Our treatment of malignant brain tumor consists of the primary extensive resection of the tumor tissues, and as an adjunct, a series of massive dose irradiation with the use of a linear accelerator. Present report describes the course it took to evolve this particular combination of treatment in our hands, supported by our own experimental data on laboratory animals.

At first, the conventional irradiation therapy with the dosage range of 100 rad daily and 4,000 to 6,000 rad in total, mainly of ^{60}Co , was found to produce very little improvement over the effectiveness of operation alone. We turned then to internal irradiation with radon seeds implanted in the surrounding tissues after the main tumor tissue had been resected. It soon became apparent that the radon seeds were too bulky to be accommodated in a sufficient number calculated from theoretical dosage requirement in the limited space for their implantation.

The only advantage this method offered was that the implanted radon seeds were visible on plain skull film and served as convenient landmarks for follow-up post-operative growth of the remaining tumor and also for planning and targetting for further irradiation with a linear accelerator.

In order to probe the practicability and efficiency to the irradiation of increasing dosages, in vitro and in vivo experiments were carried out. In the experiments using cultured brain tumor tissues, 700 rad was found to be an adequate single dose of a series of irradiation (JINNO et al., 11th Congress, Japanese Neurological Society). In the in vivo experiments using 203 T glioma in C 5713 mice (kindly supplied by Gunma University, School of Medicine), a balance was struck around 500 rad between therapeutic efficacy to the tumor tissue and destruction of the surrounding normal brain tissue.

On the basis of these preliminary studies, a clinical dosage schedule was developed as follows: using a linear accelerator with precise planning, a single dose was increased to 300 rad, with a frequency of 2 to 3 times a week. With this dosage schedule, clinical efficacy has been satisfactory. In cases where the total dosage approached 8,000 to 10,000 rad range and irradiation necrosis became an imminent possibility, more critical focussing was necessary and every effort was made to limit the total dosage at minimum.

Overall efficacy of our method of treatment leaves much to be improved and other approaches such as immunotherapy are now under consideration.

E-5. Boron-10-Slow Neutron Capture Therapy for Unexcisable Brain Tumors First Report—A Case of Pontine Glioma and Future Prospect of the Therapy

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^{10}B -Mercaptoundecahydrododecaborate has been used to treat tumor cells selectively while preserving normal brain tissues, by a nuclear reaction of low energy neutron and the non-radioactive isotope of Boron with a mass number 10 which is incorporated into brain tumor tissue. Some other boron compounds like RS-4508 and phosphate esters of B_{10}H_7 are also promising compounds for the therapy because of their appreciable uptake by tumors and considerably low toxicities.

Epithermal neutron with an energy range of 1–1,000 eV is necessary to treat deep-seated brain tumors, but its use so far has not been planned from mainly financial reasons, and thermal neutron with a less energy (0.025 eV) has been practically used. (So far 8 cases of brain tumors have been treated.)

Pontine gliomas have been incurable because of their vital seat that does not allow direct surgical excision. Conventional radiotherapies have not been effective, either because they inevitably give damages to brain matters as well as to the tumor tissue, or because they cannot cure tumors with sublethal doses to avoid brain damages.

Preliminary Clinical Results

Massachusetts General Hospital (1960–61)	University of Tokyo Hospital (1971)
18 cases (17 glioblastoma & 1 medulloblastoma) 16 were not pre-treated by Cobalt-60. after reactor treatment: 4 survived more than 6 months. No case survived a year. Average: 5.3 months. Pathology: Colloid necrosis of the brain matter, Destruction of cerebral capillary walls.	8 cases (6 glioblastoma, 1 pons glioma & 1 meningeal sarcoma) 6 were pre-treated by Cobalt-60. after reactor treatment: More than 3 survived more than 6 months. 2 cases so far survived more than a year. Average: More than 8 months. Pathology: No serious injury to the brain matter, nor to cerebral capillary walls, Despite previous intraarterial infusion of Vincristine, 5-FU, & BudR, and intensive radiation therapy.

By Boron-neutron capture therapy, however, even with presently available thermal neutron, a fairly selective treatment of the pons tumors is feasible, if neutron beam is given through a “transpharyngeal and transclival approach”.

An 8 year old girl with a pons tumor was treated by the authors. As the nuclear reactor available then for the treatment could not afford a high enough neutron flux, only an unsatisfactory dose of neutron was radiated through a ^6Li -plastic collimator placed in the oral cavity transpharyngeally. The estimated effective doses in the pontine region were, 1,300 rem for tumor tissue and 750 rem for brain matter, respectively, by the single radiation at the reactor. Additional radiations were done with Betatron and Co-60 to obtain a therapeutic effect by sparing the normal brain functions. In 3 months after the reactor treatment, the patient could ride a bicycle, and is alive and well as of 10th postoperative month.

Although the case was not at all satisfactorily treated in view of the true Boron-

neutron capture therapy because of the theoretically insufficient neutron intensity, the future of such a therapy for surgically inoperable brain tumors is promising, on conditions, that specifically designed nuclear reactors are built, and that the patients to be treated were not previously treated by conventional radiotherapy.

The indications are, 1) infiltrative tumors, like gliomas, 2) inoperable tumors, like pontine gliomas or thalamus tumors, 3) incompletely excisable tumors, like parasagittal meningiomas, 4) intramedullary tumors, and 5) inevitably complicating tumors, like some acoustic neurinomas.

E-6. Studies on the Uptake of Anticancer Drug into Brain Tumor Tissue

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In case of the systemic chemotherapy of brain tumor, uptake of sufficiently high concentration of the chemotherapeutic agent into the tumor tissue must be necessary, before the toxic side-effects of the drug will appear. For such uptake of the drug, its affinity to the tumor tissue or a breakdown of the blood-brain barrier are thought to be beneficial.

Bleomycin, an antitumor antibiotic specially accumulating into the skin, lung etc., has been used in 120 cases of brain tumor by the authors. Because it gives excellent results that had never been attained with the chemotherapeutic agents heretofore introduced, its concentration in the tumor tissue was measured by bioassay. No uptake of Bleomycin level either into the tumor tissue or brain tissue could be found in all of the 12 cases of meningioma and meningosarcoma. It was, however, found at a level of 0.3 γ /ml in the encysted fluid and 0.9 γ /mg in the tumor tissue in only one case of astrocytoma, grade 3 out of 10 cases of glioma. In this particular case, nearly the same concentration was detected in encysted fluid examined one year ago. Bleomycin was also detected in the cystic fluid of each one case of granuloma and congenital subarachnoidal cyst.

According to the study on the protein fraction of encysted fluid of 10 cases of brain tumor including 6 cases of glioma, cyst formation of the tumor is thought to be caused by diffusion of plasma from the capillaries of the tumor by a manifestation of the blood-brain barrier phenomenon. Then, detection of Bleomycin in the cyst fluid of the brain tumor can be explained by its penetration of the blood-brain barrier.

Result of the comparative studies on brain scintiscanning, concentration of chemotherapeutic agent and protein fraction of the cyst fluid on 12 cases of cystic brain tumor is not constant. Moreover, positive brain scanning can be obtained more frequently in cases of malignant brain tumors such as glioblastoma and metasta-