701819 PNL-9507

Journal of Bioengineering (,1. 1 pp 369-380, 1977. Pergamon Pl s, Inc.
Printed in the United States

^{170}Tm IN VITREOUS CARBON AS A FULLY PORTABLE EXTRACORPOREAL BLOOD IRRADIATOR*,**

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(Received in Final Form 9 June 1977)

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ABSTRACTS. Extracorporeal irradiation of blood has shown promise in suppressing early rejection of renal allografts and in treating chronic lymphocytic leukemia. Previously, nearly all blood irradiation has involved brief intermittent exposures with high dose rates. The small amount of data available involving continuous irradiation of blood suggests that doses given chronically at lower rates are more effective in suppressing graft rejection. However, no suitably portable device has been available to permit evaluation of effects from chronic irradiation. Our work has been directed toward developing a fully portable (wearable) blood irradiator. After preliminary testing of a variety of source materials, ^{170}Tm was selected for its favorable beta energy, low cost, and compatibility with the fabrication requirements. The body of the irradiator is cast from polyfurfuryl alcohol with subsequent high-temperature conversion to vitreous carbon. By sequential layering of the alcohol and suspending of $^{169}Tm_2O_3$ in the midlayer, a unit is produced without any radiation exposure during fabrication and with the source material contained on both a macro and a microscale. Exposure of the unit to reactor neutrons produces ^{170}Tm without activation of the vitreous carbon. Units now being tested weigh 500 g and have an external surface dose rate of about 50 mR/hr. Effects of chronic extracorporeal irradiation of blood are now being studied in large animals.

* This paper is based on work performed under U.S. Energy Research and Development Administration Contract EY-76-C-06-1830.
** This blood irradiator is patented under US Patent NO. 3,927,325.

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INTRODUCTION

Blood irradiation has been used with modest success to minimize early graft rejection in humans (1,2) and to suppress clinical symptoms in chronic lymphocytic leukemia patients (3). In this and other work with humans and animals, most treatments have utilized large, virtually immoble irradiators giving relatively high exposure rates, with the doses administered intermittently to the subjects. A need for fully portable irradiators has been recognized, and many attempts have been made to develop such units (4-10). In nearly all portable and semiportable units, ^{90}Sr-^{90}Y was used as the source material. None of these units has been developed beyond prototype models due to shielding difficulties. Since this report concerns development of a device, the extensive literature on uses of blood irradiation is omitted.

In the absence of fully portable irradiators, little information has been generated regarding the efficacy of chronic irradiation in controlling lymphocyte levels or suppressing immune responses. Storb, Ragde, and Thomas (11) observed a prompt lymphopenia in baboons exposed to continuous irradiation with cumulative doses of 145,000 to 202,000 rads over a period of 10 to 21 days. Skin allograft survival was significantly extended in all animals recovering from pretransplant exposure. Chanana et al. (12) compared kidney allograft survival in goats treated at a high (260 to 400 rads) transit dose (TD) (i.e., the average radiation dose received by a unit of blood each time it passes through the irradiator) with those treated at a low (44 to 55 rads) TD. They found that graft survival was significantly enhanced with the lower TD and ascribed this to the longer periods of irradiation used in those treatments. It is of interest that the cumulative doses in the animals showing longer allograft survival were one-half to one-sixth those in the shorter-survival group. If we assume that the prolonged kidney graft survival resulted from the longer exposure periods when lower dose rates were used, we can reasonably assume that constant irradiation might give even better results. This reasoning is also consistent with our knowledge that only a few hours are required to initiate the cellular immune response. This paper describes an irradiator which is fully portable (wearable), simple to fabricate, and therefore relatively inexpensive.

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Isotope Selection

There are rigorous constraints on both the isotope source and the irradiator device if full portability and prolonged irradiation are expected. Requirements for the isotope include:

1. The radiation must be such that primary and secondary radiations can be shielded with a sufficiently small mass to be fully portable (preferably < 1 kg).
2. The radiation must be sufficiently penetrating to pass through a blood barrier and deliver a significant dose to blood.
3. The half-life of the isotope should be sufficiently long to permit clinical usefulness.
4. The isotope should be inexpensive.

Several isotopes tested in this program were discarded due to problems such as inability to deliver an effective dose to blood (^{55}Fe, ^{147}Pm), necessity for excessive shielding (^{90}Sr-^{90}Y) or excessive cost (^{204}Th, ^{125}I). The isotope selected as most able to satisfy the above requirements is ^{170}Tm, which emits a 0.97 MeV (maximum) beta ray, has a half-life of 130 days and decays to stable ytterbium. Included with 3.3% of the decay is an 84-KeV X-ray. The ^{170}Tm is readily produced by thermal neutron activation of very pure ^{169}Tm (σ = 125 barns) and, while some ^{171}Tm is also produced, the radiations from the latter are of little consequence relative to shielding or dose to blood. The ^{170}Tm beta is sufficiently energetic to deliver a substantial radiation dose to blood, yet no high-energy bremsstrahlung is produced, thus shielding requirements are primarily dictated by the 84-keV X-ray. Bremsstrahlung radiation is also minimized by absorbing the betas in the low atomic number carbon of the body of the irradiator.

The four-month half-life of ^{170}Tm is sufficiently long to permit distribution and use of the irradiators, yet short enough that disposal of used units is a nominal problem. Finally, the large neutron cross section of ^{169}Tm is a special advantage in that no radiation exposures are necessary during construction and activation time is relatively short.

Selection of a Structural Material

The structural material of the irradiator must satisfy the following requirements:

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1. It must remain unaffected by very high cumulative doses of radiation.
2. The blood interface must be biocompatible and nonthrombogenic.
3. It must be impermeable so that no isotope migration occurs through a thin containment layer.
4. The material must be adaptable to simple construction techniques such that unit costs will not be excessive.
5. The structural material must be sufficiently pure that no significant radioactivity results from neutron activation of contaminants.
6. Low atomic number is desirable to minimize the energy of induced bremsstrahlung radiation.

Early tests showed that silicone rubber and other organic materials fail with the continuing radiation needed in our irradiators. Thus a more radiation-resistant material was needed for long-term use. It is well known from nuclear reactor technology that graphite is extremely resistant to radiation, and it is also well known that pyrolytic graphite is blood-compatible and nonthrombogenic. The more recently developed vitreous carbon appeared to offer many advantages for construction of a blood irradiator, even though its thrombogenicity was unknown at the time this work was initiated.

Vitreous carbon (VC) is derived from thermosetting resins by typical casting techniques followed by controlled pyrolysis. During pyrolysis essentially all noncarbon atoms are driven off as gases, leaving the carbon as a hard, strong, nonporous glassy material with a disordered structure. Furthermore, sequential layering of the resin does not affect the integrity of the pyrolyzed unit, i.e., no separations occur. For a more detailed description of VC see reference 13.

VC appears to meet all of the above material requirements. We have observed no radiation-induced change consequent to neutron activation or following prolonged use of activated units. We have also tested a variety of tubes and irradiators and find that pristine VC surfaces unscratched by machining or polishing are nonthrombogenic. The nonthrombogenic character may be related to its extreme smoothness (Figure 1). Tests with an electron beam microprobe indicate no movement of thulium

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FIG. 1

Scanning electron micrograph showing externally smooth surface of vitreous carbon made by free-surface casting. White spots are debris. The white bar is 1 μm long.

from its initial region of placement as Tm_2O_3 within the irradiator, nor have we observed loss of containment of ^{170}Tm from units used in animal studies. Construction is considerably simplified by using casting techniques, particularly with sequential layering to precisely position the isotope and achieve the pristine inner blood interface. Activation of VC coupons has indicated that only barely detectable traces of contamination are introduced with the resin.

The only disadvantages of VC that we have found are its ability to oxidize in air at T>500C and its glass-like nature, which must be taken into account in design of the irradiators.

Fabrication of Vitreous Carbon - ^{170}Tm (VCTm) Irradiators

Since we started to use VC and thulium, irradiator design has gradually evolved with two principal objectives in mind. First, the units must perform well with an optimum dose delivered to blood and minimum turbulence at all points of connection to minimize thrombus induction. Second, the units must be easily adaptable to clinical use with minimum potential exposure to patient or physician and easy insertion into or removal from an arteriovenous (AV) shunt.

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In the first unit tested (14), a Pyrolite[R*] tube having a 0.25 mm wall thickness served as the blood interface since it was known to be nonthrombogenic. This unit performed well and produced useful biological responses. However, coupling of the unit to the shunt was difficult and provided hazard to personnel exposed to unshielded radiation.

To overcome these problems we have designed the latest VCTm model (Figure 2) with male fittings at each end which are precisely sized to

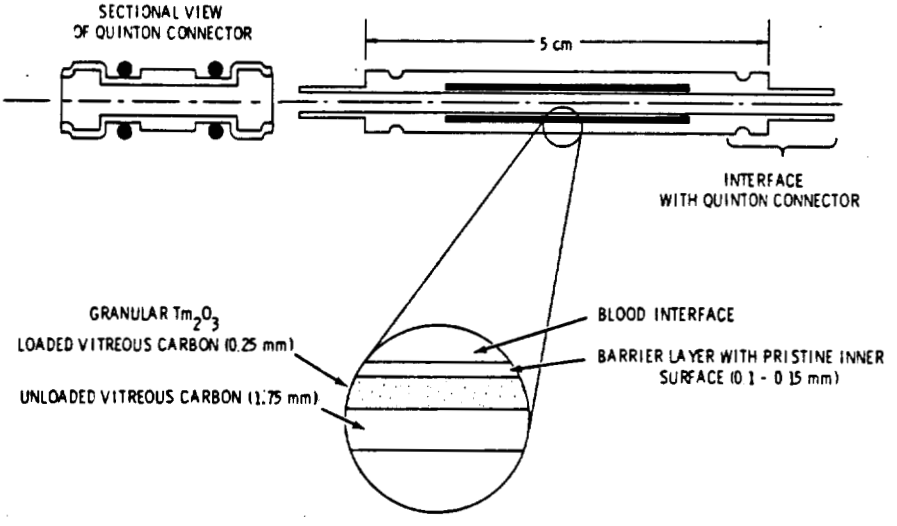

FIG. 2

Cross-sectional view of blood irradiator showing an expanded detail of the three layers.

fit commercial AV shunt hardware (Quinton Instruments**). We also found that pristine VC surfaces are nonthrombogenic, so we eliminated the Pyrolite[R] insert and now construct the irradiators as an integrated single unit. Elimination of the insert tube both simplifies the use of the VCTm units and increases the dose delivered to blood. Figure 3

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* Pyrolite is the registered trademark of Gulf Atomics.
** Quinton Instruments, Inc., Seattle, Washington.

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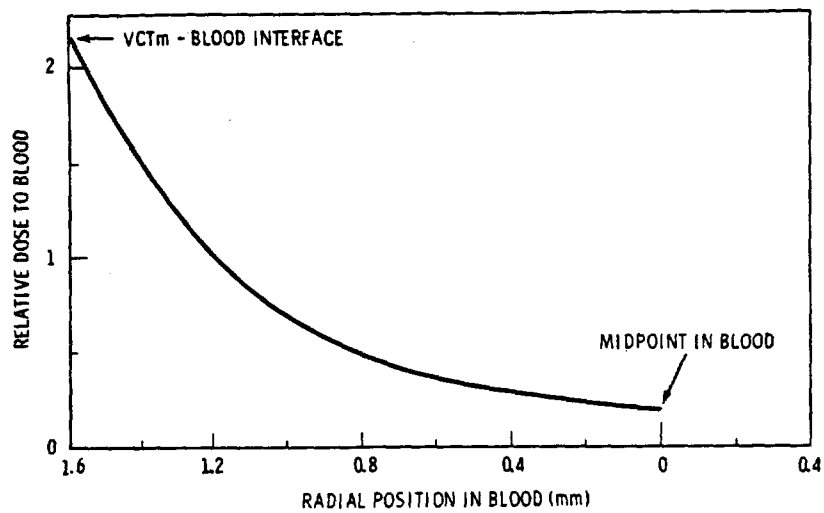

FIG. 3
Calculated blood dose profile.

shows the dose distribution in blood as calculated from a code derived from work of Slatkin and Robertson (15) and using energy distribution from ^{198}Au (0.961 MeV). It is obvious that the blood dose is maximized as the barrier layer between isotope source and blood is minimized.

Units are constructed in three steps. First, the blood interface is formed by centrifugal casting inside a sized tube, filled with a measured volume of catalyzed polyfurfuryl alcohol resin*, capped and spun at 10,000 rpm until the resin is cured. After removal, this resin tube, having a wall thickness of 0.1-0.15 mm, serves as a base to which a weighed mixture of catalyzed resin and finely powdered (< 20 μm) $^{169}Tm_2O_3$ is applied. After curing, the tube is placed in a mold and the body of the irradiator is cast around the tube. On release from the mold the ends of the irradiator are ground to a precise length and lightly coated with resin.

Carbonization of the irradiator is done in a 100 μm vacuum oven, using slowly increasing 6°C/hr) linear heating to a temperature of 1000°C. During carbonization the irradiator shrinks 21% in all dimensions and loses 50% of its mass. The Tm_2O_3 is stable, and is unaffected by

* Quaker Oats RP100A, Catalyzed with RP104B catalyst.

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this treatment. Despite the large dimensional changes, tolerances of ± 0.050 mm are routinely attained.

After carbonization the units are carefully examined for evidence of defects and those approved are cleaned in 6N HCl to remove trace contamination, and inserted into sealed capsules for neutron activation. Units containing ∿ 150 mg of Tm_2O_3 and irradiated 4 days at a neutron flux of ∿ 10^{14} n cm^{-2} sec^{-1} yield a transit dose of approximately 35 rads (assuming a flow rate of 100 ml/min). The dose rate from VCTm units can be varied by changing either the Tm_2O_3 loading, the activation time, or both. After removal from the sealed capsule, the units are cleaned in 6N HCl and washings carefully monitored for any evidence of ^{170}Tm leakage. Clean units are inserted into a heavy metal sleeve for handling and the transit dose determined by Fricke dosimetry.

The peripheral beta radiation is absorbed in the vitreous carbon body, thus minimizing production of high energy bremsstrahlung. The 84-keV X-ray of ^{170}Tm is shielded in current models by a tungsten sleeve 6.4 mm thick, a cast bismuth alloy unit to hold all parts in place and an outer aluminum sleeve (Figure 4). The total mass is 500 g. Surface doses, as measured by TLD chips, are about 50 mR/hr with the present model.

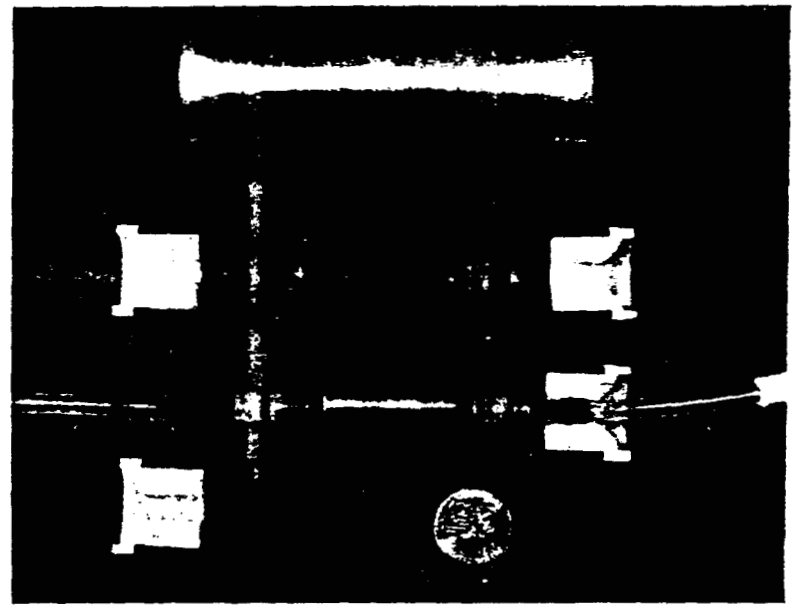

FIG. 4

Photograph of the irradiator encased in primary shielding with the midshielding open to show its use for holding the connectors in place. The silastic ends cushion against tubing collapse as animals move freely in their pens.

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Animal Testing of VCTm Irradiators

Animal response to chronic irradiation delivered by VCTm units is now being evaluated with goats. In preparation for treatment an AV shunt is installed between a carotid artery and the contralateral jugular vein. Silastic tubing, 3.18 mm ID and 15-20 cm long, is fitted with an appropriately sized cannula on one end and a Quinton extension unit on the other. Shunt preparation and implantation into the goats is done essentially as described by Boyd et al. (16), except that coumadin treatment, if used, is not initiated until recovery from surgery is nearly complete. The arterial and venous shunt tubes are joined with a connector immediately following cannula insertion and prior to closing the incision.

On recovery from surgery and when lymphocyte levels have stabilized, oral coumadin plus aspirin is given daily to attain prothrombin times of 2-3X normal. When appropriate prothrombin times are attained, the irradiator is inserted into the shunt and flow monitored daily with a doppler flowmeter. Prior to insertion the interior of the irradiator is sterilized with benzalkonium chloride solutions, rinsed with sterile saline and filled with heparin in normal saline. The irradiator is attached to and suspended by a cloth collar placed around the neck of the animal. The cloth is held in place and prevented from rotating by a dollop of silastic cement binding the dorsal neck hairs to the collar. Holding pens are made free of any protrusions liable to hook onto the irradiators, and the hind legs are hobbled. The animals are not otherwise restrained.

Figure 5 shows a typical response of circulating cells in a 50-kg goat to this chronic low dose rate regimen. With blood doses of about 1000 rads/day, lymphocyte levels fall to 25-30% of pretreatment levels within 5 days, with a subsequent slow decrease so long as the shunt remains patent. No significant change in red cell numbers has been observed nor is one anticipated with dose rates of this magnitude. Effects of heparin and coumadin on circulating lymphocytes have been examined in control animals. Coumadin appears to elevate the number of circulating lymphocytes and may thus be beneficial by moving these cells

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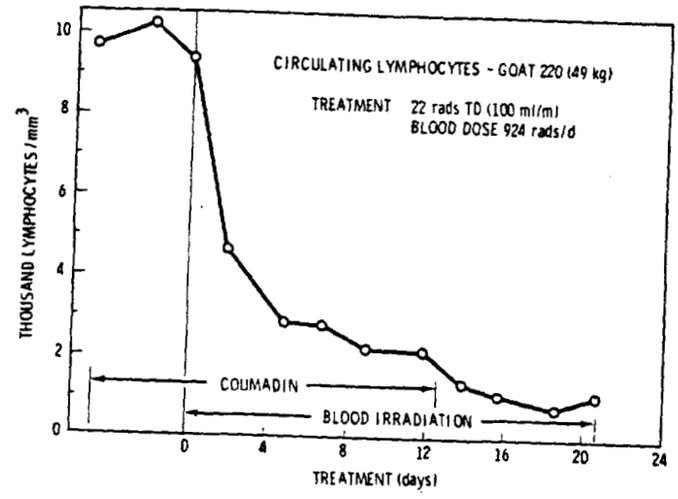

FIG. 5

A typical response of circulating lymphocytes to beta radiation from ^{170}Tm.

into the circulating pool where they are exposed to the radiation. No effect of heparin has been noted.

It is premature to comment on other biological effects now being measured since too few animals have been tested at this time. Shunt failure resulting from thrombus formation is a constant problem, with the venous cannula being the site of nearly all stoppages. It is encouraging that the new design has eliminated difficulties experienced earlier with thrombus formation at the connection sites. Furthermore, we have seen no evidence of thrombus initiation within the irradiators of the most recent design.

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