J Surg Res* 32:269–274, 1982
9. HERBERTSON BM, EVANS DB, CALNE RY, BANERJEE AK: Percutaneous needle biopsies of renal allografts: The relationship between morphological changes present in biopsies and subsequent allograft function. *Histopathology* 1:161–178, 1977
10. KIAER H, HANSEN HE, OLSEN S: The predictive value of percutaneous biopsies from human renal allografts with early impaired function. *Clin Nephrol* 13:58–63, 1980
11. BANFI G, IMBASCIATI E, TARANTINO A, PONTICELLI C: Prognostic value of renal biopsy in acute rejection of kidney transplantation. *Nephron* 28:222–226, 1981
12. HSU AC, ARBUS GS, NORIEGA E, HUBER J: Renal allograft biopsy: A satisfactory adjunct for predicting renal function after graft rejection. *Clin Nephrol* 5:260–265, 1976
13. CHURCHILL M, KLINE R, SCHWARTZ M, BIDANI A, CHURCHILL P: Kidney transplants in cyclosporine-treated Sprague-Dawley rats. *Transplantation* 49:8–13, 1990
14. AXELSEN RA, SEYMOUR AE, MATHEW TH, CANNY A, PASCOE V: Glomerular transplant rejection: A distinctive pattern of early graft damage. *Clin Nephrol* 23:1, 1985
15. COLVIN RB, COSIMI AB, BURTON RC, DELMONICO FL, JAFFERS G, RUBIN RH, TOLKOFF-RUBIN NE, GIORGI JV, MCCLUSKEY RT, RUSSEL PS: Circulating T-cell subsets in human renal allograft recipients: The OKT4 + /OKT8 + cell ratio correlates with reversibility of graft injury and glomerulopathy. *Transplant Proc* 15:1166–1169, 1983
16. FARNSWORTH A, HALL BM, NG ABP, DUGGIN GG, HORVATH JS, SHEIL ABR, TILLER DJ: Renal biopsy morphology in renal transplantation. *Am J Surg Pathol* 8:243–252, 1984
17. MARYNIAK RK, FIRST MR, WEISS MA: Transplant glomerulopathy: Evolution of morphologically distinct changes. *Kidney Int* 27:799–806, 1985
18. PETERSEN VP, OLSEN TS, KISSMEYER-NIELSEN F, BOHMAN S-O, HANSEN HE, HANSEN ES, SKOV PE, SOLLING K: Late failure of human renal transplants. An analysis of transplant disease and graft failure among 125 recipients surviving for one to eight years. *Medicine* (Baltimore) 54:45–71, 1975
19. RICHARDSON WP, COLVIN RB, CHEESEMAN SH, TOLKOFF-RUBIN NE, HERRIN JT, COSIMI B, COLLINS AB, HIRSCH MS, MCCLUSKEY RT, RUSSELL PS, RUBIN RH: Glomerulopathy associated with cytomegalovirus viremia in renal allografts. *N Engl J Med* 305:57–63, 1981
20. TUAZON TV, SCHNEEBERGER EE, BHAN AK, MCCLUSKEY RT, COSIMI AB, SCHOOLEY RT, RUBIN RH, COLVIN RB: Mononuclear cells in acute allograft glomerulopathy. *Am J Pathol* 129:119–132, 1987
21. PAUL LC, HÄYRY P, FOEGH M, DENNIS MJ, MIHATSCH MJ, LARSSON E, FELLSTRÖM B: Diagnostic criteria for chronic rejection/accelerated graft atherosclerosis in heart and kidney transplants. Fourth Alexis Carrel Conference on Chronic Rejection and Accelerated Arteriosclerosis in Transplanted Organs. *Transplant Proc* 25:2022–2023, 1993
22. MIHATSCH MJ, THIEL G, RYFFEL B: Histopathology of cyclosporine nephrotoxicity. *Transplant Proc* 3:759–771, 1988
23. MOROZUMI K, THIEL G, ALBERT FW, BANFI G, GUDET F, MIHATSCH MJ: Studies on morphological outcome of cyclosporine-associated arteriolopathy after discontinuation of cyclosporine in renal allografts. *Clin Nephrol* 38:1–8, 1992
24. NIAUDET P, NUSSENZVEIG P, HABIB R, BROYER M, DROZ D: Systematic one year renal graft biopsy in children with normal renal function, in *Transplantation and Clinical Immunology; Evaluation and Monitoring in Transplantation*, edited by TOURAINE JL et al, Amsterdam, The Netherlands, Elsevier Science Publishers, Vol XXIV, 1992, pp. 111–115
25. SOLEZ K, MARCUSSEN N, RACUSEN LC, OLSEN TS: Reproducibility of the Banff classification of early renal allograft biopsies. (abstract) *JASN* 3:882, 1992
26. STEWART S, CARY N: The pathology of heart and heart and lung transplantation—An update. *J Clin Pathol* 44:803–811, 1991
27. BESCHORNER WE, BURDICK JF, WILLIAMS GM, SOLEZ K: The presence of Leu-7 reactive lymphocytes in renal allografts undergoing acute rejection. *Transplant Proc* 17:618–622, 1985
28. COLVIN RB: Renal allografts in *Diagnostic Immunopathology*, edited by COLVIN RB, BHAN AK, MCCLUSKY RT, New York, Raven Press, 1988, pp. 151–197
29. FUGGLE SV, MCWHINNIE DL, CHAPMAN JR, TAYLOR HM, MORRIS PJ: Sequential analysis of HLA class II antigen expression in human renal allografts. Induction of tubular class II antigens and correlation with clinical parameters. *Transplantation* 42(1):144–150, 1986
30. HALL BM, BISHOP GA, DUGGIN GG, HORVATH JS, PHILIPS J, TILLER DJ: Increased expression of HLA-DR antigens on renal tubular cells in renal transplants: relevance to the rejection response. *Lancet* 2:247–251, 1984
31. KOLBECK PC, SCHEINMAN JI, SANFILIPPO F: Acute cellular rejection and cyclosporine nephrotoxicity monitored by biopsy in a renal allograft recipient: The differentiation of drug nephrotoxicity from rejection by phenotyping of cellular infiltrates. *Arch Pathol Lab Med* 10:389–393, 1986
32. SANFILIPPO F, KOLBECK PC, VAUGHN WK, BOLLINGER RR: Renal allograft cell infiltrates associated with irreversible rejection. *Transplantation* 40:679–685, 1985
33. TRUONG L, MAWAD J, HAMEED A, FARHOOD A: Tubulitis in renal diseases. (abstract) *Lab Invest* 64:99A, 1991
34. BOHMAN SO, WILCZEK H, REINHOLT F, VON WILLEBRAND E, HÄYRY P: Immunopathological patterns in long-term renal allografts. *Transplantation* 51:610–613, 1991
35. HAMEED A, OLSEN KJ, CHENG L, FOX WM III, HRUBAN RH, PODACK EF: Immunohistochemical identification of cytotoxic lymphocytes using human perforin monoclonal antibody. *Am J Pathol* 140:1025–1030, 1992
36. HAMEED A, TRUONG LD, PRICE V, KRUHENBUHL O, TSCHOPP J: Immunohistochemical localization of granzyme B antigen in cytotoxic cells in human tissues. *Am J Pathol* 138:1069–1075, 1991
37. LIPMAN ML, STEVENS AC, BLEACKLEY RC, HELDERMAN JH, MCCUNE TR, HARMON WE, SHAPIRO ME, ROSEN S, STROM TB: The strong correlation of cytotoxic T lymphocyte-specific serine protease gene transcripts with renal allograft rejection. *Transplantation* 53:73–79, 1992
38. NAKHLEH RE, KUBO SH, OLIVARI MT, MCDONALD K: Persistent histologic evidence of rejection in a heart transplant recipient without evidence of graft dysfunction. *J Heart, Lung Transplant* 11:37–41, 1992
39. CROKER BP, SALOMON DR: Pathology of the renal allograft, in *Renal Pathology With Clinical and Functional Correlations*, edited by TISHER CC, BRENNER BM, Philadelphia, J.B. Lippincott Company, 1989, pp. 1518–1554
40. NADASDY T, ORMOS J, STILLER D, CSAJBAK E, SZENOHRADSZKY P: Tubular ultrastructure in rejected human renal allografts. *Ultrastruct Pathol* 12:195–207, 1988
41. SIBLEY RK, RYNASIEWICZ J, FERGUSON RM, FRYD D, SUTHERLAND DER, SIMMONS RL, NAJARIAN JS: Morphology of cyclosporine nephrotoxicity and acute rejection in patients immunosuppressed with cyclosporine and prednisolone. *Surgery* 94:225–234, 1983
42. DAMMIN GJ: The kidney as a homograft and its host. *U Mich Med Bull* 26:278–288, 1960
43. MCKENZIE IFC, COLVIN RB, RUSSELL PS: Clinical immunopathology of transplantation, in *Textbook of Immunopathology* (2nd ed), edited by MIESCHER PA, MUELLER-EBERHARD HJ, New York, Grune and Stratton, 1976, pp. 1043–1064
44. OLSEN TS: Pathology of allograft rejection, in *Kidney Transplant Rejection: Diagnosis and Treatment*, edited by BURDICK JF, RACUSEN LC, SOLEZ K, WILLIAMS GM, New York, Marcel Dekker, Inc., 1992, pp. 333–357
45. RUSSELL PS, CHASE CM, COLVIN RB, PLATE JMD: Kidney

transplants in mice. An analysis of the immune status of mice bearing long-term, H-2 incompatible transplants. *J Exp Med* 147: 1449–1468, 1978
46. SIBLEY RK, RYNASIEWICZ JJ, FERGUSON RM, FRYD D, SUTHERLAND DER, SIMMONS RL, NAJARIAN JS: Morphology of cyclosporine nephrotoxicity and acute rejection in patients immunosuppressed with cyclosporine and prednisone. *Surgery* 94:245–254, 1983
47. HALLORAN PF, WADGYMAR A, RITCHIE S, FALK J, SOLEZ K, SRINIVASA NS: The significance of the anti-class I antibody response. I. Clinical and pathologic features of anti-class I-mediated rejection. *Transplantation* 49:85–91, 1990
48. HALLORAN PF, SCHLAUT J, SOLEZ K, SRINIVASA NS: The significance of the anti-class I response. II. Clinical and pathologic features of renal transplants with anti-class I-like antibody. *Transplantation* 53(3):550–555, 1992
49. RAPAPORT FT, CONVERSE JM, BILLINGHAM RE: Recent advances in clinical and experimental transplantation. *JAMA* 237:2835–2840, 1977
50. SANFILIPPO F: Renal Transplantation, in *The Pathology of Organ Transplantation*, edited by SALE GE, Boston, Buttersworth, 1990, p. 512
51. MATAS AJ, SABLAY L, TELLIS VA: The value of needle renal allograft biopsy. II. Reflection of acute rejection changes throughout the kidney on percutaneous biopsy. *Transplantation* 38:92–93, 1984
52. PARDO-MINDAN FJ, GUILLEN R, VIRTO R, MARIGIL MA, ERRASTI P: Kidney allograft biopsy: A valuable tool in assessing the diagnosis of acute rejection. *Clin Nephrol* 24:37–41, 1985
53. OLSEN S, BURDICK JF, KEOWN PA, WALLACE AC, RACUSEN LC, SOLEZ K: Primary acute renal failure ("acute tubular necrosis") in the transplanted kidney: Morphology and pathogenesis. *Medicine* 68(3):173–187, 1989