DOSIMETRY IN BORON NEUTRON CAPTURE THERAPY

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Abstract

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Boron neutron capture therapy is based on the irradiation of charged particles in the tumour cells. The dose in the tumour is equal to the total energy from the $^{10}B(n,\alpha)^7Li$ reaction, which is proportional to the product of the neutron fluence and the ^{10}B concentration in the tumour. Dosimetry for medical therapy implies the monitoring of the neutron fluence and the measurement of ^{10}B concentrations. The neutron fluence was determined by miniaturized silicon detectors covered with ^6LiF. The detectors are manufactured in our laboratory and have been successfully utilized for clinical purposes. The ^{10}B concentrations have, up to now, been measured by chemical analysis. Another measuring system is being studied for practical application. In this system the 0.48 MeV prompt gamma rays emitted from ^7Li nuclei are detected by Ge(Li) gamma detectors. Errors are 3% for 30 ppm of ^{10}B and 30% for 1 ppm of ^{10}B when the sample volume is 0.28 cm^3 and the counting time is 1000 seconds. Some clinical results of the boron neutron capture therapy are also described.

1. INTRODUCTION

In boron neutron capture therapy the boron-10 compound is injected before the operation [1–3]. The compound is deposited selectively in the tumour and owing to the blood/brain barrier phenomenon is not taken up in the normal brain cells. After the tumour has taken up the compound, the lesion is irradiated with thermal neutrons. The neutron capture reaction $^{10}B(n, \alpha)^{7}Li$ releases an alpha particle and a ^{7}Li ion with a mean kinetic energy of 2.33 MeV as follows:

$$^{10}B + n \longrightarrow \begin{cases} {}^{7}Li + \alpha + 2.79\ \text{MeV}\ (6.1\%) \\ {}^{7}Li + \alpha + 2.32\ \text{MeV}\ (93.9\%) \\ \quad \hookrightarrow {}^{7}Li + \gamma + 0.48\ \text{MeV} \end{cases}$$

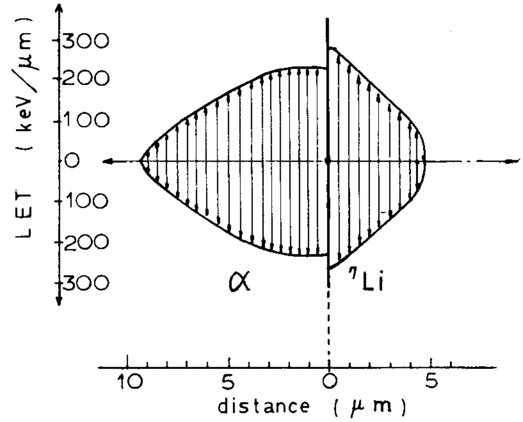
The mean kinetic energy of the alpha particle is 1.48 MeV and that of the ^{7}Li particle is 0.85 MeV. The ranges of the alpha particle and the ^{7}Li particle are 9.0 μm and 4.8 μm in water, respectively. The LET and the range of these particles are shown in Fig. 1. The value for tissue can be considered to be the same as for water. As the range of these charged particles is equal to or less than a cell diameter, nearly all the energy is absorbed in the tumour cells in which the ^{10}B compound is deposited. Some elements in the normal brain tissue also react with the thermal neutron to produce charged particles. The $^{14}N(n, p)^{14}C$ and $^{17}O(n, \alpha)^{14}C$ reactions are important in normal tissue [4]. Tables I and II show the energy released by these reactions, and other related values. The number of ^{14}N and ^{17}O nuclides shown in Table I are the values in the tissue-equivalent Rossi liquid $(C_5H_{40}O_{18}N)_n$. When the ^{10}B concentration W is larger than 3.2 μg/g of tissue, the average energy released by the $^{10}B(n, \alpha)^{7}Li$ reaction is larger than the value of other reactions. Only the dose due to the $^{10}B(n, \alpha)^{7}Li$ reaction is described here. The dose D resulting from the boron neutron reaction can be formulated as follows:

$$D = 8.61 \times 10^{-14}\, W\, \phi t$$

where D, W, ϕ and t are expressed in units of J/kg of tissue, μg/g of tissue, $n \cdot cm^{-2} \cdot s^{-1}$ and seconds, respectively.

Dose determination is divided into two parts: measurement of the ^{10}B concentration W in the tumour, and monitoring of neutron fluence ϕt.

Up to now measurements of neutron fluence were made using the gold-foil activation method. With this method the results are obtained after the irradiation is completed and cannot be used to determine the appropriate irradiation time.



Particle	Energy[a] (MeV)	Range (μm)
Alpha partice	1.48	8.95
^{7}Li ion	0.847	4.80
Total energy	2.33	13.75

[a]Weighted mean value

FIG. 1. Range and LET of alpha and ^{7}Li particles versus distance from the point of ^{10}B(n, α)^{7}Li reaction (in water).

TABLE I. NUMBER OF NUCLIDES IN THE ROSSI LIQUID

Nuclide	Natural abundance (%)	Number of nuclides per kg tissue
^{14}N	99.635	1.49×10^{24}
^{17}O	0.037	9.97×10^{22}
^{10}B		6.02×10^{19}W (see footnote a)

[a] W: ^{10}B concentration (μg/g tissue).

TABLE II. REACTION AND ENERGY RELEASED IN THE TISSUE

Nuclide	Reaction	Cross-section ($\times 10^{-24}$ cm^2)	Energy released (MeV)	(10^{16} J)	Average energy released[a] (J/kg)
^{14}N	$^{14}N(n, p)^{14}C$	1.18	0.63	1.01	$2.72 \times 10^{-13}\,\phi t$
^{17}O	$^{17}O(n, \alpha)^{14}C$	0.24	1.83	2.93	$7.00 \times 10^{-15}\,\phi t$
^{10}B	$^{10}B(n, \alpha)^{7}Li$	3837.	2.33	3.73	$8.61 \times 10^{-14}\,W\phi t$

[a] W: ^{10}B concentration (μg/g tissue); ϕ: neutron flux (n·cm^{-2}·s^{-1}); t: time (s).

Since 1977, a monitoring system which simultaneously measures neutron flux has been under development. It makes use of a miniaturized silicon detector covered with ^6LiF. The system has been effectively utilized for clinical purposes [5]. The concentration of ^{10}B in the tumour has not been measured in each case. Rather, an average value was used for the determination of the dose [6]; this average value was measured by chemical analysis.

Another measuring system for determining the concentration of ^{10}B in the tumour is now being studied for practical application. The measurement is based on the 0.48 MeV prompt gamma rays accompanying the $^{10}B(n, \alpha)^7Li$ reaction.

2. MONITORING THE NEUTRON FLUX

Clinically useful small neutron detectors were manufactured in our laboratory (Fig. 2). The size of the p-type silicon wafer is 2.5 mm in diameter and 0.5 mm in thickness. One side of the silicon wafer is etched with acid mixture CP4, while the other side is protected by wax.[1] The intact side of the wafer is connected to the centre conductor of a coaxial cable by silver paste. After drying, the silicon wafer is firmly connected to the cable with epoxy resin. Aluminium is evaporated onto the etched surface of the silicon wafer and silver paste is again used to ensure electrical contact between the evaporated aluminium electrode and the outer conductor. Five microlitres of an aqueous solution of ^6LiF, of density 1×10^{-5} g/cm^3, are placed on the surface of the aluminium electrode and dried.

[1] CP4: Chemical Polish No. 4; mixture of 5 parts of nitric acid, 3 parts of hydrogen fluoride and 3 parts of glacial acetic acid.

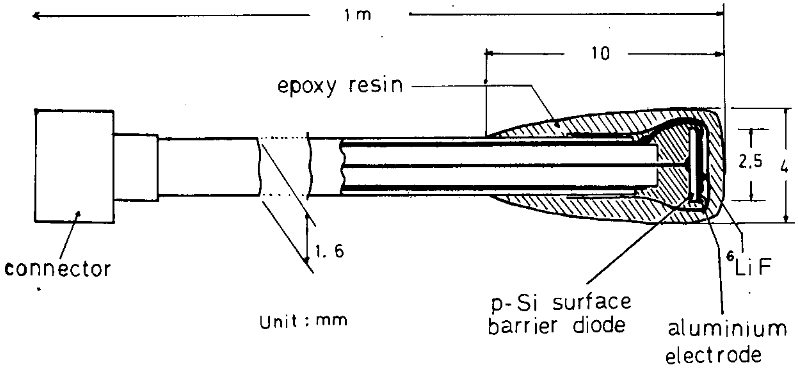


FIG. 2. Cross-sectional view of the miniaturized neutron detector.

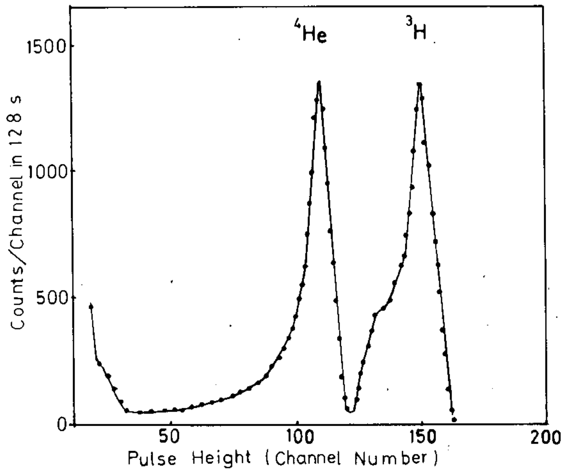


FIG. 3. Pulse-height distribution of the neutron detector. (The neutron flux is $1.4 \times 10^9\ n \cdot cm^{-2} \cdot s^{-1}$).

The detector is then encapsulated in epoxy resin. The cable is about 1 m in length and 1.6 mm in diameter. The capacitance of the cable is 65 pF, while the capacitance of the detector is 15 pF. In actual clinical application, the detector and the cable are covered by a thin rubber tube and sterilized.

Lithium-6 has appropriate characteristics for our purposes. Firstly, the neutron cross-section has 1/v dependency, as is the case for boron. Secondly, the energy released is 4.8 MeV, which is about twice that of ^{10}B. The pulse-height distribution of the neutron detector is shown in Fig. 3; the pulse height

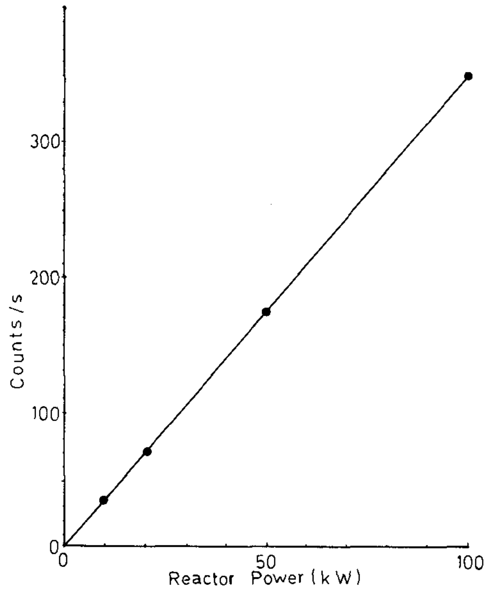


FIG.4. Relation between counte rates and neutron flux.

of the signal is seen to be high enough to be separated from noise. The signal is led to a rate meter and the counting rate is recorded for continuous monitoring. The counting rate at 100 kW full-power reactor operation is usually about one hundred counts per second, which is low enough not to require a dead-time correction. An example of the relation between the neutron flux and the counting rate is shown in Fig. 4.

The fluctuation of the recorded output of the rate meter at 100 kW reactor operation is less than 2% over 5 hours. A multichannel analyser is also connected to the detector in order to check the pulse-height distribution.

Each detector is calibrated by comparing it with activities measured using gold foils before clinical application.

3. CLINICAL APPLICATION AND INTERIM CLINICAL RESULTS

Patients are irradiated by a thermal neutron beam from the medical reactor of the Musashi Institute of Technology [7]. The cross-sectional view of the reactor is shown in Fig. 5. The irradiation port is shown in greater detail in Fig. 6 together with the neutron flux distribution. Neutron flux decreases rapidly with

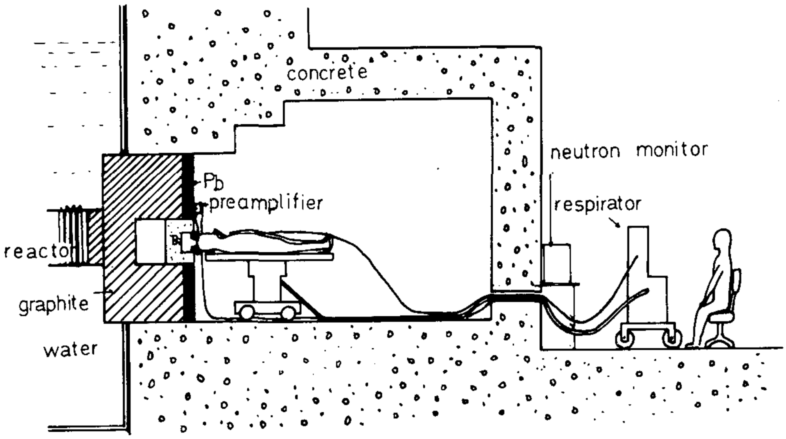


FIG.5. Schematic cross-sectional view of the irradiation room of Musashi Institute of Technology Medical Reactor (100 kW at full power).

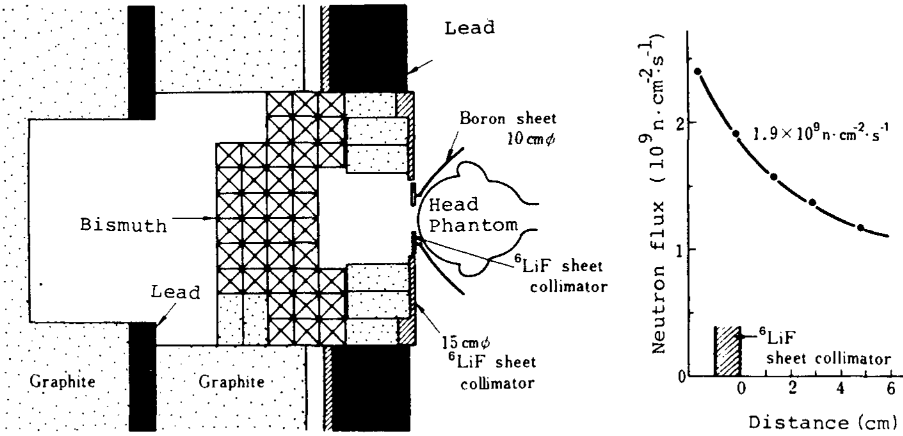


FIG.6. Detailed figure near the irradiation port with neutron flux distribution.

the distance from the port. Brain tumour patients are operated on a week or two before irradiation. The tumour is removed as thoroughly as possible, while avoiding a lobectomy, so that the good penetration of low energy neutrons is ensured. On the night before the neutron irradiation, the ^{10}B compound, $Na_2B_{12}H_{11}SH$, is infused intra-arterially and the patient is transported to the reactor by an ambulance. In the operating theatre in the reactor building, the skull is reopened for the neutron irradiation, and the neutron monitoring detector

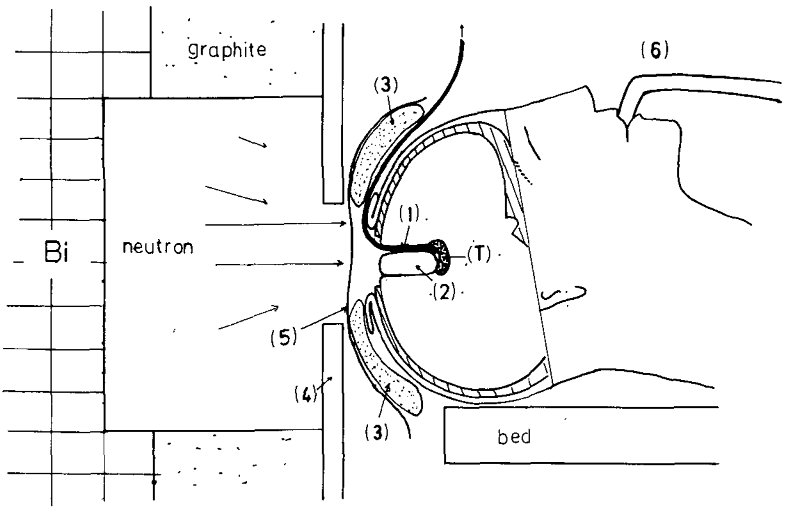


FIG. 7. Diagram of irradiation configuration: (1) neutron detectors; (2) plastic as moderator; (3) neutron shielding helmet containing ^6LiF; (4) neutron collimator; (5) sterile plastic drape; (6) endotracheal tube for general anaesthesia, (T) tumour.

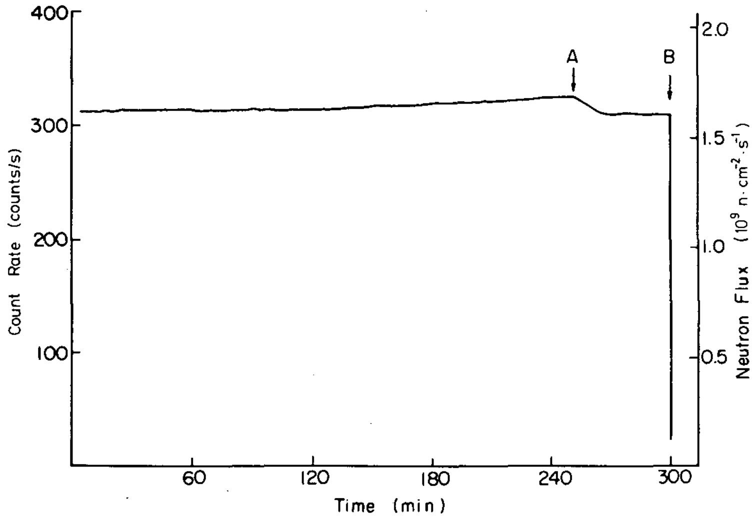


FIG. 8. Record of the count rate in the case of a patient exhibiting brain swelling during treatment. Note the steady rise in count rate. Hyperventilation was achieved at A; B shows reactor shutdown.

and gold foil are placed on the brain. Neutron irradiation is done under remotely controlled general anaesthesia. The patient and the actual application of the detector are shown in Fig. 7.

This monitor has been successfully applied in 21 operations since 1977. In one of these cases, considerable bulging of the brain mass was sensed by silicon wafer neutron detector. The count rate of the detector placed at the surface of the brain increased gradually, as shown in Fig. 8. The physicians then hyperventilated the patient, so that the brain returned to normal size. The reduction in brain bulging was confirmed by a decrease in the count rate.

Boron-10 slow neutron capture therapy has been undertaken in Japan following the return of one of the authors (H.H.) from Massachusetts General Hospital, where Professor W.H. Sweet had initiated this type of therapy in 1952.

Hatanaka treated 12 patients at the University of Tokyo Hospital under the supervision of Professor K. Sano and Professor T. Miyakawa between 1968 and 1974. Between 1974 and 1980, Hatanaka and others have also treated a total of 37 patients at the Teikyo University Hospital.

(a) The first series (1968–74) included mostly terminally ill patients and formed a Phase-1 study. The clinical result for patients with glioblastoma, recurrent after previous ^{60}Co therapy, proved that the therapy extended the lives of these patients by 21.9 ± 7.2 months after the second operation for recurrence, in comparison to 6.7 ± 0.6 months by conventionally available therapies.

(b) A patient was treated by neutron capture therapy a week after the surgical diagnosis of glioblastoma (6 cm × 5 cm × 5 cm in size) in 1972, and has been alive and well for the past 7 years with 100% mobility (Karnofsky scale). His CT scan shows complete emptiness of the tumour site.

(c) Since 1974 all new patients with supratentorial malignant gliomas at the Teikyo University Hospital have been treated by surgery plus neutron capture therapy except those who arrived when one or more of the following three conditions pertained: (i) medical reactor not in operation, (ii) ^{10}B compound not available; (iii) operating physician (H.H.) unavailable. Such patients formed a control group, and were treated by surgery plus ^{60}Co or linac therapy. This kind of patient selection may, in effect, be as valid as a 'randomized study'. The interim clinical result indicated that the neutron capture therapy patients live at least three times longer than ^{60}Co or linac therapy patients, and that their performance status is twice as good as that of the ^{60}Co and linac therapy patients on the Karnofsky scale.

Ninety-four malignant gliomas, sarcomas, inexcisable meningiomas and medulloblastomas were treated between August 1968 and August 1980, either by boron neutron capture therapy (BNCT) or with photons (^{60}Co or linac) as adjuvant therapy to surgery.

– *Supratentorial malignant gliomas:* A total of 68 cases were treated, 23 by BNCT. Average survival of BNCT cases was better than 603 days, as of 31 August 1980. Ten out of the 23 were alive, but in a state of remission. Nine were treated by BNCT after failure of photon treatment. Survival was of the order of 531 days. Half of the BNCT patients could continue at their jobs. The longest surviving glioblastoma patient has worked for over 8 years.

– *Pons-medulla gliomas:* A total of 15 cases were treated, of which 4 were treated by BNCT alone. Average survival was 232 days for BNCT cases. Ten cases were treated by photons alone; average survival was 195 days. A 3 year old girl was treated by BNCT after the astrocytoma recurred after photon treatment. She recovered from a long coma and is now attending elementary school, having survived more than 4 years (1468 days) after the first operation.

– *Sarcoma, etc.:* A total of 7 cases were treated. A rhabdomyosarcoma patient has survived over $6\frac{1}{2}$ years (2459 days). A chondrosarcoma patient has been alive and well as a teacher for more than 3 years (1111 days). Three-fifths of all meningioma cases are alive.

– *Medulloblastoma:* A total of 4 cases was treated, none by BNCT.

– *Summary:* In effect, a randomized study has been conducted since 1977. An average survival for BNCT cases, three times as long and twice as good as with conventional radiotherapy, has been observed.

4. MEASUREMENT OF ^{10}B CONCENTRATION

Up to now, the concentration of ^{10}B in the tumour has been determined by chemical analysis after post-irradiation surgical resection. In clinical applications, the ^{10}B concentrations which have been obtained in previous measurements have been adopted as the basis for determining the tumour dose. The estimated ^{10}B concentrations in the tumour are 30 to 40 $\mu g\,^{10}B/g$ of tissue and 5 to 20 $\mu g\,^{10}B/g$ in the circulating blood.

At present another measuring system is being prepared for general use [8]. In this system the intensity of the prompt gamma rays from the $^{10}B(n,\alpha)^{7}Li$ reaction is measured to obtain results at an early stage.

A collimated neutron beam from the Rikkyo reactor is impinged on sample, and the prompt gamma rays of the reaction between ^{10}B and the neutrons are detected with a Ge(Li) gamma detector. The geometry of the collimator and the position of the sample and the detector are shown in Fig. 9. The collimator is made of paraffin and lead. The beam area is about 3 cm^3 and the profile of the neutron flux is parabolic, as shown in Fig. 10. The average intensity of the thermal neutron is $3.7 \times 10^6\ n \cdot cm^{-2} \cdot s^{-1}$ and the cadmium ratio is 3.4.

The container for the sample is made of quartz. The volume of the sample is 0.28 cm^3. The position of the container relative to the detector is kept

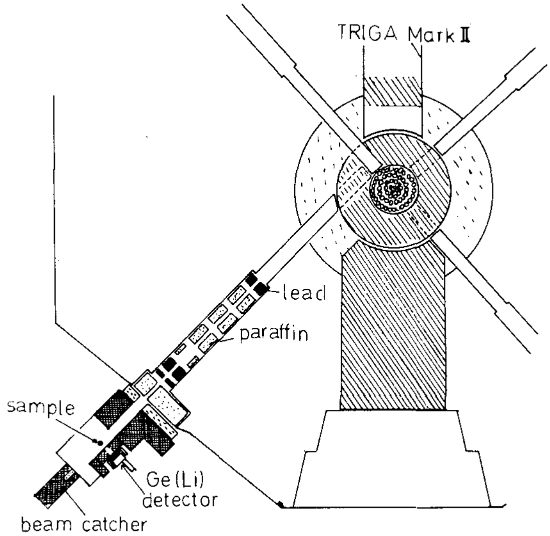


FIG.9. Geometry of the collimator, and the position of the gamma detector and the sample to be measured.

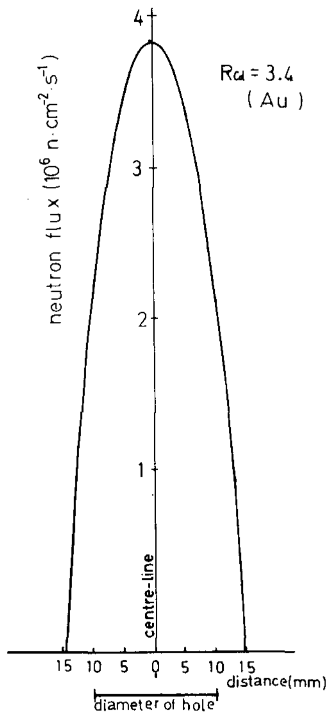


FIG.10. Profile of the thermal neutron beam from the collimator.

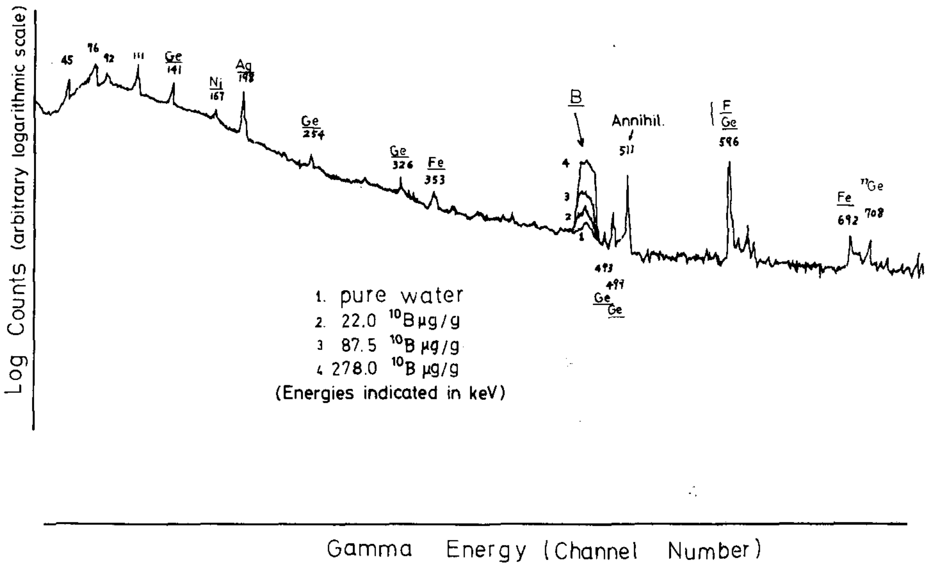


FIG.11. Prompt gamma ray spectrum of boracic acid.

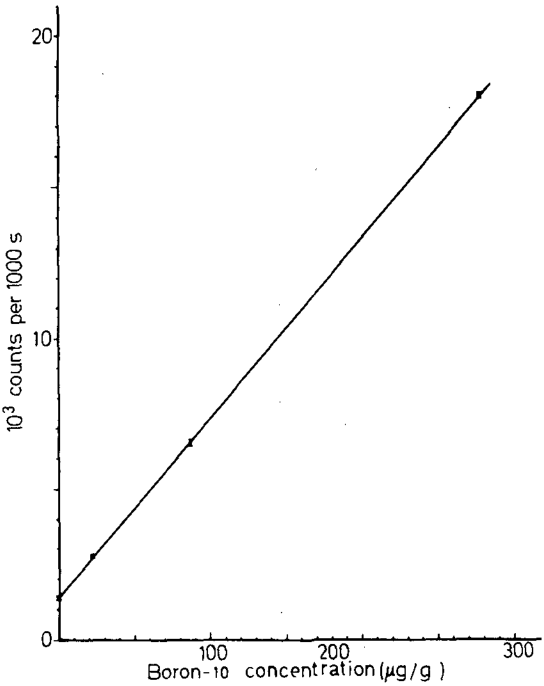


FIG.12. Linearity relation between counts and boron concentration. (The counts are calculated from the sum of those between 469 and 486 keV subtracted by the background.)

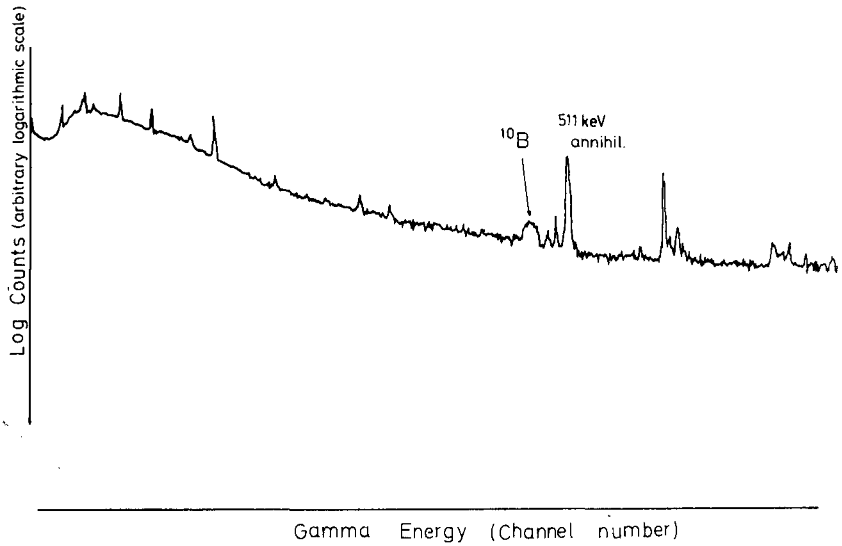


FIG.13. A prompt gamma ray spectrum of the blood of a patient.

constant at all times. The pulse-height distribution of the prompt gamma rays of boracic acid measured by the system is shown in Fig. 11. The spectral shape is distorted owing to Doppler broadening. The total count of the prompt gamma photons is proportional to the concentrations of ^{10}B in the sample, as shown in Fig. 12. The background count of blood is the same as that of water in the range of the prompt gamma rays of the $^{10}B(n, \alpha)^{7}Li$ reaction. So, the relation between the total counts and the ^{10}B concentration obtained using boracic acid can be adopted as a standard calibration curve. Figure 13 shows the pulse-height distribution for blood of a patient. In this case the ^{10}B concentration in the blood was measured to be 18.1 $\mu g\,^{10}B/g$. The preliminary measurements of the system are finished, and the system being prepared for practical application.

ACKNOWLEDGEMENTS

The authors are grateful to Professor An (University of Tokyo) and Professor T. Sato (Musashi Institute of Technology) for their constant encouragement.

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