NECROSIS OF BRAIN AND SPINAL CORD FOLLOWING X-RAY THERAPY*

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In recent years, a number of reports have appeared in the literature dealing with complications of the central nervous system, frequently fatal, following X-ray therapy for tumors or other lesions within or outside the cranium. Of the cases confirmed by biopsy or postmortem examination, we found 12 of cerebral necrosis (Fischer and Holfelder, Markiewicz, Scholz and Hsiü, O'Connell and Brunschwig, Pennybacker and Russell), 4 of brain stem (Boden) and 3 of spinal cord myelitis (Boden, Stevenson and Eckhardt). The practical significance of such undesirable complications is obvious, besides the theoretical considerations concerning the pathogenesis of the effect of X-irradiation. It is for these reasons that we wish to report the clinicopathologic findings in 2 cases.

REPORT OF CASES

Case 1. History. S.M., a negro airman, aged 22 years, had been hospitalized on April 22, 1952 because of nasopharyngeal carcinoma which had developed during the previous 4 months and later metastasized to the left posterior cervical lymph nodes. Between the 1st and 20th of May 1952, the patient was given external irradiation. This was directed through three ports, 3300 r (air) being given to the right, 1650 r (air) to the left and 1650 r (air) to the back of the nasopharynx-cervical region, over a period of 20 days (Table 1). The calculated tissue dose in the center of the field was approximately 5000 r. He was then discharged from the hospital and returned to duty. Repeated follow-up examinations during the ensuing year failed to reveal recurrence of tumor.

Readmission. On May 7, 1953, the patient was readmitted because of progressive

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<tr>
<th>Portal</th>
<th>Area</th>
<th>Field Size</th>
<th>KV</th>
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<th>Filter</th>
<th>HVL</th>
<th>TSD</th>
<th>Total Duration r (air)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>L. Nasopharynx-cervical</td>
<td>9X20 cm.</td>
<td>220</td>
<td>15</td>
<td>½ Cu 1A1</td>
<td>1.37 Cu</td>
<td>50 cm.</td>
<td>8300</td>
</tr>
<tr>
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<td>220</td>
<td>15</td>
<td>½ Cu 1A1</td>
<td>1.37 Cu</td>
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<td>1650</td>
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<tr>
<td>#3</td>
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<td>15</td>
<td>½ Cu 1A1</td>
<td>1.37 Cu</td>
<td>50 cm.</td>
<td>1650</td>
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* The statements and conclusions of the authors are the result of their own study and do not necessarily reflect the policy or opinion of the United States Armed Forces.

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weakness of his right arm and leg, and loss of temperature sensation in both legs for the previous 2 months.

Examinations. Physical examination was negative with the exception of induration of the soft tissues at the site of the previous tumor. Neurological examination revealed a spastic-ataxic gait, weakness and hyperreflexia of the right arm and leg, bilateral absence of superficial abdominal and cremasteric reflexes, and Babinski signs. There was a sensory level to pain and temperature stimulation at the inguinal ligament on the right and at D7 on the left. He was mentally clear, speech was normal and the cranial nerves were intact. X-ray films of the chest, skull and cervical spine were normal. Pantopaque and air myelograms showed no abnormalities. The spinal fluid, on two examinations, contained 55 and 65 mg. per cent of protein but was otherwise normal. Blood and urine were normal.

Course. The patient’s neurological disorder continued to progress. By May 20, there was weakness of all muscle groups, generalized hyperreflexia and a sensory level to pain and temperature sense below C6. Sphincter control was subsequently lost. On June 23, there developed impairment of the sense of position in all extremities, of vibratory sensation at both ankles and of touch sensation on the right side. Because of increasing difficulties in breathing, a tracheotomy was performed and on June 28 he was placed in a respirator. He expired on July 3, 1958.

Autopsy. The essential findings, outside the central nervous system, were fibrosis and vascular sclerosis but no tumor in the nasopharynx, and massive pulmonary atelectasis.

Central Nervous System. The brain weighed 1335 gm. and was neither grossly nor microscopically remarkable. The cervical region of the spinal cord was swollen and friable. Microscopically, all cervical segments showed widespread involvement. The white matter had undergone diffuse necrosis and demyelination which affected the
lateral, posterior and anterior columns in order of decreasing severity (Fig. 1). In the most necrotic regions there was tissue disintegration, with occasional petechial hemorrhages but no reaction. Scattered intramedullary blood vessels were thickened because of deposits of a homogeneous “fibrinoid” substance which stained reddish-blue with hematoxylin-eosin stain, and yellowish-brown with hematoxylin-van Gieson preparations, but did not stain for amyloid. This substance tended to spread

![Image](image_url)

**Fig. 2. Case 1.** (A) Necrosis of myelin and “fibrinoid” degeneration of blood vessels in cervical cord. Hematoxylin-van Gieson stain, ×100. (B) Extravasation of “fibrinoid” material from the blood vessels into the surrounding white matter. Hematoxylin-eosin stain, ×300.
from the blood vessels into the surrounding tissue, accompanied by exudation of degenerating leucocytes (Fig. 2). Despite the severe breakdown of myelin, fat deposits in phagocytes were relatively sparse, glial reaction was limited to scattered gitter cells and protoplasmatic astrocytes, and inflammatory reaction was lacking. By contrast, the grey matter of the cervical cord showed no signs of disintegration, but there were degenerative changes in neurons in the form of "axonal reaction" accompanied by a more vigorous proliferation of astrocytes and glial fibers, and by perivascular and meningeal infiltrations with lymphocytes and plasma cells (Fig. 3). Above and below the cervical region, only mild primary changes could be found in the lower part of the medulla and upper levels of the dorsal cord. There was however distinct Wallerian ascending and descending tract degeneration in all parts of the spinal cord.

Case 2. History. R.H., a white female, aged 37 years, was well until July 1946, when, following a minor head injury, headaches and right-sided Jacksonian convulsions developed. In January 1947, Dr. William T. Grant performed a left-sided frontotemporal craniotomy after ventriculography had demonstrated a shift of the ventricles to the right. At surgery, there was marked thickening of the arachnoid and cheesy material overlay the cortex. A biopsy disclosed leptomeningeal scar but no tumor tissue. The patient remained well until November 1947, when the focal convulsions began to recur. These at first responded to anticonvulsant medication, but in December 1948, they became severe enough to require hospitalization.

Examination at this time revealed aphasia, hyperactivity of all tendon reflexes, an equivocal Babinski sign on the right and slight papilloedema. The cerebrospinal
fluid showed a pressure of 250 mm. of water, a positive Pandy and a total protein of 170 mg. per cent. It was felt that there was recurrence of the lesion in the left hemisphere. However, ventriculography disclosed surprisingly a marked shift to the left.

Operation. There was a large infiltrating tumor in the right parieto-occipital region; 160 gm. of tumor were removed. Histological diagnosis was sarcoma.

Course. Postoperatively, the patient was given 20 X-ray treatments over a period of 25 days through two ports, 2650 r (air) being administered to the right and 2750 r (air) to the left temporo-parieto-occipital region (Table 2). It was calculated that the tissue dose at the midplane of the head at a depth of 7.25 cm. was 3573 r.

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<th>Portal</th>
<th>Area</th>
<th>Field Size</th>
<th>KV</th>
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<th>F.S.</th>
<th>Rate</th>
<th>Total r (air)</th>
<th>Duration</th>
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<tbody>
<tr>
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<td>R. Temporo-parieto-occipital</td>
<td>10X10 cm.</td>
<td>1000</td>
<td>3</td>
<td>2.6 mm.Pb</td>
<td>84 cm.</td>
<td>20 r/min.</td>
<td>2650</td>
<td>3800</td>
</tr>
<tr>
<td>#2</td>
<td>L. Temporo-parieto-occipital</td>
<td>10X10 cm.</td>
<td>1000</td>
<td>3</td>
<td>2.6 mm.Pb</td>
<td>84 cm.</td>
<td>20 r/min.</td>
<td>2750</td>
<td>3800</td>
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Treatments were terminated on Jan. 21, 1949 and she was discharged from the hospital.

There were no further symptoms until October 1950, 21 months later, when severe convulsions again developed, now associated with signs of progressive mental deterioration.

Examination on readmission, December 1950, disclosed marked impairment of memory, constant involuntary movements, bilateral spastic weakness with hyper-reflexia and equivocal Babinski signs, a diminution in all sensory modalities on the left side and a right homonymous visual field defect. There was, however, no evidence of increased intracranial pressure. On the assumption that there might be a recurrence of tumor, ventriculography was performed which now revealed generalized dilatation of all ventricles, more marked on the right, and only slight shift to the left. An EEG showed irritative foci in both hemispheres. The ventricular fluid contained 25 mg. per cent of protein.

Subsequent Course. The patient's condition progressively deteriorated. She became completely unaware of her surroundings, showed forced laughing, unintelligible speech, torsion movements of the head and pronounced spasticity. Towards the end there was marked difficulty in swallowing and coughing and she expired on Oct. 8, 1952, of bronchopneumonia.

Autopsy.* Central Nervous System. The brain was severely atrophied bilaterally, including the cortex, basal ganglia, and white matter; the ventricles were enlarged throughout. There was no gross evidence of tumor.

Microscopically, two tumor nodules, a few millimeters in size, were found in the putamen and substantia nigra on the right side. These showed central areas of necrosis which were bounded by round cells with hyperchromatic nuclei and frequent mitoses, and pervaded by a network of reticulin, characteristic of sarcoma (Fig. 4). The most conspicuous change, however, was widespread degeneration of both cerebral hemispheres. In the cerebral cortex, the changes were patchy and varied from areas of cystic degeneration of the tissue which was held together by glial fibers

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(Fig. 5) up to foci of diffuse depletion of neurons accompanied by proliferated micro- and macroglia. The cerebral white matter was more extensively involved. The myelin, with the exception of the U-fibers, was largely destroyed, accompanied by moderate amounts of fat droplets in gitter cells (Fig. 6). A dense gliosis replaced the white matter (Fig. 7A) but only scattered blood vessels showed sclerosis and hyalinization of their walls (Fig. 7B). There were rare infiltrations with lymphocytes of perivascular spaces and leptomeninges. Besides the cerebral white matter, the corpus cal-

Fig. 4. Case 2. Tumor nodule in brain. (A) Round cells with hyperchromatic nuclei. Hematoxylin-eosin stain, ×400. (B) Diffuse reticulin. Laidlaw stain, ×50.
Fig. 5. Case 2. Cystic degeneration of cerebral cortex. Hematoxylin-van Gieson stain, X100.

losum, both internal capsules and the right fornix were severely demyelinated. There was also bilateral severe spongy degeneration of the putamen and moderate gliosis of the caudate nucleus, globus pallidus and thalamus. The lesions extended for a short distance into the right side of the tectum and tegmentum of the midbrain but the rest of the stem showed only secondary degeneration of the pyramidal tracts. There were but mild losses of Purkinje and dentate cells in the cerebellum.

COMMENT

The 2 cases reported here illustrate the effects of X-irradiation on the central nervous system, similar to those previously described in the literature. In both, there was a latent interval following treatment, varying from 10 months in Case 1, to 21 months in Case 2, before symptoms of radionecrosis appeared. The duration of the free interval, as given in the literature, has been from 4 months to 7 years. The rapid progress in Case 1 corresponded to pathoanatomic findings of an acute necrotizing myelitis associated with fibrinoid degeneration of blood vessels and only mild glial response. The more protracted course in Case 2, on the other hand, was reflected in a chronic pathologic process of cystic degeneration and/or gliosis of grey matter, demyelination and gliosis of white matter, and sclerosis and hyalinization of blood vessels.

In any attempt at explaining such complications, besides the factor of individual susceptibility, the question of excessive dosage deserves primary consideration. Boden calculated the tolerance dose to be 4500 r in 17 days for small fields and 3500 r in 17 days for large fields, concluding that these
limits were exceeded in all reported cases of radionecrosis. There has been no general agreement, however, about such an estimate of the tolerance dose.

In experimental irradiation (Davidoff et al., Russell et al., Clemente and Holst) single high doses of 2000 r and higher were found to produce similar effects but could not very well be compared with the graded dosage over a long period of time as used in radiation therapy. In a recent communication,
Clemente and Holst found that while single doses of 4500–6000 r applied to monkeys produced immediate brain changes, chiefly in the hypothalamus and medulla, doses of 1500 r resulted in delayed effects of cortical and subcortical myelin breakdown. It would seem that the changes observed in clinical material most closely resemble the findings in chronic animal preparations as reported by Clemente and Holst. In both conditions, the effect
is delayed, diffuse and primarily on myelin with little effect on the hypothalamus or medulla.

These observations may also bear on the question of the pathogenesis of the effect of X-irradiation. In the literature, a divergence of opinion exists as to whether we are dealing here primarily with a vascular or a parenchymal effect. In our cases both phenomena were noted, but the vascular change was distinctly limited in extent compared with the widespread disintegration of the parenchyma. In some cases reported in the literature, the reverse appears to have occurred. It might be that such differences are also related to variations in dosage. Thus, with high doses, Clemente and Holst produced intense changes in the blood-brain barrier, but apparently not with lower doses, in which case a more direct parenchymal effect was noted.

Of practical importance is the question of the incidence of radiation necrosis. Boden estimated it to be as high as 25 per cent, occurring in 11 of his 41 cases of irradiation of the brain stem or cervical cord. On the other hand, Pennybacker and Russell found only 5 in 113 cases of irradiation of the brain. The latter suspected, however, that it is more common than is generally assumed but that the exact incidence is obscured by such factors as necrosis in the tumor tissue itself, the early death from malignant tumors before delayed necrosis has had time to develop and by insufficient postmortem examination.

**SUMMARY**

1. Two cases of delayed radiation necrosis of the central nervous system are reported, clinically and pathoanatomically.

2. The problems of dosage, pathogenesis and incidence of such complications are discussed in the light of a review of the literature.

**REFERENCES**


