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RADIATION NEPHROPATHY: A REVIEW

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Abstract

The marked radiosensitivity of renal tissue represents a limitation on the total radiotherapeutic dose that safely can be applied to treatment volumes that include the kidneys. Radiation nephropathy is characterized by a progressive reduction in renal hemodynamics associated with a severe anemia. The latter is often normochromic normocytic in character, but can progress to a microangiopathic hemolytic anemia. The pathogenic mechanisms responsible for the development of radiation nephropathy remain ill-defined. Experimental studies which allow serial determinations of functional, morphologic, and cell kinetic radiation-induced changes indicate that primarily glomerular but also tubular alterations occur in the primary stages of radiation nephropathy. Glomerular capillary endothelial cell loss is seen within several weeks of irradiation. Remaining endothelial cells exhibit increased permeability leading to a subendothelial transudate. Mesangiolysis also is observed. In contrast, podocytes appear to be relatively unaffected at this stage. The endothelial changes appear to resolve, but the mesangial lesions progress, with hypercellularity and/or hypertrophy, increased mesangial matrix, mesangial sclerosis, and ultimately, glomerulosclerosis. These mesangial changes are similar to those observed in other chronic glomerulopathies. Dietary protein restriction, corticosteroids, and ACE-inhibitors all can reduce the severity of experimental radiation nephropathy.

Key Words: Radiation nephropathy, renal function, renal morphology, pathophysiology, pathogenesis, glomerular capillary endothelial cell, mesangial cell, proximal tubule epithelium, vasculature, treatment of radiation nephropathy.

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Introduction

Since the earliest reports describing the effects of X-rays on the kidney [12], there have been conflicting views concerning the relative sensitivity of the organ, particularly the specific components of the nephron, to radiation. Some authors considered the kidney to be radioresistant [93, 94], leading to statements such as this by McQuarrie and Whipple [118]: "We feel confident that the clinician may use the X-rays over the kidney areas with confidence that renal tissue is resistant to the hard Roentgen rays." Others inferred from experimental observations that patients who had impaired renal function, or whose kidneys were "under special stress", should not be treated with radiation or should be followed up closely after X-ray exposure [48]. Not until the excellent experimental studies by Hartman *et al.* [65, 66], confirmed in a later clinical report [43], was it universally appreciated that renal tissue was radiosensitive. Indeed, from the standpoint of serious or fatal damage, the kidneys are probably the most radiosensitive of the abdominal organs [16].

This marked radiosensitivity frequently limits the total dose that can be safely applied to treatment volumes in which the kidneys are included. The classic study of Kunkler *et al.* [96] defined the clinical radiation tolerance of the kidney by studying a number of patients who had received bilateral renal irradiation with 250 kV X-rays during the treatment of testicular tumors. They established that a total dose of 23 Gy, given over a 5 week period, carried with it a high risk of renal damage. More recently, a tolerance dose of some 20 Gy has been proposed [95]. The recognition of this, and subsequent improvements in radiotherapeutic practice, have allowed radiation oncologists to reduce the radiation dose to which the kidney is exposed during irradiation for malignancies. This has resulted in a low incidence of radiation-induced renal morbidity (radiation nephropathy) in patients. A review of clinical accounts of renal radiation injury revealed the existence, by 1964, of only 120 cases [123]. However, the recent development of total body irradiation (TBI) for bone marrow ablation, as a prerequisite to bone marrow transplantation (BMT), has led to

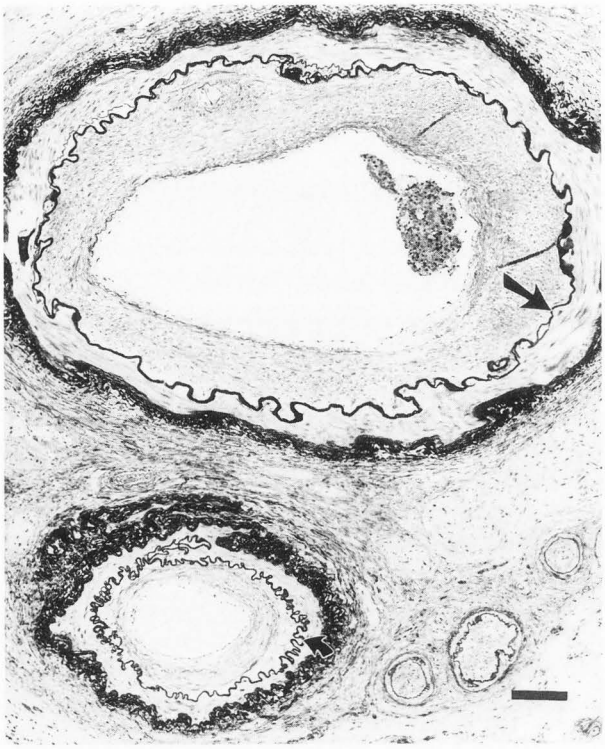

Figure 1. A nephrectomy specimen in which segmental, arcuate, and intralobular arteries show occlusive intimal thickening (arrows - internal elastic lamina) which caused renovascular hypertension in a 5-year-old, 2 years following intraoperative irradiation (dose unknown) for adrenal neuroblastoma. Elastic van Gieson. Bar = 50 μm.

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a number of reports of radiation nephropathy in long-term survivors of BMT [9, 14, 29, 32, 73, 84, 102, 105, 188, 191]. Thus, the risk of radiation nephropathy remains a limiting factor in clinical radiotherapy.

Clinical Pattern of Radiation-Induced Damage to the Kidney

Warthin [194] was the first to report autopsy findings in kidneys of 2 leukemic patients who received radiation. He described fatty degeneration, necrosis, and extensive calcification of renal tubules. However, it appears that these changes were instead those of acute uric acid nephropathy or the so-called tumor lysis syndrome [31, 130]. Probably the first accurate description of radiation-induced renal damage in a patient was published in 1927. Domagk [42] described a 9-year-old girl who received abdominal irradiation for tuberculous mesenteric lymph nodes; she died 6 months later with symptoms of renal failure. At the time of the autopsy, the kidneys were small and showed glomerular hyalinization or thickening of the Bowman's capsule, tubular atrophy or necrosis, and hyaline material in arterial walls. In the following years, there were several reports of radiation-induced renal injury (for reviews see [63, 145]), but it was Luxton [106, 107, 108], who, in a close follow-up of 58 patients arising from the irradiation study of Kunkler *et al.* [96], first classified the lesions into five categories: acute radiation nephritis, chronic radiation nephritis, proteinuria, benign hypertension, and malignant hypertension. Since, these "categories" overlap, individual cases may go through several of these phases during the course of developing renal damage.

Acute radiation nephritis (ARN) ARN usually presents after a latent period of 6-12 months in adults (so it is not acute in the usual sense), but may develop earlier in children [209, 210]. The clinical picture is one of edema, dyspnea, headaches, and moderate hypertension. A normochromic normocytic anemia may develop; in severe cases, a microangiopathic hemolytic anemia may develop, fragmented red blood cells (schistocytes) may be detectable, and thrombocytopenia and purpura may arise later. The development of anemia is indicative of severe later changes and implies a poor prognosis. The symptoms and physiological alterations are usually moderate, but may develop into severe malignant hypertension. Of 22 patients developing ARN, 12 died from the effects of renal irradiation; all that survived for an average of 16 years after radiotherapy had decreased renal function that progressed to chronic radiation nephritis.

Chronic radiation nephritis (CRN) CRN may evolve from ARN or develop in patients who have had no previous history of ARN. Although it appeared initially that the prognosis of these latter patients was better, more prolonged follow-up indicated no significant difference in the long-term survival of the two groups [107]. The clinical symptoms of CRN are albuminuria, hypertension, and a reduction in renal function. Anemia may develop.

Benign hypertension Benign hypertension may develop within 2-5 years of the completion of therapy, and may persist for several years. Patients exhibit the usual complications associated with hypertension and may succumb to cardiovascular complications.

Late malignant hypertension Late malignant hypertension may evolve from ARN or CRN and be associated with radiation nephropathy. It also may develop after irradiation of one kidney and can be relieved by removing the irradiated kidney.

Proteinuria Proteinuria, either intermittent or permanent, may develop after an average interval of 11 years following radiotherapy. Although renal function in these patients appears normal, they seem to have an

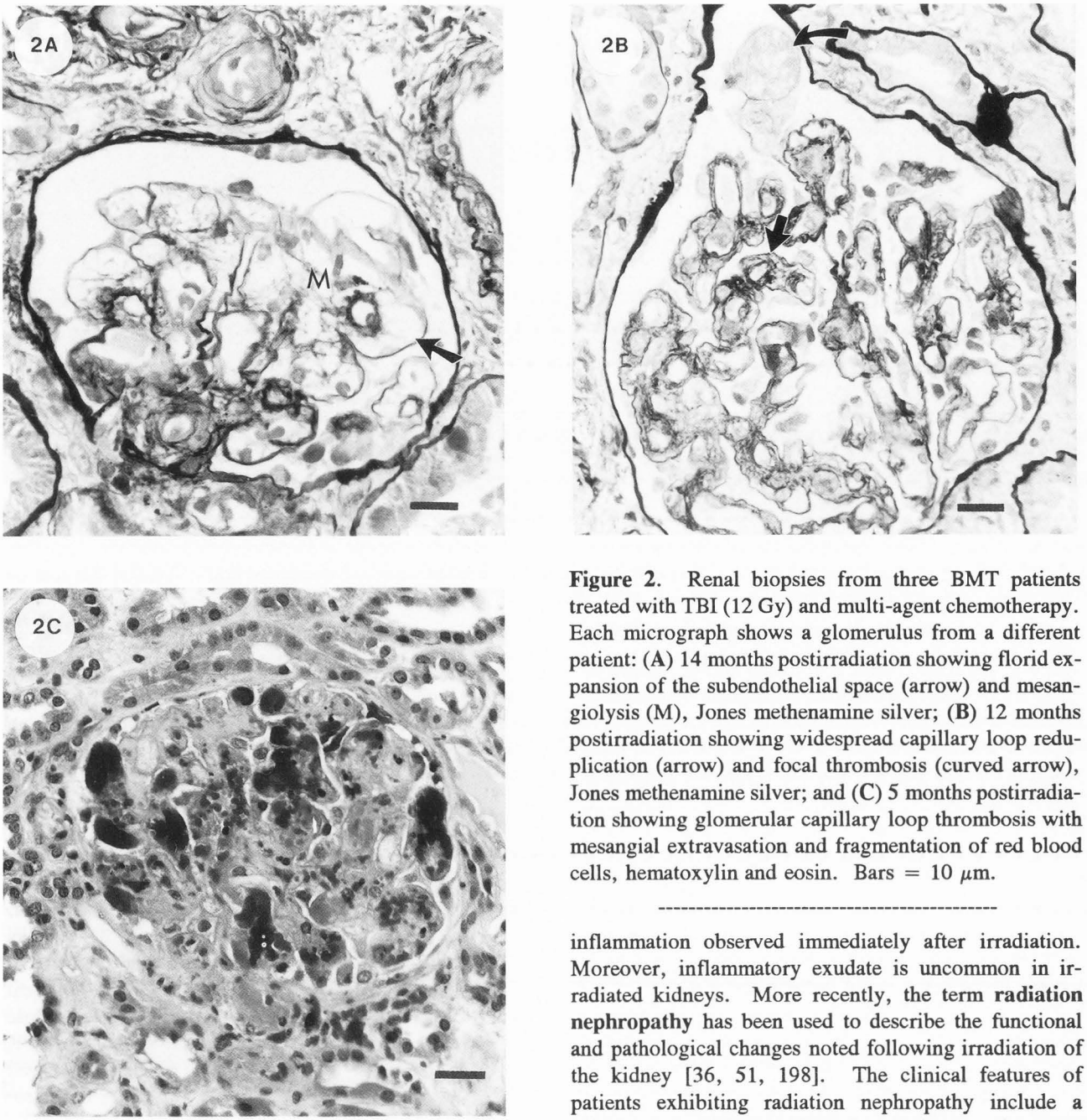


Figure 2. Renal biopsies from three BMT patients treated with TBI (12 Gy) and multi-agent chemotherapy. Each micrograph shows a glomerulus from a different patient: (**A**) 14 months postirradiation showing florid expansion of the subendothelial space (arrow) and mesangiolysis (M), Jones methenamine silver; (**B**) 12 months postirradiation showing widespread capillary loop reduplication (arrow) and focal thrombosis (curved arrow), Jones methenamine silver; and (**C**) 5 months postirradiation showing glomerular capillary loop thrombosis with mesangial extravasation and fragmentation of red blood cells, hematoxylin and eosin. Bars = 10 μm.

impaired renal reserve and exhibit temporary renal failure after stress.

Three alternative terms were proposed by Mostofi [123] who evaluated a number of human cases compiled from the Armed Forces Institute of Pathology files: nephroendotheliosis, sclerosing nephrosis, and nephroglomerulosis; these correspond to Luxton's proteinuria, CRN, and ARN, respectively. However, this terminology has not been widely adopted by workers in the field. It also should be noted that the term "radiation nephritis" (ARN and CRN) is a misnomer. There is no acute renal inflammation observed immediately after irradiation. Moreover, inflammatory exudate is uncommon in irradiated kidneys. More recently, the term **radiation nephropathy** has been used to describe the functional and pathological changes noted following irradiation of the kidney [36, 51, 198]. The clinical features of patients exhibiting radiation nephropathy include a reduction in renal hemodynamics, an increase in serum creatinine and BUN, anemia (normochromic, normocytic, or hemolytic), proteinuria, and hypertension.

Functional changes

The early investigations into the effects of radiation on renal function have been reviewed extensively elsewhere [63, 145] and will not be discussed here. There have been relatively few detailed clinical reports of the consequences of radiation on renal function, due to the practical limitations of a prolonged follow-up of patients. Avioli *et al.* [11] specifically addressed the problem of acute and chronic changes in 10 patients who had histo-

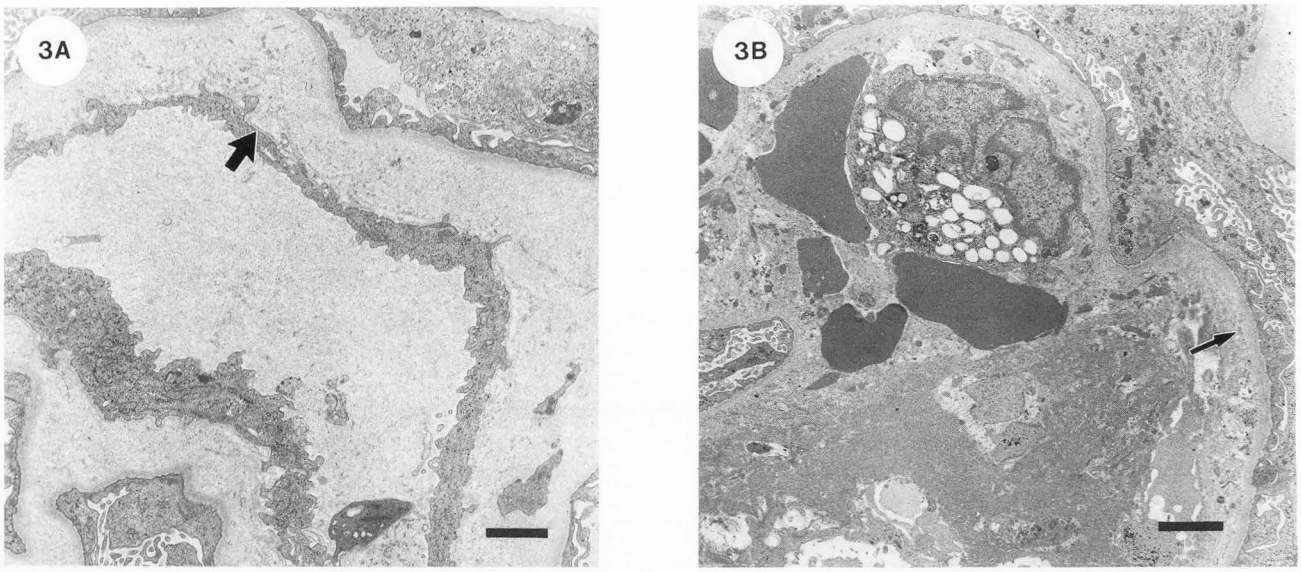


Figure 3. Renal biopsies from two BMT patients obtained 14 and 5 months, respectively, after treatment with total body irradiation (12 Gy) and multiagent chemotherapy. (**A**) A glomerular capillary showing subendothelial expansion and a thin layer of new basement membrane (arrow). (**B**) A glomerular capillary showing endothelial cell denudation (arrow), thrombosis, and fragmented red blood cells. Bars = 2 μm.

logically confirmed intra-abdominal and/or retroperitoneal malignancies with no evidence of renal disease. Standard clinical assays, such as BUN levels, urinalysis, and IVP examination, showed few changes. However, more detailed studies showed reductions in glomerular filtration rate (GFR) and renal blood flow, both during and after the completion of radiotherapy. Indeed, there was a progressive decline in GFR up to 12 months after irradiation. Thus, during the latent period, subtle subclinical alterations in renal function occurred before the clinical expression of injury. Other studies have confirmed the poor diagnostic value of routine renal function tests. When a more accurate monitoring of the functional status has been carried out, e.g., using renography or scintigraphic techniques, similar acute and long-term changes in renal function have been identified [11, 40, 88, 89, 103, 142]. This radiation-induced reduction in renal function appears to be progressive in nature [41]. However, there have been reports indicating either some recovery in function or a stabilization of renal function, albeit at levels significantly lower than those observed prior to radiation [33].

In contrast to these limited clinical data, there is a wealth of experimental data on radiation nephropathy. As observed clinically, initial findings in rodents indicated a latent period of some 6 months before any apparent change in renal function [25, 30, 200]. In contrast, studies using large animals such as the monkey [5, 144, 157], pig [148, 150], and dog [34, 120], have reported pronounced changes in GFR and ERPF within several weeks of radiation. These observations have been interpreted to be indicative of species differences in radiation sensitivity. However, recent studies, using more sensitive indices of renal function, have shown that early radiation-induced changes in renal function also are evident in mice and rats [38, 79, 177]. There is some evidence for an initial hyperemic response [144, 148, 177], also seen clinically [11, 189]. This is followed by a dose-dependent progressive decline in both GFR and ERPF, evident within some 6-8 weeks of irradiation. Minimal levels are observed approximately 12-16 weeks after irradiation; renal function then might continue to decline, might plateau, or might show an apparent recovery in function, depending on the radiation dose administered. It should be noted that a recovery in GFR and ERPF might be more apparent than real. Renal function might increase as a result of cellular hypertrophy rather than as a result of cellular repair or repopulation. The use of functional parameters, such as GFR and ERPF, that measure the overall functional capacity, cannot distinguish between these two possibilities. Recent studies in the pig have indicated that the overall time-sequence of changes in GFR and ERPF observed following unilateral [148, 149] or bilateral radiation [150], or radiation of a single hypertrophied kidney [152], is essentially the same. Indeed, a similar pattern of response has been seen following renal irradiation in the monkey [157] and rat [24]. This implies a common response to radiation, a response which is independent of any variation in the status of the renal tissue prior to

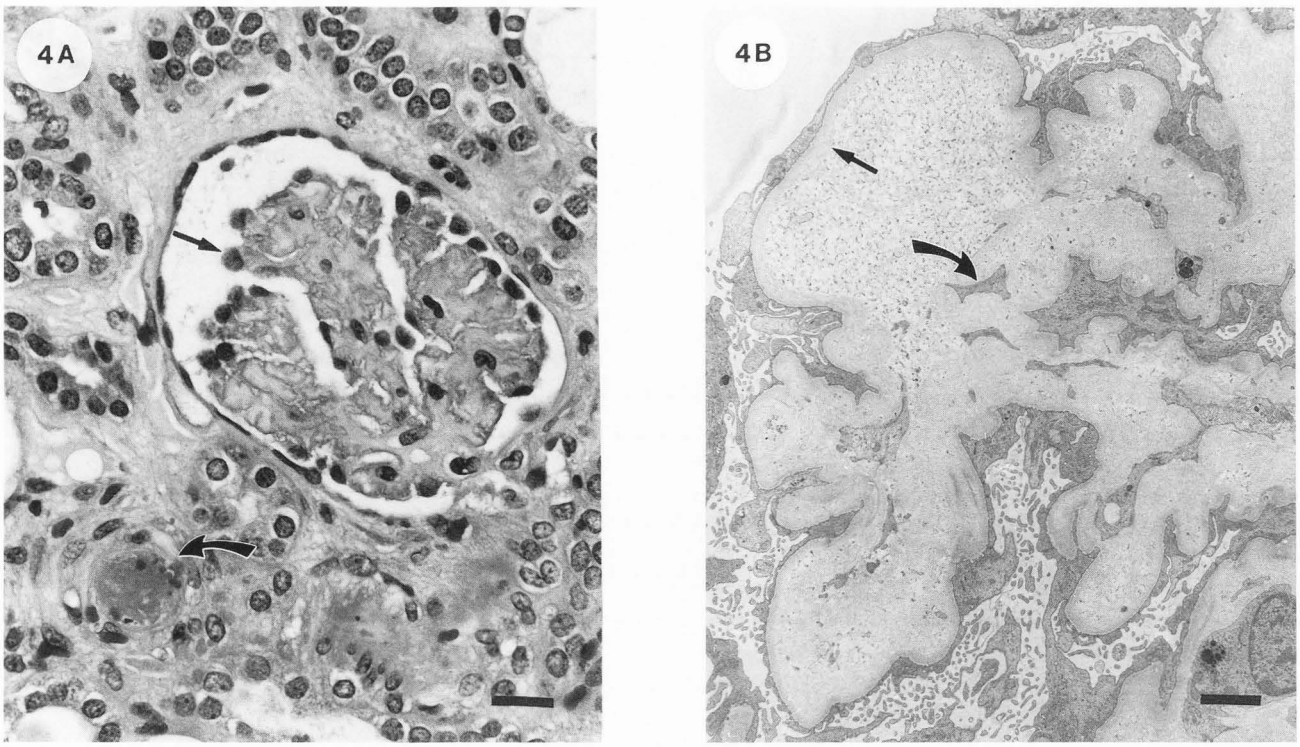


Figure 4. A renal biopsy from a BMT patient taken 5 months after total body irradiation (12 Gy) and multiagent chemotherapy. **(A)** A glomerulus with a large acellular tuft and collapsed capillary loops. Note residual podocytes (arrow) and adjacent arteriolar thrombosis (curved arrow). Hematoxylin and eosin. Bar = 10 μm. **(B)** Ultrastructural examination of a collapsed segment shows absent endothelial cells (arrow) and scant residual mesangial cell processes (curved arrow). Podocytes remain but have lost their foot processes. Bar = 2 μm.

irradiation. Thus, it is likely that common pathophysiological mechanisms are involved. What does differ in the various experimental situations is the severity of the radiation-induced decline in renal function, and the degree of improvement seen from around 16 weeks onwards.

These radiation-induced changes in renal hemodynamics are associated with a severe normochromic normocytic anemia [108, 150]; in some cases, this might progress to a microangiopathic hemolytic anemia [14, 33, 188]. The severity of the anemia is disproportionate to the degree of azotemia. Two mechanisms have been proposed to account for this radiation-induced anemia: hemolysis, and/or a reduction/inhibition in erythropoietin (Epo) production. Down *et al.* [45] noted a marked anemia in mice following TBI, with fragmented erythrocytes and reticulolysis. Later studies indicated a reduced erythrocyte life-span, with no apparent alteration in erythropoiesis [46]. Similar hemolytic changes have been seen clinically [14, 33, 188]. The critical site for initiating a microangiopathic hemolysis is believed to be the glomerular capillary tufts, which do indeed demonstrate marked disruption following irradiation [36, 51, 210]. In contrast, Luxton [108] stated that the severity of the anemia observed in radiation nephropathy implied that irradiation interfered with the production of Epo in the kidney, a conclusion reached earlier in experimental studies using the mouse [135, 136] and the dog [53]. Detailed blood analyses performed in the pig [150] showed that localized irradiation of both kidneys resulted in a normochromic normocytic anemia. Moreover, a low absolute reticulocyte count was noted, indicating that the anemia represented inhibition of erythrocyte production. Low plasma Epo levels have been reported in patients exhibiting anemia following TBI [33]. This reduced production has been interpreted as indicating damage to the juxtaglomerular apparatus [4]. The localization of these Epo-producing cells has been the focus of intense investigation. Glomerular [23, 28, 92, 97] and tubular [98] cells have been reported to be primary sites of Epo production. More recently, studies using ^{35}S-labeled antisense RNA probes specific for mRNA coding for Epo have identified interstitial peritubular cells, predominantly located in the cortical labyrinth, as the site of Epo synthesis [47]. It is likely that both hemolysis and a decreased Epo production play a role in the development of a radiation-induced anemia. The importance of the latter has been demonstrated clinically by the suc-

cessful treatment of anemia using parenteral Epo [33].

Morphologic Changes

The marked radiosensitivity of the kidneys is now clearly recognized, and the clinical characteristics of radiation nephropathy have been well described. Studies of changes in renal morphology, ideally, should help ascertain the cell type(s) at risk and, in conjunction with the observed functional data, provide a rational basis for an understanding of both the pathogenesis of radiation nephropathy and the use of interventional procedures directed at ameliorating the severity of this lesion. Clinical pathological studies have been reported (for review see [36]) but are limited by the fact that damaged kidneys seldom are evaluated before the pathological process is well advanced, thereby precluding accurate determination of primary structural alterations. Furthermore, much of the literature is from BMT patients in which nephrotoxic chemotherapeutic drugs may contribute to the renal injury. Experimental investigations on the morphologic changes seen following irradiation have yielded conflicting results. A number of earlier investigators [124], as well as recent authors [67, 81, 119, 121, 139, 203] have indicated that tubular damage is an early and prominent morphologic alteration in the irradiated kidney. Other authors have reported that glomerular lesions [35, 62, 64, 75, 76, 109, 110, 111, 129, 154, 159, 176] or vascular changes [115, 162, 193] are primarily evident. This lack of agreement has been ascribed to differences in the doses of radiation used, physiological status of the kidney at the time of radiation, the amount of kidney exposed, and the interval from radiation to morphologic evaluation; few serial sacrifice studies have been performed. Although species differences also have been implicated [124], we are of the opinion that these are of minimal importance. Another factor is the use of insufficiently sensitive histological methods. Electron microscopy studies may reveal changes not readily visible at a particular time-point using conventional light microscopy, and the use of specific stains helps to identify particular renal alterations.

Morphology of human radiation nephropathy

The kidney can be damaged either directly or indirectly during therapeutic irradiation. Indirect injury may develop in patients receiving unilateral irradiation for an abdominal tumor (Fig. 1). Progressive myointimal proliferation results in occlusive renal artery stenosis, leading to renovascular hypertension and a small atrophic kidney [37, 39, 60, 91, 117, 165, 171, 174, 192]. The hypertension can be cured by unilateral nephrectomy [39, 165, 174].

The morphologic details of direct radiation injury to the renal parenchyma were first described by Zuelzer *et al.* in 1950 [210]. Although most examples of radiation nephropathy, when encountered on biopsy or at autopsy, are complex lesions, involving glomeruli, tubules and vessels, the glomerular component is generally regarded as the most important. In rare cases, in which biopsies have been taken relatively early in the clinical course of radiation nephropathy, glomerular lesions alone are present, only later to be followed by tubulointerstitial and finally, vascular alterations [85, 86, 161]. The fine details of radiation nephropathy were first revealed in the ultrastructural study of Rosen *et al.* [160]; and confirmed and refined in the subsequent literature [85, 86].

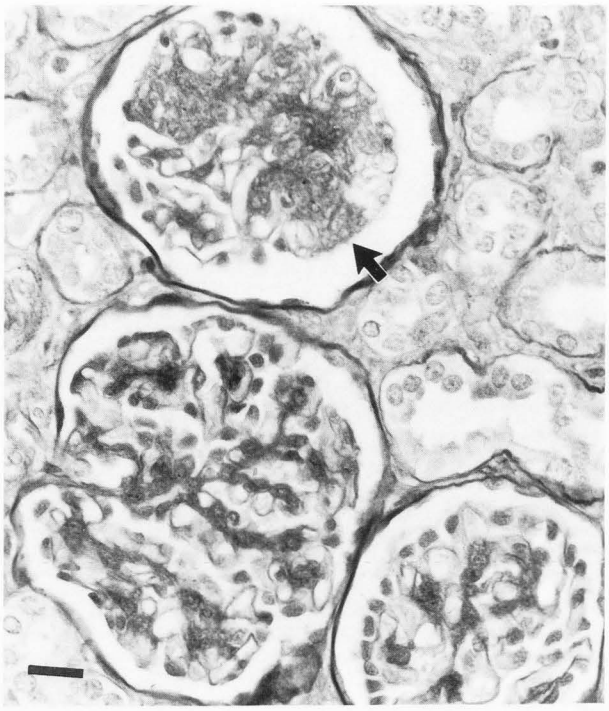


Figure 5. A nephrectomy specimen showing radiation nephropathy in a 5-year-old child, 2 years after intraoperative irradiation (dose unknown) for neuroblastoma. Extensive mesangiolysis in one glomerulus (arrow) is present while the adjacent glomeruli appear largely unaffected. Periodic acid-Schiff. Bar = 10 μm.

The most characteristic lesion observed in human radiation nephropathy affects the glomerulus. It is characterized by a spectrum of abnormalities (Figs. 2 and 3) which range from necrotizing cellular injury with thrombosis, to structural alterations of the mesangial matrix and capillary loop basement membranes. The walls of the glomerular capillary loops exhibit a prominent thickening, resulting from endothelial cell swelling and separation of the endothelial cell (EC) from the basement membrane. Often, it is associated with reduplication of the basement membrane, resulting in a double contour,

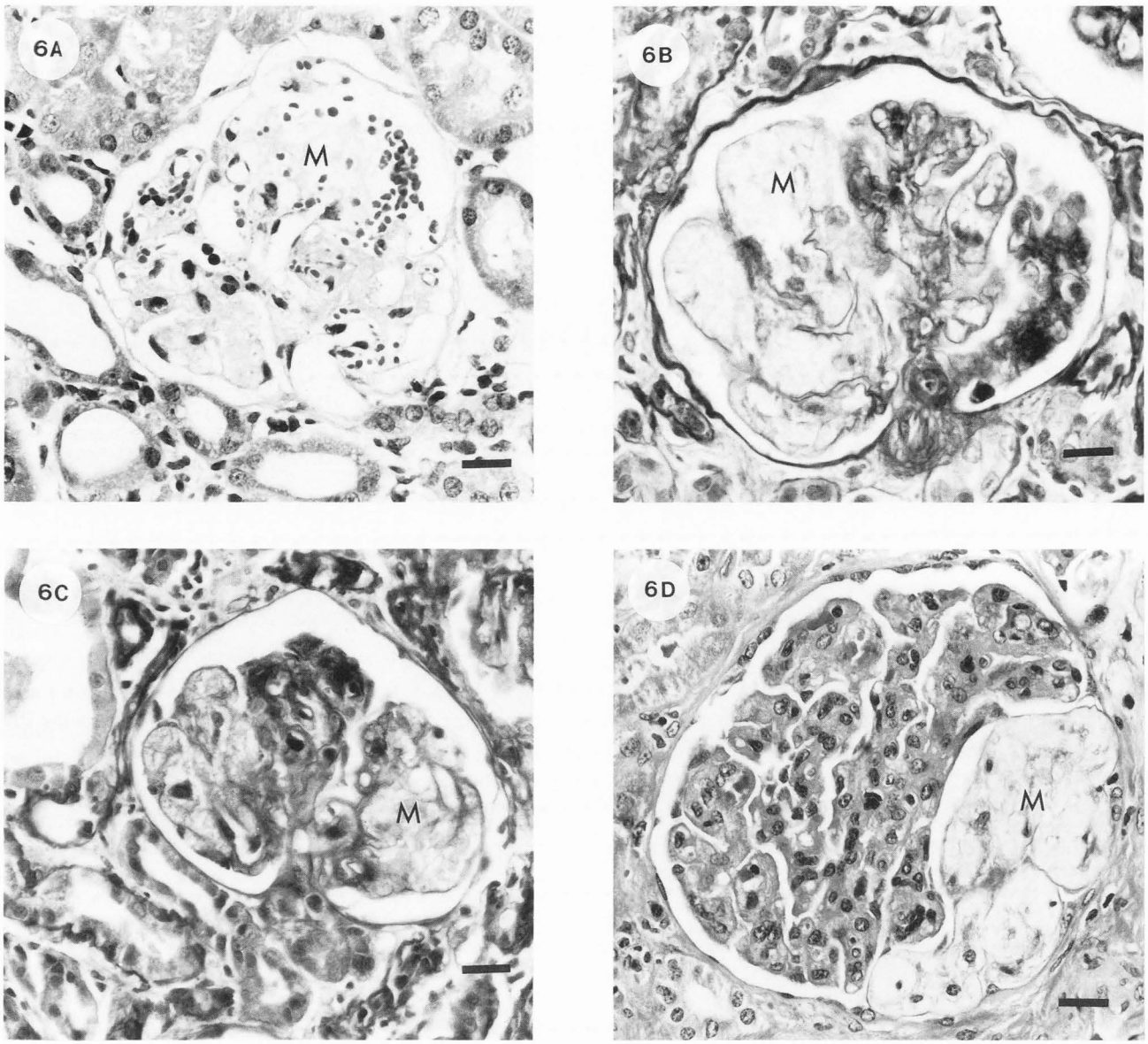


Figure 6. Experimental models of radiation nephropathy show the characteristic glomerular lesion (compare with Figure 2) characterized by segmental to global mesangiolysis (M) and subendothelial expansion. (**A**) Mouse, 15 Gy, 12 months postirradiation (PI), hematoxylin and eosin, bar = 8 μm; (**B**) rat, 15 Gy, 20 weeks PI, periodic acid-Schiff, bar = 8 μm; (**C**) pig, 9.8 Gy, 12 weeks PI, periodic acid-Schiff, bar = 10 μm; (**D**) monkey, 35 Gy, 24 months PI, hematoxylin and eosin, bar = 10 μm.

readily apparent by light microscopy with a silver stain (Figs. 2A and 2B). In its milder forms, this alteration may be visible only by electron microscopy (Fig. 3A). The mesangial areas also show prominent enlargement, with either an increase in matrix or, more characteristically, with a rarefaction of matrix, a process known as mesangiolysis (Fig. 2). This process can appear at times dramatic, with massive aneurysmal expansion of mesangial areas. In addition, confluence of capillary loops or florid expansion of the subendothelial space of the capillary loops can result in marked compromise of the capillary lumina (Fig. 2A).

Glomerular capillary loop thrombosis and arteriolar thrombosis also may develop; with extension of the thrombotic phenomena, red blood cells and red cell fragments are observed in the mesangial areas (Figs. 2C and 3B). Although morphologically acute, this abnormality is rarely detected before 6-12 months postirradiation.

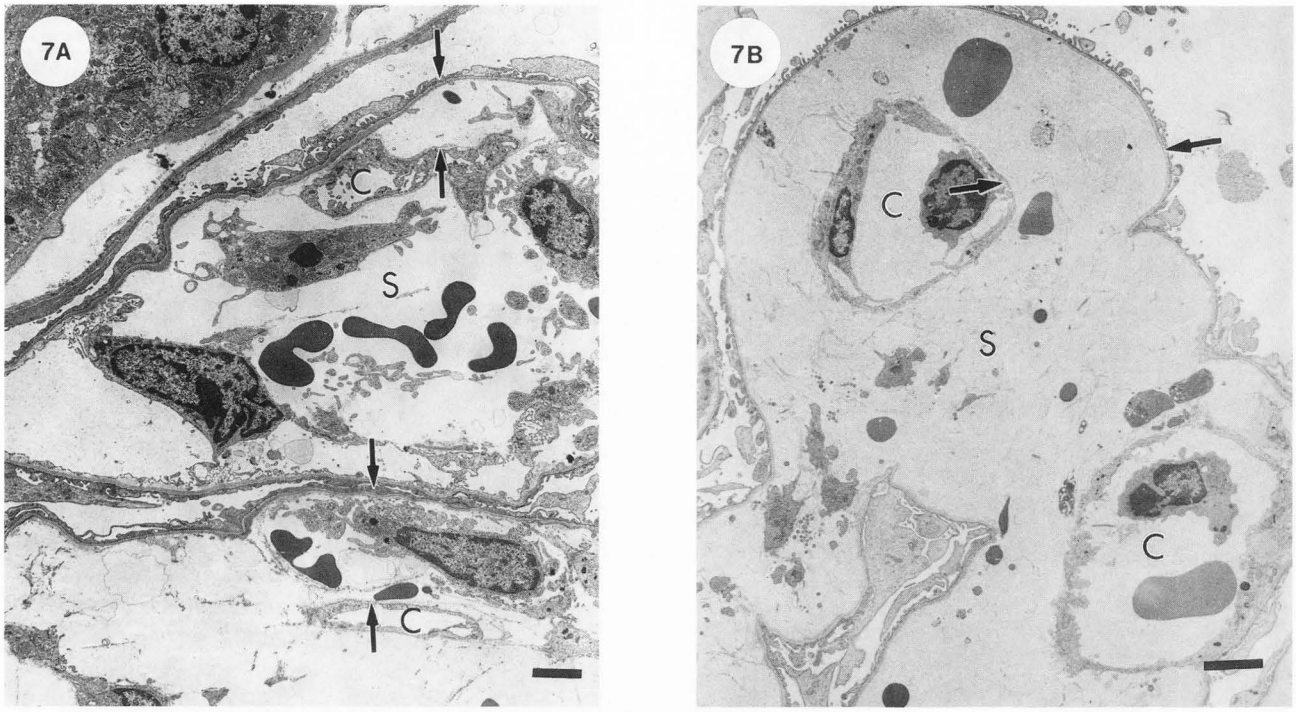


Figure 7. Glomeruli showing mesangiolysis and massive expansion of the subendothelial space (between arrows and S) with red blood cell extravasation and compromise of the capillary lumina (C). (**A**) Mouse, 15 Gy, 12 months PI, bar = 3 μm; and (**B**) pig, 9.8 Gy, 12 weeks PI, bar = 4 μm.

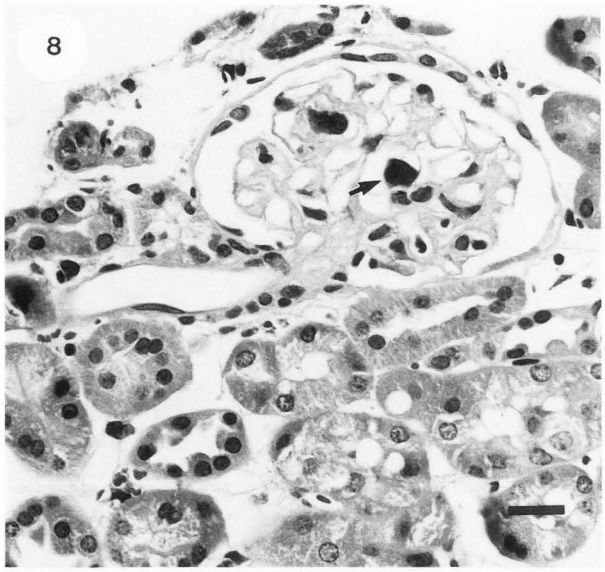
Ultrastructural studies show fibrin with very few inflammatory cells (Fig. 3B), and necrosis of cellular elements, particularly ECs but also mesangial cells (MCs). By contrast, podocytes appear to be basically intact, although they show variable effacement of their foot processes. Glomerular sclerosis characterized by mesangial sclerosis and collapse or obliteration of capillary loops, often devoid of mesangial and ECs, eventually develops in irreparably damaged glomeruli (Figs. 4A and 4B). These various lesions may affect either a portion of the glomerular tuft or the entire glomerular tuft and might co-exist within a single glomerulus. Moreover, not all glomeruli are necessarily affected in a uniform fashion. A severely damaged glomerulus may be adjacent to an apparently unaffected glomerulus (Fig. 5).

Alterations of tubules and vessels and corresponding interstitial changes usually are a prominent finding, particularly since more examples of radiation nephropathy are encountered in the advanced stage. Atrophy of tubules with thick and wrinkled basement membranes and adjacent interstitial fibrosis is invariable when renal insufficiency has developed. Accumulation of intimal foamy macrophages or intimal thickening due to myointimal cell proliferation can develop in large and medium sized arteries (Fig. 1). Small arteries and arterioles might develop either medial hyperplasia or thrombosis (Fig. 4A) with medial necrosis without a significant inflammatory response. The extent to which these tubular and vascular lesions represent a direct effect of radiation, as opposed to confounding secondary contributions from hypertension and glomerulosclerosis, is unclear.

Morphology of experimental radiation nephropathy

The morphological expression of human radiation nephropathy, as outlined above, represents the advanced stages of the lesion, generally occurring when clinical signs of radiation injury are present, about 6-18 months after treatment. It has been amply demonstrated that the glomerular lesion, so characteristic of the human disease, also predominates in experimental models, thereby validating their use. Figures 6 and 7 demonstrate radiation nephropathy produced in mouse, rat, pig, and monkey. There is variable capillary loop thickening with subendothelial expansion and basement membrane reduplication. The mesangium shows lysis of cells and matrix in continuity with the subendothelial space. Capillary loop collapse and mesangial sclerosis eventually develop. These experimentally induced glomerular lesions appear to develop regardless of the examined species (Table 1).

Sequential studies of experimental radiation nephropathy have revealed a variety of additional morphologic alterations to capillary loops and mesangium in the



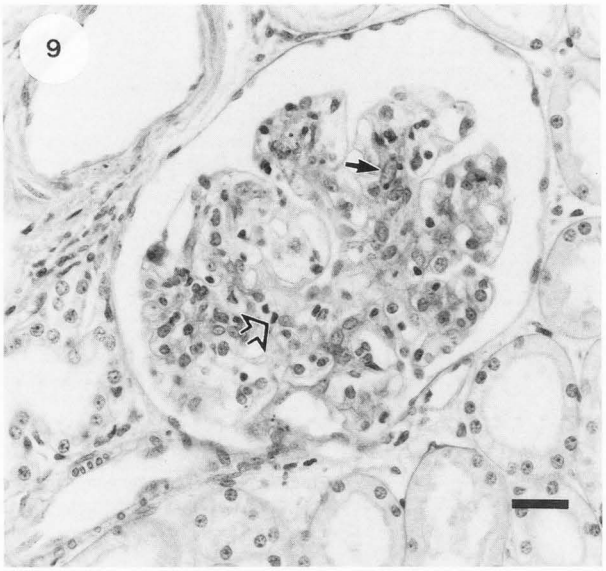


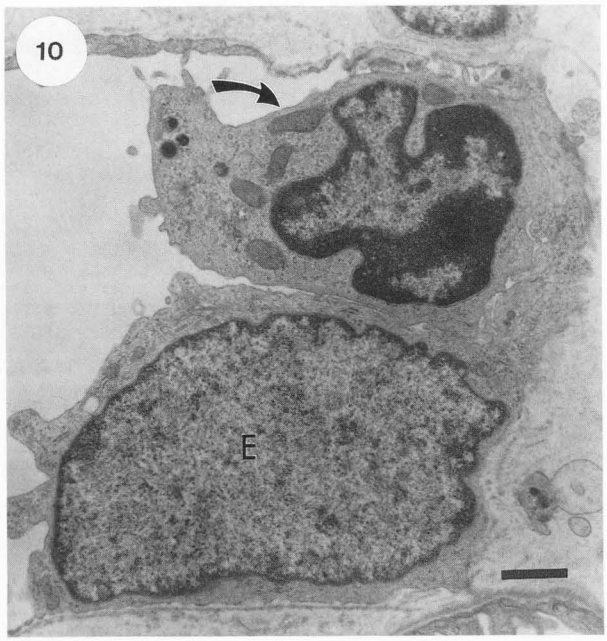
Figure 8 (at left). Hyperchromatic enlarged nuclei (arrow) in a mouse glomerulus 7 months after irradiation with a single dose of 19 Gy. Hematoxylin and eosin. Bar = 10 μm.

Figure 9 (at right). Nuclear enlargement (arrow) and a prominent lymphoid infiltrate (small dark nuclei; open arrow) in a pig glomerulus, 4 weeks after irradiation with a single dose of 9.8 Gy. Periodic acid-Schiff. Bar = 10 μm.

Table 1. The morphologic features observed in the various components of the kidney following irradiation in different species. Figures in parentheses refer to the time after irradiation at which these changes have been observed.

Species →	Mouse	Rat	Dog	Pig	Monkey	Human
Glomerular features						
nuclear enlargement	+ (> 3 months)	-	-	+ (2 weeks)	-	-
inflammation	-	-	-	+ (2 weeks)	-	-
mesangial proliferation	-	-	-	+ (6 weeks)	+ (6 months)	-
mesangiolysis/thrombosis	+ (10 months)	+ (2-3 months)	+ (2 months)	+ (3 months)	+ (6 months)	+
glomerulosclerosis	+ (10 months)	+ (2-3 months)	+ (3 months)	+ (5 months)	+ (6 months)	+
Vascular features						
thrombosis -	+ (3 months)	-	-	+ (4 months)	+	
medial hyperplasia	-	-	+ (2 months)	+ (3 months)	+ (6 months)	+
intimal thickening	-	-	-	-	+ (6 months)	+
Tubular/interstitial features						
reactive changes	+ (6 months)	+ (6 weeks)	+ (2 weeks)	+ (6 weeks)	+ (4 months)	+
tubulolysis(6 months)	+ (6 weeks)	+ (4 weeks)	-	-	-	
tubular atrophy/ interstitial fibrosis	+ (6 months)	+ (2-3 months)	+ (2 months)	+ (3 months)	+ (4 months)	+

initial phases of radiation injury. Both mice and pigs show prominent nuclear enlargement in a subset of glomerular, presumably endothelial, cells [62, 64, 76, 110, 111, 154, 159] (Figs. 8 and 9). Infiltration of glomerular capillary loops by mononuclear cells, presumably lymphoid in nature, consistently occurs in pigs [76, 154] (Figs. 9 and 10). In addition, there are pronounced changes in the mesangium. Diffuse and severe mesangial hypercellularity is observed in monkeys, but appears to be more focal in pigs (Figs. 11-15). In our experience, there is little evidence of mesangial hypercellularity in mice or rats, although other studies have reported



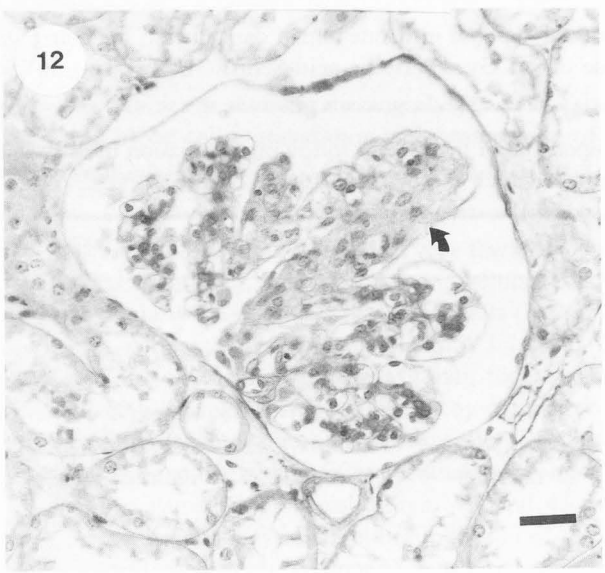
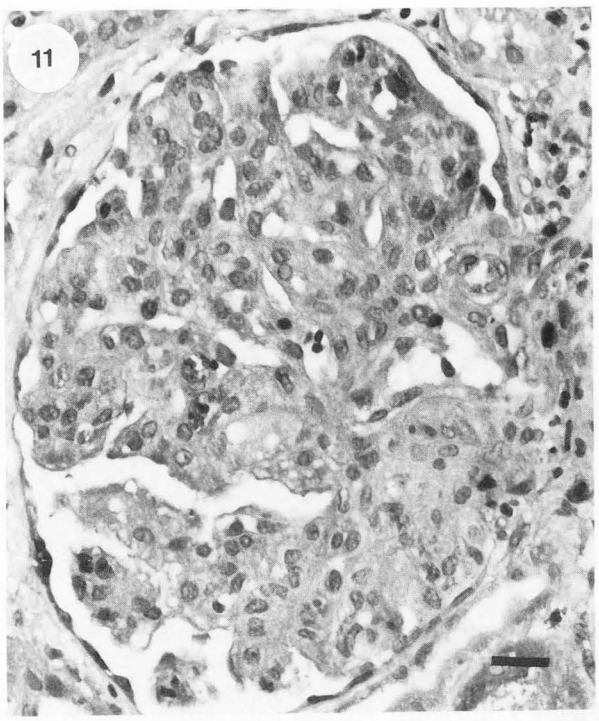


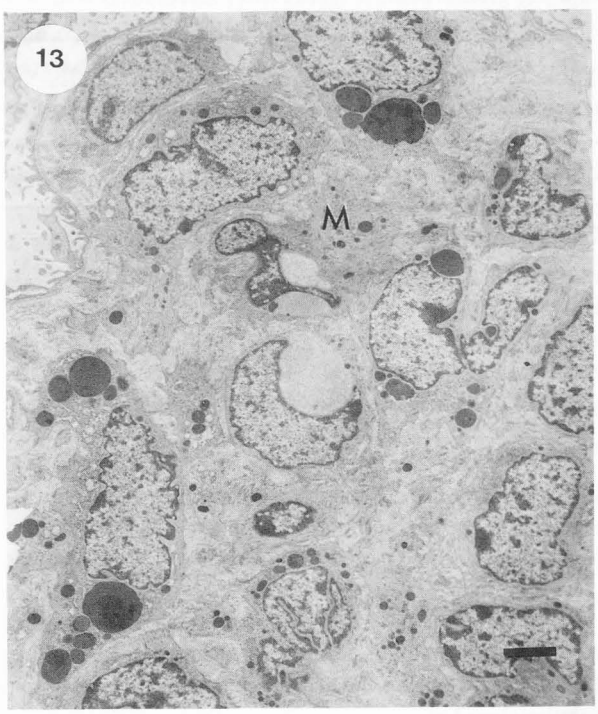
Figure 10. An electron micrograph showing a lymphocyte (arrow) adherent to a glomerular capillary endothelial cell (E). Pig, 9.8 Gy, 9 weeks PI. Bar = 2 μm.

Figure 11. Global mesangial hypercellularity in monkey, 44 Gy, 45 weeks PI. Hematoxylin and eosin. Bar = 10 μm.

Figure 12. Segmental mesangial hypercellularity (arrow) in pig, 9.8 Gy, 4 weeks PI. Hematoxylin and eosin. Bar = 12 μm.

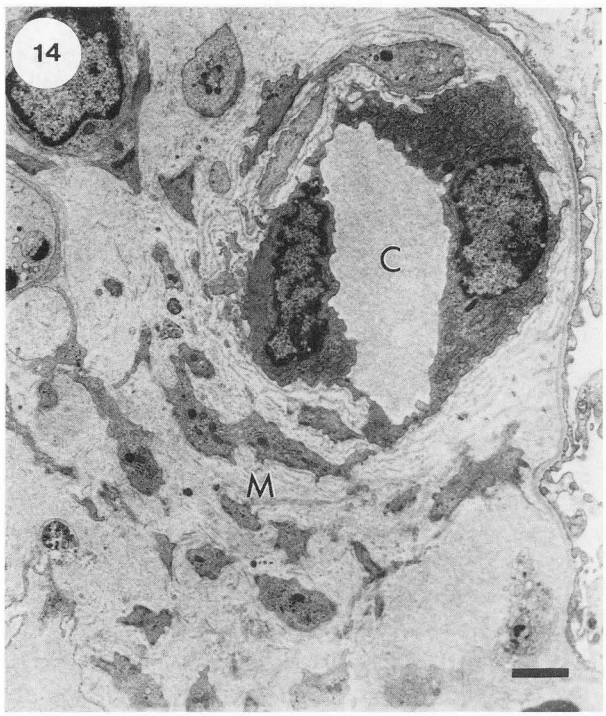
Figure 13. Electron micrograph depicting mesangial cell proliferation in pig, 9.8 Gy, 12 weeks PI. Bar = 5 μm.





increased MC proliferation [110, 112]. However, all species exhibit mesangial sclerosis.

Although prominent mesangial and endothelial alterations are observed consistently in radiation nephropathy, the podocytes appear less affected. Focal loss of foot processes certainly develops. However, many glomeruli may show good retention of their foot processes



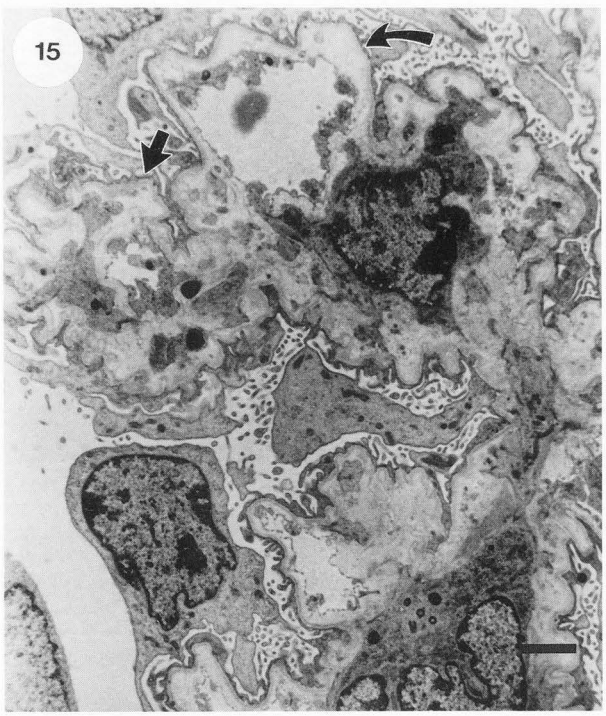


Figure 14 (at left). Electron micrograph showing mesangial matrix (M) increase (i.e., mesangial sclerosis). Compare with mesangiolysis seen in Figure 7 (C-capillary lumen). Pig, 9.8 Gy, 12 weeks PI. Bar = 2.5 μm.

Figure 15 (at right). Electron micrograph showing segmental collapse of capillary loops (arrow) and subendothelial expansion (curved arrow). Pig, 9.8 Gy, 24 weeks PI. Bar = 2.5 μm.

(Fig. 16). Denudation or necrosis of podocytes is not observed, even following capillary loop collapse or complete glomerulosclerosis.

Both vascular and tubular interstitial injury contribute to the renal dysfunction clinically defined as radiation nephropathy (Table 1). The respective contribution of these lesions and the role that irradiation plays in their development impart an additional layer of complexity yet to be unraveled. It long has been recognized that the morphologic parameter in the majority of human renal diseases most closely related to azotemia is tubulointerstitial disease [17, 52]. Although tubular atrophy may be a primary event in many diseases, atrophy invariably ensues following glomerular sclerosis, regardless of the initial insult. Furthermore, hypertension has been shown to develop and presumably, to produce occlusive vascular lesions in irradiated kidneys. Both glomerular sclerosis and tubular atrophy can develop as a consequence of hypertension [193]. Therefore, it is unclear to what extent radiation directly produces tubular or vascular injury, since each may develop for other reasons.

In early phases of radiation injury, small cortical foci of reactive appearing tubular epithelium is seen. These are characterized by nuclear enlargement, nuclear predominance, and basophilic cytoplasm (Fig. 17). In advanced stages, tubular atrophy develops, characterized by small tubular cells enveloped by a thick, irregular basement membrane, which, in our experience, does not develop in the absence of significant glomerular alterations. A distinctive subcapsular accentuation of these tubular alterations is prominent in pigs [154], and also has been reported in humans [85]. Although its distribution corresponds to a vascular pattern, the basis for the pattern is not clear.

A third distinctive form of tubular injury develops in mice and rats; we have called this lesion tubulolysis. Here, there is apparent lysis of tubular cells [81, 110], leaving an empty or denuded profile of tubular basement membrane (Figs. 18 and 19). These tubules lack the thick, wrinkled basement membranes characteristic of atrophic tubules. Tubulolysis has not been observed in pigs or monkeys, nor has it been described in humans. In contrast, interstitial fibrosis with mild interstitial inflammation is a common feature of advanced disease in all species.

Diverse vascular lesions develop in radiation nephropathy. In humans, both thrombotic lesions in arterioles (Fig. 4A) and arteries occur and intimal occlusive vascular lesions of large arteries (Fig. 1) can develop. Experimental animals demonstrate the same range of

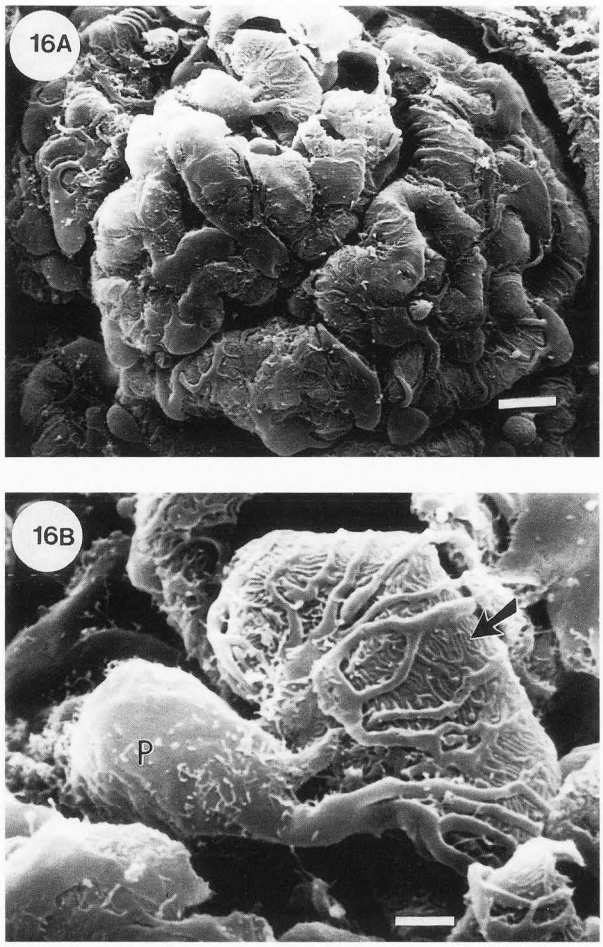


Figure 16. Scanning electron micrographs of a pig glomerulus 24 weeks PI 9.8 Gy, showing podocytes with intact foot processes (arrow; P: podocytes cell body). Bars = 10 μm (**A**) and 2.5 μm (**B**).

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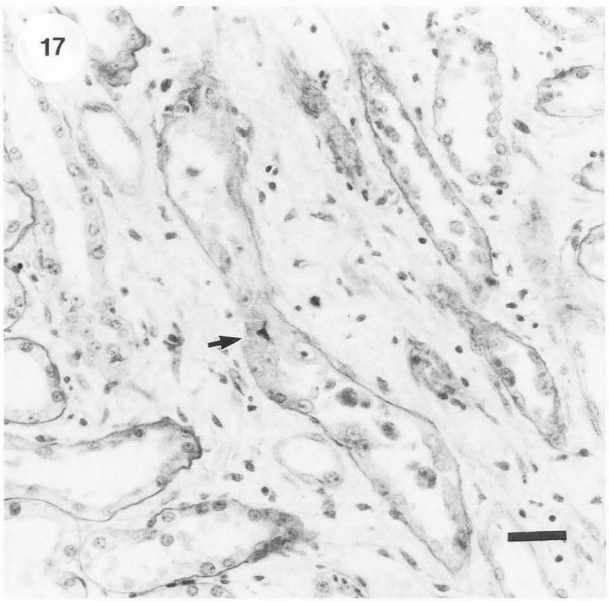
lesions, but show marked interspecies variation. Arteriolar and arterial thrombosis develops in parallel with glomerular thrombosis in both rats and monkeys (Figs. 20 and 21), particularly at high radiation doses. Thrombotic lesions are very rare in mice, even following high radiation doses, and have not been reported to develop in pigs. Occlusive but non-thrombotic vascular disease also develops in pigs, rabbits [166], dogs [125], and monkeys, but differs in the arterial layer affected. Pigs, rabbits, and dogs develop arteriolar and arterial medial hyperplasia. In pigs, medial hyperplasia develops only in the unilateral irradiation model; it is not evident in the bilateral irradiation model (Fig. 22). In contrast, monkeys develop occlusive intimal thickening without medial alterations (Fig. 23). However, rats and mice have not been reported to develop either of these chronic occlusive vascular lesions following kidney irradiation.

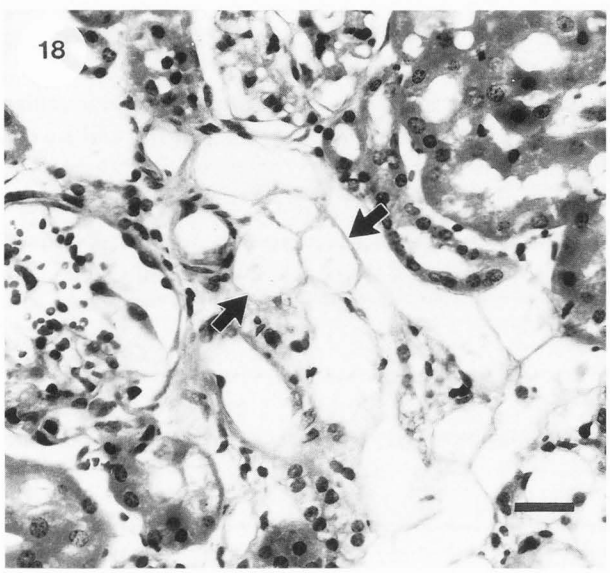
Pathogenesis

Studies on the pathogenesis of radiation nephropathy have been plagued by controversy centered on the specific target cell(s) and pathophysiological mechanism(s) involved in the development of this lesion. Arguments have revolved around two opposing schools of thought concerning the primary site of renal injury, namely, vascular versus parenchymal. Rubin and Casarett [162] proposed that the principal lesion was arterionephrosclerosis, with extra-glomerular vascular injury leading to vessel occlusion, ischemia, and **secondary** tubular atrophy and degeneration. However, arteriolar changes are an uncommon feature of experimental and clinical radiation nephropathy [36] in the absence of systemic arterial hypertension. Indeed, arteriolar lesions are less severe as compared with tubular or glomerular lesions or may even be absent [202]. Thus, the classical hypothesis that tubular degeneration occurs only secondary to injury of the vasculature and thrombosis is no longer tenable.

Diametrically opposed to the vascular hypothesis is the parenchymal hypothesis, proposed by Withers *et al.* [203]. Based upon observations of irradiated kidneys of a specific strain of inbred mice, they concluded that radiation nephropathy results from tubule cell depletion alone. This hypothesis, a bench-mark in radiation biology, served to stimulate a shift of emphasis from vascular injury as the *sine qua non* to explain the pathogenesis of late radiation injury *per se*. However, this hypothesis ignores the wealth of data not only from experimental studies involving a variety of species including other murine strains [34, 62, 64, 129, 159], but also from clinical studies involving localized [85, 86, 160, 161] or TBI [9, 33, 73, 75, 188] that show glomerular damage occurring either before or concomitantly with the development of tubular damage. Although it is certainly the case that proximal tubule epithelial cells are radiosensitive, with cell loss being evident within several weeks of irradiation, they are not the only target cells involved in the development of radiation nephropathy. Thus, the classical view that radiation nephropathy involves vascular or parenchymal cell loss alone is simplistic.

In recent years, the characterization of radiation-induced normal tissue morbidity has undergone a paradigmatic shift. Pathophysiological data from a variety of late-responding normal tissues indicate that the expression of radiation-induced normal tissue injury involves complex and dynamic interactions between several cell types within a particular organ [76, 163, 170]. These cells are viewed now not as **passive** observers, merely dying as they attempt to divide, but rather as **active** participants in an orchestrated response to injury. The central dogma of radiation biology, in which irradiation causes damage to DNA, leading to death of the cell





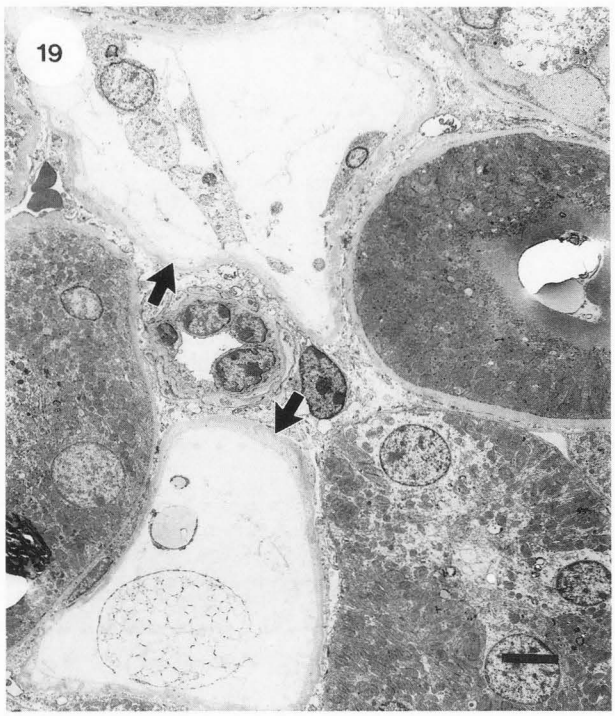


Figure 17. Deep cortical medullary ray of a pig showing reactive tubular epithelium, a cell in mitosis (arrow), and interstitial edema. 9.8 Gy, 6 weeks PI. Periodic acid-Schiff. Bar = 10 μm.

Figure 18. Tubulolysis (arrows) in mouse characterized by total disappearance of tubular cells leaving naked tubular basement membranes. 15 Gy, 12 months PI. Hematoxylin and eosin. Bar = 15 μm.

Figure 19. Electron micrograph of mouse kidney showing tubulolysis (arrows). 15 Gy, 12 months PI. Bar = 10 μm.

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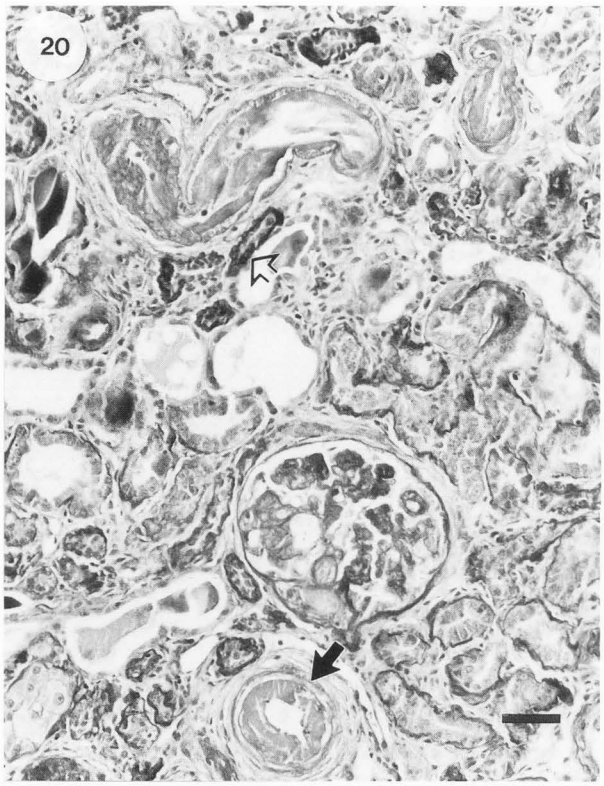
when it attempts to divide, now is seen as only one part of the overall picture. Ionizing radiation appears to cause a marked alteration in the phenotype of cells, due to activation of transcription and signal transduction pathways. Thus, *in vitro*, radiation has been shown to activate early-response genes, such as c-*jun*, Egr-1, c-*fos*, and NFκB (for review see [195]) via activation of kinases including protein kinase C and tyrosine kinase. The products of these early response genes may serve to regulate downstream genes, such as cytokines and growth factors that could play a role in cell and organ response to radiation injury. The importance of this new paradigmatic approach to radiation-induced morbidity, and specifically, radiation nephropathy, is that research is now being directed to consider the radiation response of the various cell types in terms not solely of survival, but also of altered cellular behavior.

To fully understand the pathogenesis of radiation nephropathy, it is necessary to consider the response of, not one, but several cell types. We propose that these are primarily the glomerular capillary ECs and MCs, and, albeit to a lesser extent, the proximal tubule epithelium. The morphologic and functional data presented in this review suggest that glomerular capillary endothelial cell damage represents an important primary event in renal radiation injury. Radiation-induced increases in the labeling index of these cells occur within two weeks of radiation [156], confirming that the microvascular ECs appear to be the most radiosensitive of the vascular wall components [146]. Although the direct effects of radiation on glomerular capillary EC function and/or functional changes resulting from cell loss remain ill-defined,



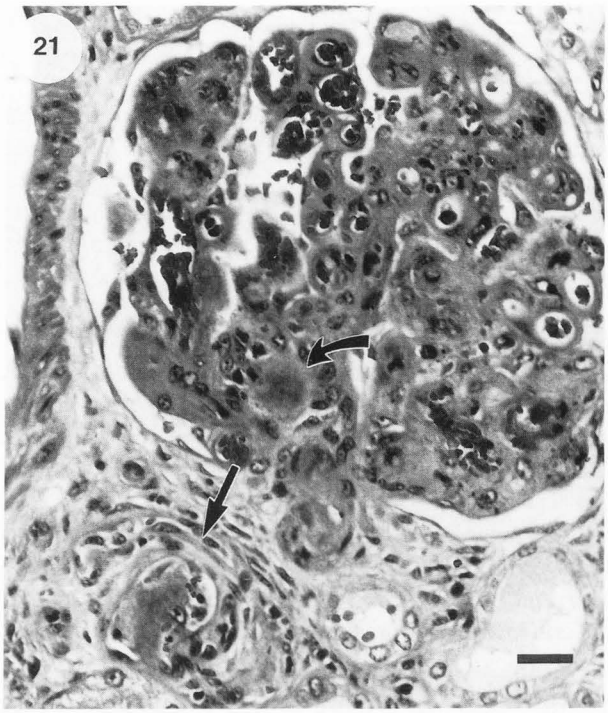


Figure 20. Arterial (arrow), arteriolar, and glomerular thrombosis, segmental glomerular sclerosis, and severe tubular atrophy (open arrow) in a mouse kidney. 19 Gy, 12 months PI. Periodic acid-Schiff. Bar = 15 μm.

Figure 21. Arteriolar (arrow) and glomerular capillary thrombosis (curved arrow) in a monkey kidney. 44 Gy, 45 weeks PI. Periodic acid Schiff. Bar = 15 μm.

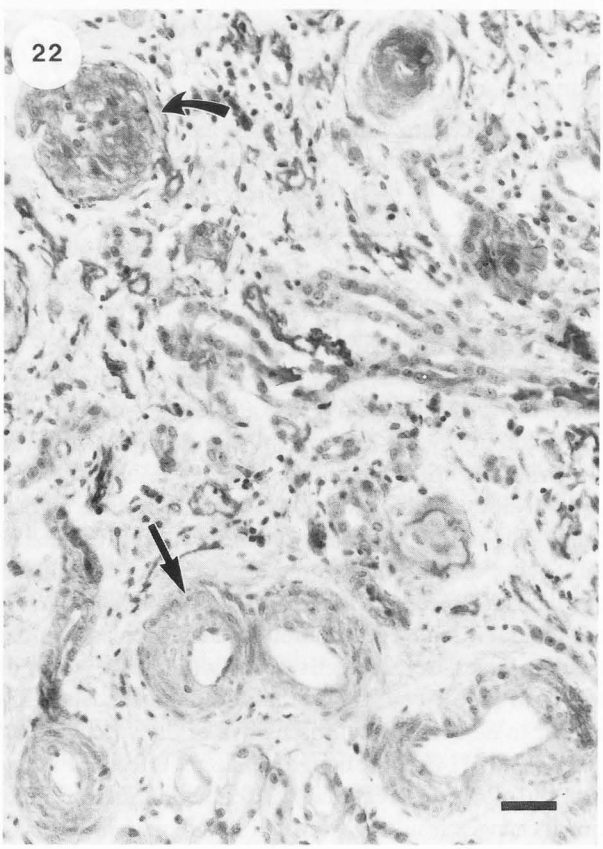


Figure 22. Pig kidney showing medial hyperplasia of both arteries and arterioles (arrow) in the peripheral cortex associated with glomerulosclerosis (curved arrow) and tubular atrophy. 9.8 Gy, 20 weeks PI. Periodic acid-Schiff. Bar = 20 μm.

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one of the earliest morphological changes appears to be the attachment of leukocytes to the glomerular capillary endothelium [76]. Endothelial cells irradiated *in vitro* release a chemotactic factor, which appears to be a lipid product of the lipoxygenase pathway [49]. Furthermore, irradiation has been shown to modulate EC/leukocyte interaction by causing a marked release of 13-hydroxyoctadecadienoic acid (13-HODE) [21], a chemorepellant believed to act as an internal regulator influencing the expression of adhesive molecules on the EC surface [22]. Thus, radiation may cause increased production of EC-derived chemoattractants, reduction in EC-derived chemorepellants, and loss of down-regulation of the cell adhesion surface, effectively promoting endothelial/leukocyte interaction. This event also may reflect a radiation-induced increase in the synthesis and/or upregulation of endothelial surface leukocyte adhesion molecules,

such as E-selectin and ICAM-1 [173]. Radiation-induced activation of adhesion molecules *in vitro* has been reported following radiation of normal and malignant glial cells and human cerebral microvascular ECs [207; Brayton *et al.*, unpublished observations]. Furthermore, glomerular capillary ECs often appear swollen with the appearance of increased metabolic activity at this time, an appearance which is associated with endothelial activation [140].

In addition, radiation appears to cause a profound increase in the permeability of the glomerular capillary endothelium, as evidenced by both transudation and emigration of plasma and red blood cell components into the subendothelial and mesangial compartments. These events lead to marked pericapillary edema and reduction in lumen cross-sectional diameter. It is of interest to note that experimental [57, 76, 110] and clinical studies [86] suggest that the podocytes appear relatively unaffected at this time; the minimal degree of proteinuria found at these times is consistent with this observation. These findings suggest radiation-induced glomerular EC damage without either concomitant basement membrane damage or altered permeability; irradiation of ECs *in vitro* is associated with increased transendothelial movement of albumin [184]. This subendothelial widening also may represent loss of adhesive interaction between the EC and the glomerular basement membrane via altered integrin expression. Integrins are a family of matrix receptors [2] that play an important role in cell-cell and cell-matrix interaction in several systems, including the kidney [1]. Immunoelectron microscopic studies of human kidney have demonstrated increased density of β_1 integrins on the portion of glomerular capillary EC facing the glomerular basement membrane [87]. Furthermore, integrin antibodies alter EC permeability properties and their capacity to retain macromolecules [100]. Radiation might cause a loss of these receptors, with subsequent loss of cell-cell adhesion and increased permeability, leading to marked widening of the subendothelial space. At present, such a proposal is purely speculative, and requires experimental verification.

These alterations in glomerular EC permeability and subendothelial transudation occur concomitantly with a significant reduction in GFR [76], indicating a possible causative relationship. However, the regulation of glomerular capillary hemodynamics and filtration is multifarious. Both glomerular ECs and MCs elaborate and respond to a host of vasoactive factors important in regulating capillary hemodynamic and filtration properties. These include prostacyclin (PGI_2), nitric oxide, and endothelin [138]. The mesangium, by virtue of its contractile properties, is intimately involved in the regulation of glomerular blood flow. As such, it responds directly or indirectly to circulating and locally synthesized

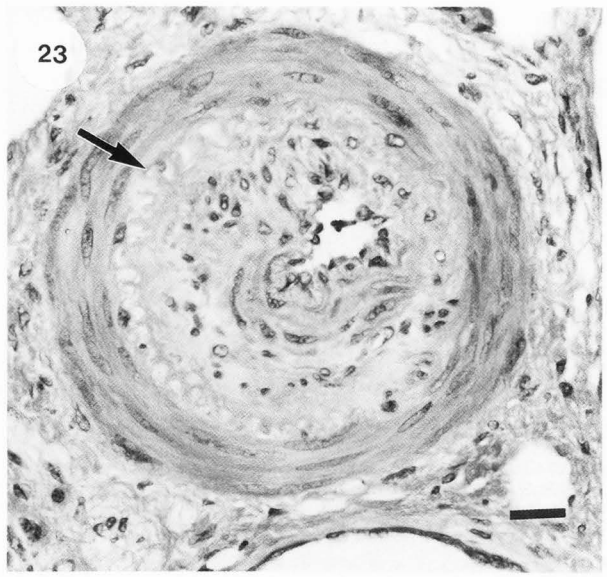

Figure 23. Monkey kidney showing florid arterial occlusive intimal thickening (arrow) without medial alterations. 44 Gy, 23 weeks PI. Hematoxylin and eosin. Bar = 10 μm.

vasoactive substances such as angiotensin II (AII), vasopressin, platelet activating factor (PAF), thromboxane A_2 (TXA_2), and prostaglandin E_2 by contraction, and results in reduced glomerular filtration surface area and ultrafiltration coefficient [167]. In response to AII and vasopressin, mesangial cells also produce PGI_2, which causes mesangial relaxation and may modulate contractility [187].

A radiation-induced reduction in PGI_2 production has been observed *in vitro* [3] and *in vivo* [172], possibly reflecting damage to the enzymatic machinery required for PGI_2 production [50]. Renal irradiation, as either localized [196] or TBI [168] leads to excessive levels of TXA_2, resulting in increased vasoconstriction. Excess TXA_2 production also will render the endothelium more thrombogenic. Thus, the microthrombi seen in more severe radiation nephropathy may further reflect radiation-induced perturbations in EC eicosanoid metabolism.

These initial, primarily EC alterations, are augmented at later times by a progressive mesangial involvement, evidenced by mesangial hyperplasia and/or hypertrophy with increased matrix formation. This leads to progressive obliteration of glomerular capillaries and sclerosis, and appears to play a key role not only in radiation nephropathy, but also in other forms of chronic renal injury [74, 90, 143]. Mesangial proliferation may occur in response to a variety of growth factors and cytokines released by injured or stimulated ECs, podocytes, and MCs themselves, as well as infiltrating cells

and platelets [186]. Although there is, as yet, no information available regarding the effect of radiation on MCs, irradiation has been shown *in vitro* to cause release of mitogens from ECs, including platelet-derived growth factor and fibroblast growth factor-like substances [49]. Renal irradiation also leads to tubular damage. This may result from direct radiation-induced cell kill, may in part be secondary to the initial glomerular injury, and may reflect the presence of significant extraglomerular lesions.

Radiation, thus, damages both glomerular and tubular components. The resulting lesions will interact and will further exacerbate the overall pathology. Associated with these changes will be the added complication of late vascular damage, resulting in secondary ischemic insult and the possible development of hypertension [199]. Moreover, the progressive nature of the glomerular lesion likely leads to hypertrophy and hyperfiltration by the remaining nephrons. Both processes have been reported to cause additional glomerular injury [6, 54]. The kidney becomes locked in a pathogenic circle of increasing nephron loss and damage, the end results of which are destruction of the renal parenchyma, glomerulosclerosis, and ultimate renal failure.

In summary, although the specific pathogenic mechanisms involved remain to be defined, the classic view that radiation nephropathy involves either vascular or parenchymal cell loss **alone** is clearly oversimplistic. The renal response to irradiation is essentially identical to that observed in a number of chronic progressive nephropathies; no pathognomonic characteristics can be identified in the irradiated kidney. The resultant clinical expression of damage in the kidney involves complex and dynamic interactions between the various cell types. The lesion appears to be predominantly glomerular in nature.

What direction does research in this area need to take? Clearly normal renal function is the result of precise and complex interactions between the various cell types. Specific biomolecules produced by the cells regulate cellular interaction and function via paracrine and autocrine mechanisms, ensuring the maintenance of function in the face of alterations to the cellular environment. Irradiation leads to both cell loss and injury. In the past, studies of radiation nephropathy, and indeed renal disease *per se*, were limited to various pharmacological mechanisms of injury, combined with assessment of the histologic and physiological consequences. Advances in molecular biology over the last few years have opened up an exciting new avenue of research in renal pathophysiology. Cellular injury leads to alterations in gene expression, e.g., upregulation of genes regulating repair and regeneration. Techniques are now available to investigate the location, structure, activity, regulation of production, and mechanism of action of these gene products [132]. Activated genes can be identified by the presence of increased messenger RNA and their specific protein products. The application of these powerful techniques to probe radiation-induced alterations in glomerular capillary EC and MC function is likely to provide significant insight into the pathogenic mechanism(s) involved in the development of radiation nephropathy. Such mechanistic data will provide clues to developing rational interventional procedures for the successful amelioration of clinical radiation nephropathy.

Influence of Dose Fractionation on the Radiation Tolerance of the Kidney

Clinically, the kidney is viewed as a radiosensitive organ, a total dose of 20 Gy being considered the upper limit of radiation "tolerance" [95]. This dose has been adopted somewhat arbitrarily, having been applied over a broad range of dose fractionation schedules. Experimental studies have indicated that the kidney has an extensive capacity for repair of sublethal radiation damage; the size of the dose of fractionated radiation markedly influences the total tolerance dose [61, 68, 151, 179, 180, 201]. There is a marked increase in the tolerance dose with decreasing size of the dose per fraction. Renal fractionation data can be analyzed using the LQ formula [44, 56]:

$$\mathbf{E = n(\alpha d + \beta d^2)} \qquad \mathbf{(1)}$$

where the effect (**E**) is a linear and quadratic function of the dose per fraction (**d**) and a function of the fraction number (**n**). This equation allows determination of the α/β ratio, a direct measure of the extent of curvature or elasticity of the underlying cell survival curve. Generally, experimental kidney fractionation data have been well described by the LQ model, with most studies indicating an α/β ratio of 2-3 Gy [81, 179, 180, 190, 201], a value typical of a late responding normal tissue. However, a value of around 5 has been reported in the irradiated mouse kidney, determined in terms of surviving tubule cells assessed 19 months after irradiation [77].

At doses of < 1-2 Gy per fraction, major deviations from the renal tolerance values predicted by the LQ model were noted [180]. This, in part, may reflect incomplete repair of sublethal damage between fractions, since short interfraction intervals of 5 hours were used. However, a reduction in repair capacity after multiple irradiations, due to diminished induction of molecular repair mechanisms [78] or the presence of a small population of radiosensitive cells, cannot be excluded.

Reirradiation and residual injury

The recurrence of a primary tumor or metastatic spread might necessitate the re-irradiation or retreatment

of a previously irradiated volume, which included the kidney. It has been suggested that renal reirradiation can be considered, since parenchymal cell depletion was negated by the repopulation of the tubules by surviving clonogens [203]. However, experimental studies refute this hypothesis [153, 158, 178, 181, 182, 183]. Studies of retreatment tolerance in the kidney indicate the virtual absence of any long-term recovery. Retreatment of the kidney appears to add to a slowly developing initial lesion, causing a more rapid expression of previously subclinical injury. This occurs despite apparent evidence for tubular regeneration [137, 154]. This tubular regeneration might be insufficient to match the rate of cell loss following irradiation. In addition, tubular proliferation might occur without a corresponding organization into functionally patent nephrons [182]. The lack of recovery also may reflect the predominant role of the glomerulus in the development of radiation nephropathy. As discussed above, the glomerular lesions observed following radiation are progressive, with no evidence of recovery.

All these hypotheses require further experimental investigations before definite conclusions can be drawn. One should note that, whatever the underlying mechanisms involved, the kidney fails to exhibit complete long-term recovery of function following irradiation. Thus, reirradiation of the kidney in patients should be undertaken with **extreme caution**, if not avoided altogether.

Treatment of Radiation Nephropathy

The incidence and severity of radiation nephropathy obviously can be reduced by limiting the volume of renal tissue irradiated and/or the amount of total dose administered. Indeed, renal shielding has successfully reduced the incidence of renal dysfunction in BMT patients receiving TBI [102]. However, any reduction in total radiotherapeutic dose clinically employed carries with it the risk of compromising tumor cell kill. An alternative approach utilizes the application of interventional procedures directed at a **selective** reduction in radiation-induced renal morbidity. This approach, if successful, will **increase** the threshold dose for radiation nephropathy and result in a clinically significant increase in therapeutic gain. Until recently, all chronic radiation-induced normal tissue morbidity was viewed to be progressive and essentially untreatable. However, the characterization of radiation-induced normal tissue injury has undergone a paradigmatic shift. The increasing awareness that such morbidity is not simply a consequence of a reduction in cell number of a particular target cell population, but rather the result of complex and dynamic interactions between particular cell types, has stimulated research in this area.

Although the successful protection of the irradiated kidney with renal arterial infusion of adrenaline has been reported clinically [175], the invasive nature of the technique precludes extensive use of such a procedure. Steroids have been reported to provide some symptomatic help [169], but did not appear to modify the progressive renal insufficiency. Although initial experimental data indicated that such treatment potentiated radiation effects on the renal vasculature [13, 25], this is now thought to reflect the high doses of steroids which were employed. More recent studies, using more appropriate doses, have shown significant attenuation of functional and morphologic parameters of radiation nephropathy in the rat and thus, have been associated with a significant increase in long-term survival [58, 59]. Placing the patient on a low protein diet may be helpful [114, 162]. A scientific rationale for the clinical use of low protein diets has come from recent studies on the consequences of reduced nephron number. This will lead to compensatory glomerular hypertrophy and/or hyperfiltration in the remaining nephrons that lead to further progressive glomerulosclerosis [20]. Low protein diets, which prevent or at least attenuate this compensatory response, have proven experimentally successful in reducing the severity of progressive glomerular injury [69]. Dietary protein restriction indeed can ameliorate the severity of radiation nephropathy in the rat [112, 113] and pig [155]. However, it remains to be determined whether such an interventional procedure will offer the prospect of significant clinical benefit.

Ongoing research into the pathogenesis and modulation of renal injury has provided exciting mechanistic insights into the renal response to injury. These advances have allowed researchers both to reevaluate their hypotheses regarding the pathogenesis of radiation nephropathy and to propose novel approaches to the future treatment of radiation nephropathy.

The Renin angiotensin system (RAS) Arruda [10] first suggested that irradiation-induced damage to the renal vasculature led to renal ischemia, renin release, increased AII production, and hypertension. As discussed above, the lack of significant vascular injury occurring as a primary event in radiation nephropathy led to a revision of this hypothesis. Thus, Robbins and Hopewell [147] hypothesized that radiation caused a relative renal cortical ischemia, which appeared to be mediated via the RAS; the angiotensin-converting enzyme inhibitor (ACEI) captopril abrogated the early radiation-induced decreases in GFR and ERPF in the pig. However, later studies failed to demonstrate a radiation-induced increased in plasma renin levels [80, 149]; the role of the RAS in radiation nephropathy appeared to be minimal. This negative conclusion was reached in view of the

dogma regarding the RAS; renin is produced and stored in the kidney and is released into the blood where AI is generated, and the latter is converted to AII by ACE present in the pulmonary vasculature. However, renin, AI, and AII now have all been identified in the juxtaglomerular cells [72]. Moreover, angiotensinogen has been detected as both mRNA and active protein in the rat kidney [26, 122] indicating the likelihood of intrarenal production of AII. Thus, localized production of AII may occur independently of changes in circulating renin. Evidence supporting this active involvement of AII in the pathogenesis of radiation nephropathy has come from more recent studies using the ACEI captopril. This compound has proven to be remarkably effective in the treatment of a variety of chronic experimental [7, 15, 197] and clinical nephropathies [70, 104, 141]. Clearly, captopril can reduce the severity of radiation nephropathy arising from both localized kidney irradiation [24, 32, 147] and TBI [126]. However, its mode of action is unresolved. Studies with other non-thiol ACE inhibitors have indicated that the thiol group of captopril is not essential for its renal action [83, 127]. Thus, its beneficial action appears to involve inhibition of AII production. It should be noted that some of the beneficial actions of ACEI could reflect accumulation of kinins, since the ACEI is also kininase II. The advent of a new class of orally active AII receptor blockers has allowed the role of AII in renal disease to be further delineated [99, 205]. Determining the therapeutic efficacy of such agents in the treatment of radiation nephropathy is eagerly awaited.

Possible mechanisms to explain the efficacy of cap topril have centered on the drug acting primarily to block the hypertensive action [7] and/or the trophic action of AgII [54, 55]. In addition to its role in modulating renal hemodynamics, it has become apparent that AII plays an equally important role in the regulation of renal cell growth. AII can be considered to be a renal cytokine, binding to specific cell surface receptors, activating several signal transduction pathways associated with cell growth, and inducing cell proliferation [131, 204]. In view of the central role of mesangial sclerosis in radiation nephropathy, it should be noted that AII effects on mesangial cells include mesangial cell hypertrophy and hyperplasia [131, 204], upregulation of extracellular matrix genes [164], activation of early growth genes [128], and generation of inflammatory mediators and other growth factors [164]. These observations, although speculative, appear to indicate a major role for AII in the pathogenesis of radiation nephropathy, thereby warranting further study.

Transforming growth factor β Any specific actions of AII in the irradiated kidney would likely be modulated via dynamic interactions with other renal cytokines. Again, although there are few data yet available from models of radiation nephropathy, particular growth factors appear very interesting. The role of transforming growth factor beta (TGF-β) in increased mesangial matrix production is well documented [133, 206]. The successful blocking of renal TGF-β activity using antibodies [18] or the proteoglycan decorin [19], a natural regulator of TGF-β, results in suppression of renal injury. A similar strategy may be of potential use in radiation nephropathy. It is interesting to note that the beneficial effect of dietary protein restriction in reducing the severity of radiation nephropathy [112, 113, 155] can be explained, in part, by the ability of protein restriction to downregulate TGF-β expression, thereby preventing increased glomerular extracellular matrix production [134]. Although there are no data as yet to show increased production of TGF-β in the irradiated kidney, abnormal radiation-induced TGF-β production has been causally linked to the development of radiation fibrosis in the skin [27, 116], lung [163], and liver [8]. Irradiation of mesangial cells *in vitro* does appear to cause upregulation of mRNA TGF-β production (Robbins, unpublished observations). The recent finding that AII induces the synthesis of TGF-β in smooth muscle cells *in vitro* [164] suggests that irradiation-induced changes in MC activity may reflect an ongoing interaction between AII and TGF-β.

Antioxidant enzymes Advances in understanding the role of renal antioxidant enzymes in the pathogenesis of reactive oxygen species (ROS)-induced renal injury suggest that the therapeutic benefit of corticosteroids in models of ROS injury may reflect, in part, a corticosteroid-induced upregulation of glomerular antioxidant enzymes [71, 208]. A potential role for ROS in the pathogenesis of radiation nephropathy is suggested by the presence in the irradiated kidney of mesangiolysis, a lesion observed in ROS models of renal injury [185]. A corticosteroid-induced upregulation of antioxidant enzymes would provide a rationale for the reported benefit of this therapy in attenuating radiation nephropathy in the rat [54, 55].

Thus, there are a number of potential interventional therapies that could prove to be beneficial in the treatment of radiation nephropathy. Further research is needed to establish whether any of these will prove ultimately to be clinically applicable. At present, patients presenting chronic radiation nephropathy and hypertension should be treated aggressively with antihypertensives; low protein diets may be useful in preventing glomerular hyperfiltration and hypertrophy. Renal dialysis or transplantation may be practicable in a patient with severe bilateral involvement. In general, the irradiated kidney should be managed by a reduction in its functional load. It may well be that the function in all irradiated

kidneys is compromised to varying degrees. Exposure of the irradiated kidney to any additional nephrotoxic insult should be viewed with extreme caution.

References

[1] Adler S. (1992) Integrin receptors in the glomerulus: Potential role in glomerular injury. Amer. J. Physiol. **262**: F697-F704.

[2] Albeda SM, Buck CA. (1990) Integrins and other cell adhesion molecules. FASEB J. **4**: 2868-2880.

[3] Allen JB, Sagerman RH, Stuart MJ. (1981) Irradiation decreases vascular prostacyclin formation with no concomitant effect on platelet thromboxane production. Lancet. **2**: 1193-1196.

[4] Alpen EL, Stewart FA. (1984) Radiation nephritis and anaemia: A functional assay for renal damage after irradiation. Br. J. Radiol. **57**: 185-186.

[5] Anderson RE, Klingler EL, Evan AP, Barkels PH, Jordan SW. (1982) The pathogenesis of radiation injury in complex tissues. An overview of problems and probes. Anat. Quart. Cytol. **4**: 165-173.

[6] Anderson S. (1988) Systemic and glomerular hypertension in progressive renal disease. Kidney Intl. **34** (Suppl. 25): S119-S121.

[7] Anderson S, Diamond JR, Karnovsky MJ, Brenner BM. (1988) Mechanisms underlying transition from acute glomerular injury to late glomerular sclerosis in a rat model of nephrotic syndrome. J. Clin. Invest. **82**: 1757-1768.

[8] Anscher MS, Crocker IR, Jirtle RL. (1990) Transforming growth factor-β1 expression in irradiated liver. Radiat. Res. **122**: 77-85.

[9] Antignac C, Gubler MC, Leverger G, Broyer M, Habib R. (1989) Delayed renal failure with mesangiolysis following bone marrow transplantation. Kidney Intl. **35**: 1336-1344.

[10] Arruda JAL. (1983) Radiation nephritis. In: Tubulointerstitial Nephropathies, Contemporary Issues in Nephrology. Vol. 10. Brenner BM, Stein JH. (eds.). Churchill Livingstone, New York. pp. 275-285.

[11] Avioli LV, Lazor MZ, Cotlove E, Brace KC, Andrews JR. (1963) Early effects of radiation on renal function in man. Amer. J. Med. **34**: 329-337.

[12] Baerman G, Linser P. (1904) Beitrage zur chirurgischen Behandlung und Histologie der roentgenulzera (Contribution to the surgical treatment and histology of radiation-induced ulcers). München Med. Wochenschr. **51**: 918-920.

[13] Berdjis CC. (1960) Cortisone and radiation. III. Histopathology of the effect of cortisone on the irradiated rat kidney. Arch. Pathol. **69**: 431-439.

[14] Bergstein J, Andreoli SP, Provisor AJ, Yum M. (1986) Radiation nephritis following total-body irradiation and cyclophosphamide in preparation for bone marrow transplantation. Transplantation **41**: 63-66.

[15] Beukers JJB, van der Wal A, Hoedemaeker PJ, Weening JJ. (1987) Converting enzyme inhibition and progressive glomerulosclerosis in the rat. Kidney Intl. **32**: 794-800.

[16] Blake DD. (1965) Radiobiological aspects of the kidney. Radiol. Clin. N. Amer. **3**: 75-87.

[17] Bohle A, Gise HV, MacKensen-Haen S, Stark-Jacob B. (1981) The obliteration of the postglomerular capillaries and its influence upon the function of both glomeruli and tubules. Klin. Woch. **59**: 1043-1051.

[18] Border WA, Okuda S, Languino L, Sporn MB, Ruoslahti E. (1990) Suppression of experimental glomerulonephritis by antiserum against transforming growth factor β1. Nature **346**: 371-374.

[19] Border WA, Noble NA, Yamamoto T, Harper J, Yamamguchi Y, Pierschbacher MD, Ruoslahti E. (1992) Natural inhibitor of transforming growth factor-β protects against scarring in experimental kidney disease. Nature **360**: 361-364.

[20] Brenner BM, Meyer TW, Hostetter TH. (1982) Dietary protein intake and the progressive nature of kidney disease. N. Engl. J. Med. **307**: 652-659.

[21] Buchanan MR, Bastida E. (1988) Endothelium and underlying membrane reactivity with platelets, leu kocytes and tumour cells: Regulation by the lipoxygenase-derived fatty acid metabolites, 13-HODE and HETES. Med. Hypotheses. **27**: 317-325.

[22] Buchanan MR, Haas T, Lagarde M, Guichardant M. (1985) 13-Hydroxyoctadecadienoic acid is the vessel wall chemorepellant factor. LOX. J. Biol. Chem. **260**: 16056-16059.

[23] Busuttil R, Roh BL, Fisher JW. (1972) Localization of erythropoietin in the glomeruli of the hypoxic dog kidney using a fluorescent antibody technique. Acta Haematol. **47**: 238-242.

[24] Bywaters T, Robbins MEC, Rezvani M. (1994) Captopril reduces the severity of radiation nephropathy in the rat (abstract). Int. J. Radiat. Biol. **65**: 129-130.

[25] Caldwell WL. (1971) The effect of prednisolone on fatal post-irradiation nephritis in rabbits. Radiology **98**: 431-433.

[26] Campbell DJ, Haebner JH. (1986) The angiotensinogen gene is expressed in multiple tissues of the rat. J. Clin. Invest. **78**: 31-39.

[27] Canney PA, Dean S. (1990) Transforming growth factor beta: A promotor of late connective tissue injury following radiotherapy? Br. J. Radiol. **63**: 620-623.

[28] Caro J, Erslev AJ. (1984) Biologic and immunologic erythropoietin in extracts from hypoxic whole rat kidneys and in their glomerular and tubular fractions. J. Lab. Clin. Med. **103**: 922-931.

[29] Chappel ME, Keeling DM, Prentice HG, Sweny P. (1988) Haemolytic uremic syndrome after bone marrow transplantation: An adverse effect of total body irradiation. Bone Marrow Transpl. **3**: 339-347.

[30] Chauser BM, Hudson FR, Law MP. (1976) Renal function in the rat following irradiation. Radiat. Res. **67**: 86-97.

[31] Cohen LF, Balow JE, Magrath IT, Poplack DG, Zeigler, JL. (1980) Acute tumor lysis syndrome. Amer. J. Med. **68**: 486-491.

[32] Cohen EP, Fish BL, Moulder JE. (1992) Treatment of radiation nephropathy with captopril. Radiat. Res. **132**: 346-350.

[33] Cohen EP, Lawton CA, Moulder JE, Becker CG, Ash RC. (1993) Clinical course of bone marrow transplant nephropathy. Nephron **64**: 626-635.

[34] Concannon JP, Summers RE, Brewer R, Weil C, Hayeslip D. (1964) High oxygen tension and radiation effect on the kidney. Radiology **82**: 508-519.

[35] Cosgrove GE, Upton AC, Smith LH. (1965) Radiation glomerulosclerosis and other late effects: Influence of radiological factors and AET. Radiat. Res. **25**: 725-735.

[36] Crosson JT, Keane WF, Anderson WR. Radiation nephropathy. (1989) In: Renal Pathology with Clinical and Functional Correlations. Tisher CG, Brenner BM. (eds.). Lippincott, Philadelphia. pp. 866-876.

[37] Crummy AB Jr., Hellman S, Stansel HC, Hulsill PB. (1965) Renal hypertension secondary to unilateral radiation damage relieved by nephrectomy. Radiology **81**: 108-111.

[38] Cullen BM, Burgin J, Reeves B, Michalowski A. (1986) Functional assessments of radiation nephropathy. Br. J. Cancer **53** (Suppl. VII): 292-294.

[39] Dean AL, Abels JC. (1944) Study by newer renal function tests of unusual case of hypertension following irradiation of one kidney and relief of patient by nephrectomy. J. Urol. **52**: 497-501.

[40] Dewit L, Anninga JK, Hoefnagel CA, Nooijen WJ. (1990) Radiation injury in the human kidney: A prospective analysis using specific scintigraphic and biochemical endpoints. Int. J. Radiat. Oncol. Biol. Phys. **19**: 977-983.

[41] Dewit L, Verhej M, Valdes Olmos RA, Arisz L. (1993) Compensatory renal response after unilateral partial- and whole-volume high-dose irradiation of the human kidney. Europ. J. Cancer. **29A**: 2239-2243.

[42] Domagk G. (1927) Roentgenstrahl-entschädigungen der Niere beim Menschen. (Radiation damage of the human kidney). Med Kliniks. **23**: 345-347.

[43] Doub HP, Hartman FW, Bolliger A. (1927) Relative radiosensitivity of the kidney to irradiation. Radiology **8**: 142-148.

[44] Douglas BG, Fowler JF. (1976) The effect of small doses of X-rays on skin reactions in the mouse and a basic interpretation. Radiat. Res. **66**: 401-426.

[45] Down JD, Berman AJ, Warhol M, van Dijken PJ, Ferrara JLM, Yeap B, Hellman S, Mauch P. (1989) Late tissue-specific toxicity of total body irradiation and busulfan in a murine bone marrow transplant model. Int. J. Radiat. Oncol. Biol. Phys. **17**: 109-116.

[46] Down JD, Berman AJ, Warhol M, Yeap B, Mauch P. (1990) Late complications following total-body irradiation and bone marrow rescue in mice: Predominance of glomerular nephropathy and hemolytic anemia. Int. J. Radiat. Biol. **57**: 551-565.

[47] Eckardt KU, Koury ST, Tan CC, Schuster SJ, Kaissling B, Ratcliffe PJ, Kurtz A. (1993) Distribution of erythropoietin producing cells in rat kidneys during hypoxic hypoxia. Kidney Intl. **43**: 815-823.

[48] Edsall DL. (1906) The attitude of the clinician with regard to exposing patients to the X-ray. J.A.M.A. **47**: 1425-1429.

[49] Eldor A, Fuks Z, Matzner Y, Witte LD, Vlodavsky I. (1989) Perturbation of endothelial functions by ionizing irradiation: Effects on prostaglandins, chemoattractants, and mitogens. Semin. Thromb. Hemostasis **15**: 215-225.

[50] Eldor A, Vladovsky I, Fuks Z, Matzner Y, Rubin DB. (1989) Arachidonic metabolism and radiation toxicity in cultures of vascular endothelial cells. Prostaglandins Leukotrienes Essent. Fatty Acids **36**: 251-258.

[51] Fajardo LF, Brown JM, Glatstein E. (1976) Glomerular and juxtaglomerular lesions in radiation nephropathy. Radiat. Res. **68**: 177-183.

[52] Fine LG, Ong ACM, Norman JT. (1993) Mechanism of tubulo-interstitial injury in progressive renal diseases. Eur. J. Clin. Invest. **23**: 259-265.

[53] Fisher JW, Roh B, Sherap K. (1964) Influence of X-irradiation of the dog kidneys on erythropoietin production. Sangre **9**: 112-117.

[54] Fogo A, Ichikawa I. (1989). Evidence for the central role of glomerular growth promotors in the development of sclerosis. Semin. Nephrol. **9**: 329-342.

[55] Fogo A, Yoshida Y, Glick AD, Homma T, Ichikawa I. (1988) Serial micropuncture analysis of glomerular function in two rat models of glomerular sclerosis. J. Clin. Invest. **82**: 322-330.

[56] Fowler JF. (1992) Brief summary of radiobiological principles in fractionated radiotherapy. Semin. Radiat. Oncol. **2**: 16-21.

[57] Gang NF, Sarophim ME, Madrazo A, Churg J. (1973) Radiation nephritis. III. Chemical, functional and morphologic correlates of the glomerular basement membrane. Amer. J. Pathol. **72**: 141-148.

[58] Geraci JP, Mariano MS, Taylor DA, Still ER. (1992) Effects of dexamethasone on late radiation injury following partial and local organ exposures. Radiat. Res.

129: 61-70.

[59] Geraci JP, Mariano MS, Jackson KL. (1993) Amelioration of radiation nephropathy in rats by dexamethasone treatment after irradiation. Radiat. Res. **134**: 86-93.

[60] Gerlock AJ Jr., Goncharenko VA, Ekelund L. (1977) Radiation-induced stenosis of the renal artery causing hypertension: Case report. J. Urol. **118**: 1064-1065.

[61] Glatstein E, Brown RC, Zanelli GD, Fowler JF. (1975) The uptake of rubidium-86 in mouse kidneys irradiated with fractionated doses of X-rays. Radiat. Res. **61**: 417-426.

[62] Glatstein E, Fajardo LF, Brown JM. (1977) Radiation injury in the mouse kidney I. Sequential light microscopic injury. Int. J. Radiat. Oncol. Biol. Phys. **2**: 933-943.

[63] Grossman BJ. (1955) Radiation nephritis. J. Pediatr. **47**: 424-433.

[64] Guttman PH, Kohn HI. (1963) Age at exposure and acceleration of intercapillary glomerulosclerosis in mice. Lab. Invest. **12**: 250-256.

[65] Hartman FW, Bolliger A, Doub HP. (1926) Experimental nephritis produced by irradiation. Amer. J. Med. Sci. **172**: 487-500.

[66] Hartman FW, Bolliger A, Doub HP. (1927) Functional studies throughout course of roentgen-ray nephritis in dogs. J.A.M.A. **88**: 139-145.

[67] Hoopes PJ, Gillette EL, Benjamin SA. (1985) The pathogenesis of radiation nephropathy in the dog. Radiat. Res. **104**: 406-419.

[68] Hopewell JW, Wiernik G. (1977) Tolerance of the pig kidney to fractionated X-irradiation. In: Radiobiological Research and Radiotherapy. Intl. Atomic Energy Agency, Vienna. pp. 65-73.

[69] Hostetter TH, Meyer TW, Rennke HG, Brenner BM. (1986) Chronic effects of dietary protein in the rat with intact and reduced renal mass. Kidney Intl. **30**: 509-517.

[70] Huisson AP, Meehan S, Keogh JA. (1991) Reduction of proteinuria with captopril therapy in patients with focal segmental glomerulosclerosis and IgA nephropathy. Irish J. Med. Sci. **160**: 319-321.

[71] Ichikawa I, Kiyama S, Yoshioka T. (1994) Renal antioxidant enzymes: Their regulation and function. Kidney Intl. **45**: 1-9.

[72] Inagami T, Mizuno K, Nakamura M, Pandey KN, Naruse M, Naruse K, Misono K, Okamura T, Kawamura M, Higashimori K. (1988) The renin-angiotensin system: An overview of its intracellular function. Cardiovasc. Drugs Ther. **2**: 453-458.

[73] Iskander SS, Browning MC, Lorentz WB. (1989) Mesangiolytic glomerulopathy in a bone marrow allograft recipient. Human Pathol. **20**: 290-292.

[74] Jacobson HR. (1991) Chronic renal failure: Pathophysiology. Lancet **338**: 419-423.

[75] Jaenke RS, Phemister RD, Norrdin RW. (1980) Progressive glomerulosclerosis and renal failure following perinatal gamma radiation in the beagle. Lab. Invest. **42**: 643-655.

[76] Jaenke RS, Robbins MEC, Bywaters T, Whitehouse E, Rezvani M, Hopewell JW, (1993) Capillary endothelium: Target-site of renal radiation injury. Lab. Invest. **68**: 396-405.

[77] Jen YM, Hendry JH. (1993) The dose-fractionation sensitivity of the kidney; assessment of viable tubule cross-sections at 19 months after X-irradiation. Br. J. Radiol. **66**: 241-244.

[78] Joiner MC, Johns H. (1988) Renal damage in the mouse: The response to very small doses per fraction. Radiat. Res. **114**: 385-398.

[79] Jongejan HTM, van der Kogel A, Provoost AP, Molenaar JC. (1987) Radiation nephropathy in young and adult rats. Int. J. Radiat. Oncol. Biol. Phys. **13**: 225-232.

[80] Jongejan HTM, van der Kogel A, Provoost AP, Molenaar JC. (1987) Hypertension after bilateral kidney irradiation in young and adult rats. Radiat. Res. **111**: 474-487.

[81] Jordan SW, Key CR, Gomez LS, Agnew J, Barton SL. (1978) Late effects of radiation on the mouse kidney. Exp. Mol. Pathol. **29**: 115-129.

[82] Jordan SW, Anderson RE, Lane RG, Brayer JM. (1985) Fraction size, dose and time-dependence of X-ray induced late renal injury. It. J. Radiat. Oncol. Biol. Phys. **11**: 1095-1101.

[83] Juncos LI, Carrasco Duenas S, Cornejo JC, Broglia CA, Cejas H. (1993) Long-term enalapril and hydrochlorothiazide in radiation nephritis. Nephron **64**: 249-255.

[84] Kamil ES, Latta H, Johnston WH, Feig SA, Bergstein JM. (1978) Radiation nephritis following bone marrow transplantation (abstract). Kidney. Intl. **14**: 713.

[85] Kapur S, Chandra R, Antonovych T. (1977) Acute radiation nephritis: Light and electron microscopic observations. Arch. Pathol. Lab. Med. **101**: 469-473.

[86] Keane WF, Crosson JT, Staley NA, Anderson WR, Shapiro FL. (1976) Radiation-induced renal disease. A clinicopathologic study. Amer. J. Med. **60**: 127-137.

[87] Kerjaschki D, Ojha PP, Susani M, Horvat R, Binder S, Hovorka A, Hillemanns P, Pytela R. (1989) A β_1 -integrin receptor for fibronectin in human kidney glomeruli. Amer. J. Pathol. **134**: 481-489.

[88] Kim TH, Freeman CR, Webster JH. (1980) The significance of unilateral radiation nephropathy. Int. J. Radiat. Oncol. Biol. Phys. **6**: 1567-1571.

[89] Kim TH, Somerville PJ, Freeman CR. (1984)

Unilateral radiation nephropathy- the long-term significance. Int. J. Radiat. Oncol. Biol. Phys. **10**: 2053-2059.

[90] Klahr S, Schreiner G, Ichikawa I. (1988) The progression of renal disease. N. Engl. J. Med. **318**: 1657-1666.

[91] Kösters S, Birzele H, Hienz HA, Baumbusch F. (1981) Kidney damage by ionizing radiation. Eur. Urol. **7**: 115-117.

[92] Koury ST, Bondurant MC, Koury MJ. (1988) Localization of erythropoietin synthesizing cells in murine kidneys by *in situ* hybridization. Blood **71**: 524-527.

[93] Krause P. (1906) Ueber die Schädigungen innerer Organe durch Roentgenbestrahlung und Schutzmassnahmen dagegen (On damage to inner organs by X-ray irradiation and protection against this damage). München Med. Wochenschr. **53**: 1745-1748 .

[94] Krause P, Ziegler H. (1906) Experimentelle Untersuchungen uber die Einwirkung der Roentgenstrahlen auf tierisches Gewebe (Experimental investigations on the effect of X-rays on animal tissue). Fortschr. Geb. Roentgenstrahlen **10**: 126-182.

[95] Krochak RJ, Baker DG. (1986) Radiation nephritis: Clinical manifestations and pathophysiologic mechanisms. Urology. **27**: 389-393.

[96] Kunkler PB, Farr RF, Luxton RW. (1952) The limit of renal tolerance to X-rays. Br. J. Radiol. **25**: 190-201.

[97] Kurtz A, Jelkmann W, Sinowatz F, Bauer C. (1983) Renal mesangial cell cultures as a model for the study of erythropoietin production. Proc. Natl. Acad. Sci. USA. **80**: 4008-4011.

[98] Lacombe C, DaSilva JL, Bruneval P, Fournier JG, Wendling F, Casadevall N, Camillera JP, Bariety J, Varet B, Tambourin P. (1988) Peritubular cells are the site of erythropoietin synthesis in the murine hypoxic kidney. J. Clin. Invest. **81**: 620-623.

[99] Lafayette RA, Mayer G, Park SK, Meyer TW. (1992) Angiotensin II receptor blockade limits glomerular injury in rats with reduced renal mass. J. Clin. Invest. **90**: 766-771.

[100] Lampugnani MG, Resnati M, Dejana E, Marchisio PC. (1991) The role of integrins in the maintenance of endothelial layer integrity. J. Cell Biol. **112**: 479-490.

[101] Lawton CA, Cohen EP, Barber-Derus SW, Murray KJ, Ash RC, Casper JT, Moulder JE. (1991) Late renal dysfunction in adult survivors of bone marrow transplantation. Cancer **67**: 2795-2800.

[102] Lawton CA, Barber-Derus SW, Murray KJ, Cohen EP, Ash RC, Moulder JE. (1992) Influence of renal shielding on the incidence of late renal dysfunction associated with T-lymphocyte deplete bone marrow transplantation in adult patients. Int. J. Radiat. Oncol. Biol. Phys. **23**: 681-686.

[103] Le Bourgeois JP, Meignan M, Parmentier C, Tubiana M. (1979) Renal consequences of irradiation of the spleen in lymphoma patients. Br. J. Radiol. **52**: 56-60.

[104] Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. (1993) The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. N. Engl. J. Med. **329**: 1456-1462.

[105] Lonnerholm G, Carlson K, Bratteby LE, Backlund I, Hagberg H., Rikner G., Smedmyr B, Oberg G, Simonsson B, (1991) Renal function after autologous bone marrow transplantation. Bone Marrow Transpl. **8**: 129-134.

[106] Luxton RW. (1953) Radiation nephritis. Quart. J. Med. **22**: 215-242.

[107] Luxton RW. (1953) Radiation nephritis. A long-term study of 54 patients. Lancet. **ii**: 1221-1224

[108] Luxton RW. Effects of irradiation on the kidney. (1973) In: Diseases of the Kidney. Strauss MB, Welt LG. (eds.). Little Brown, Boston. pp. 1049-1070.

[109] Madrazo AA, Churg J. (1976) Radiation nephritis. Chronic changes following moderate doses of radiation. Lab. Invest. **34**: 283-290.

[110] Madrazo AA, Susuki Y, Churg J. (1969) Radiation nephritis: Acute changes following high dose of radiation. Amer. J. Pathol. **54**: 507-527.

[111] Madrazo AA, Susuki Y, Churg J. (1970) Radiation nephritis II: Chronic changes after high doses of radiation. Amer. J. Pathol. **61**: 37-56.

[112] Mahler PA, Oberley TD, Yatvin MB. (1982) Histologic examination of the influence of dietary protein on rat radiation nephropathy. Radiat. Res. **89**: 546-558.

[113] Mahler PA, Rasey JW, Yatvin MB. (1987) Influence of protein nutrition on dose-survival relationship following rat kidney irradiation. Radiat. Res. **109**: 238-244.

[114] Maier JG. (1972) Effects of radiation on kid neys, bladder and prostate. Frontiers Radiat. Ther. Oncol. **6**: 196-227.

[115] Maier JG, Casarett GW. (1964) Cellular growth and tissue radiosensitivity. Tissue studies *in vivo* and the concept of radiation nephritis. Trans. N.Y. Acad. Sci. **26**: 599-627.

[116] Martin M, Lefaix JL, Pinton P, Crechet F, Daburon F. (1993) Temporal modulation of TGF-β1 and β-actin gene expression in pig skin and muscular fibrosis after ionizing radiation. Radiat. Res. **134**: 63-70.

[117] McGill CW, Holden TM, Smith TA, Ashcraft KW. (1979) Postradiation renovascular hypertension. J. Ped. Surg. **14**: 831-833.

[118] McQuarrie I, Whipple GH. (1922) Study of renal function of roentgen ray intoxication: Resistance of renal epithelium to direct radiation. J. Exp. Med. **35**:

225-242.

[119] Meistrich ML, Williams MV, Soranson JA, Fowler JF, Denekamp J. (1984) Increased collagen and fluid content of mouse kidneys at 9 months after single or fractionated X irradiation. Radiat. Res. **99**: 185-201.

[120] Mendelsohn ML, Caceres E. (1953) Effect of X-ray to the kidney on renal function of the dog. Amer. J. Physiol. **173**: 351-354.

[121] Michalowski A, Cullen BM, Burgin J, Rogers MA. (1986) Development of structural renal damage and its quantitation. Br. J. Cancer. **53** (Suppl. VII), 295-297.

[122] Morris BJ, Johnston CI. (1976) Renin substrate in granules from rat kidney cortex. Biochem. J. **154**: 625-637.

[123] Mostofi FK. (1966) Radiation effects on the kidney. In: The Kidney. International Academy of Pathology Monograph No. 6. Mostofi FK (ed.). The Williams & Wilkins Co., Baltimore. pp. 338-386.

[124] Mostofi FK, Berdjis CC. (1971) Radiopathology of kidney. In: Pathology of Irradiation. Berdjis CC. (ed.). Williams & Wilkins, Baltimore. pp. 597-635.

[125] Mostofi FK, Pani KC, Ericsson J. (1964) Effects of irradiation on canine kidney. Amer. J. Pathol. **44**: 707-719.

[126] Moulder JE, Cohen EP, Fish BL, Hill P. (1993) Prophylaxis of bone marrow transplant nephropathy with captopril, an inhibitor of angiotensin-converting enzyme. Radiat. Res. **136**: 404-407.

[127] Moulder JE, Fish BL, Cohen EP. (1993) Treatment of radiation nephropathy with ACE inhibitors. Int. J. Radiat. Oncol. Biol. Phys. **27**: 93-99.

[128] Naftlian AJ, Pratt RE, Dzau VJ. (1989) Induction of platelet-derived growth factor A-chain and c-myc gene expressions by angiotensin II in cultured rat vascular smooth muscle cells. J. Clin. Invest. **83**: 1419-1424.

[129] Nelson AC, Shah-Yukich A, Babayan R. (1984) Radiation damage in rat kidney microvasculature. Scanning Electron Microsc. **1984**; III: 1273-1277.

[130] Nomdedeu J, Martino R, Sureda H, Huidobro G, Lopez R, Brunet S, Domingo-Albos A. (1994) Acute tumor lysis syndrome complicating conditional therapy for bone marrow transplantation in a patient with chronic lymphocytic leukemia. Bone Marrow Transplant. **13**: 659-660.

[131] Norman JT. (1991) The role of angiotensin II in renal growth. Renal Physiol. Biochem. **14**: 175-185.

[132] Norwood VF, Gomez, RA. (1994) Bridging the gap between physiology and molecular biology: New approaches to perpetual questions. Amer. J. Physiol. **267**: R865-R878.

[133] Okuda S, Languino LR, Ruoslahti E, Border WA. (1990) Elevated expression of transforming growth factor-β and proteoglycan production in experimental glomerulonephritis. Possible role in expansion of extracellular matrix. J. Clin. Invest. **86**: 453-462.

[134] Okuda S, Nakamura T, Yamamoto T, Ruoslahti E. (1991) Dietary protein restriction rapidly reduces transforming growth factor β-1 expression in experimental glomerulonephritis. Proc. Natl. Acad. Sci. USA. **88**: 9765-9769.

[135] Osnes S. (1958) An erythropoietic factor produced in the kidney. Br. Med. J. **2**: 1387-1388.

[136] Osnes A. (1959) Experimental study of an erythropoietic principle produced in the kidney. Br. Med. J. **1**: 658-658.

[137] Otsuka M, Meistrich M. (1990) cell proliferation and abnormal nuclei induced by radiation in renal tubule epithelium as an early manifestation of late damage. Radiat. Res. **123**: 285-291.

[138] Pearson JD. (1990) Endothelial cell biology. Radiology. **179**: 9-14.

[139] Philips TL, Ross G. (1973) A quantitative technique for measuring renal damage after irradiation. Radiology. **109**: 457-462.

[140] Pober JS. (1988) Cytokine-mediated activation of vascular endothelium: Physiology and pathology. Amer. J. Pathol. **133**: 426-433.

[141] Praga M, Hernandez E, Montoyo C, Andres A, Ruilope LM, Rodicio JL. (1992) Long-term beneficial effects of angiotensin-converting enzyme inhibition in patients with nephrotic proteinuria. Amer. J. Kidney Dis. **20**: 240-248.

[142] Quinn JL, Meschan I, Blake DD, Witcovski RL. (1962) The usefulness of the radioisotopic renogram in radiation therapy. Radiology. **78**: 266-268.

[143] Peten EP, Striker LJ. (1994) Progression of glomerular diseases. J. Int. Med. **236**: 241-249.

[144] Raulston GL, Gray KN, Gleiser CA, Jardine JH, Flaw BL, Huchton JI, Bennett KR, Hussey DH. (1978) A comparison of the effects of 50 $MeV_{d \rightarrow Be}$ neutron and cobalt-60 irradiation on the kidneys of rhesus monkeys. Radiology. **128**: 245-249.

[145] Redd BL, Jr. (1960) Radiation nephritis. Review, case report and animal study. Amer J Roentgen. **83**: 88-106.

[146] Reinhold HS, Hopewell JW, Calvo W, Keyeux A, Reyners H. (1991) Vasculoconnective tissue. In: Radiopathology of Organs and Tissues. Scherer E, Streffer CH, Trott KR. (ed.). Springer-Verlag, Berlin. pp. 243-268.

[147] Robbins MEC, Hopewell JW. (1986) Physiological factors affecting renal radiation tolerance: A guide to the treatment of late effects. Br. J. Cancer. **53** (Suppl. VII), 265-267.

[148] Robbins MEC, Hopewell JW, Gunn Y. (1985) Effects of single doses of X-rays on renal function in unilaterally irradiated kidneys. Radiother. Oncol. **4**: 143-

151.

[149] Robbins MEC, Campling D, Rezvani M, Golding SJ, Hopewell JW. (1989) Nephropathy in the mature pig following the irradiation of a single kidney. Int. J. Radiat. Oncol. Biol. Phys. **16**: 1519-1528.

[150] Robbins MEC, Campling D, Rezvani M, Golding SJ, Hopewell JW. (1989) Radiation nephropathy in mature pigs following the irradiation of both kidneys. Int. J. Radiat. Biol. **56**: 83-98.

[151] Robbins MEC, Barnes DWH, Campling D, Hopewell JW, Knowles JF, Sansom JM, Simmonds RS. (1991) The relative biological effectiveness of fractionated doses of fast neutrons (42 $MeV_{d\rightarrow Be}$) for normal tissues in the pig. Vol. IV. Effects on renal function. Br. J. Radiol. **64**: 823-830.

[152] Robbins MEC, Bywaters T, Rezvani M, Golding SJ, Hopewell JW. (1991) The effect of unilateral nephrectomy on the subsequent radiation response of the pig kidney. Int. J. Radiat. Biol. **59**: 1441-1452.

[153] Robbins MEC, Bywaters T, Rezvani M, Golding SJ, Hopewell JW. (1991) Residual radiation-induced damage to the kidney of the pig as assayed by retreatment. Int. J. Radiat. Biol. **60**: 917-928.

[154] Robbins MEC, Wooldridge MJA, Jaenke RS, Golding SJ, Rezvani M, Hopewell JW. (1991) A morphological study of radiation nephropathy in the pig. Radiat. Res. **126**: 317-327.

[155] Robbins MEC, Bywaters T, Jaenke RS, Rezvani M, Golding SJ, Whitehouse E, Hopewell JW. (1993) Influence of a low protein diet on radiation nephropathy in the pig. Int. J. Radiat. Biol. **64**: 407-416.

[156] Robbins MEC, Soranson JA, Wilson GD, Bywaters T, Rezvani M, Golding SJ, Morris GM, Whitehouse E. Hopewell JW. (1994) Radiation-induced changes in the kinetics of glomerular and tubular cells in the pig kidney. Radiat. Res. **138**: 107-113.

[157] Robbins MEC, Stephens, LC, Thames HD, Gray KN, Peters LJ, Ang KK. (1994) Radiation response of the monkey kidney following contralateral nephrectomy. Int. J. Radiat. Oncol. Biol. Phys. **30**: 347-354.

[158] Rockwell S, Moulder JE. Biological factors of importance in split-course radiotherapy. (1985) In: Optimization of Cancer Radiotherapy. Paliwal BR, Herbert DE, Orkin CG. (eds.). American Institute of Physics, New York. pp. 171-182.

[159] Rosen VJ Jr, Cole LJ, Roan PL. (1961) Pathogenesis of postirradiation glomerulosclerosis in mice. Lab. Invest. **10**: 857-864.

[160] Rosen JS, Swerdlow MA, Muehrcke RC, Pirani CL. (1964) Radiation nephritis: Light and electron microscopic observations. Am. J. Clin. Pathol. **41**: 487-502.

[161] Rubenstone AI, Fitch LB. (1962) Radiation nephritis. Amer. J. Med. **33**: 545-554.

[162] Rubin P, Casarett GW. (1968) Urinary tract: The kidney. In: Clinical Radiation Pathology. Vol. 1. W.B. Saunders, Philadelphia. pp. 293-333.

[163] Rubin P, Finkelstein J, Shapiro D. (1992) Molecular biology mechanisms in the radiation induction of pulmonary injury syndromes: Interrelationship between the alveolar macrophage and the septal fibroblast. Int. J. Radiat. Oncol. Biol. Phys. **24**: 93-101.

[164] Ruiz-Ortega M, Gomez-Garre D, Alcazar R, Palacios I, Bustos C, Gonzalez S, Plaza JJ, Gonzalez E, Egido J. (1994) Involvement of angiotensin II and endothelin in matrix protein production and renal sclerosis. J. Hyperten. **12** (Suppl. 4), S51-S58.

[165] Salvi S, Green DM, Brecher ML, Magoos I, Gamboa LN, Fisher JE, Baliah T, Afshani E. (1983) Renal artery stenosis and hypertension after abdominal irradiation for Hodgkin disease. Urology **XXI**: 611-615.

[166] Scanlon GT. (1960) Vascular alterations in the irradiated rabbit kidney. Radiology **94**: 401-406.

[167] Schlondorff D. (1987) The glomerular mesangial cell: An expanding role for a specialized pericyte. FASEB J. **1**: 272-281.

[168] Schneidkraut MJ, Kot PA, Ramwell PN, Rose JC. (1983) Urinary prostacyclin and thromboxane levels after whole body irradiation in rats. In: Advances in Prostaglandin Thromboxane and Leukotriene Research. Paoletti R, Ramwell P. (eds.). Raven, New York. pp. 107-111.

[169] Schreiner BF, Greendyke RM. (1959) Radiation nephritis: Report of a fatal case. Amer. J. Med. **26**: 146-151.

[170] Schultheiss TE, Stephens LC. (1992) Permanent radiation myelopathy. Br. J. Radiol. **65**: 737-753.

[171] Shapiro AP, Cavallo T, Cooper W, Lapenas D, Bron K, Berg G. (1977) Hypertension in radiation nephritis. Arch. Intern. Med. **137**: 848-851.

[172] Sinzinger H, Firbas W. (1985) Irradiation depresses prostacyclin generation upon stimulation with the platelet-derived growth factor. Br. J. Radiol. **58**: 1023-1026.

[173] Springer TA. (1990) Adhesion receptors of the immune system. Nature **346**: 425-434.

[174] Staab GE, Tegtmeyer CJ, Constable WC. (1976) Radiation-induced renovascular hypertension. Amer. J. Roentgen. **126**: 634-637.

[175] Steckel RJ, Collins JD, Snow HD, Lagasse LD, Barenfus M, Anderson DP, Weisenburger T, Haukins LA, Ross NA. (1974) Radiation protection of the normal kidney by selective arterial infusion. Cancer **34**: 1046-1058.

[176] Stephens LC, Robbins MEC, Thames HD, Johnston DA, Price RE, Peters LJ, Ang KK, (1995) Radiation nephropathy in the rhesus monkey: Morphomet-

ric analysis of glomerular and tubular alterations. Int. J. Radiat. Oncol. Biol. Phys. **31**: 865-873.

[177] Stevens G, Joiner M, Joiner B, Johns H, Denekamp J. (1991) Early detection of damage following bilateral renal irradiation in the mouse. Radiother. Oncol. **20**: 124-131.

[178] Stewart FA, Oussoren Y. (1990) Re-irradiation of mouse kidneys: A comparison of re-treatment tolerance after single and fractionated partial tolerance doses. Int. J. Radiat. Biol. **58**: 531-544.

[179] Stewart FA, Soranson JA, Alpen EL, Williams MV, Denekamp J. (1984) Radiation-induced renal damage: The effects of hyperfractionation. Radiat. Res. **98**: 407-420.

[180] Stewart FA, Oussoren Y, Luts A, Begg AC, Dewit L, Lebesque JV, Bartelink H. (1987) Repair of sublethal radiation injury after multiple small doses in mouse kidney: An estimate of flexure dose. Int. J. Radiat. Oncol. Biol. Phys. **10**: 1933-1939.

[181] Stewart FA, Lebesque JV, Hart AAM. (1988) Progressive development of radiation damage in mouse kidneys and the consequences for reirradiation tolerance. Int. J. Radiat. Biol. **53**: 405-415.

[182] Stewart FA, Luts A, Lebesque JV. (1989) The lack of long-term recovery and reirradiation tolerance in the mouse kidney. Int. J. Radiat. Biol. **54**: 449-462.

[183] Stewart FA, Oussoren Y, van Tinteren H, Bentzen SM. (1994) Loss of re-irradiation tolerance in mouse kidneys with increasing time after single or fractionated partial tolerance doses. Int. J. Radiat. Biol. **66**: 169-179.

[184] Stone AM, Rubin DB, Drab EA. (1987) Increased transendothelial movement of albumen and sucrose is a direct effect of gamma irradiation *in vitro*. Fed. Proc. **46**: 418 (abstract).

[185] Stratta P, Canavese C, Dogliani M, Mazzucco G, Monga G, Vercellone A. (1991) The role of free radicals in the progression of renal disease. Amer. J. Kidney. Dis. **XVII** (Suppl. 1), 33-37.

[186] Striker LJ, Peten EP, Elliot SJ, Doi T, Striker GE. (1991) Mesangial cell turnover: Effect of heparin and peptide growth factors. Lab. Invest. **64**: 446-456.

[187] Sweeney C, Schultz P, Raij L. (1990) Interactions of the endothelium and mesangium in glomerular injury. J. Amer. Soc. Nephrol. **1**: S13-S20.

[188] Tarbell NJ, Guinan EC, Niemeyer C, Mauch P, Sallan SE, Weinstein HJ. (1988) Late onset of renal dysfunction in survivors of bone marrow transplantation. Int. J. Radiat. Oncol. Biol. Phys. **15**: 99-104.

[189] Textor SC, Forman SJ, Zipser RD, Carlson JE. (1987) Changes in renal blood flow, glomerular function, and vasoactive hormones in bone-marrow-transplant recipients after total-body irradiation. In: Prostaglandin and Lipid Metabolism in Radiation Injury. Walden TL, Hughes HN. (eds.). Plenum, New York. pp. 305-317.

[190] Van Rongen E, Kuijpers WC, Madhuizen HT. (1990) Fractionation effects and repair kinetics in rat kidney. Int. J. Radiat. Oncol. Biol. Phys. **18**: 1093-1106.

[191] Van Why SK, Friedman AL, Wei LJ, Hong R, (1991) Renal insufficiency after bone marrow transplantation in children. Bone Marrow Transpl. **7**: 383-388.

[192] Verheij M, Dewitt LGH, Valdes Olmos RA, Arisz L. (1994) Evidence for a renovascular component in hypertensive patients with late radiation nephropathy. Int. J. Radiat. Oncol. Biol. Phys. **30**: 677-683.

[193] Wachholz BW, Casarett GW. (1970) Radiation hypertension and nephrosclerosis. Radiat. Res. **41**: 39-56.

[194] Warthin AS. (1907) The changes produced in the kidneys by Rontgen irradiation. Amer J Med Sci. **113**: 736-747.

[195] Weichselbaum RR, Hallahan D, Fuks Z, Kufe D. (1994) Radiation induction of immediate early genes: Effectors of the radiation-stress response. Int. J. Radiat. Oncol. Biol. Phys. **30**: 229-234.

[196] Weshler Z, Raz A, Rosenmann E, Biran S, Fuks Z, Eldor A. (1987) Thromboxane and prostacyclin production by irradiated and perfused rat kidney. In: Prostaglandins and Lipid Metabolism in Radiation Injury. Walden TL Jr, Hughes HN. (eds.). Plenum, New York. pp. 219-224.

[197] Westenend PJ, Nooyen YA, van der Krogt JA, van Brummelen P, Weening JJ. (1992) The effect of a converting enzyme inhibitor upon renal damage in spontaneously hypertensive Fawn Hooded rats. J. Hypertension **10**: 417-422.

[198] White DC. (1975) The histopathological basis for functional decrements in late radiation injury in diverse organs. Cancer **37**: 1126-1143.

[199] Williams MV. (1986) The cellular basis of renal injury by radiation. Br. J. Cancer. **53** (Suppl. VII), 257-264.

[200] Williams MV, Denekamp J. (1983) Sequential functional testing of radiation-induced renal damage in the mouse. Radiat. Res. **94**: 305-317.

[201] Williams MV, Denekamp J. (1984) Radiation-induced renal damage in mice: Influence of fraction size. Int. J. Radiat. Oncol. Biol. Phys. **10**: 885-893.

[202] Wilson C, Ledingham JH, Cohen M. (1958) Hypertension following X irradiation of the kidneys. Lancet **1**: 9-16.

[203] Withers HR, Mason KA, Thames HD Jr. (1986) Late radiation response of kidney assayed by tubule-cell survival. Br. J. Radiol. **59**: 587-595.

[204] Wolf G, Neilson EG. (1993) Angiotensin II as a renal growth factor. J. Am. Soc. Nephrol. **3**: 1531-1540.

[205] Wong PC, Price WA, Chiu AT, Duncia JV, Carini DJ, Wexler RR, Johnson AL, Timmermans PB. (1990) Characterization of functional antagonism displayed by DuP753, an orally acting antihypertensive agent. J. Pharmacol. Exp. Ther. **252**: 719-725.

[206] Yamamoto T, Nakamura T, Noble NA, Ruoslahti E, Border WA. (1993) Expression of transforming growth factor-β is elevated in human and experimental diabetic nephropathy. Proc. Natl. Acad. Sci. USA **90**: 1814-1818.

[207] Yamanaka R, Tanaka R, Yoshida S. (1993) Effects of irradiation on the expression of the adhesion molecules (NCAM, ICAM-1) by glioma cell lines. Neurol. Med. Chir. (Tokyo) **33**: 749-752.

[208] Yoshioka T, Kawamura T, Meyrick BO, Beckman JK, Hoover RL, Yoshida H, Ichikawa I. (1994) Induction of manganese superoxide dismutase by glucorticoids in glomerular cells. Kidney Intl. **45**: 211-219.

[209] Zeigerman JH, Tulsky EG, Makler P. (1957) Post-irradiation nephritic syndrome. Obstet. Gynecol. **9**: 542-548.

[210] Zuelzer WW, Palmer HD, Newton WA Jr. (1950) Unusual glomerulonephritis in young children, probably radiation nephritis; report of three cases. Amer J. Path. **26**: 1019-1039.

Discussion with Reviewers

A.P. Evans: What types of studies should be performed to better understand the mechanisms of radiation injury in the kidney? In other words, what clinical or experimental information is lacking concerning the mechanisms of radiation injury?

Authors: Although the predominant role of the glomerular capillary endothelial cell and the mesangial cell has clearly been recognized, there is essentially no information available regarding the cellular response of these cells to irradiation. Studies need to be directed at probing radiation-induced alternations in gene expression by the use of molecular biology techniques using both *in vitro* and *in vivo* techniques. Such mechanistic data will allow the development of interventional procedures directed at ameliorating the severity of radiation nephropathy.

J.B. Reitan: Different cell types react differently to fractionation of radiation dose in radiotherapy, and tissue interaction of cell types is often overlooked in radiation pathogenesis. The appearance of radiation nephropathy may be another than the "classic" if different fractionation than the ordinary 1.8-2 Gy per fraction per day is applied. Can the uncertainty regarding the relative importance of glomerular/vascular and tubular effects be due to differences in fractionation? Is there any indication from your data or literature that hyperfractionation (smaller doses per fraction) can reduce the nephropathy problem?

Authors: We would argue that there is little uncertainty regarding the primary site renal injury in the irradiated kidney. The data presented in this review clearly demonstrate that the lesion is primarily glomerular in nature. There is no data to suggest that altering the fractionation response has any significant effect in terms of altering the pattern of the functional or morphological changes seen in the irradiated kidney. While hyperfractionation clearly results in significant sparing of the kidney, due to its extensive capacity to repair sublethal injury, such regimens still lead to the development of radiation nephropathy in some BMT patients. The kidney remains a significant dose-limiting normal tissue in radiotherapy.

V.H. Gattone: Total body irradiation (TBI) has become prominent in the clinical setting of bone marrow transplant. Based on your review of the literature, would you expect to see more favorable or detrimental renal picture after TBI in pediatric patients, especially young patients?

Authors: It is unlikely that a more favorable renal picture would be seen after TBI in pediatric patients. On the other hand, the clinical evidence for the presence of an age-effect with regard to increased susceptibility to renal injury following TBI remains equivocal. Although the best descriptions of TBI-induced nephropathy concern pediatric populations [9, 188], this might reflect closer follow up of these patients, rather than increased susceptibility of the growing kidney. Other studies have failed to show an age-effect; Lonnerholm *et al.* [105] reported renal dysfunction in 4/22 autografted children (18%) compared with 8/50 (16%) adults. Several features of radiation nephropathy suggest a careful evaluation of renal function in the young patient after TBI. The lesion is chronic, loss of renal function appears progressive, there is little significant long-term recovery of function. Improvements in cancer therapy and enhanced long-term survival of pediatric TBI patients reinforce the need for such data. Any additional nephrotoxic insult following TBI should be avoided if possible.