NRC FORM 374
(7-94)

U.S. NUCLEAR REGULATORY COMMISSION



# MATERIALS LICENSE

Amendment No. 74

Pursuant to the Atomic Energy Act of 1954, as amended, the Energy Reorganization Act of 1974 (Public Law 93-438), and Title 10, Code of Federal Regulations, Chapter I, Parts 30, 31, 32, 33, 34, 35, 36, 39, 40, and 70, and in reliance on statements and representations heretofore made by the licensee, a license is hereby issued authorizing the licensee to receive, acquire, possess, and transfer byproduct, source, and special nuclear material designated below; to use such material for the purpose(s) and at the place(s) designated below; to deliver or transfer such material to persons authorized to receive it in accordance with the regulations of the applicable Part(s). This license shall be deemed to contain the conditions specified in Section 183 of the Atomic Energy Act of 1954, as amended, and is subject to all applicable rules, regulations, and orders of the Nuclear Regulatory Commission now or hereafter in effect and to any conditions specified below.

3026/6

| Licensee | |
|---|---|
| 1. Borgess Medical Center | In accordance with letter dated May 5, 1997<br>3. License Number 21-12275-02 is amended in its entirety to read as follows: |
| 2. 1521 Gull Road<br>Kalamazoo, MI 49001 | 4. Expiration Date July 31, 2000 |
| | 5. Docket or Reference No. 030-02115 |

| 6. Byproduct, Source, and/or Special Nuclear Material | 7. Chemical and/or Physical Form | 8. Maximum Amount that Licensee May Possess at Any One Time Under This License |
|---|---|---|
| A. Any byproduct material identified in 10 CFR 35.100 | A. Any radiopharmaceutical identified in 10 CFR 35.100 | A. As needed |
| B. Any byproduct material identified in 10 CFR 35.200 | B. Any radiopharmaceutical identified in 10 CFR 35.200 | B. As needed |
| C. Any byproduct material identified in 10 CFR 35.300 | C. Any radiopharmaceutical identified in 10 CFR 35.300 | C. As needed |
| D. Any byproduct material identified in 10 CFR 35.400 | D. Any brachytherapy sources identified in 10 CFR 35.400 | D. As needed |
| E. Any byproduct material identified in 10 CFR 31.11 | E. Prepackaged Kits | E. As needed |
| F. Phosphorus-32 | F. IsoStent, Inc. ion-implanted Palmaz-Schatz Balloon-Expandable IsoStent with Delivery System. | F. See item 9.F. |

MATERIALS LICENSE
SUPPLEMENTARY SHEET

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030-02115

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| 6. Byproduct, source, and/or special nuclear material | 7. Chemical and/or physical form | 8. Maximum amount that licensee may possess at any one time under this license |
|---|---|---|
| G. Yttrium-90 | G. IsoStent, Inc. coronary artery stents in a delivery system | G. Not to exceed 20 microcuries per stent; not to exceed 10 millicuries total. |

9. Authorized Use:

A. Medical use described in 10 CFR 35.100.

B. Medical use described in 10 CFR 35.200.

C. Medical use described in 10 CFR 35.300.

D. Medical use described in 10 CFR 35.400.

E. In vitro studies.

F. For use in IsoStent, Inc. Palmaz-Schatz Balloon-Expandable IsoStent under the Investigational Device Exemption (IDE) granted by the FDA for the conduct of human clinical trials as described in letter dated July 5, 1996, and subsequent phases of the IDE process associated with the device which are approved by the FDA.

G. For research and development as defined in 10 CFR 30.4 in animal research studies as described in letter dated May 5, 1997.

CONDITIONS

10. Location of use: 1521 Gull Road, Kalamazoo, Michigan.

11. Radiation Safety Officer: Tim TenCate

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12. Licensed material listed in Item 6 above is only authorized for use by, or under the supervision of, the following individuals for the materials and uses indicated:

| | Authorized Users | Material and Use |
|---|---|---|
| A. | Gary L. Bowman, M.D. | 10 CFR 35.100, 35.200 and 31.11. |
| B. | John W. Copenhaver, M.D. | 10 CFR 35.100, 35.200, 35.500 and 31.11. |
| C. | J. Alex Gardner, M.D. | 10 CFR 35.100, 35.200, 35.500 and 31.11. |
| D. | Leonard A. Brunette, M.D. | 10 CFR 35.100, 35.200, 35.500 and 31.11. |
| E. | Arthur Gregory Laurell, M.D. | 10 CFR 35.100, 35.200, 35.500 and 31.11. |
| F. | James R. Dolan, M.D. | 10 CFR 35.100, 35.200, 35.300, 35.400, 35.500, Item 6.F. and 6.G. |
| G. | Geoffrey A. Wardwell, M.D. | 10 CFR 35.100 and 35.200. |
| H. | N. Warn Courtney, M.D. | 10 CFR 35.100, 35.200, 35.300, 31.11 and Item 6.F. |
| I. | Richard R. McConnell, M.D. | 10 CFR 35.100, 35.200, 35.300 (excluding iodine-131 for thyroid carcinoma), 35.500, 31.11 and Item 6.F. |
| J. | Edwardo R. Crotte, M.D. | 10 CFR 35.100, 35.200 and 31.11. |
| K. | David Tague, M.D. | 10 CFR 35.100, 35.200 and 31.11. |
| L. | L. Enrique Leguizamon, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| M. | Thomas McCormick, M.D. | 10 CFR 35.100, 35.200, 35.500 and 31.11. |
| N. | John E. Francis, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| O. | Kenzo Kawamura, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| P. | Dennis P. Burke, M.D. | 10 CFR 35.100, 35.200 and 31.11. |
| Q. | William B. Campbell, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |

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| Authorized Users | Material and Use |
|---|---|
| R. Umakant S. Doctor, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| S. Yoo Sup Hwang, M.D. | 10 CFR 35.400. |
| T. Khlid Altaf Mian, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| U. Evalt Ayerdi, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| V. Stephen L. Peck, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| W. Robert J. LaPenna, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| X. Benjamin A. Perry, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| Y. Robert H. Jongeward, M.D. | 10 CFR 35.100, 35.200, 35.500 and 31.11. |
| Z. George J. Balogh, M.D. | 10 CFR 35.100, 35.200, 35.500 and 31.11. |
| AA. Robert B. Davis, M.D. | 10 CFR 35.100, 35.200, 35.300, and Item 6.F. |
| BB. Katherine Gadwood, M.D. | 10 CFR 35.100, 35.200 (excluding generators) and 31.11. |
| CC. Charles Gregory Hodgman, M.D. | 10 CFR 35.100, 35.200, 35.500 and 31.11. |
| DD. Janos Gellert, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| EE. John A. Azevedo, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| FF. Sharma Saith, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| GG. Steven P. Soper, M.D. | 10 CFR 31.11. |
| HH. Bruce D. Goethe, M.D. | 10 CFR 35.100, 35.200 and 31.11. |

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| Authorized Users | Material and Use |
|---|---|
| II. Patrick A. Sorek, M.D. | 10 CFR 35.100, 35.200 and 31.11. |
| JJ. Susan J. Phelps, M.D. | 10 CFR 35.100, 35.200 and 31.11. |
| KK. David Lynn Keedy, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| LL. Douglas J. Wunderly, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| MM. Jonathan Levi, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| NN. Jim Chul Kim, M.D. | 10 CFR 35.300, 35.400 and Item 6.F. |
| OO. Heung (Henry) Shik Shin, M.D. | 10 CFR 35.300, 35.400 and Item 6.F. |
| PP. David G. Brachman, M.D. | 10 CFR 35.300, 35.400 and Item 6.F. |
| QQ. Marc Bernstein, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| RR. Anthony King, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| SS. Alicia Williams, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| TT. Antonio P. Carrillo, M.D. | 10 CFR 35.100 and 35.200 (limited to cardiovascular clinical procedures). |
| UU. Ramon Raneses, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| VV. Joel H. Reinoehl, M.D. | 10 CFR 35.200 (limited to cardiovascular clinical procedures). |
| WW. Thomas Winn, M.D. | 10 CFR 35.100, 35.200, 35.300 and Item 6.F. |

13. The licensee will establish and implement model procedure for radiation safety during implant therapy that was published in Appendix Q to Regulatory Guide 10.8, Revision 2.

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14. The licensee shall maintain records of information important to safe and effective decommissioning at the address in Condition 10. per provisions of 10 CFR 30.35(g) until this license is terminated by the Commission.

15. In addition to the possession limits in Item 8, the licensee shall further restrict the possession of licensed material to quantities below the minimum limit specified in 10 CFR 30.35(d) for establishing decommissioning financial assurance.

16. Except as specifically provided otherwise in this license, the licensee shall conduct its program in accordance with the statements, representations, and procedures contained in the documents, including any enclosures, listed below, except for minor changes in the medical use radiation safety procedures as provided in 10 CFR 35.31. The Nuclear Regulatory Commission's regulations shall govern unless the statements, representations, and procedures in the licensee's application and correspondence are more restrictive than the regulations.

    A. Application dated March 20, 1990; and

    B. Letters dated May 25, 1990 (with attachments), July 3, 1990 (with enclosures), October 17, 1990 (with attachments), December 11, 1995, July 5, 1996, and May 5, 1997.

FOR THE U.S. NUCLEAR REGULATORY COMMISSION

Date JUN 05 1997

By Evelyn R. Weaver
Nuclear Materials Licensing Branch, Region III

BETWEEN:

License Fee Management Branch, ARM
and
Regional Licensing Sections

(FOR LFMS USE)
INFORMATION FROM LTS

Program Code: 02120
Status Code: 0
Fee Category: 7C
Exp. Date: 20000731
Fee Comments:
Decom Fin Assur Regd: N

R9

LICENSE FEE TRANSMITTAL

A. REGION

1. APPLICATION ATTACHED
   Applicant/Licensee: BORGESS MEDICAL CENTER
   Received Date: 970512
   Docket No: 3002115
   Control No.: 302616
   License No.: 21-12275-02
   Action Type: Amendment

2. FEE ATTACHED
   Amount: 440
   Check No.: 245675

3. COMMENTS

Signed D. Hesser
Date 5-13-97

1997 MAY 14 PM 5:08

B. LICENSE FEE MANAGEMENT BRANCH (Check when milestone 03 is entered (✓))

1. Fee Category and Amount: 7C $440

2. Correct Fee Paid. / Application may be processed for:
   Amendment
   Renewal
   License

3. OTHER

Signed SC
Date 5/14/97

MAY 21 1997

Log May C III
Remitter
Check No. 245675
Amount $440
Fee Category 7C
Type of Fee Amd
Date Check Rec'd 5/14/97
Date Completed 5/14/97
By SC

Borgess Medical Center
1521 Gull Road
Kalamazoo, Michigan 490[illegible]640
Telephone 616-226-7000

*Member of*
*Sisters of St. Joseph*
*Health System, Inc.*
*Ann Arbor, Michigan*

May 5, 1997

U.S. Nuclear Regulatory Commission
Region III
801 Warrenville Road
Lisle, Illinois 60532-4351

BORGESS
Medical Center

License Number: 21-12275-02

We are respectfully requesting that our license be amended to allow the use of Yttrium-90 for animal research at Borgess Medical Center. As we are attempting to begin this program on or about May 15, 1997, we are requesting that this amendment be expedited.

We are asking permission to order, receive, and implant balloon expandable stents into research animals. The stents are manufactured by Isostent and contain approximately 2 - 16 microcuries of $^{90}Y$ per stent. These stents are shipped by the manufacturer in radiation shields which the stent will remain in until it is deployed in the research animal. Enclosed for your review are copies of the program which describe animal use, ordering, receipt, storage, and disposal of the research animals and the radioisotope. I have also included condensed notes regarding the specific changes to our license. Authorized user James Dolan, M.D., has been made aware of this project and addressed the issue through communication with the Radiation Safety Committee.

If you have any questions or would like to contact me, please call me in the Radiology Department at 616.226-4833

The $440 amendment fee is enclosed.

Sincerely,

Tim TenCate, RSO
Radiology Director
Borgess Medical Center
1521 Gull Road
Kalamazoo, MI 49001

Pm: 5-9-97

302616
RECEIVED
MAY 12 1997
REGION III
MAY 12 1997

**MEMORANDUM**
**BORGESS MEDICAL CENTER**
**RADIOLOGY SERVICES**

**Date:** May 6, 1997

**To:** Radiation Safety Committee
Borgess Medical Center
John. Copenhaver, M.D., Chair

**From:** James R. Dolan, M.D.
James Dolan, M.D.
Authorized User
Borgess Medical Center, NRC License Number 21-12275-02

**RE:** **Authorized Delegated Authority**

Based on my knowledge of the procedures utilizing Y-90 in animal research involving stent placement, I am delegating the responsibility for processes as they relate specifically to that project to Andrew Carter, D.O.. It is understood that Dr. Carter will follow all guidelines as they pertain to federal regulations and stipulations specified in our license amendment. Any questions should be directed to either Tim TenCate, RSO, or physicist Tracey King, M.S., Medical Physics Consultants, Inc.

**BORGESS MEDICAL CENTER**
**21-12275-02 AMENDMENT REQUEST**
(Page 1 of 2)

We have identified the items listed below as items which require modification from our existing license procedures for the radioactive stent animal research program.

| Item 5<br>Byproduct material | Item 6<br>Amount | Purpose |
|---|---|---|
| Y-90 | -up to 20 uCi per stent<br>-not to exceed 10 mCi on site at any one time. | in coronary artery stents for implantation in animals for FDA trials. |

Item 7.1

Authorized User

All work will be completed under the supervision of Andrew J. Carter, D.O.

Item 9.1

A diagram of the areas where the animals will be housed is enclosed.

Survey Meter

We will use a GM meter with a probe possessing a thin-end window or beta window to perform surveys relating to the receipt, usage, and disposal of the stents.

The meter will be calibrated according to our existing license conditions concerning survey meter operational check, use, and calibration.

Item 9.4 Personnel Monitoring

The operators and assistants in the stent implantation procedures will wear dosimetry badges. All aspects of our existing personnel monitoring program will be followed for these individuals.

Given the shallow penetration of beta particle radiation, the sealed nature of the stent, the inability of the radioactive material to leech out of the stent into the urine or feces, and the low activity involved, there will be no risk of exposure for individuals involved in the care of the animals. The animal care takers will not be monitored with dosimetry badges.

Item 10.4 Rules for Safe Use of Stents (Radioactive)

Enclosed

Item 10.5 Emergency Procedures for Loss of Stent (Radioactive)

Enclosed

Item 13 Animal Handling

A contact number for special handling of the animals will be available in the event an animal should die unexpectedly prior to the study endpoint. Following necropsy, the pathologic specimens will be transferred to the Armed Forces Institute of Pathology (Drs. Farb and Virmani) when the radiation level decays to background. Drs. Farb and Virmani are licensed to receive and handle radioactive materials. The animal carcasses will be disposed of as biologic waste and not used for human or animal consumption.

BORGESS MEDICAL CENTER
21-12275-02 AMENDMENT REQUEST

**Item 10.4** (pg 1 of 2)

## RULES FOR SAFE USE OF STENTS

The stents are supplied by the manufacturer Iso-Stent in a radiation shield. The stents are not removed from the radiation shield until it is placed directly into the patient's vessel. Therefore, we have developed Rules for Safe Use of Stents. These rules will apply only to the Stent procedure.

1. Do not examine the stent itself outside of the radiation shield at any time.

2. Do not remove the radiation shield from over the stent at any time before the delivery catheter is advanced into the body.

3. If the radiation shield accidentally comes loose and the distal end of the delivery system becomes unshielded, slide the shield back over the stent's location and tighten the Tuohy-Borst fitting on the shield to lock the shield down.

4. Make sure to advance the delivery system forward into the body following loosening of the shield Tuohy-Borst.

5. If the stent delivery system has been advanced into the body, but for any reason the stent cannot be delivered, pull back the stent delivery catheter until the stent is inside the radiation shield, lock down the shield by tightening the shield Tuohy-Borst, return the device to its package, and return the opened package to the RSO for storage and disposal.

6. If the stent comes off of the catheter due to stent embolization, the physician should retrieve the stent using forceps or other remote retrieval devices when possible.

7. Once the stent is retrieved, it should be placed inside of the radiation shield if possible. If the radiation shield cannot be used, contact the RSO for a disposal container.

8. All personnel should avoid any direct handling of the bare stent with their fingers if possible. When direct handling is absolutely necessary, the use of surgical gloves should reduce the direct contact rate.

9. Wear disposable gloves at all times while handling the stent.

10. Either after each procedure or before leaving the area, monitor your hands and clothing for contamination in a low background area.

11. Use the radiation shields provided by the manufacturer until you are ready to complete placement directly into the patient's vessel. If the patient's condition does not allow the full use of the radiation shield until placement, the radiation shield will be used as long as possible and holding of the stent by personnel will then be minimized.

12. Do not eat, drink, smoke, or apply cosmetics in an area where stents are stored or when they are being used.

13. Do not store food, drink, or personal effects in areas where stents are stored and where they are used.

14 The radiation shield and any other packaging material associated with the stent must be returned to the Nuclear Medicine Department for analysis before they can be disposed of. Place all of this material in a plastic bag or other container provided for this purpose.

15. Transport the stents from the receipt location (Nuclear Medicine Hot Lab) to the placement location only in a covered container.

16. Before transport, make a visual count of the number of stents to be transported in the container. Upon arrival at the placement location, make a visual count of the number of stents. If the number differs, implement the Emergency Stent Loss Procedure.

17. Survey the placement room after placement is completed and after the patient has left, to ensure that no stent has been left behind.

18. Store stents only in the original radiation shield and in original packaging material or other covered container. Stents will only be stored in the Nuclear Medicine Hot Lab.

BORGESS MEDICAL CENTER
21-12275-02 AMENDMENT REQUEST

**Item 10.5**

## EMERGENCY PROCEDURES FOR LOSS OF STENT

1. NOTIFY: Notify persons nearby that a stent is lost.

2. Do not allow anyone to leave the area until their clothing has been searched and they have been surveyed with a GM meter. Pay particular attention to cuffs, pockets, shoe bottoms, or any other place where a stent may be trapped.

3. Do not allow additional personnel into the area.

4. Do now allow any items to be removed from the room until they have been visually searched and surveyed.

5. Begin a systematic survey of the area to ensure that no area is missed.

6. Contact the RSO for assistance.

7. Repeat the above searches and surveys until the source is found.

8. If necessary, retrieve all items and personnel who may have left the room between the time source was lost and its loss was noticed. If the source is still not located, track the paths of these personnel and items since the time they left the room and perform searches and surveys.

9. If the source is not located through all of the above measures, a report must be filed with the RSO who will determine the additional reporting requirements. The report must contain the sequence of events that allowed the loss of a stent and the actions taken to prevent recurrence.

**PROTOCOL NUMBER:**_____

Received by LACUC___
Approved/Sent for Revision___
Received (2nd Time) by LACUC___
Date Approved/Disapproved by LACUC___
Previous Number_____
ACTIVE/COMPLETED/TERMINATED_____

PROTOCOL TITLE: The Effect of $^{90}Y$ Endovascular Irradiation on Neointimal Formation in a Porcine Model

SHORT TITLE: Endovascular radiation via a stent

PRINCIPAL INVESTIGATOR Andrew J. Carter, DO PI PHONE: 226-6826

ASSOCIATE INVESTIGATOR Tim A. Fischell

ASSOCIATE INVESTIGATOR Lynn Bailey

DEPARTMENT Cardiovascular Research DIVISION Medicine

ANIMAL REQUIREMENTS:

| Species | Strain | Age | WT | Sex (M,F,E) | Total Number | Max no. housed |
|---|---|---|---|---|---|---|
| Pig | Yucatan | | 30-60 kg | either | 64 | 40 |
| | | | | | | |
| | | | | | | |

IS SPECIAL HOUSING REQUIRED? (YES/NO) If yes, explain or cite section in protocol: No
ARE ANIMAL REQUIREMENTS RESTRICTED TO A SINGLE VENDOR? No
AGRICOLA: DTIC: WORD SEARCHED AGAINST Radiation, Stents, Restenosis
Date: 25 April 1997
Search Number_____ Search Number_____
INDEX KEY WORDS: Swine, Yucatan, coronary arteries, stents, radiation

BIOHAZARD/SAFETY ELEMENTS? Y/N BIOHAZARD NAMES:_____
BIOSAFETY LEVEL: 1, 2, 3, 4 REFERENCE PAGE IN PROTOCOL: 9
USDA CATEGORY

Number of Animals in Category

| | Year 1 | Year 2 | Y |
|---|---|---|---|
| [ ] N - Minimal, Transient, or No Pain and Distress | | | |
| [x] D - Pain, Distress Relieved by Appropriate Measures | 50 | | |
| [ ] P - Unrelieved Pain or Distress | | | |

For P, ATTACH USDA FORM 18-23 and CITE REFERENCE PAGE IN PROTOCOL): N/A

ALTERNATIVES CONSIDERATIONS: Does the protocol have any provisions that would qualify it to be identified as one that Refines, Reduces, or Replaces (3R's) the use of animals in relation to other protocols or procedures performed in the past?
YES/NO REFERENCE PAGE IN PROTOCOL:_____

PROCEDURE CODES:_____ [To be filled out by consulting veterinarian]
LOCATION CODE:_____ [To be filled out by consulting veterinarian]

**PROTOCOL TITLE:** The Effect of $^{90}Y$ Endovascular Irradiation on Neointimal Formation in a Porcine Model

**PRINCIPAL INVESTIGATOR:**

_____
Andrew J. Carter, DO
Associate Director, Cardiovascular Research

**SCIENTIFIC REVIEW:**

_____

**COORDINATION:**

A. **Attending/Consulting Veterinarian:**

_____

B. **Statistical Consultant:**

N/A

_____

C. **LACUC Representative:**

_____

25 April 1997

**PROTOCOL TITLE:** The Effect of $^{90}Y$ Endovascular Irradiation on Neointimal Formation in a Porcine Model

**PRINCIPAL INVESTIGATOR:** Andrew J. Carter, DO, Associate Director, Cardiovascular Research, 381-3963

**ASSOCIATE INVESTIGATORS**: Tim A. Fischell, MD; Director, Cardiovascular Research, Borgess Medical Center; Lynn Bailey, LATG, Research Associate, Cardiovascular Research, Borgess Medical Center

**I. NON-TECHNICAL SYNOPSIS**: A mechanical approach designed to maximize initial expansion of an arterial blockage (with an arterial stent) combined with anti-proliferative therapy (beta irradiation) to reduce subsequent narrowing may offer the ideal method to reduce the recurrence of blockage (restenosis) following balloon angioplasty. If a therapy were found to decrease the rate of restenosis, this would revolutionize the treatment of atherosclerotic coronary artery disease in this country and have a profound effect on the costs of such treatment.

## II. A. BACKGROUND:

Neointimal formation is the principle cause of restenosis after intracoronary stent placement. Endovascular radiation delivered via a stent has been shown to reduce neointimal formation after placement in porcine and rabbit iliac arteries. In previous animal experiments in our laboratory, we have demonstrated that low dose endovascular radiation via a β-particle emitting stent reduces neointimal proliferation resulting in less narrowing of the stent lumen compared to a non-radioactive stent. Subsequently, we developed a dose response relation for Palmaz-Schatz β - particle emitting stents on neointimal proliferation in a porcine restenosis model. Thirty-seven swine underwent placement of 35 non-radioactive and 39 β-particle stents with activity levels of 23.0, 14.0, 6.0, 3.0, 1.0, 0.5 and 0.15 μCi of $^{32}P$. Treatment effect was assessed by histologic analysis 28 days after stent placement. Neointimal and medial smooth muscle cell density were inversely related to increasing stent activity. The neointima of the high activity (3.0 to 23.0 μCi) stents consisted of fibrin, erythrocytes, occasional inflammatory cells and smooth muscle cells with partial endothelialization of the luminal surface. In the 1.0 μCi stents, the neointima was expanded consisting of smooth muscle cells and a proteoglycan rich matrix. The neointima of the low activity (0.15 and 0.5 μCi) stents was composed of smooth muscle cells and matrix with complete endothelialization of the luminal surface. At low and high stent activities, there was a reduction in neointimal area ($1.63 \pm 0.67$ $mm^2$, low and $1.73 \pm 0.97$ $mm^2$, high versus $2.40 \pm 0.87$ $mm^2$, control) and percent area stenosis ($26 \pm 7\%$, low and $26 \pm 12\%$, high) as compared to control stents ($37 \pm 12\%$, $p \leq 0.01$). The 1.0 μCi stents, however, had greater neointimal formation ($4.67 \pm 1.50$ mm2) and more luminal narrowing ($64 \pm 16\%$) than the control stents ($p < 0.0001$). These studies, collectively, demonstrated a 30% reduction in neointimal formation with low activities (< 0.5 μCi) of $^{32}P$ at 28 days after stent placement in normal porcine coronary arteries.

In a more recent series of experiments, we evaluated the long-term effects of stents with high activities of $^{32}P$ (3, 6 and 12 μCi) in atherosclerotic porcine coronary arteries. After six months, angiographic and histologic analysis indicated a dose dependent increase in neointimal formation and in-stent stenosis. In summary, the experimental studies with $^{32}P$ indicate a only modest reduction in neointimal formation at activities < 1.0 μCi and promotion of an atheromatous neointima at activities > 3.0 μCi.

Tierstein et al. recently reported a 60% reduction in late lumen loss and restenosis in a randomized placebo controlled clinical trial with 8 to 25 Gy irradiation delivered via an endovascular $^{192}Ir$ source in patients with refractory restenosis. These investigators prescribed a

dose of radiation that was similar to the cumulative dose provided by a 1.0 μCi $^{32}P$ radioactive stent but at a much higher dose rate. Thus, dose rate may be more important that the cumulative dose in preventing neointimal formation. A short acting isotope with a higher energy than $^{32}P$ would allow similar dose rates to be achieved with a radioactive stent. $^{90}Y$ttrium has a 64 hour half-life with a maximal energy of 2.28 MeV. A 15 mm length stent with 2 to 16 μCi of $^{90}Y$ would provide a dose rate similar to that prescribed with brachytherapy. The purpose of this study is to determine if a high dose rate radioactive stent inhibits neointimal formation after stent placement in porcine coronary arteries.

**B. Literature Search:**

1. **Literature Source(s) Searched:** DTIC, Agricola, MEDLINE, FEDRIP

2. **Date and Number of Search:** 25 April 1997

3. **Key Words of Search:** Radiation, Stents, Restenosis

4. **Results of Search:** refer to attached documents

## III. OBJECTIVE\HYPOTHESIS:

1. High dose rate endovascular irradiation will reduce neointimal formation after stent placement in porcine coronary arteries.

## IV. MATERIALS AND METHODS:

**A. Experimental Design and General Procedures:** The study will test the dose response effects of four different total stent activities of $^{90}Y$ on the degree of inhibition of neointimal formation at 1, 3 and 6 months after placement in **normal coronary arteries**. Each animal will receive one to three stents in the left anterior descending (LAD), circumflex (LCX), or right (RCA) coronary artery. This will consist of a control, non-radioactive stent, and a $^{90}Y$ stent with an activity of: 2.0, 4.0, 12.0 or 16.0 μCi. The position of these stents will be alternated for each animal, so that there will be equal distribution of each location for the five stents (randomized block design). Eight to 10 stents of each dose will be compared at each time interval to a control stent (50-60 animals, 30 control and 120 $^{90}Y$).

We will be using a 15 mm length Isostent BX balloon expandable coronary stent. The stents will be rendered radioactive by using chemical bonding techniques. $^{90}Y$ is a pure β-particle emitter (no gamma-radiation) with a maximal energy of 2.28 MeV and a half-life of 64 hours. The stents are then placed in a protective lucite shield and sterilized for use.

Animals will undergo follow-up angiography and intravascular ultrasound at 1,3 and 6 months after stent placement. The animals will be euthanized after completion of angiography for histologic analysis of the stented arteries. Angiograms will be used to confirm stent patency, and assess the degree of narrowing as well as the presence of intraluminal filling defects. Intravascular ultrasound analysis will allow quantitation of neointimal growth within the stent at the time of follow-up. Histologic analysis will include the measurement of arterial, neointimal and lumen area for comparison between the control versus β-particle emitting stents.

**B. Laboratory Animals Required and Justification:**

Yes, in view of the content of the clinical data to be obtained there is no bench or computer assisted simulation that would adequately test the effect of stent placement or local delivery of $^{90}Y$ β-particle irradiation on neointimal proliferation after placement in coronary arteries.

**2. Animal Model and Species Justification:** The Yucatan miniature swine was chosen for the animal model in this study for the following reasons: 1. The species develops intimal proliferation following coronary injury that is histologically identical to the restenosis lesion that

develops after angioplasty in humans; 2. The coronary arteries in the 30-60 kg swine approximate the size of the coronary arteries in humans (2.5-3.5 mm in diameter); 3. Previous work at this center and others has validated this model and used it to test therapies for the prevention of restenosis. 4. The size of the animal allows for use of human adult sized catheters and devices and allows for the direct transfer of the technology to human trials.

**3. Laboratory Animals:**

**a. Genus & Species:** Swine

**b. Strain/Stock:** Yucatan

**c. Source/Vendor:** Charles River or Lone Star Labs

**d. Age:** 9 to 12 months

**e. Weight:** 30-60 kg

**f. Sex:** castrated male or female

**g. Special Considerations:** N/A

**4. Total Number of Animals Required:** 66. A minimum of 60 animals will be required to assess the effect of 4 different doses of $^{90}Y$ β-particle radiation on the degree of intimal proliferation seen after stent placement in normal coronary arteries. The vessels treated with radioactive stents will be compared with vessels treated with non-radioactive stents. Assuming a 10% animal mortality associated with these procedures, a total of 66 animals will be required.

**5. Refinement, Reduction, Replacement:**

**a. Refinement:** One, 3, and 6 month endpoints will allow temporal assessment of neointimal formation, medial thickness and cell density for the control and radioactive stents. Each animal will receive two or three coronary stents. This will maximize animal utilization and provide for an adequate sample size to detect a therapeutic effect.

**b. Reduction:** Fifty to 60 animals will undergo placement of 150 stents in the coronary arteries. Each animal will receive 2-3 stents. This will consist of a control, non-radioactive stent, and/or one of four $^{90}Y$ β-particle emitting stents. Each β-particle emitting stent will deliver a different radiation activity (2.0, 4.0, 12.0, 16.0 μCi). There will be 150 treatment sites, 10 control and 10 for each radiation activity and study interval . For a type I error of 0.05, a sample size of 10 for each group will have > 90% power to detect a significant difference of 1.5 standard deviations for comparing each treatment with the controls.

**c. Replacement:** A computerized search of the medical literature (National Library of Medicine, DTIC, Agricola dated 25 April 1997) failed to reveal duplicative research aside from that mentioned in the preceding paragraphs. In view of the unique application of this device and the need to test its safety and efficacy *in vivo* in atherosclerotic coronary arteries there is no acceptable non-animal model.

**C. Technical Methods:**

**1. Prolonged Restraint: N/A**

2. **Surgery:**

All procedures will be performed in the research cardiac catheterization laboratory of Borgess Medical Center. The animals undergoing surgical procedures will have nothing by mouth for at least 12 hours prior to the procedure with the exception of preoperative medications (Aspirin 650 mg and Procardia XL 30 mg) which are administered per Os with a small amount of food (i.e., apple). All surgeries are accomplished with strict attention to sterile technique and principles of radiation safety. After sedation with 20 mg/kg Ketamine HCl and Xylazine 2 mg/kg intramuscularly (28 gauge butterfly needle) the animal will be intubated and mechanically ventilated and intravenous access (18 gauge angiocath) via an ear vein will be established. Adjunctive atropine (0.5 - 1.0 mg IV) will be administered as indicated by observed cardiac rhythm changes (bradycardia) or for excessive bronchial secretions. The animals will be placed on a warming blanket and rectal temperatures monitored as indicated. Continuous anesthesia will be maintained with Fentanyl, 75-150 mcg/kg/hour, via intravenous infusion after a bolus loading dose. A carotid artery cut down will be performed using sterile technique to gain arterial access. Electrocardiographic and arterial pressure monitoring will be continued throughout the procedure.

**Stent Placement:** The surgical techniques will follow those outlined in the prior sections. Baseline coronary angiography will be performed after the administration of 150 units/kg of intra-arterial heparin. Two hundred micrograms of intracoronary nitroglycerin will be administered to prevent vasospasm following deployment of the stents. The vessels to be treated will be sized using the guiding catheter as reference. The balloon catheter with a control or $^{90}Y$ β-particle emitting stent will then be delivered to the intended site over a guide wire using fluoroscopic guidance. The stent will be deployed by inflation to 10-14 atmospheres for 30 seconds to securely deploy the prosthesis within the vessel. This process will be completed to implant additional stents in each coronary segment 3.0 to 4.0 mm diameter by visual estimate for all animals. Following stent deployment, angiography will be performed to document stent patency. The catheter and sheath will be removed and the carotid artery repaired or ligated utilizing standard techniques. The neck incision will be repaired with interrupted suture and the skin closed with sterile staples. The animals will be recovered from the procedure and returned to care facilities by the research team. The pigs will be monitored daily by the investigators or associates for signs of postoperative complications (bleeding, infection) and pain (lack of appetite, inactivity or abnormal behavior). All animals will receive Aspirin 81 mg per Os daily and remain on a normal chow diet. The animals will receive appropriate tests or medical therapy for unexpected health problems as deemed necessary by the attending veterinarian and principal investigator or their designees.

**Follow-up Studies**: Angiography and intravascular ultrasound will be performed at a specified time interval (1,3, and 6 months) following stent placement using the techniques described above. The animals will then be euthanized by the research team. The heart will be removed immediately after death and the coronary arteries will be pressure perfused with formalin at 60-80 mm Hg for one hour. The specimens will then be delivered to the Armed Forces Institute of Pathology for further processing.

b. **Pre- and Post-operative Provisions:** All animals will be treated and evaluated in conformance with standard operating procedures to insure acceptable health for surgical procedures. This will include blood sampling for a complete blood count, serum chemistries and cholesterol. The animals will be fasted except for water and medications on the day prior to surgery. Animals will be housed at MPI research, Mattawan, MI prior to surgery. The animals will remain at the Borgess animal care facility until the radiation level has decayed to background rates.

c. **Location:** Cardiac Catheterization Laboratory, Division of Surgical Research, Borgess Medical Center

d. **Multiple Survival Surgery Procedures:**

(1) **Procedures: N/A**

(2) **Scientific Justification**: N/A

3. **Animal Manipulations**:

a. **Injections**: N/A

b. **Biosamples**: N/A

c. **Animal Identification**: Ear tag

d. **Behavioral Studies**: N/A

e. **Other Procedures**: N/A

4. **Adjuvants**: N/A

5. **Study Endpoint**: 3, 60 or 180 days

6. **Euthanasia**: Animals will be euthanized with an overdose of commercial potassium/barbiturate (Euthanasia 6 - 1 ml/10lbs IV via marginal ear vein) while fully anesthetized and subsequently will undergo necropsy with harvest of the heart intact for subsequent pressure perfusion.

7. **Pain**:

a. **USDA (Form 18-3) Pain category: Category D - (Pain Alleviated by Drugs) - (Column D, APHIS Form 7023)**

(1) **No Pain** 0 (#) 0%

(2) **Alleviated Pain** 66 (#) 100%

(3) **Unalleviated Pain or Distress** 0 (#) 0%

b. **Pain Alleviation**:

(1) **Anesthesia/Analgesia/Tranquilization**: In an experience of greater than 750 similar porcine procedures there is little discomfort associated with the postoperative recovery as can be delineated by careful observation of the animals. Should an animal appear to be in discomfort or develop a complication felt to warrant pain medication this shall be effected in the form of oxymorphine (0.15 mg/kg IM q 4 hr prn).

(2) **Paralytics**: N/A

c. **Alternatives to Painful Procedures**:

(1) **Source(s) Searched**: DTIC, Agricola, MEDLINE

(2) **Date of Search**: 25 April 1997

(3) **Key Words of Search**: stents, radiation, non-surgical models, pain

(4) **Results of Search**: No available non-surgical models

**d. Painful Procedure Justification:** This study requires post-operative animal recovery and survival for up to 6 months. Animal discomfort is expected to be minimal and when necessary completed alleviated by use of analgesia.

**D. Veterinary Care:**

**1. Husbandry Considerations:**

**a. Study Room:** The animals will be housed at MPI research, Mattawan, MI prior to surgical procedures. The animals will remain in the care facilities at Borgess Medical Center, West wing, annex, level C for the duration of the study. This facility has limited access and key coded entry by authorized personnel (research staff).

**b. Special Husbandry Provisions:** The animals will receive care in accordance with standard operating procedures for swine in accordance with 1996 NRC publication.

**2. Attending Veterinary Care:**

**3. Enrichment Strategy:** This study will not interfere with the institutional enrichment plan for swine.

**E. Data Analysis:** Quantitative angiography will be performed to measure the vessel diameter pre and post stent placement and at follow-up. The stent to artery ratio will be calculated. The angiographic percent stenosis at mid stent will be calculated from the follow-up angiogram. Histologic measurements will be made from sections from the middle of the stent. A vessel injury score will be calculated using the method described by Schwartz. The mean injury score for each arterial segment will be calculated by dividing the sum of injury scores at each wire site by the total number of wires from the mid-stent sections. Neointimal thickness will be measured at each wire site. The cross sectional areas of each mid-stent section will be measured with digital morphometry to determine the neointimal area and percent area stenosis. Investigators scoring arterial segments and performing histopathology will be "blinded" to the treatment. Data will be expressed as the mean ± SD. Statistical analysis of the histologic and angiographic data will be accomplished using analysis of variance (ANOVA). A $p < 0.05$ will be considered statistically significant.

**F. Investigator & Technician Qualifications/Training:** The principal and associate investigators have an extensive variety of clinical and research skills and experience to assure completion of the project. The investigators have experience with ongoing porcine coronary injury and atherosclerotic models similar to that described in the protocol. Lynn Bailey, LATG has assisted the investigators since 1991 with the animal care, surgery, and anesthesia. Dr. Farb and Dr. Virmani are cardiovascular pathologists at the Armed Forces Institute of Pathology. They are considered experts in coronary histopathology after angioplasty and have considerable research experience with the porcine coronary injury model and with the pathologic evaluation of endovascular prostheses. Both are licensed to receive and handle radioactive compounds.

**VI. BIOHAZARD/SAFETY:** All individuals involved in the protocol must complete a radiation safety course prior to participating in the project. The isotope stents will be sterilized by the manufacturer and packaged with the stent in a lucite cylinder and a protective metal container. The devices will be shipped to the nuclear medicine department radiopharmacy at Borgess Medical Center for inspection prior to delivery to the research lab. In accordance with our existing license, the usual storage and handling precautions for radioactive materials will be followed. The devices will be stored in the nuclear medicine isotope storage area which has limited and secured access. At the time of implantation, the stent will be maintained within the protective lucite housing until it is passed into the guiding catheter. The operator and assistants involved in the procedure will avoid direct contact with the stent and will double glove to minimize exposure. All individuals in the laboratory have received training in the use of x-ray equipment. The operators and assistants will be wearing lead aprons and dosimetry badges. The room will be screened prior to and following every procedure for evidence of radioactive contamination. Given the shallow penetration of beta particle irradiation, the sealed source, inability to leech out of the stent into the urine or feces and the low doses involved, there will be no risk of exposure for individuals involved in the care of the animals. One of the investigators will be available evenings and weekends as necessary. Follow-up angiography and necropsy will be performed using the same precautionary techniques as outlined in the implantation procedure. A contact number for special handling of the animals will be available in the event an animal should die unexpectedly prior to the study endpoint. Following necropsy, the pathologic specimens will be transferred to the Armed Forces Institute of Pathology when the radiation level decays to background (Drs. Farb and Virmani). Drs. Farb and Virmani are licensed to receive and handle radioactive materials. The animal carcasses will be disposed of as biologic waste and not used for human or animal consumption.

**VII. ASSURANCES**: As the Primary Investigator on this protocol I acknowledge my responsibilities and provide the following assurances:

**A. Animal Use:** The animals authorized for use in this protocol will be used only in the activities and in the manner described herein, unless a deviation is specifically approved by the IACUC.

**B. Duplication of Effort:** I have made a reasonable, good faith effort to ensure that this protocol is not an unnecessary duplication of previous experiments.

**C. Statistical Assurance:** I assure that I have consulted with an individual who is qualified to evaluate the statistical design or strategy of this proposal, and that the "minimum number of animals needed for scientific validity are used".

**D. Biohazard\Safety:** I have taken into consideration, and I have made the proper coordinations regarding all applicable rules and regulations regarding radiation protection, biosafety, recombinant issues, etc., in the preparation of this protocol.

**E. Training:** I verify that the personnel performing the animal procedures/manipulations described in this protocol are technically competent and have been properly trained to ensure that no unnecessary pain or distress will be caused as a result of the procedures/manipulations.

**F. Responsibility:** I acknowledge the inherent moral and administrative obligations associated with the performance of this animal use protocol, and I assure that all individuals associated with this project will demonstrate a concern for the health, comfort, welfare, and well-being of the research animals. Additionally, I pledge to conduct this study in the spirit of the fourth "R" , namely, "Responsibility" for implementing animal use alternatives where feasible, and conducting humane and lawful research.

_____

Andrew J. Carter, DO
Principal Investigator

G. **Painful Procedures: I am conducting biomedical experiments which may potentially cause more than momentary or slight pain or distress to animals that WILL BE relieved or WILL NOT (circle one) be relieved with the use of anesthetics, analgesics and/or tranquilizers.** I have considered alternatives to such procedures; however, using the methods and sources described in the protocol, I have determined that alternative procedures are not available to accomplish the objectives of the proposed experiment.

_____

Andrew J. Carter, DO
Principal Investigator

**VIII. ENCLOSURES:** 1. Bibliography; 2. CV for principal investigator

## References


1. Serruys, P.W.; De Jaegere, P.; Kiemeneij, F.; Macaya, C.; Rutsch, W.; Heyndrickx, G.; Emanuelsson, H.; Marco, J.; Legrand, V.; Materne, P.; Belardi, J.; Sigwart, U.; Colombo, A.; Goy, J.J.; Van Den Heuvel, P.; Delcan, J.; Morel, M.A.; for the Benestent Study Group.; A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N. Engl. J. Med. 331:489-495; 1994.
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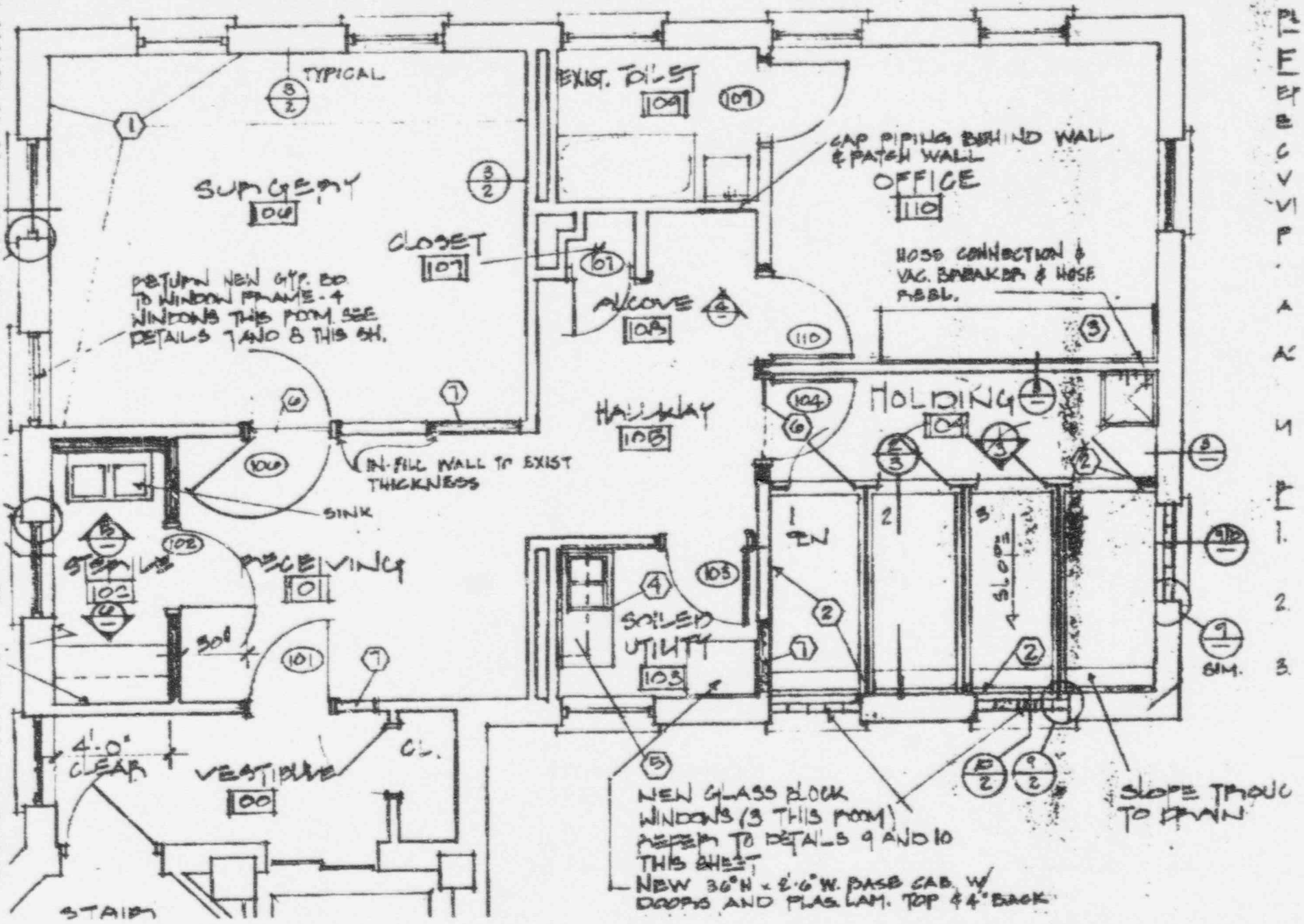

JUN 05 1997

Tim TenCate, RSO
Radiology Director
Borgess Medical Center
1521 Gull Road
Kalamazoo, MI 49001

Dear Mr. TenCate:

Enclosed is Amendment No. 74 to your NRC Material License No. 21-12275-02 in accordance with your request.

Please review the enclosed document carefully and be sure that you understand all conditions. If there are any errors or questions, please notify the U.S. Nuclear Regulatory Commission, Region III office at (630) 829-9887 so that we can provide appropriate corrections and answers.

Please be advised that your license expires at the end of the day, in the month, and year stated in the license. Unless your license has been terminated, you must conduct your program involving byproduct materials in accordance with the conditions of your NRC license, representations made in your license application, and NRC regulations. In particular, note that you must:

1. Operate in accordance with NRC regulations 10 CFR Part 19, "Notices, Instructions and Reports to Workers; Inspections," 10 CFR Part 20, "Standards for Protection Against Radiation," and other applicable regulations.

2. Notify NRC, in writing, within 30 days:

   a. When an authorized user or Radiation Safety Officer permanently discontinues performance of duties under the license or has a name change; or

   b. When the mailing address listed on the license changes. (No fee is required if the location of byproduct material remains the same.)

3. In accordance with 10 CFR 30.36(b) and/or license condition, notify NRC, promptly, in writing, and request termination of the license when you decide to terminate all activities involving materials authorized under the license.

302616

4. Request and obtain a license amendment before you:

   a. Receive or use byproduct material for a clinical procedure permitted under Part 35 but not permitted by your license issued pursuant to this Part;

   b. Permit anyone, except individuals described in 10 CFR 35.13(b), to work as an authorized user under the license;

   c. Change Radiation Safety Officers;

   d. Order byproduct material in excess of the amount, or radionuclide, or form different than authorized on the license;

   e. Add or change the areas of use or address or addresses of use identified in the license application or on the license; or

   f. Change ownership of your organization.

5. Submit a complete renewal application with proper fee or termination request at least 30 days before the expiration date of your license. You will receive a reminder notice approximately 90 days before the expiration date. Possession of byproduct material after your license expires is a violation of NRC regulations A license will not normally be renewed, except on a case-by-case basis, in instances where licensed material has never been possessed or used.

In addition, please note that NRC Form 313 requires the applicant, by his/her signature, to verify that the applicant understands that all statements contained in the application are true and correct to the best of the applicant's knowledge. The signatory for the application should be the licensee or certifying official rather than a consultant.

You will be periodically inspected by NRC. Failure to conduct your program in accordance with NRC regulations, license conditions, and representations made in your license application and supplemental correspondence with NRC will result in enforcement action against you. This could include issuance of a notice of violation, or imposition of a civil penalty, or an order suspending, modifying or revoking your license as specified in the General Statement of Policy and Procedure for NRC Enforcement Actions. Since serious consequences to employees and the public can result from failure to comply with NRC requirements, prompt and vigorous enforcement action will be taken when

dealing with licensees who do not achieve the necessary meticulous attention to detail and the high standard of compliance which NRC expects of its licensees.

Sincerely,

Original Signed By
Evelyn R. Matson
Nuclear Materials Licensing Branch

License No.: 21-12275-02
Docket No.: 030-02115

Enclosure: Amendment No. 74

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UNITED STATES
NUCLEAR REGULATORY COMMISSION
REGION III
801 WARRENVILLE ROAD
LISLE, ILLINOIS 60532-4351

May 14, 1997

Tim Tencate
Radiation Safety Officer
Borgess Medical Center
1521 Gull Road
Kalamazoo, MI 49001

SUBJECT: ACKNOWLEDGEMENT OF CORRESPONDENCE
(Letter Dated 05/05/97)

Dear Licensee:

In response to your request, we have completed the initial processing, which is an administrative review of your application for a(n):

___ New License  _X_ Amendment  ___ Renewal
___ Termination  ___ Auth User (Amendment not required)  ___ Other_
_____

No administrative deficiencies were identified during this initial review. However, it should be noted that a technical review may identify omissions in the submitted information.

It appears that your request is routine (see 1-3 below, as applicable).

1. New and amendment actions are normally processed within 90 days, unless we find major deficiencies, or policy issues requiring central program office assistance.

2. Renewal actions are normally processed within 180 days, however, under timely filing (before expiration), you may continue to operate under your existing license.

3. Termination actions are normally processed within 90 days, unless confirmatory surveys following decontamination/decommissioning activities are involved.

A copy of your correspondence has been forwarded to our Licensing Fee and Debt Collection Branch (301/415-6097) for approval of the fee category and amount, if required.

If you have a compelling safety or business-related reason for requesting expedited review, please contact the Materials Licensing Branch at (630) 829-9887. We will try to complete your request as soon as practicable. Any correspondence about this request should reference the control number.

Nuclear Materials Support Branch

Mail Control No. 302616
License No. 21-12275-02