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Hungate et al.

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[54] **TISSUE IRRADIATOR**

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[51] **Int. Cl.**[2]. **A61N 5/12;** G01N 21/24; G21G 4/00

[58] **Field of Search** ..... 117/46 CB; 250/432, 435, 250/436, 437, 438, 492, 493; 128/1.1, 1.2

[56] **References Cited**

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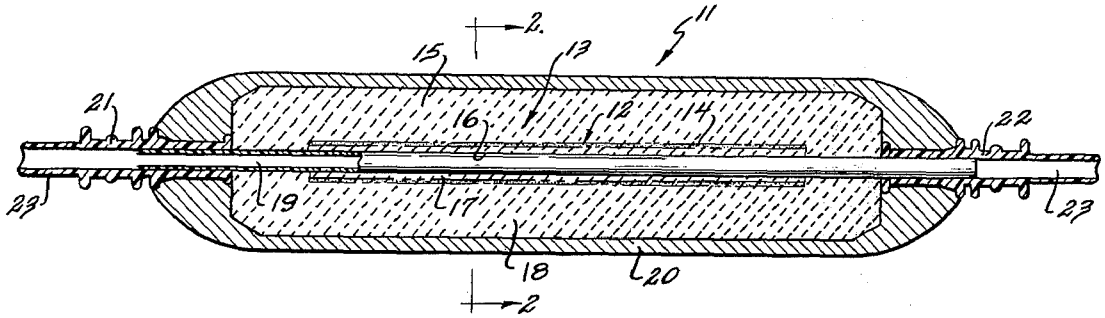
[57] **ABSTRACT**

A tissue irradiator is provided for the in-vivo irradiation of body tissue. The irradiator comprises a radiation source material contained and completely encapsulated within vitreous carbon. An embodiment for use as an in-vivo blood irradiator comprises a cylindrical body having an axial bore therethrough. A radioisotope is contained within a first portion of vitreous carbon cylindrically surrounding the axial bore, and a containment portion of vitreous carbon surrounds the radioisotope containing portion, the two portions of vitreous carbon being integrally formed as a single unit. Connecting means are provided at each end of the cylindrical body to permit connections to blood-carrying vessels and to provide for passage of blood through the bore. In a preferred embodiment, the radioisotope is thulium-170 which is present in the irradiator in the form of thulium oxide. A method of producing the preferred blood irradiator is also provided, whereby nonradioactive thulium-169 is dispersed within a polyfurfuryl alcohol resin which is carbonized and fired to form the integral vitreous carbon body and the device is activated by neutron bombardment of the thulium-169 to produce the beta-emitting thulium-170.

10 Claims, 2 Drawing Figures



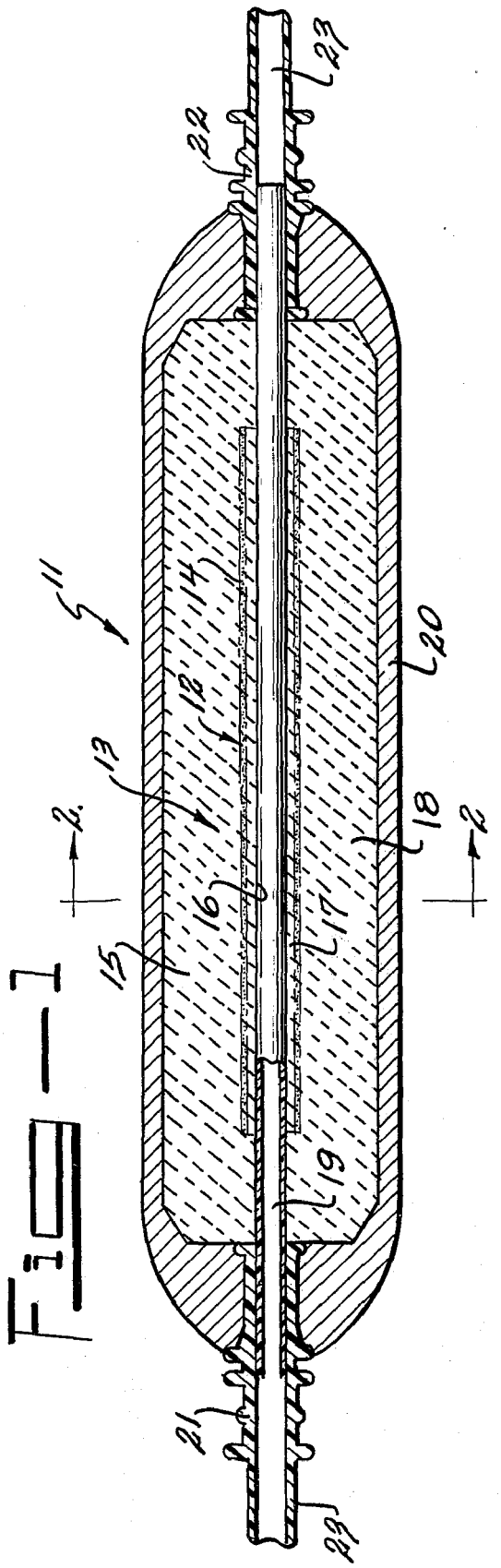


Fig. 1

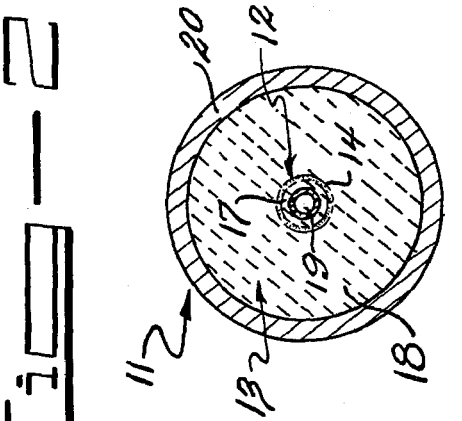


Fig. 2

TISSUE IRRADIATOR

CONTRACTUAL ORIGIN OF THE INVENTION

The invention described herein was made in the course of, or under, a contract with the UNITED STATES ATOMIC ENERGY COMMISSION.

BACKGROUND OF THE INVENTION

This invention relates to radiotherapy and to in-vivo radiation treatment of body tissues with particular emphasis directed toward in-vivo radiation treatment of blood. Specifically, the present invention is directed toward a flow-through blood irradiation device for implantation within the body, which device is both smaller and lighter than previously available flow-through radiation devices. Additionally, the development of this device has been accompanied by the development of techniques for production of the device with increased safety in dealing with the radioisotope used in the radiation device.

Radiotherapy, incuding radiation treatment of blood, as a potential cure or control for various diseases is wellknown in the art, radiotherapy being extensively used in treating various forms of cancer. Two areas to which radiotherapy has been found to be particularly adaptable are the control of leukemia and the control of immune reactions initiated by lymphocytes following tissue transplants. Suppression of lymphocyte levels in circulating blood following irradiation of the total body with low doses of ionizing radiation is well-known. It has been demonstrated that irradiation of blood in an exterior blood loop (extracorporeal irradiation of blood) suppresses lymphocyte levels without damage to other body tissues. It has consequently been shown that extracorporeal irradiation of blood is an effective adjunct or alternative to drug therapy for treating some forms of leukemia.

Immune reactions initiated by lymphocytes are usually the ultimate reason for failure of organ transplants. Current methods of suppressing these immune reactions include use of drug therapy, antilymphocyte antibodies and irradiation. Typically, more than one of these approaches is used, since there are problems associated with each. Acceptance times of skin allografts have been extended by extracorporeal irradiation of blood and this technique has been evaluated for its applicability for immunosuppression relative to renal allografts. Significant reduction in early rejection episodes and a significantly higher frequency of 6-month renal graft survival has been reported for extracorporeal irradiation of blood treated groups.

While this type of blood irradiation to suppress tissue and organ rejection and to control some blood diseases has been shown to be successful at locations fortunate enough to have irradiators, there is some evidence that continuous irradiation of blood may be more effective than periodic acute irradiations. Most treatments of both experimental animals and humans have been accomplished by shunting blood through large fixed equipment containing cobalt-60, cesium-137 or X-ray sources, thereby necessitating specialized facilities. With relatively long treatment regimes required, this severely limits the number of patients who can receive treatments and requires the inconvenience and expense of hospitalization. Efforts have been directed toward the development of small, inexpensive, portable irradiators to permit chronic exposures of patients. In particular, it is desirable to design a small, implantable irradiation device which would permit direct in-vivo irradiation of the blood. A radioisotope-coated wire for insertion diagonally across a blood vessel was previously described in U.S. Pat. No. 3,811,426, coinvented by one of the present applicants.

Another type of irradiator which has been under development is a small, tubular irradiator which provides for blood flow through the tube, the irradiator device being surgically inserted so as to serve as a small section of the blood vessel. Irradiators of this type made to date have used very energetic beta emitters, such as strontium-90-yttrium-90 or phosphorus-32. One such device contained 2 curies of strontium-90-yttrium-90 in a cylindrical zone 1 cm long within an approximately 25 mm thick outer layer of Hevimet shielding. A 0.025 mm thick layer of titanium covered the strontium-yttrium source. A thin-walled Silastic tubing, 2.64 mm inner diameter and 3.66 mm outer diameter, served to transport the circulating blood through the irradiator. The blood dose rate, estimated by passing Fricke dosimeter solution through the Silastic tubing at known flow rates and measuring the optical density change, provided a transit dose to the blood estimated to be 40 rads at a flow rate of 100 ml/min. The total weight of this irradiator was just under 2 kg. Because a device of this nature using the energetic beta emitters will induce hard bremsstrahlung, it is essential that substantial shielding be provided to protect surrounding tissues. The need for this substantial shielding results in devices which are heavy and cumbersome and such devices presently in use generally weigh several pounds. Silastic tubing is also disadvantageous in that embrittlement upon irradiation is a frequent problem.

It is an object of the present invention to provide a device for irradiation of body tissues.

It is a further object of the present invention to provide a device for in-vivo irradiation of blood.

Another object of the present invention is to provide an implantable device for continuous in-body irradiation treatment of blood flowing through the circulatory system.

Another object of the present invention is to provide a radiation device for the treatment of blood which will not give off undue irradiation to surrounding body tissues.

A further object of the present invention is to provide an in-vivo blood irradiation device for which substantial shielding is not required and which therefore permits construction of a lightweight device.

Other objects and advantages of the present invention will become apparent upon reading the following description and with particular reference to the specific embodiment described hereinbelow.

SUMMARY OF INVENTION

In accordance with the present invention, chronic in-vivo radiation treatment of tissue can be conducted by implantation of an improved lightweight portable irradiator. The tissue irradiator of the present invention has a radioisotope material contained in and encapsulated by vitreous carbon. The radioisotope is suspended in a first portion of vitreous carbon which is surrounded and encapsulated by a containment portion of the vitreous carbon. The vitreous carbon is integrally formed as a single mass with the two portions being insegmenta-

ble and indiscernible except for the presence of the radioisotope in a portion of the unit body. The formation of the vitreous carbon as a single unit provides improved containment of the radioactive material.

Particular embodiments of the invention are directed toward in-vivo irradiation of blood. In these blood irradiator embodiments, the vitreous carbon is in the form of a cylindrical body with an axial bore to permit flow of blood through the body. The radioisotope material is contained in a tubular portion of the vitreous carbon which surrounds the bore and lies fully within the vitreous carbon containment body. Means are provided for connecting this cylindrical body to blood vessels in order to pass blood through the bore. In preferred embodiments, the radioisotope is thulium-170 which preferably is present as Tm_2O_3. Use of thulium permits construction of the device employing thulium-169 which can be activated to the radioactive beta emitter thulium-170 by neutron activation after basic construction of the device has been completed.

BRIEF DESCRIPTION OF THE DRAWINGS

An understanding of the features and the advantages offered by the present invention can be obtained from a reading of the following description and with reference to the drawings, in which:

FIG. 1 is a sectional view of a device in accordance with the present invention; and

FIG. 2 is a cross-sectional view of the device taken along the line 2—2 of FIG. 1.

DESCRIPTION OF THE INVENTION

In its broadest aspects, the present invention is directed toward tissue irradiators which can be implanted for in-vivo radiation treatment of various body tissues. In accordance with the broadest aspects of the present invention, a radiation source material, such as a radioisotope, is dispersed and suspended within a vitreous carbon body. Vitreous carbon or glassy carbon is a term known in the art and refers to a glasslike form of carbon having no defined crystal structure. The vitreous carbon surrounds and encapsulates eash of the radiation source material particles and, in addition, forms a containment layer completely surrounding the radiation source material. The vitreous carbon is integrally formed as a single unit body. While the radiation source material lies in a well defined differentiable region or zone of the body, the vitreous carbon itself exists as a unit mass with the two portions, a first portion containing the source material and a containment portion surrounding the first portion, being insegmentable and indiscernible as separate layers except for the presence of the source material. Other features of the particular irradiator will depend upon the type of radiation desired, the strength of radiation desired and the particular tissue which is to be irradiated. The use of vitreous carbon offers several advantages. Vitreous carbon is a biocompatible material. Also, since carbon is very little affected by irradiation, even at intensities near the core of nuclear reactors, there will be little change in the properties of the irradiator after long periods of time. Problems could develop with previous types of irradiators in that components of the irradiator body could become embrittled upon prolonged exposure to radiation. Additionally, since the vitreous carbon is a low Z material (low atomic weight), there will be a minimum amount of bremsstrahlung radiation produced from this device. This permits construction of a device without the need for extra shielding material to prevent bremsstrahlung radiation damage to surrounding tissues.

The present invention has been found to be particularly adaptable to embodiment as an in-vivo blood irradiator. While the invention will be described with reference to this specific embodiment, the invention is not limited to this particular embodiment but should be construed with the broader aspects of the invention as herein discussed. For example, the irradiator could be shaped as a flat plate for tissue or organ irradiation, or as a solid needle for intra-tissue irradiation.

Referring now to the drawings for assistance in the description of the specific embodiment of the present invention, there is shown in FIG. 1 and FIG. 2 a blood irradiator indicated generally at **11**. A radiation source material **12** is contained in and encapsulated by a unit mass of vitreous carbon **13**. The vitreous carbon mass **13** consists of a tubular first portion **14** which contains the radiation source material **12** and encapsulates on a microscale each of the particles of the radiation material **12** and a containment portion **15** insegmentable from first portion **14** and indiscernible therefrom except for the presence of the suspended radiation source material **12**. The containment portion **15** encapsulates the radiation source material **12** on a macroscale. The containment portion **15** forms a cylindrical body having an axial bore **16**. The first portion of vitreous carbon **14** in which the radiation source material is dispersed and suspended lies cylindrically about bore **16** and is fully surrounded and encapsulated by the containment portion **15**. A thin layer **17** of the containment portion **15** lies interiorly to the tubular first portion of vitreous carbon **14**. The tubular first portion of vitreous carbon **14** is surrounded exteriorly by a thick layer **18** of the containment portion of vitreous carbon **15**. The layer **17** is thin so as to permit penetration of the radiation from source material **12** into the bore **16** while layer **18** is thicker to provide significant shielding. While the vitreous carbon has been described as consisting of various portions, it should be understood that in actuality the vitreous carbon is integrally formed as a single unit and, while one can refer to various portions or layers for sake of description, the vitreous carbon itself is not segmented but is a single mass. In a preferred embodiment of the present invention, a pyrolytic graphite tube **19** extends through the device **11** within bore **16**. The pyrolytic graphite tube serves as a blood conduit through the device and is preferred because of the nonthrombogenic nature of pyrolytic graphite. The containment of the radiation source material within vitreous carbon offers an advantage in that the radioactive particles are encapsulated on both a microand a macroscale. The individual particles are encapsulated in what is referred to as the first portion of vitreous carbon **14**. On a macroscale this entire portion of the vitreous carbon is surrounded and encapsulated by the containment portion **15** consisting of a coating **17** interior to the tubular first portion **14** and a coating **18** surrounding the exterior of tubular first portion **14**. A loss of integrity of the unit, such as a crack through the vitreous carbon, thereby would expose only the particles of the radiation source material exposed on the surface of the crack, whereas those particles not on the surface of the crack would remain encapsulated in the vitreous carbon body.

Additional shielding to prevent stray radiation from damaging surrounding tissues can be provided, such as

by surrounding the exterior of the vitreous carbon containment body **15** with a dense metal shielding layer **20.** While the metal shielding material **20** can be chosen from a wide group of metals, lead has been found to be particularly suitable and has been used in the construction of such devices, as will be described below.

Referring now to FIG. 1 for additional description of the specific embodiment, it can be seen that means, such as connectors **21** and **22** associated with each of the two ends of the bore **16,** are provided for passing blood through the device through bore **16** such as within pyrolytic graphite tube **19.** The connectors **21** and **22** extend through the metal shielding layer **20** and communicate with each other through the bore. The connectors are adapted for connection to blood-carrying vessels, such as by Silastic tubing **23** which in turn is joined to blood vessels in accordance with techniques known in the art. There is no problem of embrittlement of the Silastic tubing at this point as it is significantly removed from the radiation source. In operation, blood flows through the device and is irradiated by irradiation emitted from irradiation source material **12.** Radiation from this material can pass through the thin inner portion **17** of the vitreous carbon and the pyrolytic graphite tube **16,** thereby irradiating blood passing within bore **16.** Irradiation damage to surrounding tissue from stray radiation or radiation emanating outward from radiation source material **12** is prevented by the shielding afforded by the thicker containment portion of vitreous carbon **15** and the metal shielding layer **20.**

The use of vitreous carbon as the containment material in this blood irradiator offers significant advantages. The advantages offered by the use of a low Z material such as carbon and the presence of the vitreous carbon as a single integral mass have been mentioned. An additional advantage is also offered in that vitreous carbon is a very hard, strong and impermeable material which offers very good containment and excellent integrity in both normal usage and in case of accident. In addition, the radiation source material can be dispersed as a fine suspension within the material which, when fired, will result in inclusion of the source material as an integral part of the vitreous carbon body. The radiation source material will then be suspended in an identifiable zone of an otherwise substantially homogeneous vitreous carbon body.

The irradiation source material will be a radioisotope which may be present as a compound and which preferably is a particulate material such as a fine powder. Choice of the particular radioisotope employed will depend upon the radiation characteristics desired. For irradiation of blood, a beta emitter is generally preferred. In the present device, since elimination of gamma irradiation is desirable in order to limit radiation damage to surrounding tissue, a fairly pure beta emitter is desired. In the practice of the present invention, thulium-170 has been found to be a particularly desirable radiation source and is preferred. The thulium-170 is incorporated into the device as a fine powder of Tm_2O_3. The use of thulium-170 is preferred for several reasons. Thulium-170 is a fairly pure beta emitter, giving off a 0.96 MeV maximum beta. In addition, thulium-170 has a 125-day physical half-life and is readily produced by neutron activation of thulium-169. This permits an additional advantage of constructing the device using thulium-169 (which is nonradioactive, thus eliminating handling of any radioactive material during construction of the device) followed by neutron activation of a portion of the thulium-169 to produce the beta-emitting thulium-170. In addition, reactivation of the device by neutron activation after the unit loses effectiveness due to the decay of thulium-170 is also possible. Using the neutron activation technique following manufacture of the device gives importance to the half-life of the radioisotope used. Thulium-170 is also preferred because of the advantageous 125-day half-life.

Suspension of the radiation source material in the vitreous carbon can be accomplished by dispersing the radiation source material through a precursor resin, surrounding this portion of the resin with additional unloaded resin and carbonizing the entire resin mass so as to produce an integral vitreous carbon unit. One consideration which must be given to the choice of the precursor resin used in forming the vitreous carbon is that it have a high carbon yield. A particular technique for forming vitreous carbon found useful in the construction of the irradiator has been adapted from previously known techniques which are discussed by Shigehiko Yamanda in an article "A Review of Glass-like Carbons," distributed through the Defense Ceramic Information Center of Battelle Memorial Institute in Columbus, Ohio, Report No. DCIC-68-2, also Report No. AD-668 465, April 1968. In accordance with this technique, polyfurfuryl alcohol is cured in the shape desired followed by carbonization of the polyfurfuryl alcohol to vitreous carbon. While other thermosetting resins can be used in the practice of this invention, polyfurfuryl alcohol is preferred.

While other prior art techniques can be used in the manufacture of irradiators in accordance with the present invention and the invention should not be limited by disclosed techniques, a blood irradiator in accordance with the present invention can be manufactured as follows. A steel mandrel was coated with paraffin and trimmed to the desired diameter. The radiation source material was mixed with some polyfurfuryl alcohol resin, resulting in the grains of the source material being individually coated. An active layer of the resin containing the source material was then painted on the paraffin. A thick containment layer of polyfurfuryl alcohol resin was cast about the active layer on the mandrel. The containment layer was cast so as to extend at least ⅛ inch beyond the active layer on each side lengthwise. The polyfurfuryl alcohol resin was then cured to rigidity by heating. The heating was sufficient to melt the paraffin which then ran out of the cured resin, permitting easy removal of the steel mandrel. Additional polyfurfuryl alcohol resin was dripped down through the tube to coat the inside of the active layer. Following coating of the inner surface, the device was fired so as to carbonize the polyfurfuryl alcohol to vitreous carbon, completely encapsulating the grains of the radiation source material on a micro- and a macroscale. It is important that the firing to carbonize the material be done in one step, as there is shrinkage of the resin at the time that it is fired. If the firing is not done in one step, shrinkage of the material will result in a separation of the layers and a breach of the integrity of the unit. Firing in one step results in the formation of an integral mass of vitreous carbon. A metal shielding material can then be placed around the single-unit vitreous carbon body. Lead in the form of a two-piece can fitting about the vitreous carbon body in clamshell fashion has been found to be particularly adaptable to construction of the device. A small layer of epoxy can

be coated about the exterior of the lead shield to insure encapsulation and integrity of the unit and provide a smooth outer surface. In the preferred embodiment, a pyrolytic graphite tube runs through the center of the device. Alternatively, a vitreous carbon blood interface tube can be formed by dripping the polyfurfuryl alcohol resin down the inside of a quartz tube until the inside is uniformly coated and curing the resin. Following firing in a furnace, which carbonizes the polyfurfuryl alcohol to vitreous carbon, the vitreous carbon tube will shrink about 20 percent, permitting easy removal from the quartz tube.

In construction of the device, thulium-169 in the form of $^{169}Tm_2O_3$ can be used as a radiation source material. This permits construction without concern for radiological hazards or exposure of personnel. In addition, construction of the device is simplified, as the complex techniques of handling and working with radioactive materials are eliminated. Following completion of the basic structure, the thulium-169 can be converted to radioactive thulium-170 by neutron activation.

A blood irradiator was constructed in accordance with the specific embodiment of the present invention. A pyrolytic graphite tube having a 0.25 mm wall thickness was used as a blood interface because of its nonthrombogenic character. The inner barrier of vitreous carbon surrounding the pyrolytic graphite tube was 0.05 mm thick. The inner barrier was surrounded by a 0.15 mm layer containing $^{169}Tm_2O_3$, a portion of which was subsequently neutron-activated to thulium-170. This was surrounded with a 2.3 mm containment layer of vitreous carbon. The total weight of the vitreous carbon unit following carbonization was 2 grams. A containment layer of 6.4 mm of lead surrounded the vitreous carbon unit and resulted in a device whose weight was 160 grams. Silastic tubing served to connect the graphite tube to arterial and venous cannulas. Following neutron activation, external dose rates were less than 50 mR per hour at the surface and a transit dose of 21 rads at a flow rate of 100 ml/min was measured by Fricke dosimetry. The device was connected to an arterial-venous shunt (common carotid artery and external jugular vein) of a 20 kg goat. Small lymphocytes dropped to 15 percent preirradiation level within 7 days and the unit was removed at 11 days. A reciprocal skin allograph performed immediately postirradiation survived twice as long (24 days) on the irradiated animal as on a nonirradiated control (12 days). Successful reduction of blood lymphocyte levels was therefore demonstrated.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A tissue irradiator comprising:

a radioisotope material contained in, dispersed through, and encapsulated by a first portion of vitreous carbon, which portion is surrounded and encapsulated by a containment portion of vitreous carbon.

2. A tissue irradiator in accordance with claim **1** for irradiating blood, wherein said containment portion of vitreous carbon is a cylindrical body having an axial bore therethrough, said radioisotope-containing vitreous carbon portion lies cylindrically about said bore and fully within said vitreous carbon containment body, and wherein said irradiator further comprises means for passing blood through said bore.

3. An in-vivo blood irradiator in accordance with claim **2** further comprising:

a metal shielding layer surrounding the exterior of said vitreous carbon containment body; and wherein said means for passing blood through said bore comprise connectors associated with each of the two ends of said bore, said connectors communicating through said bore, said connectors passing through said surrounding metal layer, and said connectors permitting connection to blood-carrying vessels.

4. The in-vivo blood irradiator of claim **3** further comprising:

a pyrolytic graphite tube passing through said bore and joining said connectors at the two ends of said bore.

5. The in-vivo blood irradiator of claim **4** wherein said radioisotope is thulium-170.

6. The in-vivo blood irradiator of claim **5** wherein said thulium-170 is present in the form of Tm_2O_3.

7. A method of making a tissue irradiator comprising:

a. dispersing a radiation source material within a curable resinous material;

b. forming a shaped body of said curable resinous material containing said radiation source material and subsequently curing said resinous material;

c. surrounding said shaped body by coating the surfaces of said body with additional amounts of said curable resinous material and subsequently curing said additional resinous material so as to contain said radiation source material within a shaped structure;

d. firing said resulting shaped structure so as to convert said resinous material to vitreous carbon thereby completely encapsulating said radiation source material within said vitreous carbon.

8. The method in accordance with claim **7** wherein said resinous material which is carbonized is polyfurfuryl alcohol.

9. The method of claim **8** wherein said radiation source material is Tm_2O_3 and which includes thulium-170.

10. The method in accordance with claim **8** wherein said radiation source material is $^{169}Tm_2O_3$ and wherein said device is bombarded with neutrons so as to convert a portion of the thulium-169 to thulium-170 through neutron activation.

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