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of the central nervous system.**

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# Review CT of the Adverse Effects of Therapeutic Radiation of the Central Nervous System

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Clinical deterioration during or after radiation of the central nervous system may be due to progression of, or a complication induced in, the lesion being treated. Deterioration may also be due to an adverse effect of the radiation on nervous tissue or vessels within the beam, to alteration in the blood-brain barrier, thus influencing the effects of drug therapy, or to a superimposed catastrophe unrelated to the treatment. Transient effects, which occur within the first 3 months of radiotherapy, include increase in symptoms suggesting enlargement of the tumor and the somnolence syndrome that occurs in children. Classical permanent radiation effects include necrosis, atrophy, calcification, necrotizing leukoencephalopathy, mineralizing microangiopathy, aneurysm formation, tumor induction, and cerebrospinal fluid fistulae. Rarely, demyelination occurs with higher doses than are currently used. The permanent effects tend to occur later than the transient ones; some are progressive and many have serious consequences. The appearances of mineralizing microangiopathy are specific; but the nature of the other complications is only evident in the clinical context, although there may be difficulty distinguishing between radiation necrosis and further growth of an intracerebral tumor. Selected cases illustrate the computed tomographic features of these entities.

Radiation of the cranium is undertaken for a variety of reasons, the usual being to reduce the mass of an inoperable intracranial tumor or to treat malignant extracranial tumors. It is currently used prophylactically in acute lymphatic leukemia and lymphoma and to sterilize the bed after macroscopic removal of malignant tumors. Previously it was also used to treat a number of benign conditions.

However much care is taken in treatment planning, normal brain tissue inevitably lies within the radiation beam. Although megavoltage therapy produces satisfactory isodose curves with sharp demarcation of the treated volume, some scattered radiation is unavoidable. The dose required for curative treatment needs to be carefully balanced against the risks to the normal brain, since the sensitivity of many tumors differs only slightly from that of the surrounding brain. By using several ports, the brain dose is limited while delivering a high tumor dose.

Radiotherapy planning and assessment of the isodose curves has been facilitated by the use of computers, but it is usually impossible to entirely eliminate "hot spots." Although the total tumor dose may be within permissible tolerance limits, it is the volume and dose of hot spots that may determine whether radiation damage will occur in normal brain. The brain appears to tolerate a daily dose of about 200 rad (2 Gy), and if this is given five times a week for 5–6 weeks it is unlikely that adverse effects will be encountered. Higher daily doses of radiation or irregular fractionation alter the biological effect in a manner that cannot be accurately controlled and may result in a dose higher than desired. The brain itself is not uniform in its response to radiotherapy. The cortex and subcortex are said to be more resistant to damage than are the white matter and hypothalamus,

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and the spinal cord is more sensitive.

During the course of radiation, with or without concomitant chemotherapy, the response of cerebral tumors is usually assessed by clinical progress, sometimes supplemented by computed tomography (CT) scanning. The development or progression of neurologic disturbance during or after radiotherapy for cerebral or extracranial lesions is a positive indication for CT. The most frequent early change of radiation damage is low attenuation in the white matter; since this is also a common accompaniment of intracranial tumors it may be misinterpreted as due to tumor progression. The importance of appreciating the CT changes in these conditions and recognizing their significance prompted this study.

### Materials and Methods

We reviewed pathology records from five London teaching hospitals for patients with proven radionecrosis. In addition, computerized record indices were studied for patients with complications of radiotherapy. All those with available CT scans are included in our study.

### Results

Most of the cases selected in this way were investigated at the Hospital for Sick Children, Great Ormond Street, and the National Hospital for Nervous Diseases, Queen Square, which are specialized referral hospitals. Unfortunately, the radiotherapy in these cases had been performed elsewhere so that the number of patients at risk could not be determined and the incidence of adverse reactions could not be meaningfully assessed. However, relatively few complications were encountered.

In one patient, the complications were temporary. A child with acute lymphatic leukemia developed somnolence syndrome. No other patients with transient deterioration during the early stages of radiotherapy had CT.

Permanent complications were found more frequently. There were no cases of acute demyelination. There were eight patients with histologically proven radionecrosis and one other who developed a meningioma in the radiotherapy field. Atrophy was observed in 13 patients treated with craniospinal prophylaxis for acute lymphatic leukemia and in two adults treated for gliomas. Three children developed calcification of the basal ganglia after radiotherapy for primary brain tumors. Necrotizing leukoencephalopathy developed in one case of lymphosarcoma, and mineralizing microangiopathy developed in three patients with acute lymphatic leukemia. Other acute complications were infarction due to radiation-induced vascular occlusion, abscess formation, and an acute agonal hemorrhage into areas of histologically proven radionecrosis.

### Discussion

Adverse clinical manifestations of radiation fall into two main groups, transient and permanent.

#### *Transient Changes*

The most common adverse effect is an increase in symptoms sufficient enough to postpone radiation. The deterioration is usually transient and the evidence available suggests that it is probably associated with a perivascular lymphocytic exudation [1] and is similar to that observed in dogs [2]. CT changes have not been described, and unless the tumor is extracranial, any abnormality is likely to be attributed to the effects of the primary lesion.

There is a characteristic clinical syndrome of somnolence, lethargy, anorexia, and irritability in more than half of the children with acute lymphatic leukemia. It occurs 6 weeks to 3 months after commencing prophylactic central nervous system radiation and lasts 1–3 weeks [3]. The radiation is given in relatively low dosage (2,400 rad [24 Gy]) and it is accompanied by intrathecal and systemic methotrexate. It is likely the combination is the major factor in producing the syndrome. However, it does occur with radiotherapy alone and was noted in 3% of children treated for trichophytosis of the scalp [4]. One child with acute lymphatic leukemia from our series was scanned during this syndrome and no abnormal CT changes were demonstrated.

Reversible CT changes were reported in one child 6 weeks after completion of radiation with 2,400 rad (24 Gy) and about 1 month after an overlapping course of intrathecal methotrexate [5]. The child developed headache and papilledema. CT showed diffuse areas of decreased attenuation of periventricular white matter. Maintenance systemic methotrexate was discontinued and dexamethasone commenced. Serial scans 3 and 6 months later showed a gradual return to normal, coinciding with resolution of the clinical changes. The exact cause is uncertain, but the patient ran a clinical course similar to the encephalopathy in children reported by Kaye et al. [6].

#### *Permanent Changes*

*Acute demyelination.* This rare complication occurs within the first 3 months after radiotherapy and it has been suggested that it is probably a progression from the transient changes previously described, which only follow very high doses [7]. Only two cases proven by autopsy have been described and in both certain areas of the brain received a dose higher than that generally used in current practice [8, 9]. These cases were reported before CT was available; microscopically there was subependymal demyelination with perivascular lymphocytic and plasma cell infiltration and pronounced microglial proliferation affecting the brain stem only.

*Necrosis.* This is characterized by an insidious onset of clinical features that may suggest tumor recurrence. It can commence as early as 1 month after completion of radiotherapy, but may develop up to 14 years later. Microscopically there may be pronounced microcytic and gliotic changes involving principally the white matter, although the gray matter can also be affected [9]. There is hyalinization and fibrosis of vessel walls with a protein-rich fluid in the



perivascular spaces extending through the parenchyma, suggesting increased vascular permeability. The CT appearances correlated reasonably well with the dose of radiation. In the series reported by Mikhael [10] all patients receiving 5,000–5,600 rad (50–56 Gy) and two who received 6,200 and 6,400 rad (62 and 64 Gy) had low attenuation areas without mass effect or abnormal enhancement. Similar appearances were reported by Martins et al. [11] in one patient after 5,000 rad (50 Gy). Enhancing masses of low attenuation were present in eight of the Mikhael cases, and have also been reported by other authors using a similar dose level after treatment with 6,000 rad (60 Gy) or more [11–13].

In our cases necrosis developed 1 month to 12 years after radiation. On plain CT there was low attenuation of the white matter sometimes extending beyond the limits of the radiation beam. There was a mass effect with compression of the ventricular system in seven patients with ring and patchy enhancement after contrast injection in all patients (fig. 1). In five patients, treatment plans were available and the dose varied between 4,800 rad (48 Gy) in 16 fractions over 28 days and 7,257 rad (72.6 Gy) in 38 fractions over 56 days.

In one patient these changes developed within 6 weeks of the commencement of radiation. In another patient with an enhancing mass in the left frontal region, follow-up scans demonstrated some resolution during the next month, only to be followed by a recurrence of the CT changes 3 months later (fig. 2).

**Atrophy.** CT appearances consistent with cerebral atrophy occur after radiation in nearly half of the patients receiving 3,000–6,000 rad (30–60 Gy) to the entire brain [14]. Atrophy was demonstrated in one-third of children with acute lymphatic leukemia treated at the Hospital for Sick Children, Great Ormond Street, with prophylactic craniospinal radiation (2,400 rad [24 Gy]) and intrathecal methotrexate [15].

Similar changes were demonstrated in two adults. One had a brain stem glioma treated with 4,000 rad (40 Gy) of radiation and three doses each of 10 mg of intrathecal

methotrexate. The other had a grade II astrocytoma incompletely removed, and was treated on the linear accelerator with a dose of 5,000 rad (50 Gy) over 5 weeks by two laterally opposed fields (fig. 3).

Wilson et al. [16] reported encephalographic changes that they considered consistent with atrophy in 17 of 40 patients with a variety of primary intracranial tumors. Only two of the patients were considered to have received more than a moderate tumor dose.

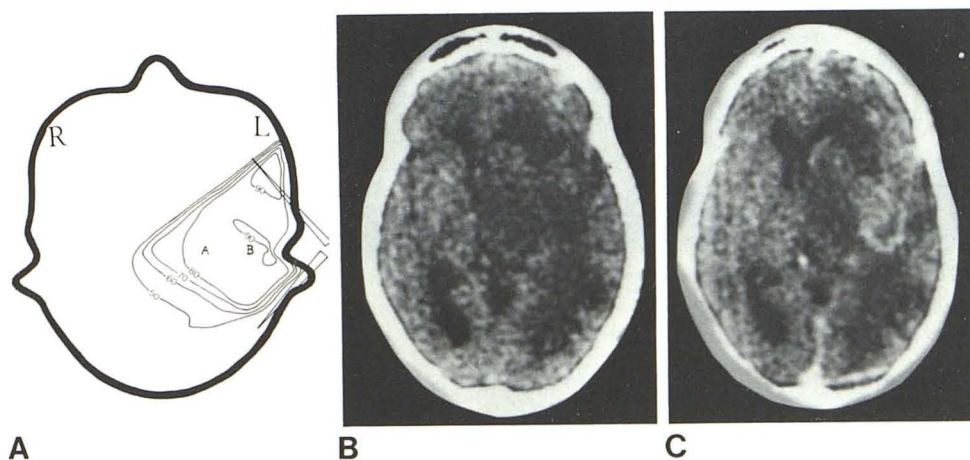
The precise mechanism of these changes has not been determined with any certainty. It is likely that in some patients there is loss of cerebral tissues, but in other cases the appearances may be due to communicating hydrocephalus from a high convexity block [17] or from the effects of steroid treatment [18].

**Calcification.** Calcification in the brain is rare after cranial radiation [19–21], but was present in the basal ganglia in three children on routine follow-up scans. All three received full courses of radiation. One had an optic chiasm glioma radiated 7 years before. The dose is unknown, but is most likely to have been at least 5,000 rad (50 Gy). The basal ganglia would certainly have been in the field of radiation (fig. 4). The other two patients with medulloblastomas received 5,000 rad (50 Gy) to the posterior fossa (fig. 5) and 3,500 rad (35 Gy) to the whole brain.

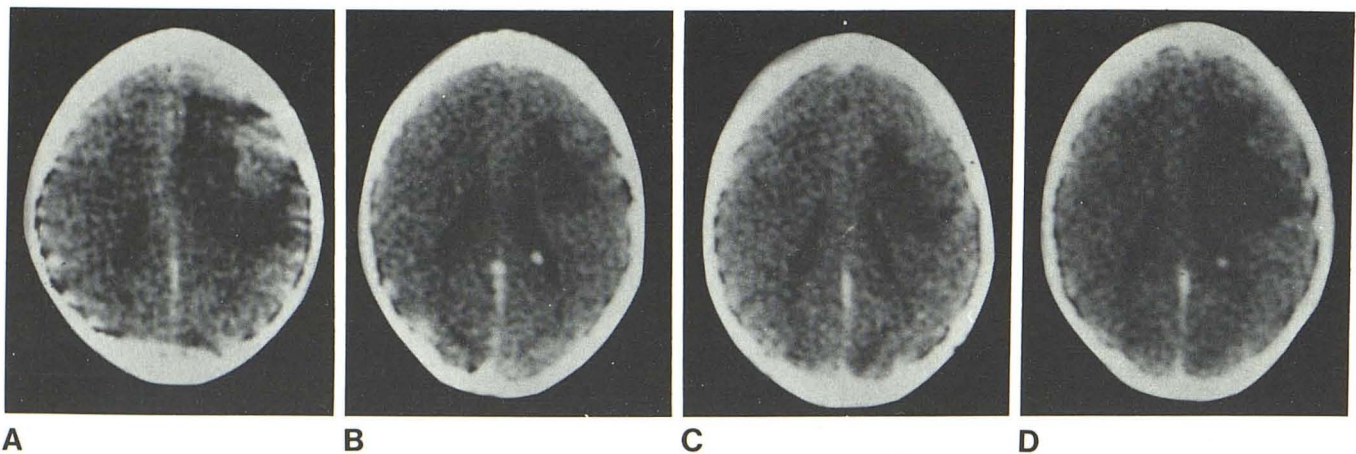
**Leukoencephalopathy.** Necrotizing leukoencephalopathy and mineralizing microangiopathy are rare conditions that occur in patients with lymphoma and acute lymphatic leukemia treated by cranial radiation combined with methotrexate. The precise relation between cranial radiation and the initiating dose of intrathecal or systemic methotrexate is as yet unresolved. Children under age 10 years are most frequently affected [22], presumably because immature tissues are particularly susceptible.

Necrotizing leukoencephalopathy may be acute or subacute. The changes, consisting of discrete multifocal coagulative necrosis, are randomly disseminated in the cerebral white matter [23]. Diffuse reactive astrocytosis may be marked [24] or absent [23]. These changes have been reported after treatment with intraventricular methotrexate

Fig. 1.—Radiation necrosis in 68-year-old woman. Squamous cell carcinoma of left external auditory meatus was treated by excision and 6,000 rad (60 Gy) in 38 fractions over 56 days. A, Isodose curves with doses of 6,700 rad (67 Gy) (A) and 7,250 rad (72.5 Gy) (B). B and C, CT scans 1 year later. Extensive low density beyond treated volume with mass effect and irregular ring enhancement in left medial temporal region. Biopsy of left temporal lobe revealed radiation necrosis only.

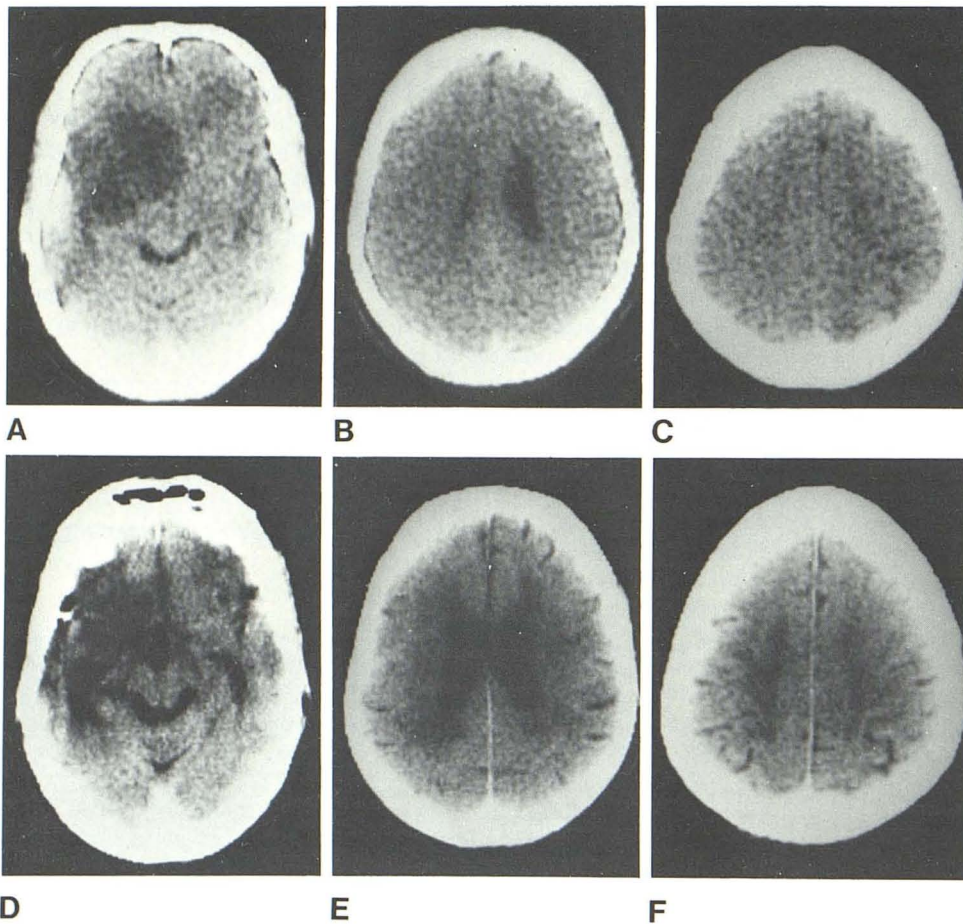






**A** Fig. 2.—Radiation necrosis in 60-year-old man with basal cell carcinoma of scalp in left frontal region. Radiation dose could not be ascertained, and 18 months later he had focal epilepsy and mild left hemiparesis. **A**, After contrast medium. Homogeneously enhancing left frontal mass with surrounding low density. He was treated with anticonvulsants and dexamethazone

with improvement. **B**, Enhanced scan 1 month later. **C**, 2 months later. Regression of lesion but recurrence of symptoms. **D**, After 4 months. Increase in extent of low density, but no abnormal enhancement. Excision biopsy showed radiation necrosis.



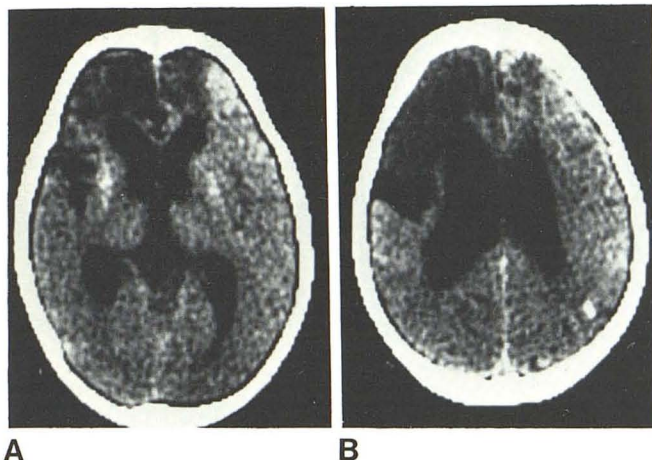
**A** Fig. 3.—Radiation atrophy in 54-year-old man with grade II astrocytoma treated with partial excision and 5,000 rad (50 Gy). **A-C**, Low density mass in right frontotemporal region. **D-F**, Sections at similar but not identical levels 18 months later. Extensive low density in white matter of both hemispheres and in right frontotemporal region without mass effect. Moderate dilatation of ventricles and subarachnoid spaces consistent with cerebral atrophy in absence of steroid therapy.

with or without central nervous system radiation [25], with intrathecal methotrexate and central nervous system radiation [6], and even with intrathecal methotrexate alone [26].

In one case of lymphosarcoma in an adult [12], CT

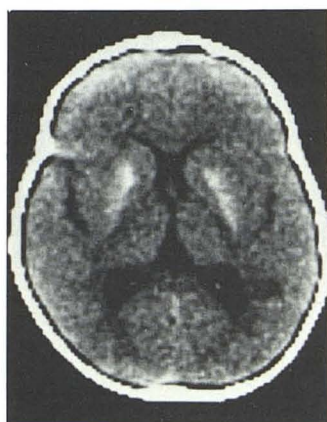
changes consisting of diffuse central low attenuation with compression of the ventricular system due to brain swelling (fig. 6) followed 3,500 rad (35 Gy) of cranial radiation together with a total of 330 mg of intrathecal methotrexate





**A** **B**  
Fig. 4.—Basal ganglia calcification in 10-year-old boy. Scans 7 years after radiation of optic chiasm glioma. Calcification in both lentiform nuclei and extensive well defined brain damage in right frontal lobe and anteromedial part of left frontal lobe. Dilatation of lateral and third ventricles and right Sylvian fissure.

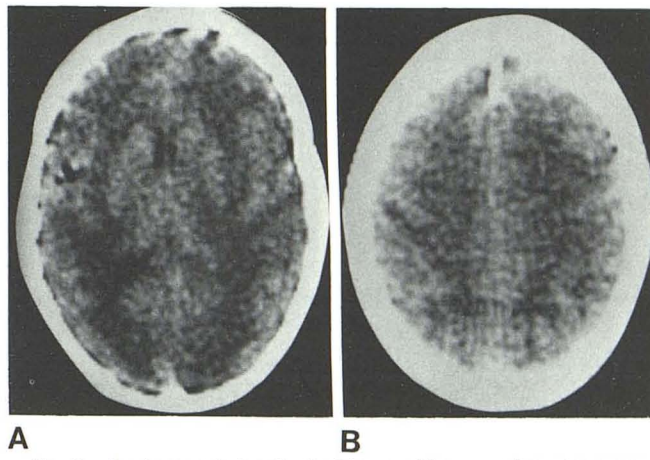
Fig. 5.—Basal ganglia calcification in 8-year-old girl treated for posterior fossa medulloblastoma with 4,000 rad (40 Gy) to the posterior fossa and 3,500 rad (35 Gy) to whole brain 3½ years previously. Scan shows extensive symmetrical calcification in lentiform nuclei.



and 1,400 mg of cytosine arabinoside in 18 months. This dose considerably exceeded that normally used.

In the more chronic form, mineralizing microangiopathy and multifocal dystrophic calcification occur predominantly in the border zone between cortical and basal perforating vessels [27] (fig. 7); it only occurs if a combination of both radiation and intrathecal methotrexate is used [22]. The calcification is well demonstrated on CT occurring in the deep hemispheric white matter as well as in the lentiform nuclei [22], where it is similar to that occurring with radiotherapy alone.

**Tumor induction.** Development of new primary tumors within the field of cranial radiation, although rare, is well recorded [28–31] and, although many pathologic types may occur, fibrosarcoma is the most common and occurs particularly within the pituitary gland following radiation for an adenoma. The mean interval between radiation and development of a tumor is about 8 years and the reported radiation doses have varied widely, but have often been multiple. The tumor usually develops within a heavily radiated area



**A** **B**  
Fig. 6.—Leukoencephalopathy in 54-year-old woman. Lymphosarcoma was diagnosed 2 years before. Neoplastic meningitis was treated with 3,500 rad (35 Gy), 330 mg of intrathecal methotrexate and 1,400 mg of intrathecal cytosine arabinoside. There was immediate improvement, but sudden deterioration and coma 16 months later. Scans show small lateral ventricles with symmetrical low density in white matter of cerebral hemispheres.

[30] but five cases of meningioma are recorded occurring many years after scalp irradiation with relatively low doses [32]. Fabrikant et al. [33] believed that the type and degree of tissue damage induced by the radiation is more important than the actual dose and that the neoplasms may develop in regenerating tissue. One of our patients developed a well differentiated meningioma in the left temporal region at the periphery of the radiation field 23 years after treatment of a grade III astrocytoma of the right frontal lobe. However, it was impossible to decide whether this was an example of tumor induction or the development of two coincidental tumors in the same patient.

Tumors that develop in the parasellar region after pituitary radiation may be confused with recurrence of the original tumor. The progressive nature of the mass and the interval between radiation and the development of the tumor would suggest that diagnosis, but diagnostic investigations are not specific and surgical exploration is necessary. When the tumor develops at a distance from the primary lesion, confusion is less likely, but a final diagnosis can only be established by surgery.

**Skull vault changes.** Plain film changes of necrosis of the overlying cranial vault were found in only one case in our study and thus seem to be an infrequent accompaniment of the underlying cerebral necrosis. Conversely vault changes may be present without evidence of intracranial pathology.

**Vascular changes.** In addition to its effects on the cerebral parenchyma, radiation affects both the small and large vessels within the field and may develop as early as 4 months or as late as 23 years after radiotherapy [34]. The changes that occur in large vessels consist of premature arteriosclerosis with vascular occlusion, which causes the strokelike signs seen in many patients.

Since arteriosclerotic changes are increasingly common with age, radiotherapy can only be incriminated if involvement is confined to a radiation field away from the usual sites of atheroma or occurs in childhood [35, 36]. One of



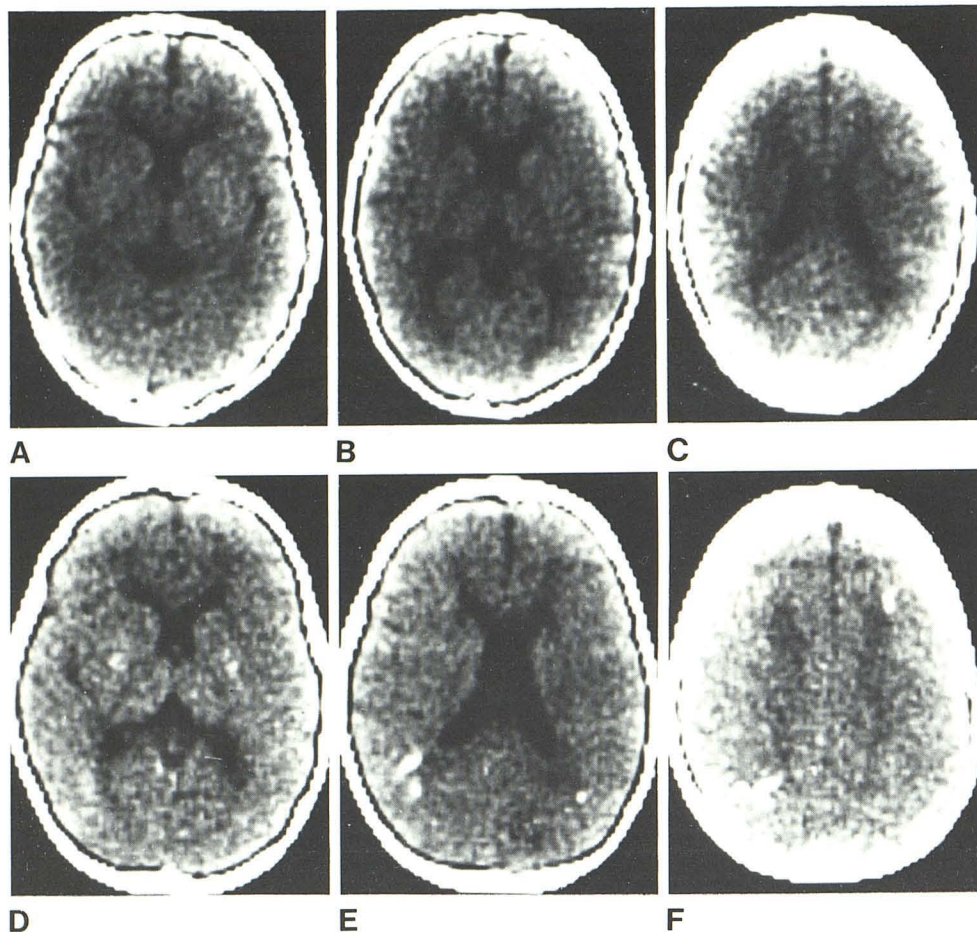


Fig. 7.—Mineralizing microangiopathy in 6-year-old girl. Acute lymphoblastic leukemia treated with 2,400 rad (24 Gy) and intrathecal methotrexate. A–C, Plain scans. Ventricles are mildly dilated and there is symmetrical low attenuation of white matter. D–F, 1 year later. Ventricle sizes unchanged. There are bilateral focal areas of calcification in the lentiform nuclei and in border zones between gray and white matter indicating mineralizing angiopathy.

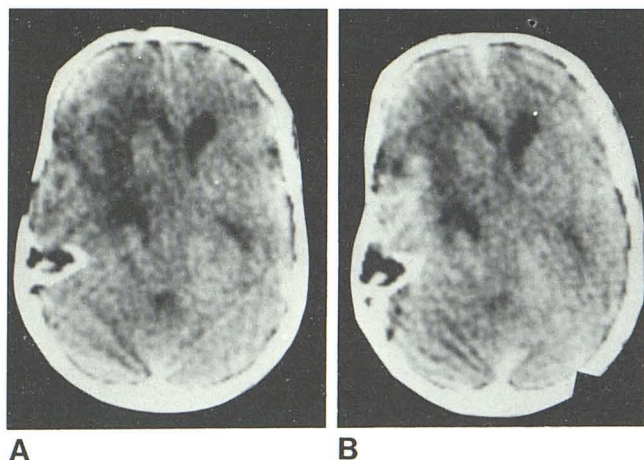


Fig. 8.—Brain abscess in 44-year-old man. Right temporal meningioma excised and irradiated (dose unknown). Admitted unconscious 12 years later with pus draining from right ear. Plain (A) and enhanced (B) scans. Focal ring of high attenuation in right temporal lobe with surrounding edema, marked mass effect, and irregular peripheral enhancement. Excision of mass showed abscess and radiation necrosis. CT after clinical improvement showed resolution of edema.

our patients had a sudden hemiparesis 20 years after treatment of a craniopharyngioma with radioactive gold implantation and postoperative radiotherapy at age 5 years. Angiography demonstrated narrowing and irregularity of the

posterior cerebral artery and CT showed an enhancing lesion in the thalamus. Extensive vascular changes involving both carotid and vertebrobasilar territories were also demonstrated on angiography in another patient (who was seen before CT was available) with failing vision 16 years after irradiation of a posterior fossa medulloblastoma.

Radiation of tumors of the neck may result in the development of aneurysmal dilatation leading to embolic occlusion of intracranial vessels and infarction. Aneurysms of the cavernous segment of the carotid artery have also occurred after yttrium implants for pituitary tumors [37]. Cerebrospinal fistulae may also occur after surgical implantation of radioactive seeds for pituitary ablation [38].

*Complications in necrotic tissue.* Hemorrhage may occur into necrotic tissue at any time after radiation. In one case of radiation necrosis reported by Brismar et al. [39], there was a hemorrhage 1 year after radiation of an arteriovenous malformation with a dose of 4,000 rad (40 Gy); one of our patients with previously diagnosed radiation necrosis was found at autopsy to have extensive hemorrhage into the necrotic tissue. Recent blood clot is readily demonstrated by CT but, unless the underlying lesion was documented previously, its nature may not be apparent.

Not surprisingly infection has also been reported in necrotic tissue [9]. One of our patients had pus draining from the ear 12 years after excision of a right temporal meningioma followed by radiotherapy of an unknown dose. CT



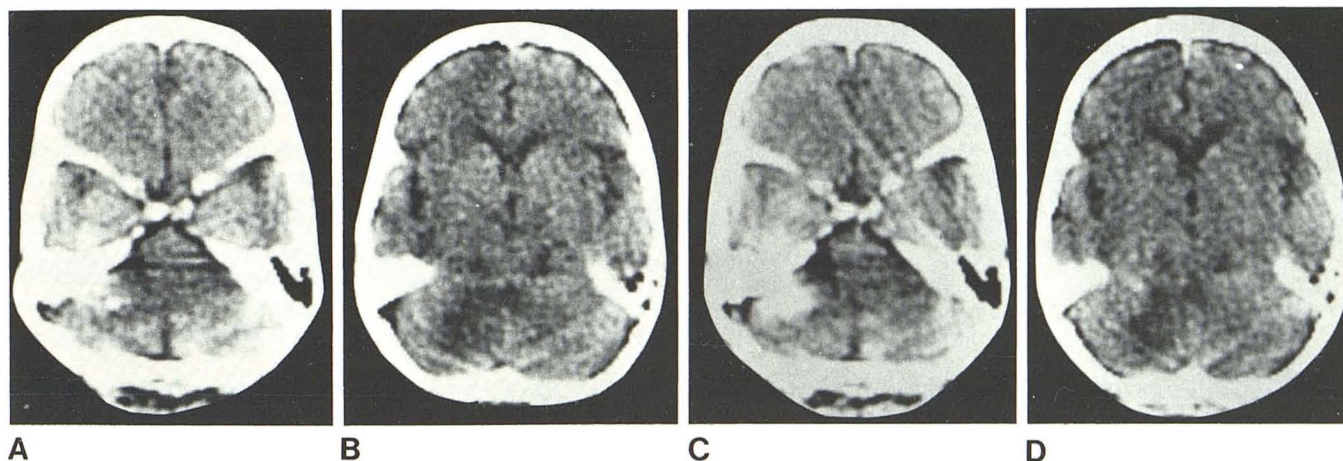
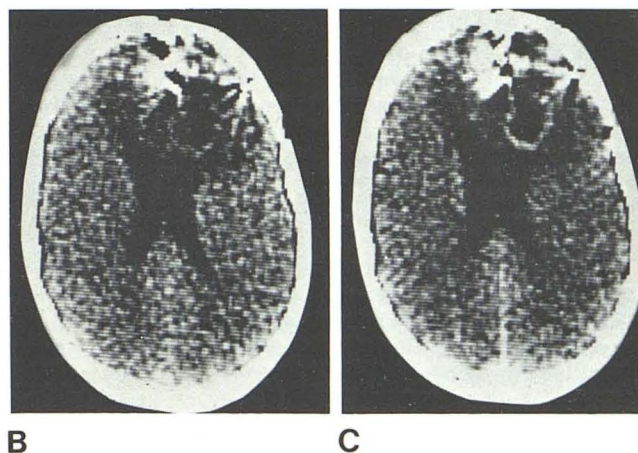
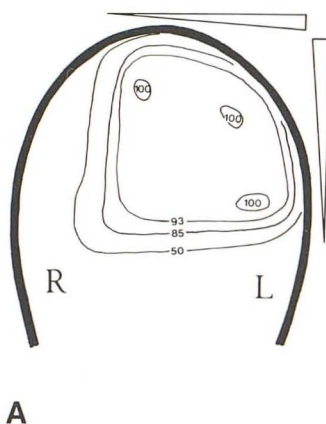


Fig. 9.—Recurrent tumor in 58-year-old woman. Excision of squamous carcinoma of right middle ear followed by 6,200 rad (62 Gy) in 20 fractions over 24 days. Cerebellar signs developed 2 years later. Plain (A and B) and

enhanced (C and D) scans. High attenuation mass medial to right petrous ridge which enhanced after contrast. Recurrent tumor diagnosed on biopsy.

Fig. 10.—Radiation necrosis in 32-year-old man. Left frontal oligodendroglioma treated with 5,000 rad (50 Gy) in 20 fractions over 35 days, as well as radon seed implantation. Severe headache and vomiting 4 years later. Isodose curve (A) and plain (B) and enhanced (C) scans. Extensive area of low density with isodense ring in left frontal region compressing left anterior horn. Marked enhancement. Lesion was excised, revealing radiation necrosis and no tumor.



showed a mixed attenuation lesion in the right temporal lobe that enhanced considerably and was surrounded by extensive edema (fig. 8). Rapid clinical recovery followed excision and drainage of the necrotic and infected tissue and this coincided with resolution of the abnormal CT changes.

Normal intracranial structures are relatively resistant to therapeutic radiation, but may react adversely in a variety of ways. Many effects of radiation with or without chemotherapy are associated with CT abnormalities but of these only mineralizing microangiopathy is specific. Therefore, it is important to consider the possibility of either recurrent tumor or necrosis in any patient who has had radiotherapy (figs. 9 and 10). However, in the clinical context and in relation to the radiation field the other abnormalities we have described will suggest the possibility of radiation changes. This is of particular importance when radiotherapy has been given for an extracranial or benign lesion, since the treatment of choice for localized necrotic tissue is surgical removal.

#### Editor's Note

A book was published recently that expands on the subject matter in this paper: Gilbert HA, Kagan AR, eds. *Radia-*

*tion damage to the nervous system. A delayed therapeutic hazard.* New York: Raven, 1980

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