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Radiation Injury of the Brain

Peter E. Valk1,2 and William P. Dillon2

The clinical, radiologic, and pathologic findings in radiation injury of the brain are reviewed. Late radiation injury is the major, dose-limiting complication of brain irradiation and occurs in two forms, focal and diffuse, which differ significantly in clinical and radiologic features. Focal and diffuse injuries both include a wide spectrum of abnormalities, from subclinical changes detectable only by MR imaging to overt brain necrosis. Asymptomatic focal edema is commonly seen on CT and MR following focal or large-volume irradiation. Focal necrosis has the CT and MR characteristics of a mass lesion, with clinical evidence of focal neurologic abnormality and raised intracranial pressure. Microscopically, the lesion shows characteristic vascular changes and white matter pathology ranging from demyelination to coagulative necrosis. Diffuse radiation injury is characterized by periventricular decrease in attenuation on CT and increased signal on proton-density and T2-weighted MR images. Most patients are asymptomatic. When clinical manifestations occur, impairment of mental function is the most prominent feature. Pathologic findings in focal and diffuse radiation necrosis are similar. Necrotizing leukoencephalopathy is the form of diffuse white matter injury that follows chemotherapy, with or without irradiation. Vascular disease is less prominent and the latent period is shorter than in diffuse radiation injury; radiologic findings and clinical manifestations are similar. Late radiation injury of large arteries is an occasional cause of postradiation cerebral injury, and cerebral atrophy and mineralizing microangiopathy are common radiologic findings of uncertain clinical significance. Functional imaging by positron emission tomography can differentiate recurrent tumor from focal radiation necrosis with positive and negative predictive values for tumor of 80–90%. Positron emission tomography of the blood-brain barrier, glucose metabolism, and blood flow, together with MR imaging, have demonstrated some of the pathophysiology of late radiation necrosis. Focal glucose hypometabolism on positron emission tomography in irradiated patients may have prognostic significance for subsequent development of clinically evident radiation necrosis.

Recognition of injury to normal brain as a complication of cerebral radiation therapy has increased since the advent of noninvasive imaging and the use of more aggressive schemes of irradiation and chemotherapy. This probably reflects a true increase in the prevalence of cerebral radiation injury, as well as an increase in the rate of diagnosis. Delivery of higher radiation doses causes more injury to normal as well as to abnormal tissue, while improvement in long-term survival increases the time available for development of late radiation effects. CT and MR imaging have increased the recognition rate of radiation injury when it occurs.

Cerebral radiation injury has been classified according to time of appearance of symptoms after therapy. Acute injury appears during radiation therapy as a transient worsening of symptoms, and has little prognostic significance. Early delayed injury occurs a few weeks to 3 months after therapy and also is transient in most cases. By contrast, late radiation injury, which occurs a few months to 10 or more years after therapy, is irreversible, progressive, and sometimes fatal, and constitutes the major, dose-limiting complication of cerebral irradiation [1]. There are two main forms of late radiation injury, which may occur separately or together: focal injury

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and diffuse white matter injury. The basic pathology is probably the same in both instances, but the clinical manifestations and radiologic findings of the two syndromes differ sufficiently to warrant separate consideration.

Prevalence of Symptomatic Late Radiation Injury

The prevalence of radiation injury is difficult to determine and few reliable figures have been reported. Marks et al. [2] followed a population of 139 patients who had received photon therapy for primary brain and pituitary tumors. Seven patients (5%) developed histologically documented radiation necrosis. Marsa et al. [3] found necrosis in 10 (15%) of 66 autopsied patients, out of a total population of 256 patients (4%) irradiated for tumor. These figures are bound to be underestimates, since patients who died without autopsy and patients who survived without a tissue diagnosis were not included. Hohweiler et al. [4] studied 76 patients with primary brain tumors and found 10 patients with clinical and CT evidence of necrosis, including eight who were alive and had no evidence of tumor. The overall prevalence was 14%, with a 50% prevalence in surviving patients. An even higher rate of neurologic complications has been reported after chemotherapy combined with prophylactic cranial irradiation for small cell carcinoma of the lung. Frytak et al. [5] found neurotoxicity in 37% of patients who survived 1½ years or longer, and Laukkanen et al. [6] reported neuropsychological impairment and CT abnormalities in seven of 12 patients who survived 2 years or more. Imaging abnormalities without clinical manifestations are more frequent still, but the clinical significance of such findings has not been determined and prospective studies of irradiated patient groups are needed.

The term “injury” is used here to describe all degrees of injury, from asymptomatic edema to necrosis. The most frequent clinical, pathologic, and radiologic features of symptomatic radiation- and drug-related cerebral injury are summarized in Table 1.

Focal Injury

Clinical Manifestations

Focal radiation injury of the brain was recognized clinically by Fischer and Hoffelder [7] in 1930. Focal necrosis presents as a mass lesion, with focal neurologic abnormalities and evidence of raised intracranial pressure. Unilateral motor or sensory loss, aphasia, disturbance of consciousness, and seizures are common. Although symptoms may develop from 3 months to more than 10 years after irradiation, approximately 70% of all cases occur during the first 2 years [1]. The clinical course is unpredictable. Changes are usually irreversible and frequently progressive, and extension of necrosis leads to death in many cases [1, 8]. However, resolution of a mass lesion is encountered occasionally [9], and some patients stabilize clinically with permanent neurologic deficits [10, 11]. Surgical removal of the necrotic mass is the treatment of choice and may be lifesaving [11–13].

Radiologic Findings

The angiographic [9, 12, 14] and CT [10, 11, 15–17] features of focal radiation necrosis are well known. On angiography, the injured area most commonly appears as an avascular mass, with no specific features, and in some cases the angiogram is normal. Unenhanced CT shows a low-density region, with surrounding vasogenic edema and variable mass effect. Following contrast administration, irregular enhancement is seen at the margins of the mass.

These radiologic features can be interpreted most readily when injury follows irradiation of an extracerebral or extracranial lesion (Fig. 1) [10, 11, 14] or when it occurs at a distance from an intracerebral tumor [2]. When injury occurs at the site of an intracerebral tumor, it is not possible to differentiate the effects of radiation from those of residual or recurrent tumor on the basis of angiographic or CT findings. MR imaging provides no additional differentiating information (Fig. 2). MR spectroscopy may become useful in the future, but limited volume resolution at present precludes its use in most patients. In both conditions, increase in tissue water content causes increase in mobile hydrogen density and prolongation of T1 and T2 relaxation times. These changes result in decreased signal on T1-weighted images and increased signal on T2-weighted and proton-density images (Fig. 3). The blood-brain barrier (BBB) defect results in enhancement following the administration of paramagnetic contrast material.

When necrosis follows irradiation for cerebral tumor, it

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<th>TABLE 1: Clinical Syndromes of Treatment-Related Cerebral Injury</th>
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* Necrosis is the most common finding when biopsy or autopsy is performed in diffuse white matter injury with frank dementia. However, the pathologic findings are unknown in most patients.
occurs most frequently at or near the site of the tumor [18], even after whole-brain irradiation. Tissue adjacent to the tumor appears to be rendered more susceptible to injury, possibly by the vasogenic edema that usually surrounds the lesion [19]. However, focal injury also can occur at a distance from the primary lesion, and radiation necrosis contralateral to the lesion has been described after whole-brain irradiation [2].

Necrosis is the most common clinically recognized form of focal radiation injury, but recent studies after focal charged-particle therapy have revealed a higher prevalence of lesser, subclinical injury [20]. MR (Fig. 3) and CT changes are similar to those of radiation necrosis, with the exception of contrast enhancement, which is not seen in these asymptomatic patients. In our experience, an asymptomatic focal increase in signal on T2-weighted MR images has been a common incidental finding following focal or limited-field photon irradiation.

Hemorrhagic focal radiation injury has been reported by Woo et al. [21]. They found radiation-induced telangiectasia at the margin of a region of cerebral hemorrhage, in associa-

Fig. 1.—Focal radiation necrosis following extracerebral irradiation. Lesion detected 6 months after irradiation of overlying plasmacytoma of the skull. Contrast-enhanced CT scan shows left frontal hypodensity with central area of enhancement. Diagnosis was confirmed by surgical biopsy.

Fig. 2.—A and B, Focal radiation necrosis. Contrast-enhanced CT scan (A) and proton-density MR image, 2000/33 (B), 11 months after external irradiation and interstitial brachytherapy of glioblastoma multiforme. CT shows hypodensity in left frontoparietal region, with central area of ring enhancement. MR shows diffuse increase in signal in region of CT hypodensity, consistent with edema. On follow-up, there was no further deterioration and the patient was alive 9 months later without antitumor therapy. This excludes a diagnosis of tumor recurrence and establishes radiation necrosis as the most probable cause of CT change.

C and D, Recurrent malignant glioma. Contrast-enhanced CT scan (C) and proton-density MR image, 2000/33 (D), 8 months after external irradiation and interstitial brachytherapy of anaplastic astrocytoma. CT shows left occipital hypodensity and mass lesion with irregular contrast enhancement at margins. MR shows diffuse increase in signal in region of CT hypodensity, consistent with edema. The patient continued to deteriorate, clinically as well as radiologically, and antitumor chemotherapy was commenced 3 weeks later with positive response. Deterioration with response to chemotherapy established diagnosis of tumor recurrence.

The CT and MR findings in these two patients are nonspecific and do not help differentiate radiation necrosis from recurrent tumor.
tion with evidence of late radiation necrosis. We have now seen five cases of radiation-associated focal hemorrhage on MR, unaccompanied by other manifestations of radiation necrosis. These patients had been treated with conventional doses of photon radiation. MR revealed multiple foci of hemosiderin, mixed with subacute hemorrhagic change (Fig. 4). Some of the lesions appeared calcified and showed contrast enhancement, similar to cryptic vascular malformations. These lesions probably were radiation induced, as they occurred only within the irradiated volume of brain and in one case were not present before radiation therapy.

**Pathologic Findings**

Focal necrosis affects white matter more severely than gray [10, 19, 22]. Hyalinization and fibrinoid necrosis of small arteries and arterioles are the most characteristic findings, together with narrowing of the lumen and endothelial prolif-

eration (Fig. 5). A perivascular mononuclear inflammatory response may be seen. White matter changes vary from rarefaction of myelin and reactive gliosis to coagulation necrosis and cavitation. The microscopic appearance of severely affected regions does not vary with lesion topography, and the same histologic changes may be seen in focal and diffuse forms of injury [8]. De Reuck and Eecken [8] have suggested that the topography of damage may be determined by the distribution of vascular lesions, with occlusion of deep perforating arteries producing focal lesions in the corresponding vascular territories, and more generalized disturbances of cerebral perfusion producing lesions in the periventricular arterial end and border zones. The relatively rich blood supply of the cortex and subcortical white matter could explain the relative sparing of those regions.

The pathology of subclinical focal radiation injury has not been determined, since patients with these lesions have no symptoms and no histologic diagnosis is obtained.

![Fig. 3.](image1.png) Focal radiation injury, asymptomatic. A and B, T1-weighted, 600/30 (A), and proton-density, 2000/30 (B), MR images 2 years after focal helium ion irradiation of a right temporal arteriovenous malformation (AVM). AVM vasculature is seen as foci of flow void in right temporal lobe, surrounded by extensive zone of increased signal on proton-density image. Prolongation of T1 relaxation by edema has reduced white matter signal on T1-weighted image, thereby reducing gray-white differentiation. MR changes reflect degree of edema, rather than underlying tissue disease, and cannot be used to differentiate asymptomatic edema from radiation necrosis.

![Fig. 4.](image2.png) Hemorrhagic radiation injury, asymptomatic. A and B, T2-weighted, 2800/80 (A), and enhanced T1-weighted, 600/20 (B), MR images through temporal lobes in patient who had received helium ion irradiation for nasopharyngeal carcinoma 3 years earlier. Increased signal in right temporal white matter is consistent with focal radiation injury or tumor spread. Three hypointense abnormalities, two in the right and one in the left temporal lobe, probably represent hemorrhagic radiation damage. The largest of these has a complex appearance and shows enhancement following administration of gadopentetate dimeglumine. This lesion may consist of focal necrosis or metastatic tumor, as well as hemorrhagic cerebral injury.
The most prominent clinical features of severe diffuse white matter injury involve impairment of mental function: personality change, impairment of memory, confusion, learning difficulties (in children), and frank dementia, leading to death in the most severe cases [23–26]. Seizure disorders and motor abnormalities may occur also. These manifestations are usually irreversible. Neurologic symptoms commonly develop when the underlying tumor is cured or in remission, particularly after treatment for childhood leukemia [27–30]. While the fiber tracts of the deep, periventricular white matter include the short and long commissural networks; the ipsilateral association pathways; and the main motor, sensory, visual, and language tracts [31]; dysfunction related to these pathways is seen in only a fraction of the patients affected, even of those with the most severe lesions on imaging. Most patients with periventricular MR abnormalities are asymptomatic and have no clinical abnormality.

Prior to CT, there was no diagnostic method for premortem demonstration of diffuse white matter disease. The CT findings of diffuse white matter injury (Fig. 6) were first reported by Martins et al. [10], who described six patients with radiation injury, including one with diffusely reduced attenuation in both frontal lobes. Mikhael [16] subsequently reported eight patients with bilateral, diffuse, low-density lesions involving much of the hemispheric white matter, with no contrast enhancement and no localized mass. Awareness of diffuse white matter injury grew with the advent of MR imaging, which is extremely sensitive to increased water content within the white matter. The first description of postradiation MR findings [32] included five patients with diffusely increased signal in the deep periventricular white matter on T2-weighted images and no focal abnormalities. Since then, more extensive studies have confirmed this finding and have related the MR appearances to clinical manifestations [23, 33, 34].

Periventricular white matter lesions appear as high-signal areas on proton-density and T2-weighted images, varying in
extent from small foci at the angles of the frontal and occipital horns to a confluent band of hyperintensity extending from the ventricular lining to the corticomedullary junction (Figs. 7–10). As in the case of focal injury, there is increase in mobile hydrogen density and prolongation of T1 and T2 relaxation times. The lesions are best seen on proton-density, 2000/30 (TR/TE), or T2-weighted, 2000/80–100, images. The abnormalities are usually symmetric and are indistinguishable from the deep white matter changes seen in ostensibly normal older people and in patients with risk factors for cerebral vascular disease [35–37].

Constine et al. [23] reported periventricular white matter abnormalities on MR in all of 41 irradiated brain tumor patients, but only 32% (56% of adults and 20% of children) showed severe abnormalities. The prevalence of severe abnormalities increased with age, volume of brain irradiated, radiation dose, and interval between irradiation and imaging. Fifty percent of patients who had received whole brain irradiation showed severe abnormalities, compared with 14% of patients treated with local fields. Six patients were imaged before irradiation and five had no pretreatment abnormality. After treatment, all patients showed abnormalities that were mild to moderate in extent, indicating that these changes were caused by irradiation.

Other investigators have reported a lower prevalence of radiation-related white matter lesions on MR. Tsuruda et al. [34] found probable radiation-related lesions in 36 (38%) of 95 irradiated patients, while Curran et al. [33] found lesions in 24 (43%) of 56 patients. Tsuruda et al. also found an increase in the prevalence and severity of lesions with age, with no lesions seen before the age of 20. They attributed the absence of lesions in young patients to shorter follow-up.
Fig. 8.—Moderate diffuse white matter change, asymptomatic.
A-C, T2-weighted, 2000/80, MR images (A and B) and CT image (C) 20 months after regional photon irradiation for brainstem glioma. On MR, there is slight increase in periventricular white matter signal bilaterally, most marked around posterior horns, but also extending anteriorly. Abnormality is mild in degree and moderate in extent. CT image shows no white matter hypodensity.

Fig. 9.—Severe diffuse white matter change, asymptomatic.
A and B, Proton-density axial MR images, 2000/30, 14 months after whole-brain photon irradiation for malignant glioma. There is diffuse increase in white matter signal bilaterally, extending from ventricular lining to corticomedullary junction. The patient had no intellectual or neurologic abnormality.
(18 months average vs 42 months average in adults) and a high rate (45%) of limited-field irradiation for posterior fossa lesions. The reason for the higher prevalence of MR abnormalities in the patients reported by Constine et al. [23] was not apparent. In our experience, the majority of patients irradiated for posterior fossa tumors will develop focal white matter hyperintensities near the trigones of the lateral ventricles, best seen on T2-weighted images. The rate at which these changes develop is variable, but appears time and dose dependent.

Curran et al. [33] described the MR findings of 24 patients as mild (six patients), moderate (nine patients), or severe (nine patients), and found that seven of eight patients with symptomatic radiation injury had severe MR abnormalities. Three of these patients underwent craniotomy and were found to have coagulation necrosis and perivascular fibrosis, without evidence of tumor. No patients with mild abnormalities and only one patient with moderate abnormalities had symptoms of injury. Constine et al. [23] found a less clear-cut relationship between severity of MR abnormality and clinical injury. Mental dysfunction attributable to radiation was found in seven adults, and five of these had severe MR changes. However, four of 14 asymptomatic adults also had severe changes, while three patients with seizures and one patient with hemiparesis had only minor changes. It is significant that some of the patients with the most severe changes were asymptomatic.

It is clear that severe MR changes do represent clinically significant white matter disease in some cases, but the significance of early changes is more doubtful. No direct association between mild white matter changes and abnormal clinical findings has been reported. However, Constine et al. [23] performed follow-up MR imaging in 13 patients and reported progression of changes in six, over intervals of 8–20 months, suggesting that mild white matter lesions may progress to symptomatic lesions in some patients.

In a study of 31 survivors of malignant glioma, 13 younger and 18 older than age 40, Styloposoulos et al. [38] found an association between postirradiation CT abnormality, mental status, and age. By 2 years postirradiation, all of the older group and over half of the younger group had white matter hypodensities on CT, and all patients who survived 4 years or more developed this finding. CT evidence of white matter injury and cerebral atrophy was always more severe in the older patients. More importantly, the younger survivors maintained a nearly normal mental status despite white matter abnormalities, while those over 40 showed progressive decline.

All studies that compared MR and CT in irradiated patients found that the sensitivity of MR for detecting white matter lesions was two- to threefold higher [23–25, 33] and that CT abnormalities were more closely associated with clinical evidence of injury. CT white matter lesions and early MR lesions probably represent different stages of the same pathologic processes, the CT lesions being more advanced, with more clinical manifestations.

Diffuse white matter injury appears to be a complication of large-volume or whole-brain irradiation. The group studied by Tsuruda et al. [34] included 16 patients who had been irradiated for pituitary tumors, using limited treatment fields. These patients showed no significant increase in the prevalence of diffuse white matter lesions, compared with a nonirradiated control group with pituitary tumors. This observation is consistent with the findings of Rodriguez et al. [20] and Marks et al. [39], who found no diffuse white matter abnormalities following focal irradiation with charged particles.

The nonspecificity of MR imaging led Curran et al. [33], Tsuruda et al. [34], and Constine et al. [23] to exclude the actual tumor site from their studies, since the cause of an abnormality at this site could not be established. As this was frequently the site of highest radiation dose, the results were bound to underestimate focal white matter injury. Exclusion of the primary site also would exclude most cases of focal necrosis, which usually is centered on the primary lesion. However, none of the patients reported by Constine et al. or Tsuruda et al. had clinical findings suggesting focal necrosis.

Focal and diffuse white matter injury may occur together (Fig. 11). On CT examination, some patients have bilateral, diffuse white matter hypodensities, as well as a focal enhancing mass [4, 8, 10, 24]. The focal and diffuse lesions usually occur at the same time [8, 10, 24], but one may follow the other. Cases have been reported where resolution or resection of a mass lesion was followed by development of bilateral white matter hypodensities at a later time [4, 10, 40].

Deterioration of intellectual function with no associated MR abnormality has been reported in survivors of childhood acute lymphoblastic leukemia [41]. All patients had been treated with intrathecal methotrexate and whole-brain irradiation with doses of 18–24 Gy. No patients showed white matter abnormality on MR imaging, but seven of the 10 were below
Fig. 11.—Concurrent focal and diffuse white matter injury, symptomatic. A–E, T2-weighted MR images, 2000/80, 6 (A and B) and 11 (C and D) months after irradiation of left-sided intraventricular neurocytoma and T1-weighted enhanced image, 600/20 (E), at 11 months. The patient developed weakness of the right arm 6 months after irradiation, and MR imaging showed severe white matter changes in the left hemisphere, as well as mild changes on the right. During the next 5 months, the patient developed dementia and the motor lesion progressed to right hemiparesis. T2-weighted images at this time (C and D) showed severe white matter changes bilaterally and imaging with gadopentetate dimeglumine (E) demonstrated a focal blood-brain barrier (BBB) defect on the left. Positron emission tomography with $^{18}$F-FDG showed low activity at the site of the BBB defect, confirming the diagnosis of radiation necrosis, rather than tumor recurrence.

Pathologic Findings

Diffuse white matter injury, as demonstrated by CT and MR, can reflect a wide spectrum of disease. All stages of radiation injury have in common an increase in free tissue water, which produces hypodensity on CT and increased signal intensity on T2-weighted MR images. This may result from endothelial cell damage, causing increased capillary permeability and vasogenic edema, or from demyelination, leading to replacement of hydrophobic myelin by water [44]. The tissue changes that accompany the increase in water content may vary from minimal change to coagulation necrosis. The MR abnormality is related to water content, rather than tissue damage, and the extent of edema produced by a given lesion may vary from patient to patient. This could explain the finding of severe MR changes in some patients.
who have no clinical abnormality, and the occasional finding of only mild changes in symptomatic patients [23, 33]. When necrosis occurs, the pathologic findings are identical to those seen in focal injury: vascular lesions, demyelination, gliosis, and necrotic foci coalescing to form large necrotic areas. Necrosis is the usual autopsy or biopsy finding in patients with frank dementia and diffuse white matter hypodensity on CT [2, 8, 25]. Diffuse white matter necrosis also may be associated with contrast enhancement on CT [2, 25].

There are fewer reports of histologically documented diffuse white matter necrosis than focal necrosis, possibly owing to differences in clinical and radiologic presentations. Focal necrosis presents as a mass lesion, which often must be differentiated from recurrent tumor, and this leads to surgery and biopsy in many cases. On the other hand, diffuse white matter necrosis presents with dementia and bilateral imaging abnormalities, and biopsy usually is not undertaken.

The pathologic findings in patients with mild MR changes, with or without some intellectual deterioration, have not been determined, as such patients rarely come to biopsy or autopsy. The mild changes are identical to those seen in some ostensibly normal people over the age of 65. It has been proposed that these age-related lesions may represent zones of perivascular atrophic demyelination or small areas of infarction resulting from vascular insufficiency [45, 46]. Early lesions of radiation injury may represent similar effects, accelerated by radiation [34].

Caveness and Carsten [47] reported sequential histologic changes in monkeys that were subjected to whole-brain irradiation within the therapeutic range. They found minute foci of necrosis throughout the white matter, which underwent healing or multiplied and coalesced, depending on dose and individual susceptibility. Caveness and Carsten suggested that a large number of acute foci may produce sufficient breakdown in the BBB to cause vasogenic edema, while a large number of healed lesions may produce a loss of brain substance and cerebral atrophy.

**Necrotizing Leukoencephalopathy**

Necrotizing leukoencephalopathy is the term used to describe diffuse white matter injury that follows treatment with chemotherapeutic agents, with or without associated radiation. This condition was first reported in survivors of childhood leukemia who had been treated with intrathecal methotrexate [48]. Subsequently this entity was also described after combined radiation and chemotherapy in adult leukemia [49–51], glioma [52, 53], bone or soft tissue sarcoma [26], and small cell carcinoma of the lung [6, 54]. Necrotizing leukoencephalopathy shows similar changes on CT and MR (Fig. 12) and clinical manifestations similar to those seen in postradiation diffuse white matter injury [26, 31, 55]. Initially, it may be manifested as excessive drowsiness [26]. Focal necrosis also may occur after chemotherapy, and we have seen this complication together with diffuse necrotizing leukoencephalopathy, as well as alone.

The prevalence of injury following either treatment method alone is low; when the two are used together, the rate of injury increases markedly [27]. Prophylactic whole-brain irradiation has caused clinical radiation injury with doses as low as 24 Gy, when used together with IV and intrathecal chemotherapy [56].

Most cases of drug-related white matter injury have been described in children, whereas diffuse white matter radiation injury alone is seen mainly in adults. Diffuse injury in adults is manifested primarily by personality change, impairment of memory, and confusion, progressing to frank dementia, whereas injury in children presents with learning and speech difficulties and often is associated with neuroendocrine abnormalities [28].

The latent period between treatment and onset of symptoms is shorter after chemotherapy than after radiation. A group of 39 adult cancer patients with treatment-related white matter hypodensities on CT was studied by Lee et al. [26]. Clinically evident white matter injury developed in seven pa-

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**Fig. 12.—Diffuse necrotizing leukoencephalopathy, symptomatic.**

A and B, CT scan (A) and T2-weighted MR image, 2000/80 (B), 10 months after treatment with doxorubicin (Adriamycin) and whole-brain irradiation for adenocarcinoma of the lung. Both studies show evidence of white matter edema, as hypodensity on CT and increased signal on MR, which is most marked anteriorly and extends posteriorly to parietal regions. Clinically, the patient had mild intellectual impairment. CT and MR findings in diffuse necrotizing leukoencephalopathy are similar to the diffuse white matter changes seen after radiation alone.
tients: in one patient after radiation only, in two after chemotherapy only, and in four after radiation and chemotherapy. In the patients who had chemotherapy only, clinical onset was acute, occurring 1–3 weeks after treatment, and was accompanied by CT changes in two of the three cases. In those who were treated by radiation and chemotherapy, chemotherapy followed radiation by 1–4 years; onset of symptoms followed chemotherapy by 2–4 months. Less frequently, leukoencephalopathy may occur as an acute syndrome, within 12–24 hr of intrathecal or high-dose IV therapy with methotrexate or cytosine arabinoside [26]. Acute symptoms usually resolve within hours to days after cessation of therapy, but some neurlogic deficit may persist.

The pathologic findings in necrotizing leukoencephalopathy resemble those of radiation-related white matter necrosis (Fig. 5). Axonal swelling, multifocal demyelination, coagulation necrosis, and gliosis are seen in the periventricular regions and centrum semiovale in both conditions [26, 27, 49, 50]. However, hyalination and fibrinoid necrosis of arterioles are not seen consistently after chemotherapy, while axonal dysplasia is more common [26, 27, 49, 50].

Mineralizing Microangiopathy

Mineralizing microangiopathy with dystrophic calcification is the most commonly seen neuroradiologic abnormality in children who have been treated for cancer [28, 57, 58]. Approximately 25–30% of patients who survive more than 9 months after intrathecal methotrexate and cranial irradiation have evidence of intracerebral calcification on CT examination [27]. This is usually seen after combined chemotherapy and radiation, but may occur after radiation alone [27]. Calcification occurs in the basal ganglia, particularly in the putamen, and in the border zone between basal ganglia and cortical perforating vessels [59]. Cortical calcification also may be seen. These findings are frequently associated with evidence of cortical atrophy, as well as white matter hypodensity on CT [29, 59, 60]. Pathologically, there is deposition of calcium in small blood vessels, which are surrounded by varying amounts of mineralized necrotic brain. It is uncertain whether these lesions produce any abnormal clinical manifestations. Price and Birdwell [57] found premortem evidence of abnormal neurologic function in only four of 28 patients who had mineralizing microangiopathy at autopsy, and even in these patients the relationship between the symptoms and the histologic lesions was unclear.

Cerebral Atrophy

Cerebral atrophy is a frequent late finding after irradiation, almost certainly related to diffuse white matter injury. Contine et al. [23] found enlarged sulci and dilated ventricles in approximately one half (50% by CT and 60% by MR) of 41 irradiated brain tumor patients. Curnes et al. [25] reported MR and CT evidence of atrophy in six of nine patients with symptoms of radiation injury, and Packer et al. [24] found atrophy in all of 11 symptomatic children studied by MR imaging. Microscopically, the lesion of radiation injury involves mainly white matter, whereas CT and MR imaging studies have shown evidence of both white and gray matter atrophy. Injury to deep perforating arteries is one possible mechanism for causing cortical atrophy secondary to white matter disease. The clinical significance of cerebral atrophy, as demonstrated by MR or CT, is uncertain. Evidence of atrophy usually accompanies the clinical syndrome of diffuse white matter injury; however, atrophy also is seen commonly in patients who have no demonstrable intellectual compromise [23]. It must be remembered that corticosteroids and inanition also may lead to the appearance of atrophy on CT and MR studies in brain tumor patients.

Radiation Injury of Large Arteries

Damage to small and medium-sized arteries of the brain is a prominent feature of late radiation injury, but damage to larger arteries also may be seen [61–65]. Pathologically, fibrinoid necrosis of vessels may occur, but more commonly the changes are those of atherosclerosis, with vascular narrowing and occlusion [66]. Since such changes are common in the general population and the prevalence increases with age, radiation can be implicated as the cause only when vascular disease occurs in childhood [63, 67, 68] or is seen in a radiation field that is away from the usual sites of atheroma. Following focal charged-particle therapy, vascular radiation injury has caused brain necrosis that was remote from the site of irradiation [39]. The diagnosis is made by angiography, which may show stenosis or occlusion of a major artery or narrowing of smaller cortical vessels [65].

In our own experience, we have noted several instances of a moyamoya-like syndrome [69] in young patients treated for craniohypophryngiomata with focal irradiation to the sellar and suprasellar regions. This entity may be diagnosed by MR imaging, which demonstrates occlusion of the supraclinoid carotid artery and associated watershed infarctions.

Early Delayed Radiation Injury

Early delayed radiation injury was first described clinically in 1963 by Rider [70]. He reported two patients who had received radiation therapy for extracranial lesions and 10 weeks later developed brainstem and cerebellar symptoms. Recovery took 10–12 weeks and was spontaneous and complete in both cases; both patients were alive and well 6 years later. Subsequent reports [71–73] have confirmed the usually transient nature of this reaction, which occurs most frequently in the second month after radiation and usually improves within 6 weeks [70]. However, the syndrome can be more severe and has been fatal in extreme cases [73, 74]. Pathologic examination in these cases showed disseminated demyelination.

The main significance of early delayed radiation injury lies in the need to differentiate this condition, which is transient and requires no therapy, from late radiation injury and tumor progression. CT shows nonspecific low-density changes involving the basal ganglia, cerebral peduncles, and deep white matter bilaterally; these resolve completely without treatment.
[75]. The early delayed reaction should be suspected when symptoms develop within 3 months of treatment, but the diagnosis can be established only in retrospect, after spontaneous recovery has taken place.

Early CT changes, occurring within a few weeks to months of irradiation, may be due to tumor necrosis alone, without associated cerebral injury. Graeb et al. [76] described three cases in which irradiation was followed by CT changes suggesting tumor progression: increase in central necrosis, new or increased contrast enhancement, and adjacent low-density change. These changes appeared 3 weeks to 3 months after radiotherapy. However, there was no clinical deterioration, and repeat CT study 3–6 months later, without change in therapy, showed regression of the abnormal findings. These early, transient changes almost certainly were due to tumor necrosis, without injury to normal brain.

**Positron Emission Tomography (PET) in the Differentiation of Radiation Necrosis from Recurrent Tumor**

Radiation necrosis following irradiation of cerebral tumor presents a problem in diagnosis as well as therapy. Clinical deterioration or change in CT appearance, occurring months to years after irradiation, may be due to tumor recurrence or to radiation necrosis, and it is generally not possible to differentiate the two on radiographic or clinical grounds. PET using the glucose metabolic tracer $^{18}$F-2-fluoro-2-deoxyglucose ($^{18}$F-FDG) provides a functional approach to the problem. The potential usefulness of this technique was demonstrated by Patronas et al. [77] and Doyle et al. [78] and was confirmed in later more extensive studies [79, 80].

We performed 38 PET studies in patients who had been treated for malignant glioma by interstitial brachytherapy [79, 81]. Following initial stabilization after irradiation, PET examination was carried out when the CT appearance changed or there was clinical deterioration. Imaging was performed with the Donner 280-crystal positron tomograph, which has in-plane resolution of 8 mm and axial resolution of 11 mm, full width at half maximum [82]. Rubidium-82 was used as a BBB tracer, to define the extent of the lesion in terms of BBB defect. The sensitivity of $^{82}$Rb to change in BBB permeability in our experience is comparable to that of X-ray contrast material used in CT studies. $^{18}$F-FDG was then injected IV and a comparison was made of $^{18}$F-FDG uptake in the lesion and in the immediately adjacent cortex. Active tumor was diagnosed when lesion activity was equal to or greater than adjacent activity; lower lesion activity was interpreted as radiation injury (Figs. 13 and 14). The tumor often was surrounded by a region of metabolic suppression involving the adjacent cortex, and tumor activity was frequently less than contralateral cortical activity but usually greater than adjacent activity. Low lesion activity cannot distinguish radiation injury from other nonfunctioning lesions, such as hematoma or metabolically inactive tumor. However, in this clinical context, exclusion of tumor recurrence does establish radiation injury as the likely cause of posttreatment deterioration.

To determine the prognostic value of the PET diagnosis, we compared the PET result with a clinical diagnosis of tumor recurrence or no tumor recurrence, which was established by following the patient's progress and response to therapy after the PET study [79]. Clinically, it was clear that in some patients tumor was proliferating, while in others it was not. The PET result agreed with the follow-up diagnosis in 15 of 17 cases of tumor recurrence and in 17 of 21 cases of radiation injury. On this basis, the overall accuracy of the PET examination was 84% and the positive and negative predictive values were 79% and 89%, respectively. PET examination frequently provided the only effective means of prospectively differentiating tumor recurrence from necrosis in this patient group. A histologic diagnosis was obtained at reoperation after 18 of the 38 PET studies and apparently viable tumor cells as well as necrotic tissue were seen in all cases, regardless of clinical outcome. This lack of correlation between histologic appearance and biological behavior has been observed also by other investigators [83] and may reflect difficulty in differentiating radiation-induced cytolytic changes and reactive gliosis from tumor.

Di Chiro et al. [80] studied 95 patients with a variety of primary and secondary cerebral tumors who had been referred for evaluation of posttreatment deterioration. They found PET evidence of necrosis in 10 irradiated patients, and these findings were confirmed at surgery or at autopsy. They also found necrosis in four patients who had received chemotherapy only; two of these patients had residual or recurrent tumor as well. In an earlier study of tumor metabolism, Di Chiro et al. [84] found that only high-grade gliomas showed $^{18}$F-FDG uptake equal to or greater than that of normal gray matter and that low-grade gliomas usually showed less, suggesting that the $^{18}$F-FDG technique may not be applicable to low-grade tumors. However, recurrence of low-grade glioma has been demonstrated by PET with $^{18}$F-FDG in a small number of cases [77], so that recurring tumor may show higher $^{18}$F-FDG uptake than a primary lesion does. At the present time there are insufficient data regarding the metabolic level of recurrent low-grade gliomas to use this technique for clinical diagnosis.

**PET and MR Imaging of Focal Radiation Injury**

Most studies of radiation injury in humans have involved whole-brain or large-volume photon irradiation, usually given for treatment of intracerebral tumor. In many instances, it has not been possible to differentiate radiation effects near the site of the lesion from the effects of the lesion itself, and in several imaging studies the actual tumor site has been excluded from consideration for this reason [33, 34]. Patients with surgically inoperable cerebral arteriovenous malformations (AVMs) are now being treated with focal irradiation [85], and at the Lawrence Berkeley Laboratory a group of these patients is being followed long-term by MR imaging and PET. These patients present a unique opportunity to study the effects of radiation on normal brain tissue within and immediately around the target region. The AVM is localized, nongrowing, and produces no distant effects. The main local complication is hemorrhage, which usually can be identified.
Fig. 13.—Recurrent malignant glioma. A–C, Positron emission tomographic (PET) studies of three patients who had been treated for malignant glioma by interstitial brachytherapy. \(^{82}\)Rb and \(^{18}\)F-FDG were used as tracers of blood-brain barrier (BBB) and glucose metabolism. In each case, the patient had stabilized after brachytherapy and then showed deterioration on CT 7–15 months later. BBB defects on \(^{82}\)Rb images (top row) have been outlined by regions of interest (ROI) superimposed on \(^{18}\)F-FDG images (bottom row) in order to define extent of lesions. Maximum lesion activity on \(^{18}\)F-FDG images is greater than activity in immediately adjacent brain region, suggesting a diagnosis of tumor recurrence. In each case, there is peritumoral metabolic suppression. In A, maximum lesion activity is less than contralateral normal activity, while exceeding immediately adjacent activity. Clinical follow-up confirmed the PET diagnosis in all cases.

by characteristic clinical features and MR findings [86]. Any other changes detected after therapy are likely to be due to radiation, rather than to the AVM itself. Irradiation is performed with a stereotaxically directed helium ion beam, so that the dose is sharply localized, with the 10% isodose contour placed at the periphery of the lesion [85]. Fifteen to 25 Gy is given in a single day, or in two doses given on two consecutive days.

Neurologic deficits related to focal charged-particle therapy have developed in approximately 8% of cases so far [20]. Marks et al. [39] have reported CT and MR findings in seven AVM patients who developed new neurologic and imaging abnormalities 4–22 months after therapy. Five patients had findings consistent with late radiation injury, including low attenuation on CT, high signal on T2-weighted MR images, and mass effect. The abnormality was centered in the target region, but extended beyond the 10% isodose contour in all cases. The pattern of abnormality was consistent with edema, extending out from the injured region along white matter fiber tracts. Abnormal contrast enhancement was also seen, indi-
cating breakdown in BBB. This breakdown was localized to the irradiated region itself and was consistent with radiation necrosis within the target volume. Follow-up imaging showed partial or complete resolution of the CT or MR abnormality in four patients, but significant clinical improvement was seen in only one. This combination of permanent neurologic changes with focal BBB defect and transient edema, occurring several months or more after irradiation, is characteristic of late radiation injury. The remaining two patients had radiation injury of large arteries.

PET studies of BBB, metabolism, and blood flow in irradiated AVM patients have demonstrated some of the pathophysiology of radiation injury. The tracers used were $^{82}$Rb for BBB breakdown, $^{18}$F-FDG for glucose metabolism, and $^{123}$I-HIPDM for perfusion. MR and PET findings in a patient with late radiation necrosis are shown in Figure 15. Nine months after irradiation of a large right thalamic AVM, the patient experienced gradual onset of left hemiparesis and left homonymous hemianopia. MR examination 6 months after clinical onset showed edema and mass effect in the right hemisphere, and a repeat study 6 months later showed persisting edema involving areas of cortex as well as white matter. The AVM appeared obliterated. On PET examination 15 months after commencement of symptoms, $^{82}$Rb uptake showed a region of defective BBB, and $^{18}$F-FDG activity within this region was markedly reduced. There was also markedly reduced metabolism in most of the ipsilateral cortex, where the BBB was intact. The $^{123}$I-HIPDM blood flow study showed that reduced perfusion accompanied the cortical hypometabolism.

The clinical and imaging findings supported the diagnosis of late radiation necrosis. The BBB defect followed the outline of the target region, as shown by isodose contours, and $^{18}$F-FDG uptake here was markedly reduced. The extensive reduction in metabolism and perfusion of the right cerebral cortex probably was due to diaschisis (deafferentation) secondary to destruction of the right thalamus or white matter tracts [87, 88]. A second PET study, performed 1 year after the first, showed more complete metabolic suppression in the right cortex, together with crossed cerebellar diaschisis. There had been interval reduction in $^{18}$F-FDG and $^{82}$Rb accumulation in the irradiated region, probably due to progressive gliosis and loss of vascularity at this site. This sequence of PET and MR findings is consistent with primary radiation necrosis and gliosis in the target area, secondary vasogenic edema spreading through the adjacent white matter, and diaschisis affecting the ipsilateral cortex and contralateral cerebellum.

![Fig. 15.—Focal radiation necrosis. The patient was treated with focal helium ion irradiation for arteriovenous malformation (AVM) in right thalamic region and 9 months later experienced gradual onset of left-sided weakness. Neurologic examination 15 months after irradiation showed a severe left hemiparesis and left homonymous hemianopia. A-C. Proton-density MR images, 2000/33. Pretreatment MR image (A) shows numerous small AVM vessels in right thalamic region. Image 15 months later (B) shows increased signal throughout much of right-sided white matter, also involving gray matter, and mass effect. At 21 months (C), swelling has resolved, but extensive hyperintensity persists in white matter and cortex. AVM is no longer seen. D. Positron emission tomographic (PET) studies 21 months (top row) and 33 months (bottom row) after irradiation. At 21 months (12 months after onset of hemiparesis), $^{82}$Rb image shows blood-brain barrier (BBB) defect limited to treated area and $^{18}$F-FDG uptake in this region is markedly reduced. There is also markedly reduced $^{18}$F-FDG and $^{123}$I-HIPDM uptake throughout most of right cortex, indicating reduced glucose metabolism and perfusion, with no associated BBB defect. MR and PET findings probably represent radiation necrosis in irradiated region, white matter injury in right hemisphere, and diaschisis affecting right cortex. (Crossed cerebellar diaschisis was also present.) Twelve months later there is decrease in $^{82}$Rb and $^{18}$F-FDG accumulation at site of primary injury, as well as further decrease in $^{18}$F-FDG uptake in right cortex. This probably represents progressive gliosis and reduced vascularity of irradiated tissue. Deafferentation of cortex is more complete.
Asymptomatic MR hyperintensity is seen more frequently than radiation necrosis. Over 200 AVM patients have been followed for 2 or more years after treatment and evidence of edema has been seen on routine follow-up MR imaging in approximately 40% of asymptomatic patients [20]. The edema is centered on the region of maximum dose and may be restricted to the treated volume or may extend further. Typically, edema becomes apparent during the second post-treatment year and regresses after persisting for a variable period of time. Total resolution has been seen in most cases. The extent of edema that may be seen without clinical manifestations has been surprising: the MR images in Figure 16 show increased signal throughout much of the white matter of the affected hemispheres in two asymptomatic patients.

When neurologic deficits develop in association with an MR abnormality, MR evidence of edema precedes clinically manifested injury in most patients (Fig. 17) [89]. At present, it is not possible to predict which patients with focal edema will develop a neurologic deficit, and we are evaluating the use of PET metabolic studies for this purpose. We found extensive suppression of $^{18}$F-FDG metabolism in the two asymptomatic patients shown in Figure 16. The BBB was intact; we have seen BBB breakdown only in association with clinical neurologic abnormality. Seventeen months later, one of these patients developed expressive dysphasia, difficulty with handwriting, and increased frequency of seizures. These symptoms gradually worsened over a 6-month period. Repeat PET study showed no significant change in the extent of hypometabolism. Rubidium-82 PET and gadopentetate dimeglumine–enhanced MR imaging now showed evidence of a BBB defect. The diagnosis of radiation necrosis was confirmed by histologic examination of tissue obtained at surgery. This case history suggests a possible predictive relationship between metabolic suppression and clinically evident radiation injury. We are performing prospective PET studies of irrad-

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**Fig. 16.—Focal radiation injury, asymptomatic.**
A-D, High-resolution positron emission tomographic (PET) and MR images in two patients with arteriovenous malformations (AVMs) 25 (A and B) and 29 (C and D) months after helium ion irradiation. AVMs are still visible in left parietal and left temporal lobes, respectively. T2-weighted, 2000/100 (B), and proton-density, 2000/30 (D), MR images show large areas of hyperintensity around AVM, extending beyond irradiated region. In one patient (A and B) there was mass effect and abnormal signal involved gray matter as well as white. In both cases, there was marked suppression of cortical glucose metabolism on affected side, and this suppression was similar in extent to MR abnormality. The second patient (C and D) had no abnormal clinical findings, while the first had a minimal upper motor neuron weakness in the right leg that had been present before irradiation. This patient subsequently developed memory deficit, right hand clumsiness, and increased frequency of seizures. The diagnosis of radiation necrosis was established at surgery.

**Fig. 17.—Focal radiation injury, symptomatic.** T2-weighted MR images (2000/80) were obtained in a 15-year-old girl who had received focal helium ion irradiation for a large left temporoparietal arteriovenous malformation (AVM).
A, 13 months after treatment. Region of markedly increased signal is in left hemispheric white matter. No neurologic abnormality was present at this time.
B, 20 months after treatment, following development of right hemiparesis. Edema is more extensive, involving gray matter as well as white; mass effect is present. Steroid therapy was commenced and the neurologic deficit gradually improved.
C, MR image 30 months after treatment shows marked resolution of edema.
D, Further resolution is seen at 34 months. At this time, only slight weakness of dorsiflexion of the right foot remained.
ated patients to investigate this possibility. Steroid therapy has been effective in the treatment of late radiation injury in some cases [13, 20] and difluoromethylornithine has shown promise as an agent for reducing postradiation edema [90]. Prediction of neurologic abnormality would allow therapeutic trials with these or other drugs before irreversible effects develop.

Conclusions

The radiographic findings of focal radiation necrosis are well recognized. Diagnosis presents a problem only when necrosis occurs at the site of an irradiated cerebellar tumor. Tumor recurrence and focal cerebellar necrosis cannot be differentiated by CT or MR, but functional imaging by PET now presents an effective means of differential diagnosis. Diffuse white matter injury has been generally recognized only since the advent of MR imaging, which is extremely sensitive to changes in white matter water content. A high rate of bilateral, periventricular MR abnormalities has been found in irradiated patients, but the clinical significance of such findings is still uncertain. Diffuse white matter abnormality on MR imaging may represent a spectrum of disease, ranging from white matter necrosis to minimal lesions that could be related to diffuse vascular disease. Prospective studies of irradiated patient populations are required to establish the relationship between these radiologic appearances and clinical manifestations of radiation injury. Punctate foci of hemorrhage in irradiated brain associated with telangiectasia of blood vessels may represent an unusual vascular response to radiation.

PET has been useful in demonstrating some of the pathophysiologic changes associated with radiation necrosis, and for determining the functional significance of abnormal anatomic images. Metabolic PET abnormalities, occurring in asymptomatic, radiation-treated patients, may have prognostic significance for development of clinically manifested late radiation injury. Confirmation of diagnosis after the onset of symptoms has limited value, as no effective therapy of established neurologic injury exists. Prediction of impending neurologic abnormality is needed to allow evaluation of early therapy with steroids and possibly other drugs, prior to the development of irreversible changes.

REFERENCES