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RADIATION NEPHRITIS

Radiation nephritis has not had wide attention in the medical literature. Many physicians have erroneously considered the kidney to be resistant to the effects of irradiation. This illusion is partly due to the fact that the clinical signs of renal impairment are often subtle and therefore overlooked, or are mistakenly attributed to the primary condition for which radiotherapy was given. Furthermore, many patients die of their primary disease (usually a malignancy) before clinical evidence of nephritis occurs.

Because of the widespread use of radiotherapy in practice today, a review of the previous experience with radiation nephritis was undertaken, and two patients with radiation nephritis are presented. Both were studied in detail, particularly with respect to their refractory anemia.

CASE REPORTS

Case 1—R.S.B. (HFH #119 59 04), a 30 year old white man, had a left orchidectomy for seminoma in June of 1959. Intravenous pyelography prior to radiotherapy depicted a marked displacement of the left ureter and hydronephrosis in the upper pole of the left kidney. The right kidney was slightly larger than normal, with a bifid pelvis and ureters. No blood chemistry values were available at that time.

Radiotherapy was initiated on 2/4/60 at another hospital. Treatment was given with 250 KV 3 mm Cu half value layer to several fields including the peri-aortic and inguinal nodes. Because of displacement of the upper ureters side-by-side fields were used in the upper abdomen. The best estimate that can be made of kidney dose is 3,100r in 20 treatments to the left, and 2,100r in 14 treatments to the right. The entire course of therapy was completed in 14 weeks. A comment was made of an unusually severe skin reaction on the left. Unfortunately the records available are insufficient to permit more accurate estimates.

The patient remained well until 9/29/61, when he received further radiotherapy (2,400r in 7 weeks) to the mediastinum for recurrent meta- until July, 1965, when he was referred to the Henry Ford Hospital because

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of severe generalized throbbing headaches, unrelieved by aspirin. Ten days stases, at another hospital. The patient returned to apparent normal health prior to the examination, he had noted blurred vision, and daily epistaxis. Moderate dyspnea on effort, lassitude, and nausea were present, but no urinary symptoms or hematuria. There was no personal or family history of hypertension or renal disease.

Physical examination revealed a pale young man with a trace of pedal edema. The blood pressure was 220/130 mm. Hg. and there was bilateral papilledema with retinal hemorrhages and exudates. The heart was moderately enlarged; no cardiac murmurs were heard. No abdominal masses were palpated, but radiation changes of the skin of the abdomen were visible. This clinical picture suggested the diagnosis of malignant hypertension and raised the question of radiation nephritis as an underlying cause.

Laboratory studies showed the following: hemoglobin 6 gm/100 ml., Hct. 22 vol. per cent; and white blood count 5,450/mm.^{3} with 73 per cent neutrophils, and 15 per cent lymphocytes. The platelets were plentiful and a reticulocyte count was 4.3 per cent. The urinary specific gravity was 1.005. Proteinuria was present and microscopy of the sediment revealed a few erythrocytes and leukocytes, and scanty casts. The blood urea nitrogen (BUN) was 68 mg/100 ml., the creatinine, 9.2 mg/100 ml., and the creatinine clearance, 8.3 ml/minute (volume 2,720 cc.). The total serum proteins were 5.7 gm/100 ml., (albumin 2.91 gm/100 ml., alpha 1 globulin 0.53 gm/100 ml., alpha 11 globulin 0.68 gm/100 ml., beta globulin 0.90 gm/100 ml., and gamma globulin 0.68 gm/100 ml.). The serum electrolytes were: sodium 131 mEq/L., potassium 3.3 mEq/L., chloride 95 mEq/L., CO_2 combining power 19.2 mEq/L. The serum calcium was 8.0 mg/100 ml. and the serum phosphorus 5.3 mg/100 ml. The alkaline phosphatase was 6.4 Bodansky units and the uric acid was 9.9 mg/100 ml.

The chest X-ray revealed slight cardiomegaly, and the electrocardiogram showed left ventricular hypertrophy. A retrograde pyelogram ruled out an obstructive uropathy, although the left kidney appeared small with blunted calyces. A urine culture was sterile.

A month later symptoms of hypertensive cardiac failure appeared. Specific treatment was given for hypertension, and the anemia was treated by blood transfusions. The patient became clinically worse. The BUN was 129 mg/100 ml., and the creatinine was 15.9 mg/100 ml. Proteinuria persisted. Liver function tests were normal with the exception of a slightly prolonged prothrombin time. An upper gastrointestinal X-ray was unremarkable, but the small bowel series demonstrated a prolongation of the transit time. An I^{131} renogram revealed marked bilateral renal impairment.

Intermittent dialysis was initiated, but rapid progress of congestive failure led to death on 8/29/66. Table 1 summarizes the hematologic data obtained on this patient in February 1966, prior to the use of dialysis. The bone marrow sample was obtained from the sternum, and presumed to be free of significant radiation effect.

At post mortem examination there was no evidence of recurrent seminoma. The serous cavities contained excessive amounts of serosanguineous fluid. The heart weighed 650 gm., and showed bi-ventricular hypertrophy. The lungs were congested. The right kidney weighed 80 gm., the left 60 gm. There was a bifid right ureter. The right renal capsule was thickened and stripped with difficulty. The left kidney was surrounded by adherent fibrous tissue in which was imbedded the left adrenal gland. The left renal artery was partially occluded by an adherent thrombus (Fig. 1). Histologically the glomeruli were decreased in number and showed irregular thickening of their basement membranes. The tubules depicted alternate areas of dilitation and atrophy. Much interstitial fibrosis was seen through-

TABLE 1. HEMATOLOGICAL DATA

	Case 1 (R. S. B.)	*Case 2 (W. A.)*
RBC (ml./mm³)	2.1	2.31
Hgb. (gm./100 ml.)	6.0	6.4
Hct. (vol. %)	19	20
Retic. ct. (%)	3	1.6
WBC (mm³)	5,250 (Polys. 58%)	5,050 (Polys. 57%)
Platelets (mm³)	210,000	Adequate numbers
Bone marrow	Hypocellular fatty particles	Generally hypocellular; myeloid : erythroid ratio = 3.8 : 1
Serum iron (μg/100 ml.)	80	95
T.I.B.C. (μg/100 ml.)	202	315
Plasma iron clearance (Normal T ½ = 90 min.)	128	270
Plasma iron turnover (Normal = 32-52 mg. iron/d.)	21.7	9.24
RBC utilization of iron (Normal = 80%)	42.6	48.5
RBC turnover of iron (Normal = 30-50 mg. iron/d.)	9.24	4.48
Plasma erythropoietin activity	Not done	Zero

out. Endarteritis fibrosa of the renal arterial vessels was present. All these changes seemed to be more marked in the left kidney. The myocardium appeared to be hypertrophied. The lungs revealed changes of organized fibrosis and numerous hemosiderin-laden macrophages. Hemosiderin was also prominent in the spleen and liver where it was present in macrophages and hepatic parenchymal cells. The sections of vertebral bone depicted patches of sclerotic bone with absence of hematopoiesis.

Comment on Case 1

After a latent period of five years from the start of radiotherapy, anemia, hypertension, proteinuria, edema, and impaired renal function were observed. Symptoms were due mainly to the elevated blood pressure, which with the anemia and azotemia were severe and refractory. At the onset of symptoms the BUN was 68 mg/100 ml., and hemoglobulin 6 gm/100 ml. Left ventricular failure, hypertension, and uremia led to death 12 months after symptoms started. The autopsy findings showed the gross and microscopic changes previously described in chronic radiation nephritis.

Case 2—W.A. (HFH #043 78 40), 21 year old white male, printing press operator, was found to have a neuroblastoma of the left adrenal gland at age three months. Immediate orthovoltage radiotherapy was begun, and the patient was given an estimated tumor dose of 1,600r (20 treatments in five weeks). Two months after the first course, he was given a second course of an estimated tumor dose of 1,250r (16 treatments in three weeks). The field size varied from 8 by 10 cm. to 15 by 15 cm. At the age of 11 months, the mass in the left upper quadrant could no longer be felt and the liver was normal size.

The patient did well until the age of 3½ years, (Fig. 2) when another mass was palpable in the upper abdomen, and an intravenous pyelogram depicted displacement of the left kidney. A third course of roentgen therapy was administered, delivering an estimated tumor dose of 1,400r (13 treatments in two weeks).

The patient again did well until the age of 11 years, at which time it was established that his growth was below the lower limit of normal. At age 14, occasional episodes of abdominal pain, nausea, and vomiting developed superimposed upon persistent anorexia. At this time, the patient showed a striking degree of dwarfing in the abdomen and lower thorax where he had received the radiation therapy. The hemoglobulin was found to be 10.5 gm/100 ml. and the blood urea nitrogen (BUN) 60 mg/100 ml. Despite a normal urinalysis and blood pressure, the possibility of radiation nephritis was entertained. A program of high fluid, low salt, and low pro-

tein diet was initiated. At age 15, (Figs. 3, 4) the patient was admitted to the hospital in uremia. The blood pressure was 118/90. The hemoglobulin was 9.7 gm/100 ml. The BUN was 81 mg/100 ml., and there was 1+ proteinuria. An intravenous pyelogram revealed prompt excretion of dye on the right without gross abnormality, but only questionable visualization of the left kidney. The patient continued having intermittent episodes of azotemia for the subsequent five years, promptly relieved by increasing the fluid intake on each occasion. The lowest recorded BUN during this time was 32 mg/mm^3.

During hospitalization at age 20, the following pertinent data were obtained: blood pressure 120/100 mm. Hg.; hemoglobulin 9 gm/100 ml.; white blood count 9,950/mm^3; and the differential white count in per cent, bands 13, neutrophils 73, lymphocytes 9, and monocytes 5. The platelets were adequate. Blood chemistry determinations included the following: BUN 94 mg/100 ml., creatinine 5.2 mg/100 ml., sodium (Na) 149 mEq/L., potassium (K) 5.4 mEq/L., chloride (Cl) 111 mEq/L., and the CO_2 combining power 13.5 mEq/L. The serum calcium was 9.6 mg/100 ml., the serum phosphorus 6.6 mg/100 ml., the alkaline phosphatase 16.2 Bodansky units/100 ml. and the total serum bilirubin 0.32 mg/100 ml., the direct reacting fraction being 0.16 mg/100 ml. Serum protein electrophoresis showed: a total protein of 8.0 gm/100 ml., with 4.03 gm. of albumin, 0.32 gm. of alpha 1 globulin, 0.90 gm. of alpha 11 globulin, 1.08 gm. of beta globulin, and 1.65 gm. of gamma globulin. The urinalysis revealed a specific gravity of 1.006, a pH of 5, and a protein of 1+. There were 1-2 WBCs and 0-2 RBCs found in the sediment. The urine culture was negative. The creatinine clearance was 4 ml/min. (volume 530 cc.). The 24-hour urine calcium was 9 mg/vol. and phosphate 375 mg/vol. (volume 1,020 cc.).

The spine and pelvis X-rays showed post-radiation changes, and some evidence of secondary hyperparathyroidism with erosions in the left femur and in the clavicles.

His most recent admission at age 21 occurred in September, 1966. The patient complained of leg weakness and appeared pale. Pertinent hematological data are presented in Table 1, under case 2. The bone marrow was obtained from a non-irradiated site. Urinalysis showed a specific gravity of 1.005, gross proteinuria, and a few leukocytes in the sediment. The BUN was 114 mg/100 ml. and the serum creatinine was 10.8 mg/100 ml. The serum electrolytes were: Na^+ 142, K^+ 5.3, Cl^- 112, CO_2 12 mEq/L. The serum calcium was 9.0 mg/100 ml., and the PO_4 7.0 mg/100 ml. Serum protein electrophoresis now showed a total of 6.2 mg/100 ml. with a uniform mild decrease in all fractions from the determinations of the previous

year. The serum oxalic glutamic acid, bilirubin, and bromsulphaphthalein values were normal. The prothrombin time was 15 seconds compared with a control of 12 seconds. The serum carotene was 8 μg/100 ml. The D-xylose test showed 0.69 gm. excretion (normal, 4.0 gm.) and the Schilling test yielded 6.5 per cent excretion of the administered cyanocobalamin in a total urine volume of 2,300 cc. (normal 8% or greater). Several stools were negative for occult blood. Mucosal biopsy and X-rays of the small bowel were not obtained due to the precarious clinical status.

The patient was treated with blood transfusions, low protein diet, and high water intake, with a subsequent fall in the BUN to 45 mg/100 ml.

Currently the patient is living a sedentary existence, under strict dietary and fluid instructions.

Comment on Case 2

This patient was first found to have evidence of impaired renal function 11 years after last receiving radiotherapy. There had been no clinically recognizable acute radiation nephritis in the early post-irradiation period. His subsequent course has been one of progressive deterioration of renal function with a slowly rising diastolic level of blood pressure and cardiomegaly, but without an indication of malignant vasculitis so far. Of coincidental interest is the evidence of intestinal malabsorption, reflected in the very low serum carotene level, the markedly impaired D-xylose excretion, and the mildly abnormal Schilling test result. The possibility exists that late functional impairment of absorption as a sequela of radiation damage to the small bowel is also present.

HEMATOLOGIC CONSIDERATIONS

The refractory and often severe anemia that accompanies radiation nephritis may contribute significantly to the patient's symptoms and have an unfavorable influence on the length of his survival. The severity of the anemia in radiation nephritis tends to be greater than in other forms of renal insufficiency.[1] The physician must face the issue of when and to what extent blood replacement should be used in the presence of renal failure. Often this is a difficult decision to reach because of the complexity of factors involved.

The etiology of the anemia of radiation nephritis is multifactorial. One component is the element of shortened red cell survival, which has been described in association with chronic renal insufficiency.[2,3] Studies to demonstrate low grade hemolysis usually require the use of isotope tagging of red cells, since simpler signs of red cell destruction are absent. The presence

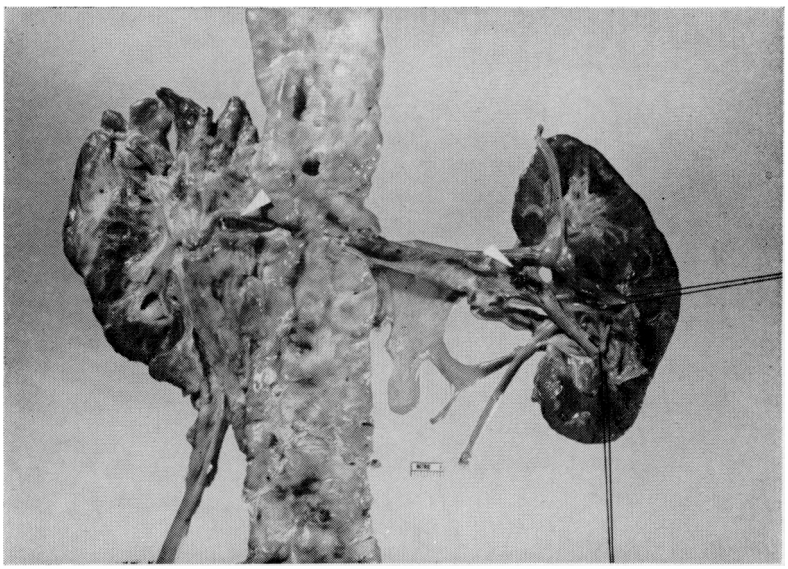


FIG. 1. Gross autopsy specimen from Case no. 1. Posterior-anterior view of the kidneys attached to the aorta by their vascular pedicles. The dense perirenal fibrosis on the left made dissection all but impossible; the left adrenal is imbedded in this tissue. The severe loss of kidney mass bilaterally can be appreciated. Note absence of hydronephrosis and hydroureter, and moderate to marked arteriosclerosis of aorta. The arrows point to thrombi in the left renal artery and a lobar branch of the right renal artery respectively.

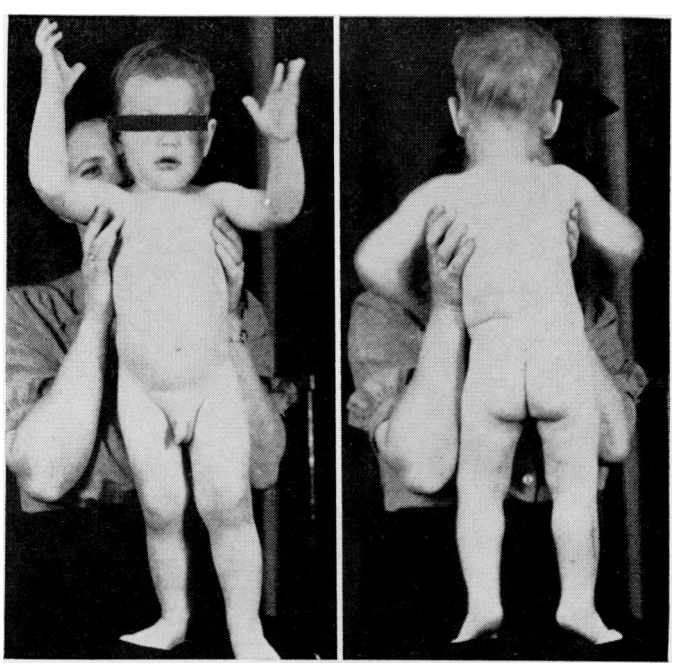
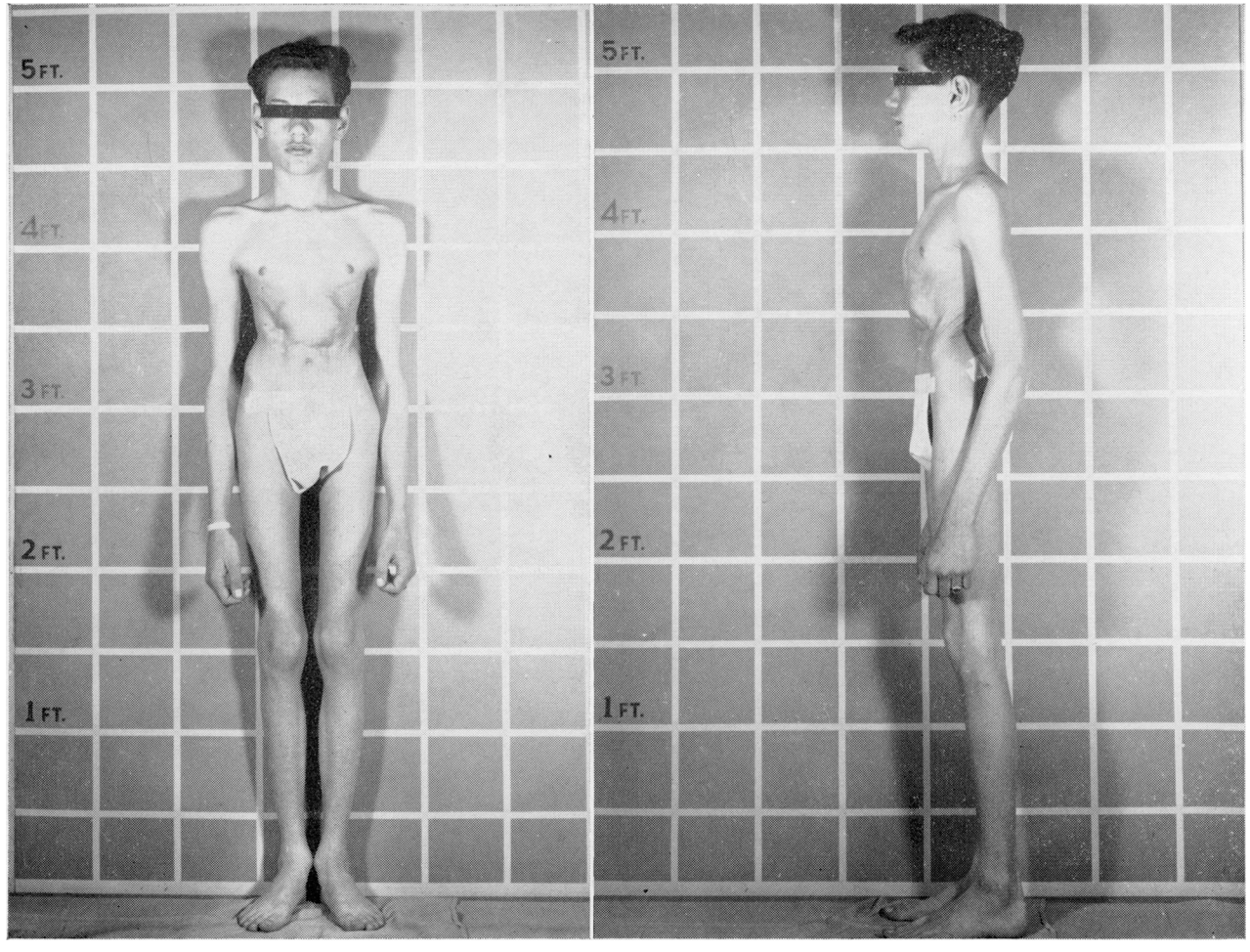


FIG. 2. Case 2. The patient (WA), at age 3½ years. (The Figure is reprinted from the article, "Neuroblastoma" by S. M. Beck and P. J. Howard, by courtesy of *The American Journal of Diseases of Children,* 1951, *82,* 325-334.)



FIGURES 3 and 4. The patient (WA), at age 15 years. Note the disproportionate development of the trunk and extremities as a result of radiation effects on the lower dorsal and lumbar vertebra and pelvic bones. The chronic radiation skin changes can be seen on the abdomen.

of burr cells, so common in the peripheral smear of patients with uremia, may be an indicator of microangiopathic lesions causing trauma to red cells in their course through the small blood vessels. This possibility was advocated by Brain, Dacie, and Hourihan,[4] who have also noted the presence of schistocytes (helmet cells, fragment forms) in the blood of patients with glomerulonephritis and malignant hypertension.

The association of defective erythropoiesis with chronic renal insufficiency has been previously established,[5] and possibly is the most important factor. It is generally characterized by marrow red cell hypoplasia, with sparing of granulocytic and megakaryocytic elements, although occasionally the marrow is normal or even hyperplastic. Random aspiration sites may differ in their appearance due to an inherent "spotty" nature of the marrow in this disorder, and probably accounts for the disparity in reported findings. Ferrokinetic studies consistently show an impaired plasma iron turnover rate and a poor utilization of iron by developing red cells in renal insufficiency,[6] and our patients' results conform to this pattern (see Table 1). It would be convenient to ascribe this depression of erythropoiesis to the lack of active circulating erythropoietin, since this has been observed in most cases of renal failure.[7,8] No discernible erythropoietin could be found in one of our cases studied.* However, lack of an activator of erythropoiesis is not solely responsible for the hypofunction of the bone marrow, since Erslev[10] has shown that in experimentally induced renal failure in rabbits there is no response to infusions of a potent erythropoietic extract. The mechanism is, therefore, incompletely understood. This is particularly so in patients with chronic renal disease and refractory anemia, but without azotemia, who generally have normal or increased levels of plasma erythropoietin.[7,11]Failure of adequate marrow response has been ascribed to an inhibition of normal erythropoietin stimulation by ill-defined circulating substances presumed to be present in azotemia, but this hypothesis is unconfirmed.

In radiation nephritis there is the further consideration of damage to significant portions of the hematopoietic marrow included in the irradiated field. Estimated from statistics on bone volumes recorded by Trotter,[12] at least 50 per cent of the normally active marrow in our cases was irradiated. Although significant marrow injury due to either myelotoxic drugs or to extensive irradiation of hematopoietic marrow usually produces pancytopenia, in our cases the granulocytes and platelets were not appreciably affected.

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* The plasma erythropoietin assay of Adamson, *et al.*[9] was performed by Dr. Joseph W. Eschbach at the Univ. of Washington, Seattle, Wash. The test animals were five protein-starved, hypoxic, polycythemic mice.

DISCUSSION

The possibility of renal damage resulting from therapeutic irradiation was pointed out soon after discovery of roentgen rays by Roentgen[13] in 1895. Although the effects of ionizing radiation on the kidney have been investigated in animals, there has remained a widespread belief that renal tissue was remarkably insensitive to radiation damage.

Patho-physiology

In 1926 and 1927, Hartman, Bolliger, and Doub[14–16] studied the effects of radiation on the renal tissue of dogs. They showed that the renal parenchyma was sensitive to radiation and that nephritis could be produced by a broad range of doses, in some instances so low that epilation did not follow the exposure. The lesions produced closely resembled the pathologic findings that were recognized later in humans. Others[17,18] reported that pathologic changes noted in the kidneys following radiation exposure were of a progressive nature. Desjardins[19] considered the kidney to be less sensitive to irradiation than lymphoid tissue, skin or liver, but more sensitive than muscle and nervous tissue. In 1942 Warren[20] reviewed the current literature on radiation nephritis and emphasized that renal tissue should be considered radiosensitive. Employing the electron microscope, Scherer and Vogell[21] in 1957 observed changes in the mitochondria of the hepatic and renal cells following total body irradiation of mice.

Redd[22] has recently described primarily glomerular damage after renal irradiation, but Bianchi[23] found the major change in the tubules in experimental studies. Indeed, clinical cases show this difference in the lesions produced by irradiation. Rubenstone and Fitch[24] did much to clarify the dilemma in an excellent clinicopathologic study in which they demonstrated the variability of lesions that are produced. Gross perirenal or capsular fibrosis frequently occurs, but there may also be one of three types of intrarenal change: (1) interstitial fibrosis of the cortex with atrophy of the tubules, (2) glomerular changes with cellular proliferation, or hyaline crescent formation, or total destruction by fibrosis, and (3) intralobar and intralobular arteriolar damage characterized by fibrinoid necrosis of the vessel wall, and lipid-filled histiocyte deposits in the media and intima. The differences in the type of pathologic response are apparently not dose related.

Rosen[25] and co-workers studied two fatal cases of acute radiation nephritis by means of electron microscopy of renal biopsy and autopsy specimens. They demonstrated the presence of a basement membrane-like material on the endothelial side of the glomerular capillaries. Occasionally entrapment

of endothelial cells in this lamina densa-like material was seen. They are of the opinion that this glomerular capillary lesion represents the dominant and initial pathologic change produced by irradiation of the kidney.

The most recent major review of the pathophysiology of radiation effects on the kidney was by Mostofi.[26] Cognizant of Rosen's electron microscopic findings, and conceding that in a few instances the glomeruli are involved early, he concludes from his own extensive study that the damage to the endothelium of renal blood vessels and to the epithelium of the convoluted tubules is the primary and basic lesion. Atrophy of tubules, interstitial fibrosis, and sclerosis of vessels ensue, followed later by glomerular fibrosis and hyalinization.

Clinical experience

Domagk[27] in 1947 was probably the first to describe a case of fatal renal damage: a nine year old girl who erroneously received a large dose of unfiltered radiation over the kidney area in the treatment of mesenteric lymphadenitis. Other reports of fatal radiation nephritis occurring from four to twelve months after exposure have been by Zuelzer[28] (three cases), Grossman,[29] Beck,[30] and Schreiner and Greendyke.[31] The radiation was administered for adrenal, ovarian, and renal malignancies.

Another group of case reports is concerned with the late appearance of chronic radiation nephritis, often accompanied by severe hypertension.[32,33] In 1944 Dean and Abels[34] reported the development of hypertension in a 20 year old woman, eight years after intensive irradiation of a lymphomatous mass in the left upper quadrant. Removal of the shrunken left kidney resulted in correction of the hypertension. Of particular interest in the light of our case, was the report of Levitt and Oram[35] describing a man with severe hypertension that developed after abdominal radiation for metastatic seminoma of the testis. Decreased function of the left kidney was demonstrated, and nephrectomy relieved the hypertension. Wilson[36] and co-workers report that radiation to the kidney in man might produce hypertension without the florid histological changes. Two other cases have been reported within the past five years in which the renal radiation damage was predominantly unilateral, and nephrectomy reversed the hypertension.[24,37]

Different degrees of renal damage, ranging from the early occurrence of advanced renal sclerosis to subclinical nephritis discovered in the post-irradiation period, have been described by other authors.[38-40] Of interest in this regard, Avioli[41] and co-workers in 1963 consistently showed alteration of renal function as an acute result of kidney irradiation in 10 patients under treatment for intra-abdominal malignancy. The renal plasma flow pro-

gressively fell after 400 rads exposure, whereas the glomerular filtration rate (GFR) transiently decreased at 400 rads, but increased above pre-irradiation levels after 550 to 1,625 rads. Cumulative doses of 2,000 to 2,400 rads resulted in a progressive decrease in GFR which persisted for at least a year. Tubular function as measured by the maximum excretory capacity for para-aminohippuric acid (TM_{PAH}) was variable in its response. These changes occurred without any associated abnormality in the clinical signs and commonly used laboratory tests indicative of renal disease. Most clinical reports, however, fail to draw a clear relationship between the severity of renal damage and the dose of radiation received.

The classic study of Luxton[42] in 1953 was responsible for reviving interest in the problem of radiation nephritis. He reported on a group of patients who developed radiation nephritis following treatment by roentgen ray "bath" for seminoma of the testis. Approximately 20 per cent of the patients exhibited evidence of renal damage. He emphasized the hazard of damage to one or both kidneys from a dose exceeding 2,300r given within a period of five weeks or less.

Preceding December 1966, 122 cases of radiation nephritis had been reported in the literature. British radiotherapists use more widespread radiation to the abdomen than do the Americans. This would tend to increase the cases in which both kidneys received significant radiation and may account for the greater incidence of nephritis in the British literature.

Clinical types of radiation nephritis

Many cases of chronic radiation nephritis are probably overlooked because of the long latent period. A long-term follow-up of 54 cases collected by Luxton[43] forms the current basis for the subdivision of radiation nephritis into four clinical types. While the majority of cases can be classified according to these four types, some pass through several phases in their evolution.

1. *Acute radiation nephritis* characteristically appears six months to a year after irradiation. Although the development of symptoms is gradual, most patients are incapacitated within one month. The most common clinical features are related to hypertension, congestive heart failure, uremia, and marked anemia. A rise in the BUN above 100 mg/100 ml. at any time during the first three months or the development of pleural effusions without generalized edema are signs of a poor prognosis. The urinary changes consist of proteinuria, rarely greater than 5 gm. per day, and epithelial, hyaline, or granular casts with occasional erythrocytes in the sediment. The blood pressure varies; usually it is highest within six months after the

onset of symptoms. A severe normochromic, normocytic anemia, refractory to all forms of therapy is the rule in acute, as well as chronic radiation nephritis in the presence of azotemia. In Luxton's series, five of the thirteen patients died within four months after onset of symptoms, and one after a year. Death was due to hypertension, cardiac failure, hypertensive seizures, and renal failure. The remainder improved about six months after the onset of symptoms, but were left with evidence of chronic nephritis.

2. *Chronic radiation nephritis* may follow acute radiation nephritis or may develop insidiously 18 months to several years after irradiation. The clinical features include hypertension, proteinuria, cylindruria and anemia, and impaired renal function. In some instances there has been no further deterioration, but most patients with the primary type develop progressive hypertension and slowly increasing azotemia. There is a suggestion that the ultimate prognosis is better in the insidious type, but this was not so in either of our cases who fall into this clinical category.

3. *Benign hypertension* was the clinical picture in four patients from Luxton's series. Persistent hypertension and slight proteinuria are the only findings and seem to develop on the average about eight months after the start of radiotherapy.

4. *Late malignant hypertension* may evolve from any of the preceding clinical types or appear *de novo* in explosive fashion. Four of Luxton's patients developed this picture long after radiotherapy. Death usually occurred within a few weeks.

Prevention

Once radiation nephritis occurs, no specific measures seem to modify the course, although the possible benefit from corticosteroids given concomitantly with the radiotherapy or in the early phase of clinical radiation nephritis has not been evaluated to date.[44] Furthermore, removal of a unilaterally damaged kidney may be curative of the hypertension, but efforts directed toward prevention of radiation damage to the kidney are more worthy than attempts at reparation.

If a dose of 2,300r or more is to be delivered to both kidneys, the risk of subsequent renal failure can best be minimized by shielding one third of the total mass of healthy kidney tissue.[45] Therefore, knowledge of the exact location and functional status of the kidneys is an obvious prerequisite to initiating abdominal radiotherapy. Certain clinical factors predispose to radiation nephritis, such as congenital renal lesions, malposition of one or both kidneys, tumor masses adjacent to the kidney which may interfere with its blood supply, and pre-existing acquired kidney disease.

Asscher[46] has shown in rats that intraperitoneal injections of cysteamine (decarboxylated cysteine) prior to irradiation of the kidneys significantly protects them from the damage demonstrated in saline treated controls. However, since cysteamine also prevents depilation and radiation sickness, it is probable that this substance produces a temporary radio-resistance of the whole organism, thereby impairing the therapeutic effect on neoplastic tissue.

Recently Steckel and co-workers[47] have demonstrated striking renal protection to radiation effects in dogs by infusing the renal artery with epinephrine via a percutaneous catheter just before and during irradiation. They also demonstrated the practicality of using this adjunctive technique clinically in one patient in whom the catheter was kept in situ for 16 days while radiotherapy was given. If further experience validates the efficacy and safety of this method, it will undoubtedly require a reassessment of the safety limits of radiation dosage cited above.

SUMMARY

Two patients with chronic radiation nephritis, one of whom died of renal failure and hypertension, are reported. Anemia in this disease is usually more severe than in other forms of chronic nephritis, and has multiple causes. Ferrokinetics and plasma erythropoietin assay indicated an erythropoietic depression. The associated radiation of vertebral and pelvic marrow contributes an additional effect not seen in other types of renal failure.

Recognition of radiation nephritis is important because of the possible benefit from cortico-steroid therapy in the evolutional stage, and because removal of a unilaterally damaged kidney may cure the associated hypertension. Better prophylactic techniques for protection of the kidney are under investigation, and may eventually reduce the incidence and severity of this iatrogenic disorder.

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