

BNL--47087

DE92 011552

NEUTRON CAPTURE THERAPY: YEARS OF EXPERIMENTATION — YEARS OF REFLECTION¹

Lee Edward Farr, M.D.²

December 16, 1991

¹Invited lecture; Medical Department, Brookhaven National Laboratory
²Chairman, Medical Department, Brookhaven National Laboratory, 1949-1962.
Present Address: 2502 Saklan Indian Drive #2, Walnut Creek, California, 94595-3001

MEDICAL DEPARTMENT

BROOKHAVEN NATIONAL LABORATORY
UPTON, LONG ISLAND, NEW YORK 11973

EXACTER

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

fp

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, nor any of their employees, nor any of their contractors, subcontractors, or their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise, does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency, contractor or subcontractor thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency, contractor or subcontractor thereof.

Printed in the United States of America
Available from
National Technical Information Service
U.S. Department of Commerce
5285 Port Royal Road
Springfield, VA 22161

NTIS price codes:
Printed Copy: A03; Microfiche Copy: A01

Prologue

In this lecture, I shall discuss our early research on neutron capture therapy over a number of years, beginning in 1950, speaking briefly of patient treatments but dwelling mostly on interpretations of our animal experiments. This work was carried out over eighteen years, beginning over forty years ago (1). Yet, it is only fitting to start by relating how neutron capture therapy became part of Brookhaven's Medical Research Center program.

In September 1948, after numerous calls from and conferences primarily with Harvard's two representatives to the board of Associated Universities, Inc. [AUI], Edward Reynolds, Administrative Vice President of Harvard University (President of AUI) and A. Baird Hastings, Professor of Biochemistry at the Harvard Medical School (a Trustee of AUI), I agreed to come to Brookhaven to develop a medical research center. For the remainder of 1948, and for the first six months of 1949, I commuted three days each week from Wilmington, Delaware to Brookhaven, familiarizing myself with its administration organization, its planned facilities, and the scientists on the staff of the few departments already organized. With my assumption of full-time duties in September 1949, I began to recruit a seasoned scientific staff for the Medical Department from leading medical institutes and universities. We were committed to explore and develop the medical applications primarily of short half-life radioisotopes; this included capture reactions.

In the spring of 1950 we began screening vital dyes to use as a target unit for what was to be known as neutron capture therapy. Since some dyes have an almost specific affinity for malignant tumors, the use of such as a carrier of the target atom appeared to be advantageous, whatever target atom or reaction was sought. For the dye, I chose bismarck brown, which had most

of the desired characteristics. Winton Steinfield joined our group in February, 1952 and undertook to determine a methodology to insert boron or uranium into the dye molecule without changing its physicochemical characteristics. He had the advice and guidance of Donald D. Van Slyke, my former mentor, who came to Brookhaven at the same time as I. After some months of failure, Steinfield told me that at last he knew how to accomplish his objective. However, before writing up the procedure, he wished to go to Baltimore and sail back a boat which he had just bought. In the spring of 1953, he and his wife left Baltimore on the boat, made contact with the Coast Guard in New Jersey, and were never seen again. I had all his notes but neither I nor Van Slyke could decipher them; it was a "Love's Labour's Lost".

Baird Hastings had told me late in 1950 about William Sweet's work at the Massachusetts General Hospital on the distribution of borates in patients with glioblastoma multiforme as a prelude to proposed thermal neutron exposures for boron neutron capture therapy [BNCT], and suggested that Sweet and I get together to discuss our common interests. I had been cautious about using borates because of their reported toxicity, but Sweet's work showed his patients tolerated therapeutic doses well. I had already interested my friends and colleagues, Lyle Borst and Marvin Fox, who were completing final construction of the Brookhaven Graphite Research Reactor [BGRR], in the possibilities inherent in capture reactions as a therapeutic measure. So, not only was it easy for Sweet and me to agree to a joint study on the application of this reaction in the treatment of glioblastoma multiforme, but Fox was also willing to modify the shielding on the top of the BGRR to give us a facility for patient trials.

Shortly after coming to the Department in 1949, William Hale, Head of the Division of Bacteriology and Immunology, developed a transplantable,

malignant, methylcholanthrene-induced brain tumor in mice that could be used as an experimental model. A little later, researchers at Argonne National Laboratory showed that this tumor was exceedingly radioresistant. Suppression of tumor growth and its elimination could be attained only with concomitant widespread and deep destruction of abutting normal tissue.

James S. Robertson, a physician and mathematician who was also well versed in physiology, and Elmer E. Stickley, a physicist, were the experts in dosimetry both present and forthcoming. They went on to establish many of the design criteria for the Brookhaven Medical Research Reactor [BMRR] (2). Victor Bond, who joined us a bit later, was periodically consulted in these initial endeavors. Our core team of scientists was now in place except for Otho Easterday, who would concentrate on boron toxicology and pharmacology (3, 4). As soon as we had started to look at boron, I began, with Bernice Antal, to evolve a simpler, yet accurate and reliable, method for boron analysis. In November, 1956, Tadeusz Konikowski, a skilled pharmacist with a master's degree, became my technical assistant. He took over this pursuit of a better analytical method which was later achieved (5,6,7).

Clinical Studies

William Sweet and his colleagues had some data on the distribution of boron between brain and tumor during a short period after injection. These data seemed to indicate that there was a very sharp rise in tumor boron concentration after injection, peaking within a few minutes and then falling abruptly. With this knowledge in hand, a series of studies was begun at the Medical Department on the time course of boron neutron-capture effects on the pig. Radiation effects were evident in the exposed regions of these animals. This was really the first demonstration at Brookhaven of in vivo effects of this reaction (8,9).

After several conferences and consultations, Sweet and I decided we should begin a trial on ten of Sweet's patients. Herbert Locksley, one of Sweet's assistants, was added to our staff to care for the patients sent us from the Massachusetts General Hospital. At the end of 1950, authorization for a clinical trial of neutron capture therapy was received from Shields Warren, Director of the AEC's Division of Biology and Medicine. Sweet transferred to the Brookhaven Medical Research Center patients whose glioblastoma multiforme brain tumors had exhausted current therapeutic efforts and who were in a terminal phase of their disease, to continue under Locksley's care.

On February 15, 1951, we began to treat these ten patients, using sodium tetraborate (borax) as the boron-10 [^{10}B] carrier. During these clinical trials, Locksley made observations on toxic effects of the borax administrations (10). Fortunately, the effects were not very severe and were transitory, disappearing in all patients by the fifth day. There was no evidence of a decrease in tolerance with successive doses. Hadley Conn found that intravenous injection of these doses of borax caused consistent but very transient abnormalities in the electrocardiogram (11); he thought these might be accounted for by cell hypoxia, resulting from entrance of the borate into the heart muscle. All patients were normal 24-48 hours after injection. The paucity of adverse effects after doses of borax corresponding to 32 and 50 mg of boron per kilogram body weight was surprising.

The results of the first trial were clinically encouraging (12, 13), but histological study of specimens did not show those cellular changes which, generally, are used as criteria for irradiation effects (14). Evidence had begun to accumulate that our hypotheses of the distribution of boron could be erroneous. I shall interject here the pathological findings of the series of

about fifty patients who were sent to us later from several neurosurgical services, and who were cared for by the neurosurgeons H. James Bagnall and Y. Lucas Yamamoto during and after treatment at the BGRR (1951-1959) and later (1959-1961), at the new Brookhaven Medical Research Reactor [BMRR] (2,15). These treatments were all carried out using an aqueous solution containing sodium pentaborate and glucose in the molar ratio 2:1. Pentaborate is less toxic than tetraborate (borax) and a further decrease in toxicity was achieved by the addition of glucose to pentaborate in that molar ratio (16). Specimens from those patients were studied extensively by Paul Yakolev of Harvard and Webb Haymaker of the Armed Forces Institute of Pathology as well as by W.G. Calvo and W. Kahle, who were from leading West German university clinics, together with Stuart Lippincott of Brookhaven National Laboratory (7,8,9). Each independently evaluated the effects of neutron capture therapy in those patients. Discouragingly, in no case did anyone find specific changes characteristic of radiation exposure which could be expected after neutron capture therapy (17,18,19,20,21,22). The findings in this major extension of patient studies were in full agreement with Brookhaven's John Godwin's postmortem appraisal of the first eight patients receiving this treatment (14). I can attest to the careful, meticulous studies carried out by these experts because I, too, examined the specimens which were specially prepared to bring out any unusual histopathological effects.

Experimental Studies

Using the Medical Department's port at the graphite reactor in the mid-1950s, Konikowski and I began our extensive series of studies on neutron capture therapy in mice. The malignant methylcholanthrene-induced transplantable tumor, induced by Hale, was the object of our studies with pentaborate as the boron-10 carrier. Thus began the experiments to gain more

information on boron distribution and radiation effects so that the most potent borate dose and neutron fluence could be selected. We also sought to learn if various residence times of boron in the tumor before irradiation changed the degree of tumor regression after the treatment. The first experimental neutron capture trials used young mice with intracranial tumor implants. When the tumors had grown sufficiently to be easily detected, a borate injection was given intravenously in a tail vein. The mouse then was exposed to an adequate thermal neutron fluence. Three days later, the animal was killed and the tumor tissue residue, or what was believed to be that, was removed and minced using sterile precautions. The separated tumor cells were then injected intracranially into ten mice. If none of the mice died from tumors, the result was positive. But with ten animals injected for each exposed tumor, the logistics became difficult, for this meant injecting one hundred test mice for ten treated ones. Another disadvantage was that all tumor remnants were lost by the mincing, leaving none for histological study.

We then tried implantation of the tumor into thigh muscles. After no longer than three weeks, death resulted from tumor growth. Growth was rapid in ten to twelve days to diameters averaging 1.0 centimeters, and in this period no central necrosis was ever found; thus, the tumor was a useful tool for this study, for it could be used, in part, for chemical analysis, still leaving adequate specimens for histological appraisal. A viable brain-to-brain mouse tumor colony was maintained by intracranial implantation of 0.02 ml of inoculum in 4-to-6-week old mice every eight days which contained equal parts of minced tumor and saline. It also could be used for a thigh intramuscular transplant. The intracerebral take rate was 90% to 100%. When this tumor preparation was implanted in the thigh, 0.06 ml was used. Thereafter, two successive thigh-thigh transplants furnished experimental

material. Minced thigh tumor mixed with an equal amount of saline provided the 0.06 ml inoculum. The thigh tumor take rate in this methodology was 79% to 90% (7). If thigh-to-thigh transplants were continued, it was found that tumor invasiveness increased. To maintain constant invasiveness, after two thigh-to-thigh transplants, the next transplant used a brain tumor preparation and the above-referenced protocol was followed. This general procedure was followed throughout the entire period of experimentation. A viable mouse tumor, free of visible necrosis, was maintained by thigh or brain transplantation in 4-to-6-week old mice every eight days. Since our criteria for evaluation of the treatment were based on an assumption of an intact tumor, necrosis introduced an uncertainty in classifying results, as it falsified the amount of tumor mass actually present. At the same time, the tumor had to be kept free of viral and bacterial contaminants, a most demanding task. The animals used in specific experiments received thigh implants with enough animals being inoculated to provide in addition a small group for tumor colony maintenance (7). Konikowski maintained the tumor line and provided reproducible thigh tumors for our experiments first at Brookhaven and later at the M.D. Anderson Cancer Center in Houston, Texas for more than sixteen years in an impeccable manner. He kept the colonies in isolation and took care of the animals himself. For our studies, the boron dose had to be delivered without leakage in a tail vein. At this Konikowski was also a master, and could inject mice at a rate of almost one a minute with virtually no failures.

The first definitive experiments using thigh tumor implants were to determine what effects, if any, a simple injection of borate or just thermal neutron exposure might have upon tumor growth and development. Borate injection alone had no effect, and exposure to thermal neutrons slightly retarded the growth rate [Figure 1] (7).

With this fundamental information at hand, Konikowski and I continued a long, systematic series of studies which, over fifteen years, ultimately included observations on over six thousand mice with thigh tumor implants treated with neutron capture therapy; each tumor-bearing mouse treated by BNCT was followed throughout its life. For the mice in which neutron capture therapy caused permanent regression of the thigh tumor, there was no reduction in life span compared with unirradiated animals that had received no tumor transplants.

By now, the method for boron analysis had been markedly improved, simplified and tested (5) so that we could, with confidence, begin studies on the distribution of boron among the blood, tumor, muscle, and skin tissues of the mouse (23). In all our subsequent studies on the boron content of blood and other tissues, each point in the reported graphs is the average of observations on ten animals [Figure 2]. There was gratifyingly little scatter in the data, and the results were reproducible.

An early objective was to learn what effect varying tumor diameters, from 8 mm to more than 17 mm, had upon results with a constant thermal neutron fluence at the reactor port (24). For these observations, typically, we irradiated right thigh tumors five days after transplantation and we used a constant dose of boron³, 35 micrograms per gram of mouse body. It was clear that as the diameter of the tumor increased, a greater incident thermal neutron fluence was required to effect complete regression of the tumor. With tumors of these diameters the range of effective incident fluences was from 0.30 to 2.80×10^{12} per square centimeter.

³In this lecture, numerical 'boron' doses refer to doses of boron-10, a stable isotope of boron. Preparations of borax and pentaborate were 95 ± 1 atom% enriched in boron-10.

Our next study determined the effect of increasing the boron dose. Many studies were done at 25 and 35 micrograms boron per gram mouse body weight; fewer studies were made at 50 and 100 micrograms boron per gram mouse body weight. In these observations, the incident thermal neutron fluences ranged from 1.0 to $2.0 \times 10^{12}/\text{cm}^2$. The results showed that increasing boron dosage from 25 to 50 micrograms per gram of mouse did not increase tumor regression significantly; this also was true between the 50 and 100 microgram per gram dose levels. Fifty percent of the mice receiving the 25 $\mu\text{g/g}$ dose showed complete regression (cure) (92 of 184 tumors so tested), as did 48% of those that received 50 $\mu\text{g/g}$ (119 of 124 neoplasms tested) (24). These data reinforced our rationale for using 35 micrograms boron per gram body weight as the standard experimental test dose in mice. Moreover, this dose is equivalent to 35 milligrams boron per kilogram body weight, which was used in the large series of adult patients who were treated at the BMRR from 1959 to 1961 (25).

It is useful here to recall the data on the malignancy and histology of the experimental mouse tumor. Over the years of experimentation there was no decrease in the invasiveness of this tumor by virtue of our transplantation procedures; neither was there any change in its macroscopic growth characteristics [Figure 3a, unirradiated mouse on left] or in its histological appearance [Figure 3b]. After neutron capture therapy, the tumor did not regress immediately. At no time did we find necrosis to be a consequence of the irradiation. Histological studies made 24-48 hrs after treatment demonstrated some increase in cytoplasm, but there was no multinucleation, cellular inclusions or other change. There was some degree of cellular edema in the tumor. Mitotic figures were rare. Subsequently, regression and resorption took place. There was never any formation of scar tissue. After

the tumor had regressed, the muscle at the site of tumor implantation was histologically normal. Moreover, the overlying skin was neither epilated nor apparently affected in any fashion (23).

By 1968 we had accumulated a massive amount of data and studies on the effect of varying the interval between injection and exposure were in progress. But we had no assurance that we could rightfully use all the data or even any specific part in a summation analysis. We were eager to learn if there were demonstrable differences in the results when different reactors were used with different exposure times, from over 20 minutes at the BGRR to one hundred milliseconds at the TRIGA pulsed reactor. The extensive studies at the BMR^P fell between these extremes, at 100 to 300 seconds.

Up to this time we had routinely calculated entrance fluence by measuring activation of gold wires inserted in various segments of the mouse thigh tumor. Useful as these experiments had been, they gave no information on the effect of various tumor diameters upon outcome. We had neglected approximation of exit dose studies at presumably maximum diameters. These we now determined to examine. Fortunately, in all of our tests, we had implanted gold wires and foils distal to the neutron flux entrance, so their activation gave a better measurement to establish the effective average neutron fluence to the most distant region of the tumor. These so-called exit data were now calculated. It was clear that a knowledge of the attenuation factor of neutron fluence by tumor size was needed to compare the results from tumors of different diameters. At this point, Konikowski undertook the arduous task of reexamining all the data obtained with the several boron doses of 25, 35, and 50 micrograms per gram body weight. He also determined the flux fall-off half-distance for thermal neutron penetration into the tumor, 6.7 mm, which was needed in our calculations. The attenuation factor for neutron flux from

the nearest surface to the deepest penetration of the tumor is given by the following equation:

$$f = \exp[-(\text{maximum tumor depth in mm}) \times 0.693/6.7].$$

The values for f range from 0.44 for a tumor 8 mm in maximum depth, to 0.32 for an 11 mm-deep tumor, to 0.26 for a 13 mm-deep tumor, and so on.

We were also interested in estimating the radiation dose at the deepest margin of the tumor. For this estimate we modified the formula of Brownell and Hines (using 10^{12} neutrons per cm^2 as the unit of fluence), making the formula:

$$\text{Dose (rad)} = 8.67 [^{10}\text{B micrograms per gram tumor}] [\text{neutron fluence}]$$

For our purposes, the boron concentration used is what we term the most probable concentration [MPC]. This value is obtained from the composite graphs of tumor concentration for each ten-minute interval after injection, up to over one hour. Since the final computed unit would have some dimension of rad, we called it the Exit Rad Index [ERI]. This index is calculated with the following formula:

$$\text{ERI} = 8.67 [\text{MPC}; ^{10}\text{B micrograms per gram}] [f] [\text{surface fluence}]$$

The Exit Rad Index is a convenient index with which we can compare our numerous experimental trials. ERI must be some approximation to the minimum dose or the dose at the exit of the slow neutron beam as it passed through the tumor, although we did not explore this aspect of dosimetry further.

When we plotted all the data from the various studies using the Exit Rad Index as the reference dose unit, we observed that the data for different doses at different reactors showed a remarkable fit to a standard format (26) [Figures 5, 6, and 7] despite marked variations in the numbers of animals, the results from which are plotted using the standard axes. Representative data from the Brookhaven Graphite Research Reactor [BGRR], the Brookhaven Medical Research Reactor [BMRR] and the General Atomics TRIGA Pulsed Reactor are presented in the figures. Unpublished data from the reactor at the Kernforschungsanlage at Jülich near Cologne, West Germany, also fell on a similar line as did a few data obtained at the Texas A & M Reactor. Comparison of Figs. 4, 5, and 6 indicate no therapeutic advantage to delivering equivalent radiation in ever-decreasing exposure times, as had been postulated. On the contrary, the prolonged irradiations at the BGRR, in retrospect, were no less efficient overall than those performed more rapidly at the other reactors. The number of animals observed with tumor regression at zero per cent and one hundred per cent is small, since these points are absolute and can be determined with only a minimal number of test subjects. In every experiment that we carried out, the animals treated had tumors of various diameters. Consequently, we do not have a single experiment in which all animals showed permanent regression (cure) of the tumor. This result could have been attained by restricting a study to tumors of a single diameter less than 1.0 cm, but that would not have been as informative as using tumors of multiple sizes. It is important to remember that these studies were done over almost two decades, using a variety of reactors, at several of which rather makeshift or jerry-built devices were used to hold the animals for irradiation. Taking into account the general factor of biological variation, the graphs show, gratifyingly, a consistent, uniform pattern. This uniformity

bespeaks a validity for using all of our data when we examine the totality of results for their compatibility with our original hypotheses.

It is now evident that the most significant of all our studies was the one in which we observed the effects using a series of ten-minute sequences for beginning the exposure after boron injection. Before these experiments, we could only predict most generally the outcome in any situation. We had noted that this seemed to be in some way related to the time of exposure after injection, but there was no good evidence to sustain this contention. When data from such studies became available, we learned that despite a flat boron concentration in the tumor after the first ten minutes (we irradiated no animals before ten minutes after injection), the incidence of complete regression of tumors in the exposed population changed remarkably with each sequential injection-exposure time interval. For the groups shown in Figure 7, the number of animals ranged from 53 to 112. For the group exposed from 7 to 11 minutes after injection, 58% showed a complete regression of their tumor; among the group exposed 13 to 23 minutes after injection, 70% showed complete regression of their tumors; in the 25 to 36-minute group, 75% showed complete regression. The mice in the 38 to 48-minute group showed the maximum response of 86% with complete regression. Thereafter, there was a stepwise decline for the 50 to 60-minute group to 58%, the 62 to 72-minute group to 50%, the 74 to 80-minute group to 26%, and the 82 to 92-minute group to 22%. We found this pattern could also be described for each boron dose that we used (27). From this information, we know that some observations in previous studies believed to be deviations were not necessarily due to experimental error. With the development of the Exit Rad Index, we learned that the lesser regression of tumors with greater diameters, which were much more difficult to assess in relation to desired position, really responded in like manner to

smaller tumors where complete regression was frequent. But this did not account for differences in regression rates after varying time of exposure following the boron injection.

One fact became crystal clear. Within the range of our experiments there was no good correlation between boron concentration in the tumor and the extent of regression, regardless of the thermal neutron fluence. When the dose of boron was increased from 25 to 50 micrograms per gram of mouse, only a very small increase was seen in the percentage of tumor regressions when identical neutron fluences were employed. The Exit Rad Index gave us no explanation of this phenomenon. We were also puzzled by failure to see any epilation or changes in the skin that lay over the tumor when analyses of the epidermis showed that there was sufficient boron concentration to cause damage. To destroy the skin, we had found that a very much greater thermal neutron fluence was needed. But the most puzzling observation was the changing effects upon the tumor with differing intervals between injection and exposure, despite an almost constant MPC.

The results at the BGRR and at the BMRR show a pleasing consistency. When we take into account the marked differences in durations of exposure, over 20 minutes at the BGRR and only 23 to 300 seconds at the BMRR, it becomes clear why we did not anticipate such similarity. There is no reason to believe that similar, stepwise-effects would not have occurred at the BGRR had we used variable injection-exposure time in intervals there. It was by pure chance that we began exposure at the BGRR at an interval that was the most effective for tumor regression. I suspect that the scatter of results in the TRIGA experiments was due in large part to uncertainty in placing the animals in the path of the beam. Yet, taking all this into account, as well as the small number of animals exposed at the TRIGA pulsed reactor in a fraction of

one second, there are no good grounds for believing that the 300-millisecond TRIGA exposures were any more efficacious than the BMRR exposures.

Discussion

One major puzzle which these data present can be stated succinctly. The $^{10}\text{B}(n,\alpha)^7\text{Li}$ reaction must occur when thermal neutrons come into juxtaposition to a boron-10 atom. Yet, when these data are examined with respect to complete tumor regression following several different injection-radiation intervals, a paradox is evident. Tumor elimination was not consistent with the observed boron concentration and the neutron fluence. This inconsistency is clearly shown in Figure 7, and is also suspected from a study of various relationships between the ERI and the probability of tumor regression. In studies at the BCRR, Figures 5(a) and 5(d), the curves shown are very similar with respect to slope and to the ERI, 100 to 120, at the 100% tumor regression point. The boron dose administered and, hence, the average tumor boron concentration for Fig. 5(d) were much larger than for Fig. 5(a). Yet, in both series, some animals showed completely regressed tumors at an ERI below 50. Figures 4(b) and 5(c) show two different series studied at the BMRR at injection-irradiation intervals of 26-38 and 26-30 minutes, respectively, with almost identical boron concentrations, where the ERI for 100% tumor regressions was 165-170. Some mice showed complete regression in each series at an ERI of 50. The 100% value for ERI at the TRIGA reactor was about 170 [Fig. 5(b)] and the slope of the curve approaches the slopes seen for the BMRR. In Figs. 4(c) & 4(d), in which the intervals were 40-92 and 52-92, respectively, at an ERI of 50 no animals showed regression. With longer intervals, injection to irradiation, at the BMRR, the ERI also shows a decrease in the efficacy of the treatment. The ERI curve for the BMRR study

with an injection-irradiation interval of 7-25 minutes [Fig. 4(a)] paralleled, but was not congruent with, the ERI curve for the BGRR study at 20-30 minutes [Fig. 5d]. In the former, the 100% tumor control point was reached at an ERI of about 150, and an estimated lowest control point was probably reached at an ERI of about 50.

No matter how the experimental data are approached, all reactors exhibit a similar picture. For some reason, in certain animals the tumor is more readily affected by this reaction than in apparently similar animals when the expected reaction intensities should be identical. Further, in all of these studies, the disappearance of the tumor, though complete and not recurring in the animal's lifetime, was not accompanied by scar formation nor by any detectable residua of tumor or irradiation (26, 27). Such regression might be compared to the disappearance of hypertrophied tissue when the stimulus to hypertrophy has gone. When much larger radiation exposures were given to the skin than were used in these studies, both epilation and scarring followed, yet exposures of this intensity caused no changes in muscle tissue sections taken from exposure sites.

How can we explain these paradoxes? Our data give no clue to the answer. There are a number of possible hypotheses which come to mind, but in the absence of much more data on the pharmacodynamics and pharmacokinetics of the borate ion, no selection among these hypotheses can be made today.

Epilogue

I look to researchers at Brookhaven National Laboratory to continue work on experimental neutron capture therapy and its application to patient therapy. In so doing, I trust you will explain the paradoxes I have outlined.

Acknowledgment

The assistance of the late Mr. Tadeusz Konikowski in performing these clinical and experimental studies of BNCT was invaluable. I thank Dr. Daniel Slatkin for delving into the archives at Brookhaven to enable me to present the correct chronology of our beginning efforts in this program. Thanks are also due to the late Professor Dr. H. W. Knipping of the University of Cologne and the Kernforschungsanlage, Jülich, Germany, for work at the latter facility, and to the staff of the General Atomics Corporation, La Jolla, California, for splendid cooperation at their TRIGA pulsed reactor facility. This work was initiated and conducted in large part at Brookhaven National Laboratory, Upton, New York under the aegis of the U.S. Atomic Energy Commission. After 1962, substantial support was also provided by the M.D. Anderson Cancer Hospital, Houston, Texas.

References

1. Farr, L.E., and Robertson, J.S., Neutron Capture Therapy, in Encyclopedia of Medical Radiology, Vol.16/2. Springer Verlag, Berlin, 1971, pp. 68-92.
2. Robertson, J.S., Stickley, E.E., Bond, V.P., and Farr, L.E., The Proposed Brookhaven Medical Research Reactor, Nucleonics, 13:64, 1955.
3. Easterday, O.D., Constant Temperature Apparatus for Increasing the Solubility of Drugs for Injection. Arch. Int. Pharm., 137:2, 1957.
4. Easterday, O.D., and Hamel, H., Acute Intravenous and Intraperitoneal Toxicity Studies on Sodium Pentaborate Decahydrate and Sodium Tetraborate. Arch. Int. Pharmacodyn., 143:144, 1963.
5. Konikowski, T., and Farr, L.E., Determination of Microgram Quantities of Inorganic Boron in Mammalian Specimens. Clin. Chem., 11:378, 1965.
6. Farr, L.E., and Konikowski, T., Renal Clearance of Sodium Pentaborate in Mice and Man. Clin. Chem., 9:717, 1963.

7. Farr, L.E., and Konikowski, T., The Effect of Regional Thermal Neutron Exposure Upon the Growth and Transplantability of an Induced Malignant Tumor in the Mouse, Proceedings of the Symposium on Biological Effects of Neutron and Proton Irradiations, Brookhaven National Laboratory, Upton, New York, Oct. 3-11, 1963, Vol. 2, IAEA, Vienna, pp. 157-172.
8. Farr, L.E., The Impact of Nuclear Science on Medicine, Am. Scientist, 41:556, 1953.
9. Lippincott, S.W., Robertson, J.S., Bond, V.P., Cronkite, E.P., Easterday, O.D., and Farr, L.E., Effects of Thermal Neutrons and of Heavy Particles from $^{10}\text{B}(n,\alpha)^7\text{Li}$ Reaction on Pig Skin, AMA Arch. Path., 68:639, 1959.
10. Locksley, H.B. and Farr, L.E., Tolerance of Large Doses of Sodium Borate Given Intravenously by Patients Receiving Neutron Capture Therapy, J. Pharmacol. Exp. Ther., 114:484, 1955.
11. Conn, H.B., Antal, B.B., and Farr, L.E., Effects of Large Intravenous Doses of Sodium Borate on Human Myocardium as Reflected in the Electrocardiogram, Circulation, 12:1043, 1955.
12. Farr, L.E., Sweet, W.W., Robertson, J.S., Foster, C.G., Locksley, H.B., Sutherland, D.L., Mendelsohn, M.L., and Stickley, E.E., Neutron Capture Therapy with Boron in the Treatment of Glioblastoma Multiforme, Am. J. Roent. Ther. Nucl. Med., 71:279, 1954.
13. Farr, L.E., Robertson, J.S., and Stickley, E.E., Physiology of Neutron Capture Therapy, Proc. Natl. Acad. Sci. USA, 40:1087, 1954.
14. Godwin, J.T., Farr, L.E., Sweet, W.W., and Robertson, J.S., Pathological Studies of Eight Patients with Glioblastoma Multiforme Treated by Neutron Capture Therapy Using Boron-10, Cancer, 8:601, 1955.
15. Farr, L.E., and Lippincott, S.W., The Medical Uses of Nuclear Reactors, Bruxelles-Médicale, 37:843, 1957.
16. Easterday, O.D., and Farr, L.E., Alteration of Borate Toxicity by d-Glucose. J. Pharmacol. Exp. Ther., 132:392, 1951.
17. Farr, L.E., Calvo, W.G., Haymaker, W.E., Lippincott, S.W., Yamamoto, Y.L., and Stickley, E.E., Effect of Thermal Neutrons on the Central Nervous System (Apparent Tolerance of Central Nervous System Structures in Man), Arch Neurol., 4:246, 1961.
18. Lippincott, S.W., Calvo, W.G., Backer, E.P., Jesseph, J.E., Jansen, C.R., and Farr, L.E., Effects of Heavy High Energy Charged Particles. AMA Arch. Path., 76:543, 1963.
19. Farr, L.E., Nuclear Reactor Radiology in Clinical Medicine. Northwest Medicine, 59:1121, 1960.

20. Farr, L.E., Lippincott, S.W., Kahle, W., Haymaker, W.E., and Yakolev, P.I., The Neuropathological and Topographical Study of Whole Brains Following Neutron Capture Therapy for Glioblastoma Multiforme, Proc. III Cong. Intl. de Neuropathologie, Brussels, Belgium, July 25, 1957.
21. Farr, L.E., Robertson, J.S., Stickley, E.E., Bagnall, H.J., Easterday, O.D., and Kahle, W., Recent Advances in Neutron Capture Therapy, Progress in Nuclear Energy. Series VI. Vol. 2. Medical Sciences, Eds. Bugher, J.E., Coursaget, J., Loutit, J.F., Pergamon Press, London & New York, 1959, pp. 128-138.
22. Lippincott, S.W., Yamamoto, Y.L., and Farr, L.E., Radiation Effects of Neutron Capture Therapy on a Malignant Vascular Neoplasm of the Cerebellum, AMA Arch. Path., 69:44, 1959.
23. Farr, L.E., and Konikowski, T., Skin Lesions in the Mouse from Alpha Particle Formation by the Thermal Neutron Boron-10 Reaction. Radiat. Res., 19:245, 1963.
24. Farr, L.E., and Konikowski, T., Effects of Varying Boron-10 Dose, Thermal Neutron Fluence and Reactor Employed on Results of Neutron Capture Therapy of a Transplantable Mouse Neoplasm. Int. J. Appl. Radiat. Isot., 19:495, 1968.
25. Slatkin, D.N., A History of Boron Neutron Capture Therapy of Brain Tumors: Postulation of a Brain Radiation Dose Tolerance Limit. Brain, 114:1609, 1991.
26. Farr, L.E., and Konikowski, T., Long Range Effects of Neutron Capture Therapy of Cancer in Mice. I: Correlation between the time of intracellular residence of $^{10}\text{B-Na}$ pentaborate and the regression of the tumor. Int. J. Nucl. Med. Biol., 3:1, 1976.
27. Farr, L.E., and Konikowski, T., Long Range Effects of Neutron Capture Therapy of Cancer in Mice. II. Dose Effect. Int. J. Nucl. Med. Biol., 5:3, 1978.

Legends for Figures

- Figure 1. Effect of exposure to a mainly thermal neutron beam at the BGRR is only moderate growth retardation. (A) Untreated tumor. (B) Tumor after irradiation at the reactor.
- Figure 2. Distribution of boron-10 with time after intravenous injection in mice of sodium pentaborate:glucose (molar ratio 2:1).
- Frame 2a: 50 $\mu\text{g } ^{10}\text{B}$ per gram of body weight
Frame 2b: 35 $\mu\text{g } ^{10}\text{B}$ per gram of body weight
Frame 2c: 25 $\mu\text{g } ^{10}\text{B}$ per gram of body weight
- Figure 3a. Typical appearances of experimental mice 18 days after tumor implantation in the right thigh: left, unirradiated; right, 13 days after BNCT. (BNL #10-380-91)
- Figure 3b. Microscopic view magnification (X1200) of a thin stained section from an unirradiated tumor in mouse thigh muscle ten days after its implantation. (BNL #10-380-91)
- Figure 4. Exit Rad Index versus Percent Tumor Regression for several BMRR studies using intravenously injected sodium pentaborate:glucose (molar ratio 2:1). Dose: 35 $\mu\text{g } ^{10}\text{B}$ per gram of body weight. The number of animals used for a point is shown near that point.
- Frame 4a: Leg tumor diameters: 8-15 mm
Average tumor- ^{10}B concentration at time of treatment: 24.8 $\mu\text{g}/\text{gm}$
Injection-irradiation intervals: 7-25 minutes
Thermal neutron exposure time: 23 seconds
Number of animals treated: 374
- Frame 4b: Leg tumor diameters: 8-17 mm
Average tumor- ^{10}B concentration at time of treatment: 29.0 $\mu\text{g}/\text{gm}$
Injection-irradiation intervals: 26-38 minutes
Thermal neutron exposure times: 23-300 seconds
Number of animals treated: 926
- Frame 4c: Leg tumor diameters: 8-15 mm
Average tumor- ^{10}B concentration at time of treatment: 25.8 $\mu\text{g}/\text{gm}$
Injection-irradiation intervals: 40-92 minutes
Thermal neutron exposure time: 23 seconds
Number of animals treated: 898

Frame 4d: Leg tumor diameters: 8-17 mm
Average tumor-¹⁰B concentration at time of
treatment: 26.5 μg/gm
Injection-irradiation intervals: 52-92 minutes
Thermal neutron exposure times: 100-300 seconds
Number of animals treated: 684

Figure 5.

Exit Rad Index versus Percent Tumor Regression for some
BGRR, TRIGA, and BMRR experiments using pentaborate:glucose
(molar ratio 2:1). The number of animals used for a point
is shown near that point.

Frame 5a: Reactor: BGRR
Leg tumor diameters: 8-17 mm
Dose: 25 μg ¹⁰B per gram of body weight
Average tumor-¹⁰B concentration at time of
treatment: 20.5 μg/gm
Injection-irradiation intervals: 20-30 minutes
Thermal neutron exposure time: 22 minutes
Number of animals treated: 62

Frame 5b: Reactor: Pulsed TRIGA: General Atomics Jackson
Laboratory
Leg tumor diameters: 8-17 mm
Dose: 35 μg ¹⁰B per gram of body weight
Average tumor-¹⁰B concentration at time of
treatment: 28.8 μg/gm
Injection-irradiation intervals: 28-38 minutes
Thermal neutron exposure time: 100 milliseconds
Number of animals treated: 36

Frame 5c: Reactor: BMRR
Leg tumor diameters: 8-17 mm
Dose: 35 μg ¹⁰B per gram of body weight
Average tumor-¹⁰B concentration at time of
treatment: 30.0 μg/gm
Injection-irradiation intervals: 26-30 minutes
Thermal neutron exposure times: 100-300 seconds
Number of animals treated: 611

Frame 5d: Reactor: BGRR
Leg tumor diameters: 8-17 mm
Dose: 50 μg ¹⁰B per gram of body weight
Average tumor-¹⁰B concentration at time of
treatment: 30.2 μg/gm
Injection-irradiation intervals: 20-30 minutes
Thermal neutron exposure time: 22 minutes
Number of animals treated: 108

Figure 6.

Exit Rad Index versus Percent Tumor Regression for other studies at the BGRR using intravenously injected sodium pentaborate:glucose (molar ratio 2:1).

Leg tumor diameters: 8-17 mm

Dose: 50 μg ^{10}B per gram of body weight

Average tumor- ^{10}B concentration at time of treatment: 31.9 $\mu\text{g}/\text{gm}$

Injection-irradiation intervals: 31-50 minutes

Thermal neutron exposure time: 22 minutes

Number of animals treated: 140

Figure 7.

BMRR study. Percentage of mice exhibiting permanent tumor regression plotted against serially increasing injection-to-exposure time intervals.

All treated neoplasms: 9-11 mm diameter

(n): Number of animals used for the indicated injection-to exposure time interval

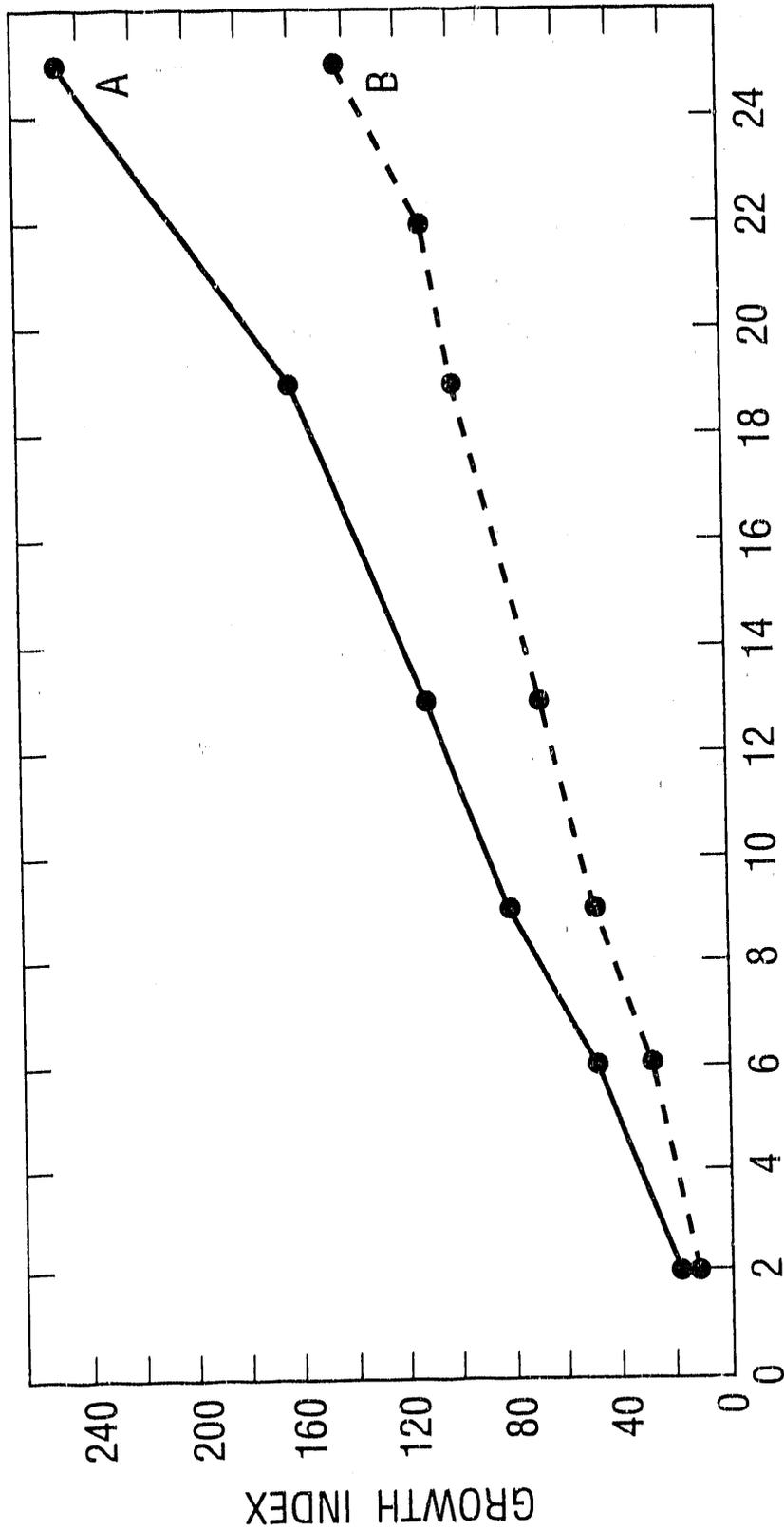
Thermal neutron fluences: 1.41 to 1.67 $\times 10^{12}/\text{cm}^2$

Thermal neutron exposure time: 23 seconds

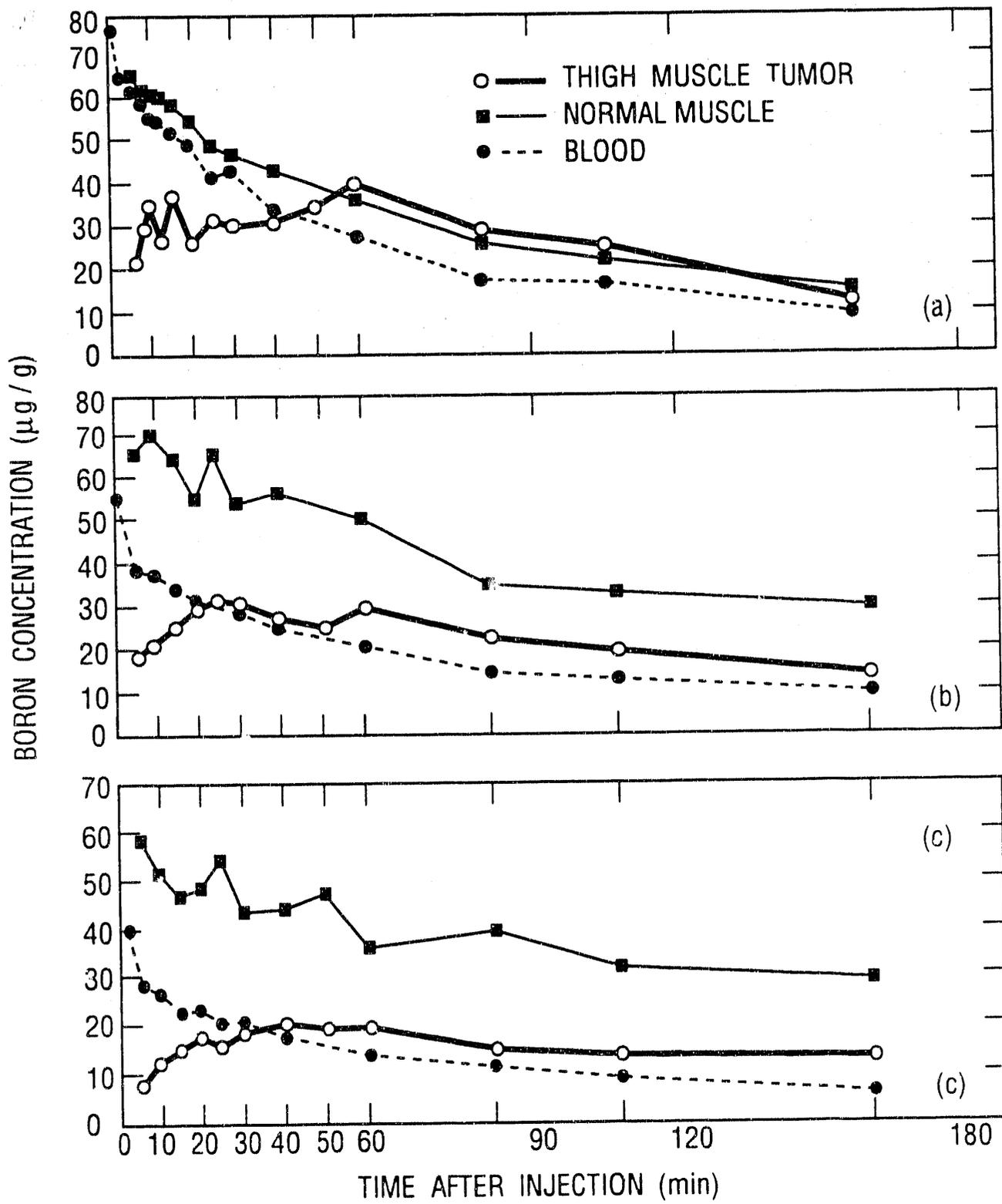
Drug: Sodium ^{10}B -pentaborate:glucose (molar ratio 2:1)

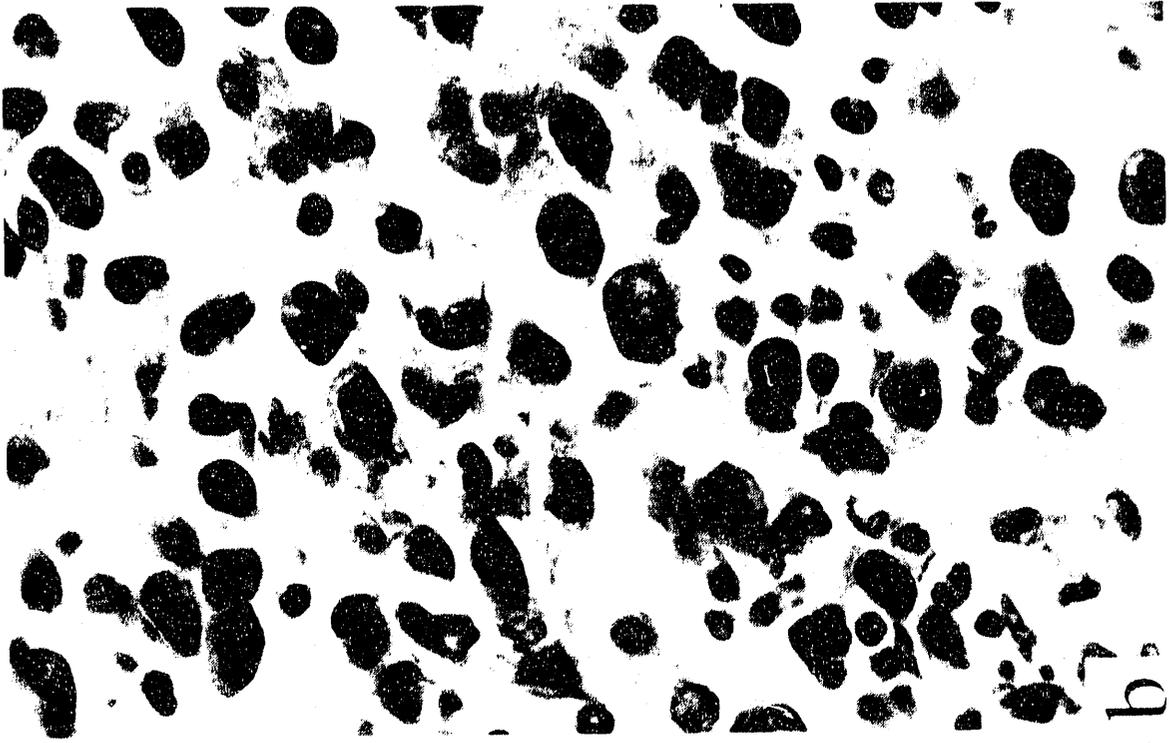
Dose (intravenous): 35 μg $^{10}\text{B}/\text{g}$ body weight

Number of animals treated: 652

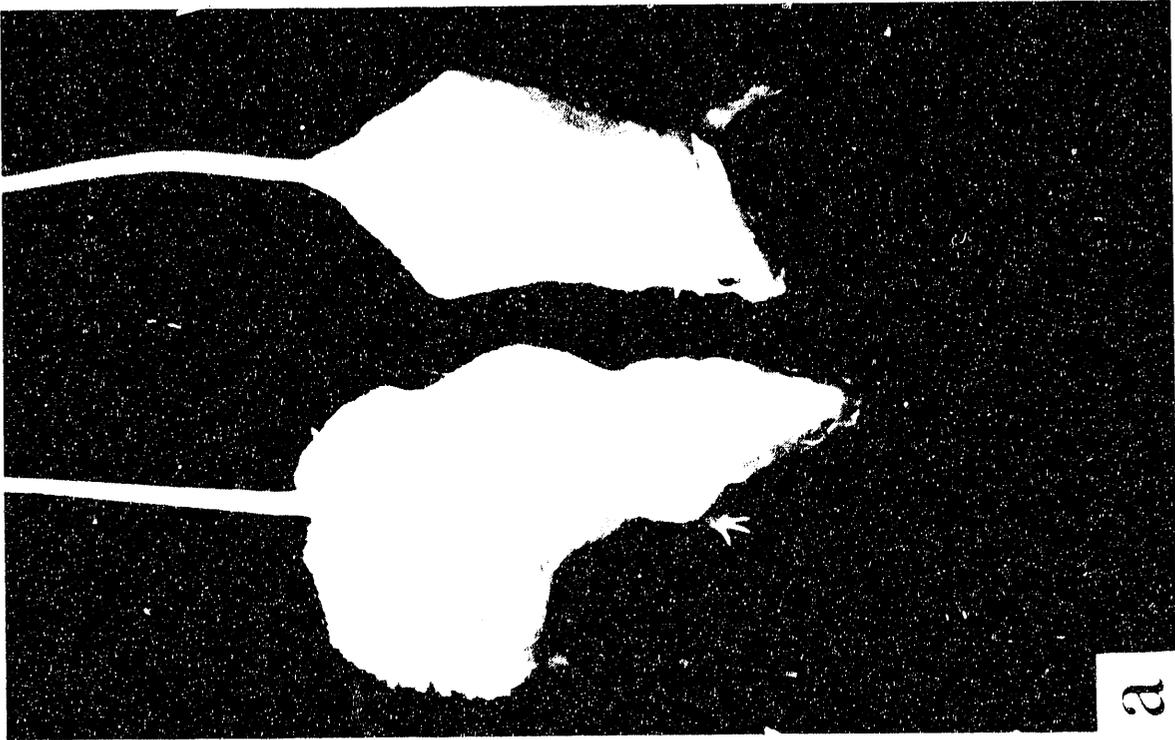


DAYS AFTER IRRADIATION AT A THERMAL NEUTRON PORT
OF THE BROOKHAVEN GRAPHITE RESEARCH REACTOR

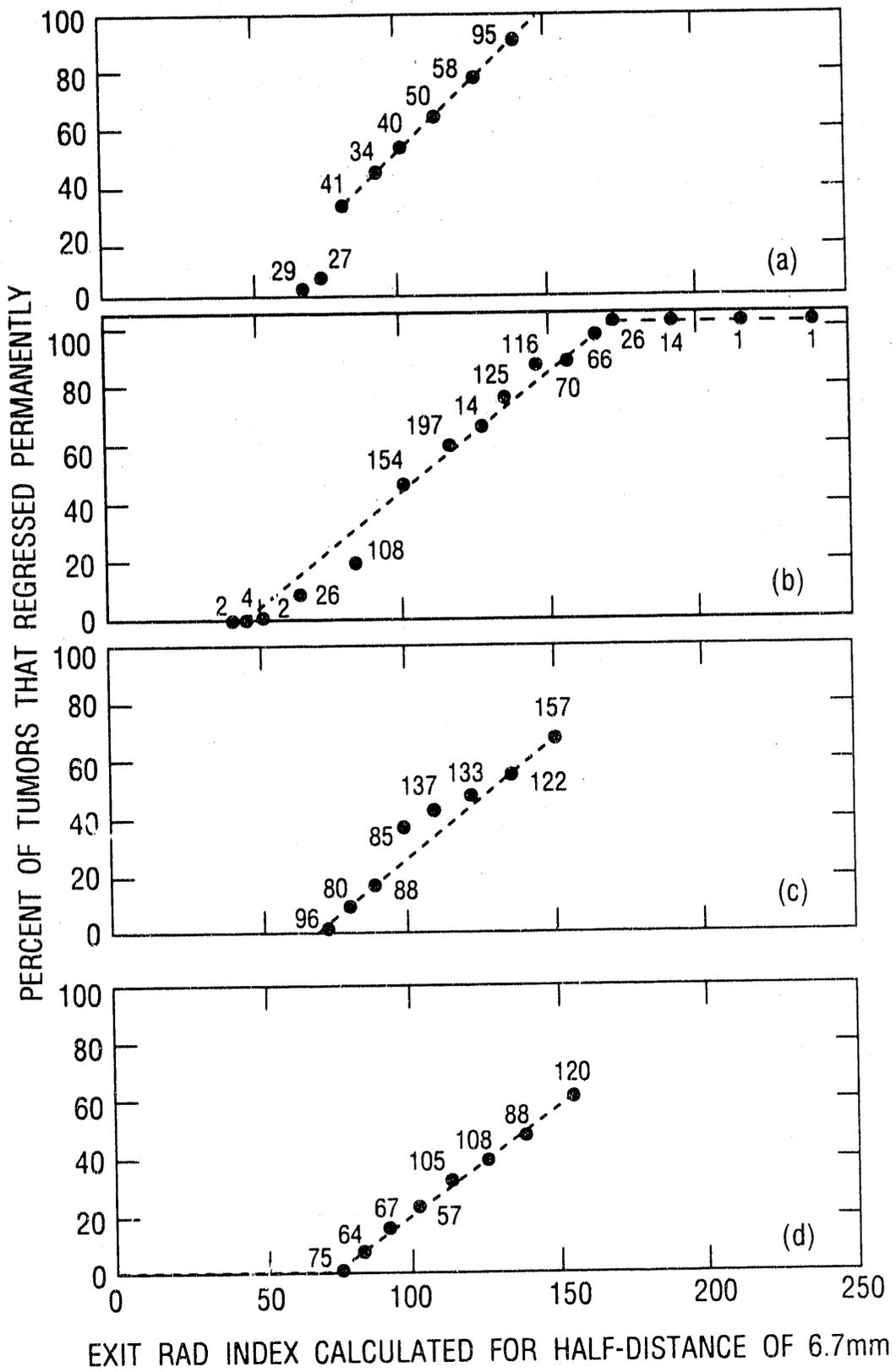


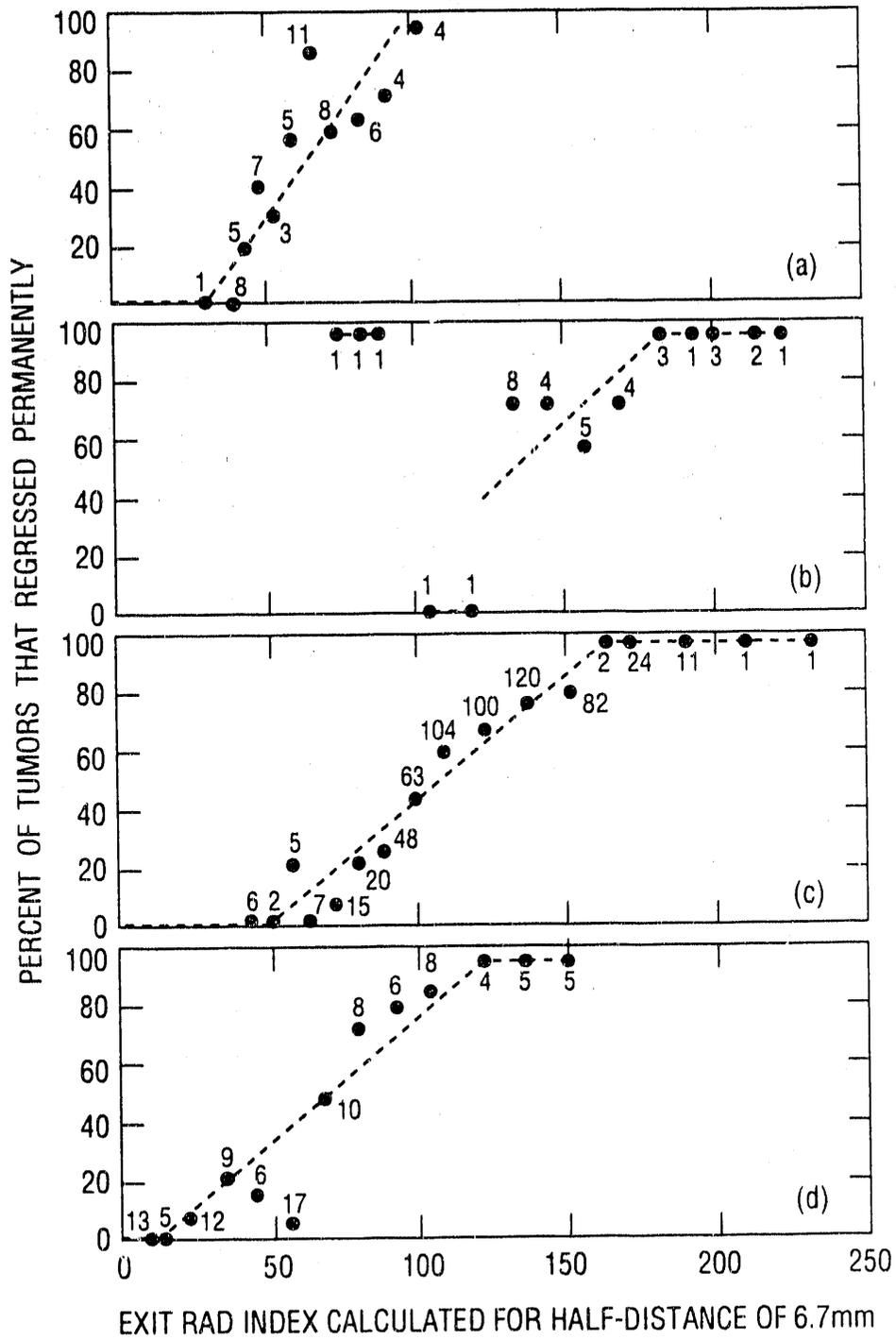


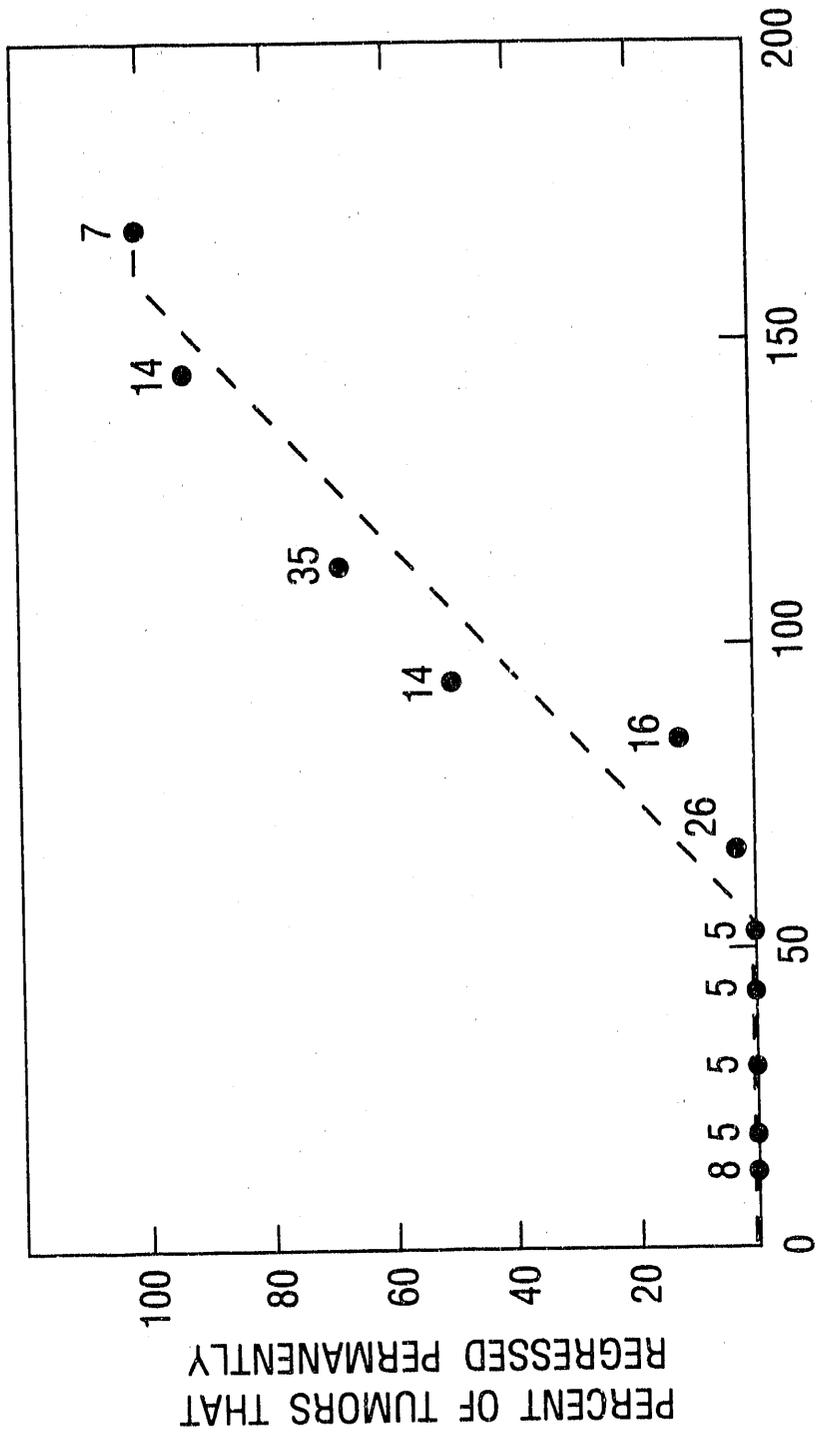
b

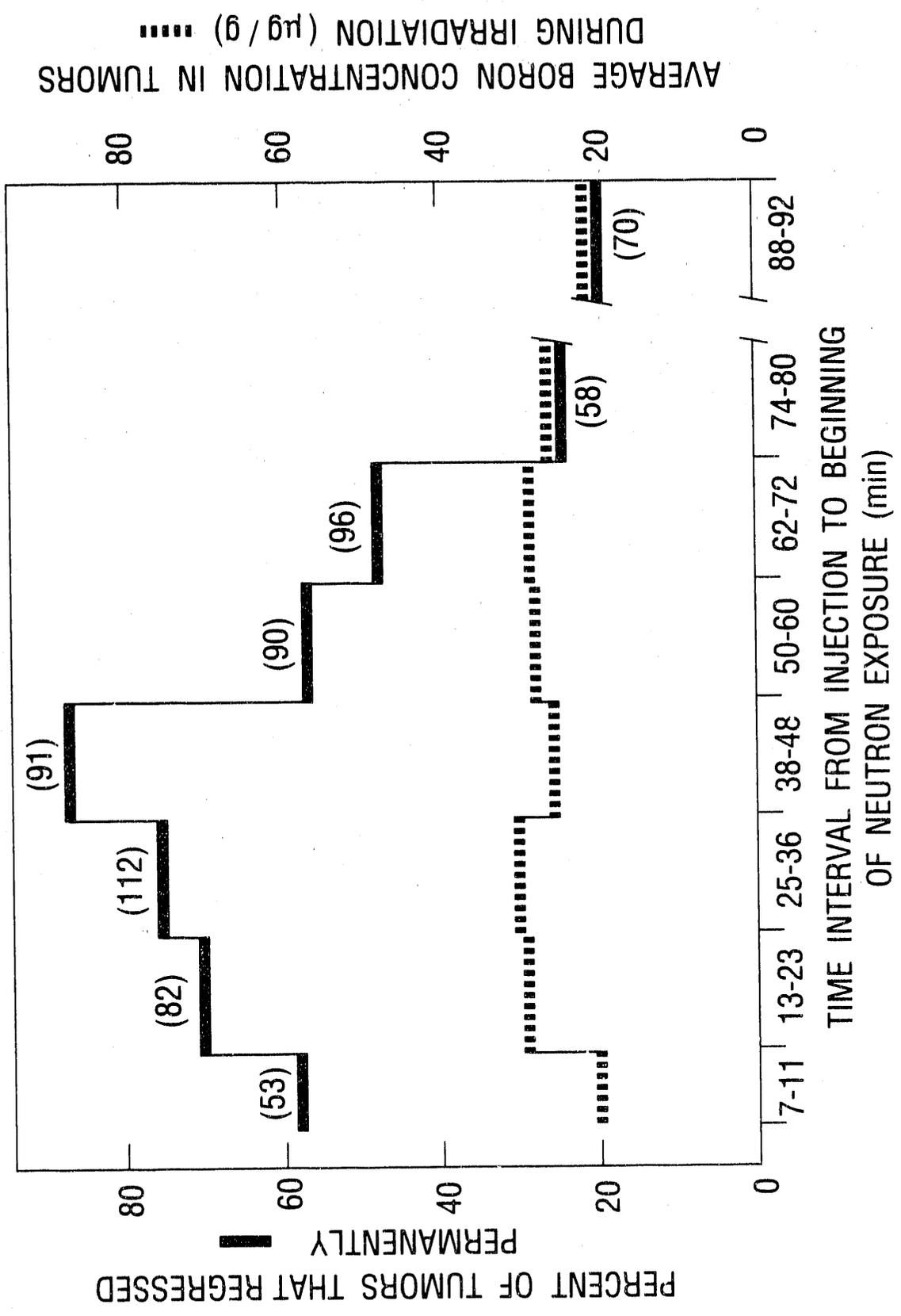


a









END

**DATE
FILMED**

6/10/92

