ATOMIC ENERGY COMMISSION

[10 CFR Parts 31, 32 and 35]

Group Licensing for Certain Medical Uses

The Atomic Energy Commission has under consideration amendments to its regulations in 10 CFR Parts 31, 32 and 35 to expand its licensing of groups of medical uses of byproduct material which have similar requirements for licensee qualifications, to specify licensing requirements for the distribution of byproduct material to such licensees and to add new byproduct material to the general license for certain in vitro clinical and laboratory testing.

In 1967 the Commission added sections 35.14 and 35.100 to its regulations in 10 CFR Part 35 to simplify its procedures for licensing certain diagnostic of radioisotopes. Under these sections a number of the more common diagnostic uses were divided into two groups on the basis of similar requirements for user training and experience, facilities and equipment, and radiation safety procedures. Group I included diagnostic uses characterized as uptake, dilutic and excretion studies. Group II consisted of scanning (now called imaging) and tumor localization studies. Under the procedures set out in section 35.14 an application for a specific license for a diagnostic use of byproduct material specified in Group I or Group II is considered by the Commission as an application for all of the uses within the group.

The amendments proposed herein would add some diagnostic uses to Groups I and II of section 35.100 Schedule A and would establish three new groups of medical uses of radioisotopes as follows:

Group III. Use of generators and reagent kits for the preparation and use of radiopharmaceuticals containing byproduct material for certain diagnostic uses,

Group IV. Use of prepared radiopharmaceuticals for certain therapeutic uses, and

Group V. Use of sources and devices containing byproduct material for certain medical uses.

Under this proposed expansion of group licensing, physicians and medica institutions would be licensed to use the byproduct materials for the medica uses designated in one or more of the groups for which the applicant has appropriate facilities, equipment, operating procedures and trained personnel (both physicians and paramedical) to perform the medical procedures and handle the radioisotopes designated in the group or groups.

The groups of licensed uses would be amended from time to time to add new radiopharmaceuticals, sources, devices, and uses as they are developed. would authorize automatically the new uses and materials for persons license to perform the uses specified in the group or groups without the need for filing an application and receiving a license amendment. In addition to the

publication of such amendments in the FEDERAL REGISTER, notices of additions to the groups would be mailed to all medical licensees of the Commission.

Persons using radiopharmaceuticals, generators and reagent kits containing byproduct materials, or sources and devices, under the licensed groups would be required to obtain such products from manufacturers licensed by the Commission pursuant to section 32.72, 32.73 or 32.74, respectively, or by an Agreement State pursuant to equivalent Agreement State regulations. Although the Commission does not regulate the manufacture and distribution of reagent kits which do not contain radioactive material, it does regulate the use of such reagent kits for the preparation of radiopharmaceuticals by licensees of the Commission as part of its licensing and regulation of the users of the byproduct material. Users of such reagent kits to prepare radiopharmaceuticals pursuant to a Group III license would be required to use reagent kits which are approved by the Commission or by an Agreement Sta Manufacturers of such reagent kits who desire to have their reagent kits approved by the Commission for use by Group III licensees would be permitte to submit the pertinent information specified in section 32.73 for Commissi consideration.

In the exercise of the Commission's regulatory program, licensing of the use of radiopharmaceuticals has included considerations of patient safety a drug effectiveness. This procedure has been followed since the Food and Dr Administration (FDA) regulations, 21 CFR 130.3, New Drugs for Investigation Use in Human Beings, which were issued in 1963 contained an exemption from

those regulations for radiopharmaceuticals which are regulated by the AEC and Agreement States. The Chairman of the Commission, in a letter to the Department of Health Education and Welfare commenting on their proposal to grant that exemption, expressed the view that eventually an appropriate balance with respect to the regulation of drugs containing byproduct materia would involve FDA regulations controlling the pharmaceutical quality of drugs and the safety and efficacy of drugs with respect to the patient, whil AEC regulatory controls would govern radiation safety of employees and the public during manufacture and use of the drugs.

The Commission and the FDA are coordinating their respective regulatory programs to provide for a transition from the Commission to the FDA of the regulation of pharmaceutical quality, safety and efficacy of radiopharmaceut in such manner as to minimize duplication of regulatory activities, to accomplish the objectives of protecting public health and safety without und inhibiting the use of radioactive materials in medicine and to assure no disruption in the supply of these drugs which are of vital importance in man medical applications during the transition period.

On November 3, 1971, the FDA published in the FEDERAL REGISTER (36 FR 2 a notice of termination, effective December 2, 1971, of the exemption from FDA investigational new drug regulations for AEC and Agreement State regulat radiopharmaceuticals for well established uses and provided for regulation by the FDA of such radiopharmaceuticals (21 CFR 130.49 - Requirements regard certain radioactive drugs.) It is expected that the FDA will similarly terminate the exemption for radiopharmaceuticals for investigational uses at an early date.

The groups of use in §35.100 would include medical uses of radiopharmaceuticals for which safety and effectiveness have been established and those which are undergoing investigation to establish such safety and effectiveness. For the investigational radiopharmaceuticals and uses included in the licensed groups, a licensee would be required to register with the Commission prior to use of each different type of investigational u to identify the radiopharmaceutical, its intended purpose, and the supplier, and to certify that he would be using the radiopharmaceutical pursuant to a "Notice of Claimed Investigational Exemption for a New Drug" (IND) that has been accepted by the FDA.

The new §§32.72 and 32.73 which contain criteria for licensing the distribution of radiopharmaceuticals, and generators and reagent kits for preparation of radiopharmaceuticals, to group-use licensees would require manufacturers to furnish evidence that the radiopharmaceuticals, generators and reagent kits will be manufactured, packaged, and labeled under an effective New Drug Application from FDA, a Biologic Product License from FDA or a "Notice of Claimed Investigational Exemption for a New Drug" that has been accepted by FDA.

Section 31.11 of 10 CFR Part 31, which provides a general license to physicians, clinical laboratories and hospitals for use of certain radioisotc for in vitro clinical or laboratory testing, would be amended to add hydroger (tritium) and iron 59 to the general license. Section 32.71 of 10 CFR Part

would be amended to add these isotopes to the provisions for licensing their manufacture and distribution for in vitro use under the general license.

Pursuant to the Atomic Energy Act of 1954, as amended, and section 553 of title 5 of the United States Code, notice is hereby given that adoption of the following amendments to 10 CFR Parts 31, 32 and 35 is contemplated. All interested persons who desire to submit written comments or suggestions for consideration in connection with the proposed amendments should send them to the Secretary of the Commission, U. S. Atomic Energy Commission, Washington, D. C. 20545, Attention: Chief, Public Proceedings Staff, by March 7, 1974 . Copies of comments received on the proposed amendments may be examined at the Commission's Public Document room at 1717 H Street, NW, Washington, D. C.

1. Section 35.14 of 10 CFR Part 35 is amended to read as follows:

§35.14 Specific licenses for certain groups of medical uses of byproduct material.

(a) Subject to the provisions of paragraphs (b), (c) and (d) of this section, an application for a specific license pursuant to §35.11, §35.12 or §35.13 for any medical use or uses of byproduct material specified in one or more of Groups I to V, inclusive, of §35.100 will be approved for all of the uses within the group or groups which include the use or uses specified in the application if:

(1) The applicant satisfies the requirements of §35.11, §35.12, or §35.13;

(2) The applicant, or the physician designated in the application as the individual user, has adequate clinical experienc in the types of uses included in the group or groups;

(3) The applicant or the physicians, technologists, radiological safety personnel and other paramedical personnel who will use the byproduct material have adequate training and experience in the handling of radioactive material appropriate to the uses included in the group or groups;

(4) The applicant's radiation detection and measuring instrumentation is adequate for conducting the procedures involved in the uses included in the group or groups;

(5) The applicant's radiation safety operating procedures are adequate for handling and disposal of the radioactive material involved in the uses included in the group or groups.

(b) Any licensee who is authorized to use byproduct material pursuant to one or more groups in §§35.14(a) and 35.100 is subject to the following conditions:

(1) For Groups I, II, and IV, no licensee shall receive, possess or use byproduct material except as a radiopharmaceutical manufactured in the form to be administered to the patient, labeled, packaged, and distributed in accordance with a specific license issued by the Commission pursuant to §32.72 of this chapter or in accordance with a specific license issued to the manufacturer by an Agreement State pursuant to equivalent State regulations.

(2) For Group III, no licensee shall receive, possess, or use generators or reagent kits containing byproduct material except generators or reagent kits which are manufactured, labeled, packaged, and distributed in accordance with a specific license issued by the Commission pursuant to §32.73 of this chapter or in accordance with a specific license issued to the manufacturer by an Agreement State

pursuant to equivalent State regulations and no licensee shall use reagent kits which do not contain byproduct material to prepare radiopharmaceuticals containing byproduct material except reagent kits which are approved by the Commission or by an Agreement State for use by persons licensed pursuant to this §35.14 and Group III of Schedule A, §35.100, or equivalent Agreement State regulations.

(3) For Group V, no licensee shall receive, possess, or use byproduct material except as contained in a source or device which has been manufactured, labeled, packaged, and distributed in accordance with a specific license issued by the Commission pursuant to §32.74 of this chapter or in accordance with a specific license issued to the manufacturer by an Agreement State pursuant to equivalent State regulations.

(4) For the investigational uses in §§35.100(a)Group I(19), (b)Group II(25), (c)Group III(3), and (d)Group IV(9), the licensee shall, prior to the use of each different type of investigational radiopharmaceutical, or generator or reagent kit for the preparation and medical use of investigational radiopharmaceuticals, and prior to use of such investigational radiopharmaceutical, generator or reagent kit obtained from each different supplier, file Form AEC-___ "Registration Certificate - Medical Use of Investigational

Radiopharmaceutical Under Group License," with the Materials Branch, Directorate of Licensing, U. S. Atomic Energy Commission, Washington, D.C. 20545, and receive from the Commission a validated copy of the Form AEC-_____ with registration number assigned. The licensee shall furnish on Form AEC- _____ the following information and such other information as may be required by that form:

(i) Name, address and license number of the licensee;

(ii) Name of the radiopharmaceutical, generator, or reagent kit to be used;

(iii) The radionuclide, chemical form, and proposed use of the radiopharmaceutical to be used or prepared and used;

(iv) Name of the manufacturer of the radiopharmaceutical, generator or reagent kit to be used;

(v) Certification that he has in his possession, and will follow, a copy of the plan of investigation outlined in the "Notice of Claimed Investigational Exemption for a New Drug" (IND) which has been accepted by the Food and Drug Administration (FDA).

The Commission will not validate a Form AEC- _____ until it has confirmation from FDA that the registrant is an identified investigator in the IND or has otherwise been accepted by FDA as a participant in the investigation.

(5) Any licensee using investigational pharmaceuticals who is required to file Form AEC- _____, "Registration Certificate - Medical Use of Investigational Radiopharmaceutical Under Group License," pursuant to paragraph (b)(4) of this section shall report in duplicate to the Materials Branch any changes in the information furnished by him in the "Registration Certificate - Medical Use of Investigational Radiopharmaceutical Under Group License," Form AEC- _____. The report shall be submitted within 10 days after the effective date of such change.

(6) For Group III, any licensee who uses generators or reagent kits shall follow the instructions for eluting the generator or processing radioactive material with the reagent kit which are approved by the Atomic Energy Commission or an Agreement State and are furnished by the manufacturer on the label attached to or in the leaflet or brochure which accompanies the generator or reagent kit.

(7) For Group IV, any licensee who possesses and uses radiopharmaceuticals for therapy shall assure that patients containing more than 8 millicuries of iodine 131 for the treatment of thyroid carcinoma or patients containing more than 23 millicuries of gold 198 shall be hospitalized.

(8) For Group V, any licensee who possesses and uses sources or devices containing byproduct material shall assure that:

(i) Each source or device containing more than 100 microcuries of byproduct material with a half-life greater than thirty days, except iridium 192 seeds encased in nylon ribbon, shall be tested for contamination and/or leakage at intervals not to exceed six months; and a source or device shall be so tested prior to its first use unless the supplier furnishes a certificate that the source or device has been so tested within six months prior to the transfer;

(ii) The test required by paragraph (b)(8)(i) of this section shall be capable of detecting the presence of 0.005 microcurie of radioactive material on the test sample. The test sample shall be taken from the source or from the surfaces of the device in which the source is permanently or semipermanently mounted or stored on which one might expect contamination to accumulate. Records of leak test results shall be kept in units of microcuries and maintained for inspection by the Commission;

(iii) If the test required by paragraph (b)(8)(i) of this section reveals the presence of 0.005 microcurie or

more of removable contamination, the licensee shall immediately withdraw the source from use and shall cause it to be decontaminated and repaired or to be disposed of in accordance with Commission regulations. A report shall be filed within 5 days of the test with the appropriate Atomic Energy Commission Regulator Operations Regional Office listed in Appendix D of Part 20 of this chapter, describing the equipment involved, the test results, and the corrective action taken;

(iv) The radiation safety and handling instructions approved by the Atomic Energy Commission furnished by the manufacturer on the label attached to the source, device or permanent container thereof, or in the leafle or brochure which accompanies the source or device, are followed and that such instructions are maintained in a legible and conveniently available form;

(v) A quarterly physical inventory is conducted to account for all sources and devices received and possessed. Records of the inventories shall be maintained for inspection by the Commission and shall include the quantities and kinds of byproduct material, location of sources and devices, and the date of the inventory;

(vi) Needles or standard medical applicator cells containing cobalt 60 as wire shall not be opened by the licensee unless specifically authorized by a condition of a license issued to him by the Atomic Energy Commission;

(vii) Patients containing cobalt 60, cesium 137 and/or iridium 192 implants shall remain hospitalized until the implants are removed.

(c) Any licensee who is licensed pursuant to paragraph (a) of this section for one or more of the medical use groups in §35.100 also is authorized to use byproduct material under the general license in §31.11 of this chapter for the specified in vitro use without filing Form AEC-483 as required by §31.11(b); Provided, the licensee is subject to the other provisions of §31.11.

(d) Any licensee who is licensed pursuant to paragraph (a) of this section for one or more of the medical use groups in §35.100 also is authorized to receive, possess, and use for calibration and reference standards any byproduct material with an atomic number not higher than 83 in amounts not to exceed 15 millicuri total of materials with half lives not longer than seven days and not to exceed 200 microcuries total of materials with half lives longer than seven days.

2. Section 35.100 of 10 CFR Part 35 is amended by changing the title and subtitles, by adding certain new uses to the present paragraphs 35.100(a)Group I and (b)Group II, and by adding new paragraphs 35.100(c)Group III, (d)Group IV and (e)Group V. The section, as amended, will read as follows:

§35.100 Schedule A - Groups of medical uses of byproduct materia

(a) Group I. Use of prepared radiopharmaceuticals for certain diagnostic studies involving measurements of uptake, dilution and excretion. This group does not include uses involving imaging and tumor localizations.

(1) Iodine 131 as sodium iodide (NaI^{131}) for measurement of thyroid uptake;

(2) Iodine 125 as sodium iodide (NaI^{125}) for measurement of thyroid uptake;

(3) Iodine 131 as iodinated human serum albumin (IHSA) for determinations of blood and blood plasma volume;

(4) Iodine 125 as iodinated human serum albumin (IHSA) for determinations of blood and blood plasma volume;

(5) Iodine 131 as labeled rose bengal for liver function studies;

(6) Iodine 125 as labeled rose bengal for liver function studies;

(7) Iodine 131 as labeled fats or fatty acids for fat absorption studies;

(8) Iodine 125 as labeled fats or fatty acids for fat absorption studies;

(9) Iodine 131 as labeled iodopyracet, sodium iodohippurate sodium diatrizoate, diatrizoate methylglucamine, sodium diprotrizoate, sodium acetrizoate, or sodium iothalamat for kidney function studies;

(10) Iodine 125 as labeled iodopyracet, sodium iodohippurate sodium diatrizoate, diatrizoate methylglucamine, sodium diprotrizoate, sodium acetrizoate, or sodium iothalamat for kidney function studies;

(11) Cobalt 58 as labeled cyanocobalamin for intestinal absorption studies;

(12) Cobalt 60 as labeled cyanocobalamin for intestinal absorption studies;

(13) Chromium 51 as sodium chromate for determinations of red blood cell volume and studies of red blood cell survival time;

(14) Chromium 51 as labeled human serum albumin for gastro-intestinal protein loss studies;

(15) Iron 59 as chloride, citrate, or sulfate for iron turno studies;

(16) Potassium 42 as chloride for potassium space determinatic

(17) Sodium 24 as chloride for sodium space determinations;

(18) Xenon 133 as gas, free or in solution, in prepackaged individual doses only, for blood flow and pulmonary function studies;

(19) Any byproduct material in a radiopharmaceutical and for a diagnostic use involving measurements of uptake, dilution, or excretion for which a "Notice of Claimed Investigational Exemption for a New Drug" (IND) has been accepted by the Food and Drug Administration (FDA); Provided, that the registration requirements of paragraph 35.14(b)(4) are complied with.

(b) Group II. Use of prepared radiopharmaceuticals for diagnostic studies involving imaging and tumor localizations.

(1) Iodine 131 as sodium iodide for thyroid imaging;

(2) Iodine 131 as iodinated human serum albumin (IHSA) for brain tumor localizations and cardiac imaging;

(3) Iodine 131 as iodinated human serum albumin (IHSA) for cisternography;

(4) Iodine 131 as macroaggregated iodinated human serum albumin for lung imaging;

(5) Iodine 131 as colloidal (microaggregated) iodinated human serum albumin for liver imaging;

(6) Iodine 131 as labeled rose bengal for liver imaging;

(7) Iodine 131 as iodopyracet, sodium iodohippurate, sodium diatrizoate, diatrizoate methylglucamine, sodium diprotrizo or sodium acetrizoate for kidney imaging;

(8) Iodine 131 as sodium iodipamide for cardiac imaging;

(9) Iodine 131 as iodinated human serum albumin (IHSA) for placenta localization;

(10) Chromium 51 as sodium chromate for spleen imaging;

(11) Chromium 51 as labeled human serum albumin for placenta localization;

(12) Gold 198 in collodial form for liver imaging;

(13) Mercury 197 as labeled chlormerodrin for kidney and brain imaging;

(14) Mercury 203 as labeled chlormerodrin for brain imaging;

(15) Selenium 75 as labeled seleno-methionine for pancreas imagi

(16) Strontium 85 as nitrate or chloride for bone imaging in patients with suspected or diagnosed cancer;

(17) Technetium 99m as pertechnetate for brain imaging;

(18) Technetium 99m as pertechnetate for thyroid imaging;

(19) Technetium 99m as pertechnetate for salivary gland imaging;

(20) Technetium 99m as pertechnatate for blood pool imaging othe than placenta localization;

(21) Technetium 99m as pertechnetate for placenta localization;

(22) Technetium 99m as labeled sulfur colloid for liver and spleen imaging;

(23) Technetium 99m as labeled macroaggregated human serum albumin for lung imaging;

(24) Xenon 133 as gas, free or in solution, in prepackaged individual doses only, for heart and lung imaging;

(25) Any byproduct material in a radiopharmaceutical and for a diagnostic use involving imaging for which a "Notice of Claimed Investigational Exemption for a New Drug" (IND) has been accepted by the Food and Drug Administration (FDA) Provided, that the registration requirements of paragraph 35.14(b)(4) are complied with.

(c) Group III. Use of generators and reagent kits for the preparation and use of radiopharmaceuticals containing byproduct material for certain diagnostic uses.

(1) Molybdenum 99/technetium 99 generators for the elution of technetium 99m as pertechnetate for:

(i) brain imaging;

(ii) thyroid imaging;

(iii) salivary gland imaging;

(iv) blood pool imaging other than placenta localization;

(v) placenta localization;

(vi) use with reagent kits for preparation and use of radiopharmaceuticals containing technetium 99m as provided in paragraphs (c)(2) and (3).

(2) Reagent kits for preparation of technetium 99m labeled:

(i) sulfur colloid for liver and spleen imaging;

(ii) iron-ascorbate-diethylenetriamine pentaacetic acid complex for kidney imaging;

(iii) diethylenetriamine pentaacetic acid (Sn) for kidney imaging and kidney function studies;

(iv) diethylenetriamine pentaacetic acid (Sn) for brain imaging;

(v) human serum albumin microspheres for lung imaging;

(vi) polyphosphates for bone imaging;

(vii) macroaggregated human serum albumin for lung imaging;

(viii) disodium etidronate for bone imaging.

(3) Any generator or reagent kit for preparation and diagnostic use of a radiopharmaceutical containing byproduct material for which generator or reagent kit a "Notice of Claimed Investigational Exemption for a New Drug" (IND) has been accepted by the Food and Drug Administration (FDA); Provided that the registration requirements of paragraph 35.14(b)(4) are complied with.

(d) Group IV. Use of prepared radiopharmaceuticals for certain therapeutic uses.

(1) Gold 198 as colloid for intracavitary therapy of malignant effusions;

(2) Gold 198 as colloid for interstitial therapy of cancer;

(3) Iodine 131 as iodide for therapy of hyperthyroidism and angina pectoris;

(4) Iodine 131 as iodide for therapy of thyroid carcinoma;

(5) Phosphorus 32 as soluble phosphate for therapy of polycythemia vera;

(6) Phosphorus 32 as soluble phosphate for therapy of leukemia and bone metastases;

(7) Phosphorus 32 as colloidal chromic phosphate for intracavita therapy of malignant effusions;

(8) Phosphorus 32 as colloidal chromic phosphate for interstitial therapy of cancer;

(9) Any byproduct material in a radiopharmaceutical and for a therapeutic use for which a "Notice of Claimed Investigation Exemption for a New Drug" (IND) has been accepted by the Foo and Drug Administration (FDA); Provided, that the registrati requirements of paragraph 35.14(b)(4) are complied with.

(e) Group V. Use of sources and devices containing byproduct materi for certain medical uses.

(1) Americium 241 as a sealed source in a device for bone mine analysis;

(2) Cesium 137 encased in needles and applicator cells for top: interstitial, and intracavitary therapy of cancer;

(3) Cobalt 60 encased in needles and applicator cells for topic interstitial, and intracavitary therapy of cancer;

(4) Gold 198 as seeds for interstitial therapy of cancer;

(5) Iodine 125 as a sealed source in a device for bone mineral analysis;

(6) Iridium 192 as seeds encased in nylon ribbon for interstiti therapy of cancer;

(7) Strontium 90 sealed in an applicator for therapy of superficial eye conditions.

3. Section 31.11 of 10 CFR Part 31 is amended by adding new paragraph 31.11(a)(4) and (5), by amending the first sentence of paragraph 31.11(b), and by amending paragraphs 31.11(c)(1) and (d)(1) to read as follows:

§31.11 General license for use of byproduct material for certain in vitro clinical or laboratory testing.

(a) A general license is hereby issued to any physician, clinical laboratory or hospital to receive, acquire, possess, transfer, or use, for any of the following stated tests, in accordance with the provisions of paragraphs (b), (c), (d), (e), and (f) of this section, the following byproduct materials in pre-packaged units:

* * * *

(4) Hydrogen 3 (tritium), in units not exceeding 50 microcuries each for use in in vitro clinical or laboratory tests not involving internal or external administration of byproduct material, or the radiation therefrom, to human beings or animals.

(5) Iron 59, in units not exceeding 20 microcuries each for use in in vitro clinical or laboratory tests not involving inter or external administration of byproduct material, or the radiation therefrom, to human beings or animals.

(b) No person shall receive, acquire, possess, use, or transfer byproduct material pursuant to the general license established by paragraph (a) of this section until he has filed Form AEC-483, "Registration Certificate-In Vitro Testing with Byproduct Material Under General License", with the Materials Branch, Directorate of Licensing, U. S. Atomic Energy Commission, Washington, D. C. 20545, and received from the Commission a validated copy of Form AEC-433 with registration number assigned or until he has been authorized pursuant to §35.14(c) of this chapter to use byproduct material under the general license in this §31.11. * * *

(c) A person who receives, acquires, possesses, or uses byproduct material pursuant to the general license established by paragraph (a) of this section shall comply with the following:

(1) The general licensee shall not possess at any one time, pursuant to the general license in paragraph (a) of this section, at any one location of storage or use a total amount of iodine 125, iodine 131, and/or iron 59 in excess of 200 microcuries.

* * * *

(d) The general licensee shall not receive, acquire, possess, or use byproduct material pursuant to paragraph (a) of this section:

(1) Except as prepackaged units which are labeled in accordan with the provisions of a specific license issued under th provisions of §32.71 of this chapter or in accordance wit the provisions of a specific license issued by an Agreemer State, which authorizes manufacture and distribution of iodine-125, iodine-131, carbon-14*, hydrogen-3 (tritium), or iron-59 for distribution to persons generally licensed by the Agreement State.

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*See Notice of Rule Making, 38 F.R. 34110, December 11, 19

4. Section 32.71 of 10 CFR Part 32 is amended by adding new paragraphs 32.71(b)(4) and (5) and by amending paragraph 32.71(c)(1) to read as follows:

§32.71 Manufacture and distribution of byproduct materials for certain in vitro clinical or laboratory testing under general license.

An application for a specific license to manufacture or distribute byproduct material for use under the general license of §31.11 of this chapter will be approved if:

* * * * *

(b) The byproduct material is to be prepared for distribution in prepackaged units of:

* * * * *

(4) Hydrogen 3 (tritium) in units not exceeding 50 microcuries each;

(5) Iron 59 in units not exceeding 20 microcuries each.

* * * * *

(c) Each prepackaged unit bears a durable, clearly visible label:

(1) Identifying the radioactive contents as to chemical form and radionuclide, and indicating that the amount of radioactivity does not exceed 10 microcuries of iodine 131, iodine 125, or carbon 14;* 50 microcuries of hydrogen 3 (tritium); or 20 microcuries of iron 59; and

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*See Notice of Rule Making, 38 F.R. 34110, December 11, 197

5. A new §32.72 is added to 10 CFR Part 32 to read:

§32.72 Manufacture and distribution of radiopharmaceuticals conta byproduct material for medical use under group licenses.

An application for a specific license to manufacture and distribut radiopharmaceuticals containing byproduct material for use by pers licensed pursuant to §35.14 of this chapter for the uses listed in Group I, Group II, or Group IV of Schedule A, §35.100 of this chapter will be approved if:

(a) The applicant satisfies the general requirements specified in §30.33 of this chapter;

(b) The applicant submits evidence that the radiopharmaceutical cor taining byproduct material will be manufactured, labeled, and packaged in accordance with

(1) An effective new drug application (NDA) or a Biologic Produ License from the Food and Drug Administration (FDA); or

(2) A "Notice of Claimed Investigational Exemption for a New Drug (IND) that has been accepted by the FDA;

(c) The applicant submits information on the radionuclide, chemical and physical form, packaging including maximum activity per package, and shielding provided by the packaging of the byprodu material which is appropriate for safe handling and storage of the radiopharmaceuticals by group licensees; and

(d) (1) The label affixed to each package of the radiopharmaceutic contains information on the radionuclide, quantity, and da of assay and the label affixed to each package, or the leaflet or brochure which accompanies each package, contair a statement that the radiopharmaceutical is licensed by the U. S. Atomic Energy Commission for distribution to persons licensed pursuant to §35.14 and §35.100 Group I, Group II, or Group IV of 10 CFR Part 35, as appropriate, or under equivalent licenses of Agreement States;

(2) The labels, leaflets or brochures required by this paragrapl are in addition to the labeling required by the Food and Dru Administration (FDA) and they may be separate from or, with the approval of FDA, may be combined with the labeling required by FDA.

6. A new §32.73 is added to 10 CFR Part 32 to read:

§32.73 Manufacture and distribution of generators or reagent kits for preparation of radiopharmaceuticals containing byproduc material.

An application for a specific license to manufacture and distribute generators or reagent kits containing byproduct material for preparation of radiopharmaceuticals by persons licensed pursuant to §35.14 of this chapter for the uses listed in Group III of Schedule A, §35.100 of this chapter will be approved if: (See Note

(a) The applicant satisfies the general requirements specified in §30.33 of this chapter;

Note 1. Although the Commission does not regulate the manufacture and distribution of reagent kits which do not contain byproduct material it does regulate the use of such reagent kits for the preparation of radiopharmaceuticals containing byproduct material as part of its licensing and regulation of the users of the byproduct material. Any manufacturer of reagent kits which do not contain byproduct material who desires to have his reagent kits approved by the Commission for use by persons licensed pursuant to §35.14 and Group III of Schedule A, §35.100 of this chapter may submit the pertinent information specified in this §32.73.

(b) The applicant submits evidence that the generator or reagent k: is to be manufactured, labeled and packaged in accordance with

(1) An effective New Drug Application (NDA) or a Biologic Prod License from the Food and Drug Administration (FDA), or

(2) A "Notice of Claimed Investigational Exemption for a New Drug (IND)" that has been accepted by the FDA;

(c) The applicant submits information on the radionuclide, chemical and physical form, packaging including maximum activity per package, and shielding provided by the packaging of the byprodu material contained in the generator or reagent kit;

(d) The label affixed to the generator or reagent kit contains information on the radionuclide, quantity, and date of assay; and

(e) The label affixed to the generator or reagent kit, or the leaflet or brochure which accompanies the generator or reagent kit, contains:

(1) adequate information, from a radiation safety standpoint, on the procedures to be followed and the equipment and shie ing to be used in eluting the generator or processing radio active material with the reagent kit, and

(2) a statement that this generator or reagent kit (as appropri is approved for use by persons licensed by the U. S. Atomic Energy Commission pursuant to §§35.14 and 35.100 Group III of 10 CFR Part 35 or under equivalent licenses of Agreement States.

The labels, leaflets or brochures required by this paragraph are in addition to the labeling required by FDA and they may be separate from or, with the approval of FDA, may be combined with the labeling required by FDA.

7. A new §32.74 is added to 10 CFR Part 32 to read:

§32.74 Manufacture and distribution of sources or devices contain byproduct material for medical use.

An application for a specific license to manufacture and distribute sources and devices containing byproduct material to persons licens pursuant to §35.14 of this chapter for the uses listed in Group V c Schedule A, §35.100 of this chapter will be approved if:

(a) The applicant satisfies the general requirements in §30.33 of this chapter;

(b) The applicant submits sufficient information regarding each typ of source or device pertinent to an evaluation of its radiation safety, including:

(1) The byproduct material contained, its chemical and physical form, and amount;

(2) Details of design and construction of the source or device;

(3) Procedures for, and results of, prototype tests to assure that the source or device will maintain its integrity under stresses likely to be encountered in normal use and accident

(4) For devices containing byproduct material, the radiation profile of a prototype device;

(5) Details of quality control procedures to assure that product sources and devices meet the standards of the design and prototype tests;

(6) Procedures and standards for calibrating sources and devices;

(7) Legend and methods for labeling sources and devices as to their radioactive content;

(8) Instructions for handling and storing the source or device from the radiation safety standpoint; these instructions ar to be included on a durable label attached to the source or device or attached to a permanent storage container for the source or device; Provided, instructions which are too leng for such label may be summarized on the label and printed i detail on a brochure which is referenced on the label;

(c) The label affixed to the source or device, or to the permanent storage container for the source or device, contains informatio on the radionuclide, quantity, and date of assay, and a statement that the (name of source or device) is licensed by the U. S. Atomic Energy Commission for distribution to persons licensed pursuant to §§35.14 and 35.100 Group V of 10 CFR Part 35 or under equivalent licenses of Agreement States; Provided, such labeling for sources which do not require long term storage (e.g. gold 198 seeds) may be on a leaflet or brochure which accompanies the sources.

(Sec. 81, 161, 182, 183, Pub. Law 83-703, 68 Stat. 935, 948, 953, 954, as amended (42 U.S.C. 2111, 2201, 2232, 2233))

Dated at Germantown, Md. this 15th day of January 1974.

For the Atomic Energy Commission.

Gordon M. Grant
Acting Secretary of the Commission

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DAVID A. CUNNINGHAM

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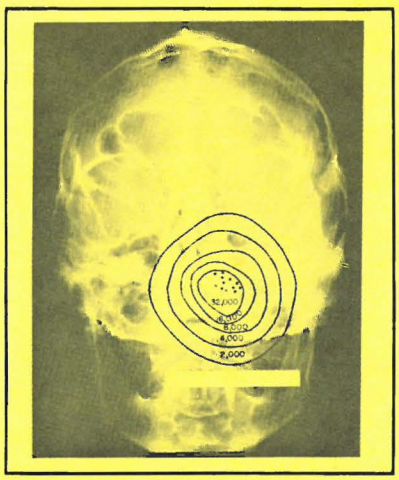
IODINE - 125

PERMANENT IMPLANT SEEDS.
AN IDEAL ISOTOPE FOR INTERSTITIAL
RADIATION THERAPY PROVIDING INTENSE LOCALIZED
X-RADIATION WITH UNIQUE HANDLING CONVENIENCE.



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Iodine-125 Seeds - Since 1965(1) Iodine-125 seeds have been used routinely as permanent interstitial implants. The procedure has proved to be outstandingly safe and effective. Successful results have been demonstrated in the treatment of a wide range of tumors, including those of the head and neck, lung, bladder, and prostate. Most significantly, the use of Iodine-125 has resulted in a major reduction of the radiation exposure to operating room personnel.

Simplified Radiation Protection - The combined effect of the unique absorption characteristics of 30 keV X-rays, low half value layer (lead HVL - 0.025 mm) and low activity of each seed (0.4 to 0.8 mCi) facilitates the reduction of radiation exposure to operating room and nursing personnel when Iodine-125 is used to replace Radon-222, Gold-198, or Iridium-192. For example, a thin lead foil of only 0.25 mm reduces radiation from Iodine-125 by 99.9%. Equivalent radiation protection for Radon-222 requires more than 130 mm of lead. Gold-198 or Iridium-192 requires 38 mm or more.

The 30 keV X-rays from Iodine-125 are reduced to less than 10% by 7 cm of tissue. Consequently, most patients represent little radiation exposure risk to their associates, and may use multiple occupancy rooms during their period of hospitalization.

Long Shelf Life - Iodine-125 has a half life of 60 days. At the time of shipment each seed has a nominal activity of 0.65 mCi. The seeds are considered effective down to 0.3 mCi. The useful shelf life is therefore more than two months. Supplies of the seeds may be conveniently stored in the surgical suite or radiation therapy department to simplify implant scheduling, and provide immediate clinical availability when required for use by the surgeon or attending radiation therapist.

Optimum Time-Dose Relationship - The 60-day half life of Iodine-125 produces a time-dose relationship which lies in the most effective region between the maximum tissue tolerance and the minimum tumor lethal dose.(2) The therapeutic ratio is high and the precision required for dosimetry is less critical than for radioisotopes with shorter half lives. (Fig. 1).

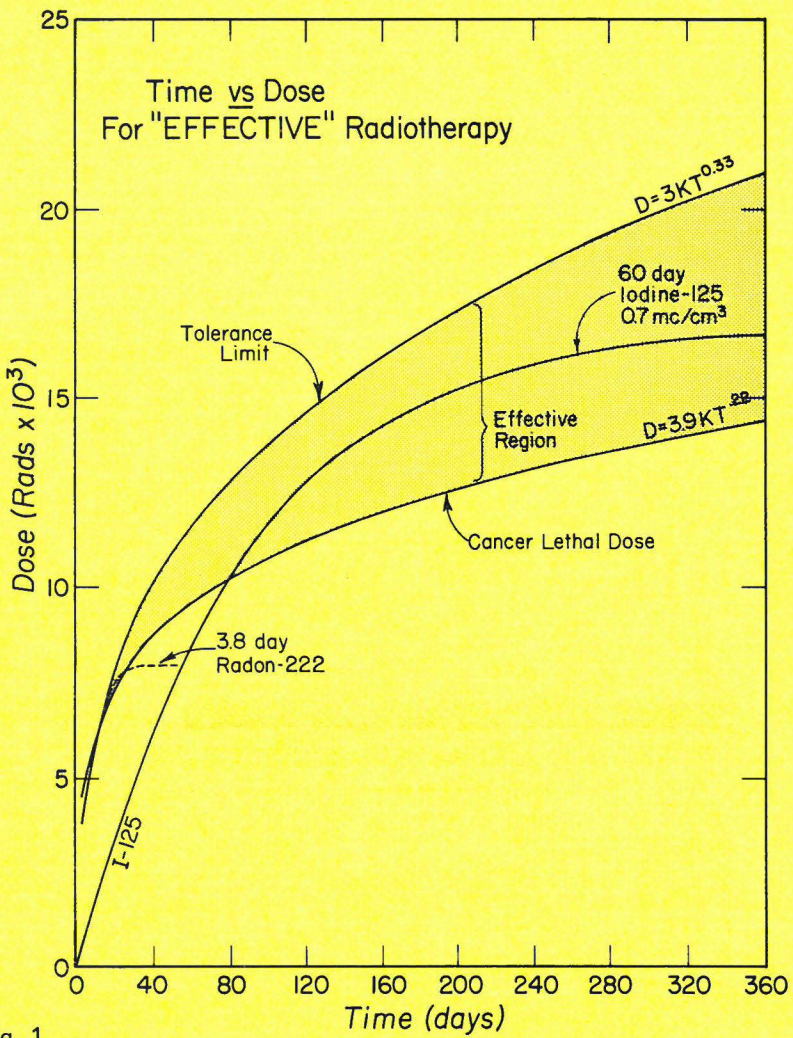


Fig. 1

Time-Dose Relationship for permanent implants, developed from Cohen.(2)

Implant Technique - Iodine-125 is supplied as a titanium capsule, or "seed", small enough (4.5 mm x 0.75 mm) to be injected using a standard No. 17 needle. Several simple applicators are available and make the procedure very fast. (A modification of the Scott Applicator(3) is supplied by Lawrence Soft Ray Corporation).

Calculation of the quantity of activity to be employed for each tumor is simple, as Iodine-125 conforms to the Dimension Averaging rules developed by Henschke.(4)

The tiny implanted source is well tolerated by the body. The permanent implant technique requires only one surgical procedure and minimizes the risks of infection and tumor trauma associated with removable implants such as Iridium-192. Hospitalization of patients may be shortened and many cases treated on an outpatient basis.

Clinical Applications - Implants of Iodine-125 offer significant benefits, primarily in the management of head and neck, intrathoracic and intraabdominal cancers. Many tumors which are localized and readily accessible may be successfully treated with the implant alone. Superficial tumors may be treated using Iodine-125 in a surface applicator.

Iodine-125 is also frequently employed to augment surgery, chemo-therapy or external beam therapy.

Surgical Procedures - A surgical operation, such as thoracotomy, often discloses an unresectable tumor and the surgeon is forced to leave a significant portion of the tumor intact. Iodine-125 seeds offer the potential to convert these essentially useless operations into effective treatments. The patient benefits both physically and emotionally where this positive alternative is available. The results of Iodine-125 implants under these conditions are most encouraging.(6), (7)

External Beam Therapy - External beam radiation therapy can be greatly enhanced by the simultaneous application of Iodine-125 implants. The combination protocol permits very high local tumor doses (over 20,000 R) to be safely employed while retaining the benefits of external beams in controlling cell colonies in nodal sites or in tissue adjacent to the bulk of the tumor. Iodine-125 implants may be utilized at the completion of a course of external beam treatments in order to control small residual radio-resistant masses.

Iodine-125 emits 30 keV X-rays having a half value layer (HVL) of only 2 cm in tissue. The dose distribution around each seed is uniform and tightly localized. Interstitial implants compare very favorably with the most complex external beam geometries in establishing high tumor doses with minimum dose to surrounding healthy tissue. (See Frontpiece, Fig. 2 and Fig. 3).

In addition, the Iodine-125 seeds contain a gold X-ray marker which serves as an excellent basis for tumor localization in subsequent treatment planning.

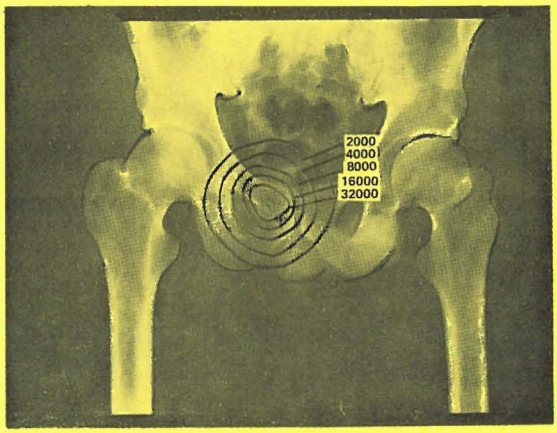
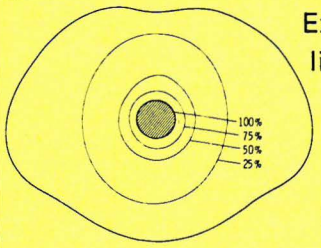


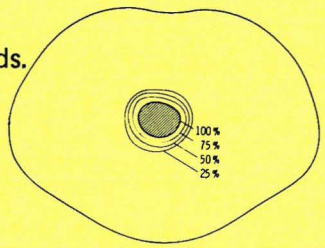
Fig. 2 Computer-calculated isodose curves for prostate implanted with 19 Iodine-125 seeds.(5)

Fig. 3 Pelvic cross-sections comparing 6 MV vs. Iodine-125 isodose curves.(5)



External beam 6 MV linac, optimum setup, 360° rotation, 6 x 6 cm. Rectum and bladder receive over 65% maximum dose.

Interstitial implant with Iodine-125 seeds. Rectum and bladder receive less than 30% maximum dose.(6)



Iodine-125 Compared to Gold-198, Radon-222, and Iridium-192 - Table 1 shows the physical characteristics of the four principle radioisotopes used for permanent implants. It can be seen that Gold-198 and Radon-222 have short half lives compared to Iodine-125 and Iridium-192. Consequently, they have little shelf life. Gold-198, Radon-222, and Iridium-192 all emit high-energy beta radiation which may complicate therapy and dosimetry. Most significantly, Gold-198, Radon-222, and Iridium-192 all emit high-energy gamma radiation while Iodine-125 emits only X-rays of approximately 30 keV. This energy is more than adequate to penetrate and destroy the implanted tumor, but minimizes the dose to surrounding healthy tissue. Iodine-125 thus provides improved isodose characteristics combined with an optimum time dose relationship (Fig. 1) and simple radiation protection.

TABLE 1.

Isotope	Half Life (days)	Emitted Energy			Half Value Layer (lead)	Half Value Layer (tissue)
		Alpha	Beta (Max.)	Gamma		
Iodine-125	60	none	none	27-35 keV	0.025 mm.	2 cm.
Iridium-192	74.4	none	670 keV	300-610 keV	4.5 mm.	6 cm.
Gold-198	2.7	none	960 keV	410 keV	4.5 mm.	6 cm.
Radon-222	3.8	+	70-3260 keV	50-2440 keV	13 mm.	10 cm.

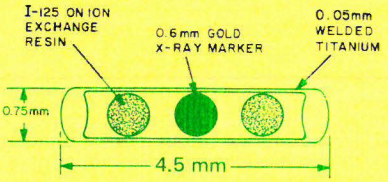


Fig. 4. Iodine-125 seed.

SPECIFICATIONS:

Nominal Activity - 0.65 mCi on Ion Exchange resin.

Seed Dimensions - 4.5 mm x 0.75 mm (0.05 mm welded type A-40 Titanium wall) with 0.6 mm gold X-ray marker.

Emission Energy - 27.4 to 35.4 keV X-rays. No other significant alpha, beta, or gamma radiation. (Iodine-126 content less than 1.5%).

Half Life - 60 days.

Gamma Constant - 1.7 Rads - cm^2/hr — mCi. (3,525 Rads/mCi I-125 destroyed at 1 cm vs. 1,050 Rads/mCi Rn-222 destroyed).(6)

Testing - Includes calibration, rigid microscopic and X-ray inspection as well as the AEC-required leak test. All seeds are autoclaved prior to the final leak test. A leak test certificate is provided with every shipment.

Delivery - Within 30 days on initial order and within ten days on subsequent orders, FOB Mountain View, California. Initial order must contain verification of Radioactive Materials License.

Shipment - Via Airfreight, both domestic and international.

(Specifications subject to change without notice).

For further information write or call:
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Mountain View, California 94040
(415) 967-2861

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U. S. Patent No. 3,351,049
British Patent No. 1,133,219
Canadian Patent No. 830,573

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Mortimer Heller, Ph.D.

3) Charlotte Memorial Hospital (S)
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4) Veterans Administration Hospital
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K. Charyulu, M.D.

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TECHNIQUES OF INTERSTITIAL AND INTRACAVITARY RADIATION

BASIL S. HILARIS, MD*

Interstitial implantation and intracavitary applications occupy a definite position in the curative management of cancer. With these techniques a much higher dose can be delivered to the tumor than possible with external radiation. At the same time, a much lower dose is given to the adjoining normal tissue avoiding severe complications and late damage of the normal tissue and organs. The high doses delivered with internal radiation are tolerated well because the irradiated volumes are very small compared to the volumes which are irradiated with external radiation therapy even with small-field technique. However, the methods and the radioisotopes which are commonly used in interstitial and intracavitary radiation therapy are complicated and unsatisfactory from the radiation safety point of view. For this reason new methods with artificial radioisotopes were developed at Memorial Hospital for interstitial and intracavitary radiation. These techniques include the remote afterloader with which all intracavitary applications were carried out since July 1967 and the use of low energy ^{125}I seeds for interstitial implants. The clinical experience with both techniques indicates that most of the drawbacks of the older methods are eliminated while their proven therapeutic value is retained.

INTERSTITIAL AND INTRACAVITARY IRRADIATION are of special value for curative radiation therapy. These techniques permit the irradiation of localized tumors with much higher doses than can safely be given by external radiation therapy; at the same time they provide better sparing of the surrounding normal tissue. Figures 1, 2 and 3 illustrate these points with roentgenograms of some of our intracavitary applications and interstitial implants; we have superimposed isodose curves calculated by a computer.

Figure 1 shows an intracavitary application for a carcinoma of the uterine cervix. The area within which all stage I and most of the stage II carcinomas of the cervix are located receives between 16,000 and 8000 rads. This dose is tolerated by the adjacent normal organs without complications because of the rapid falloff of the dose. With external radiation therapy, on the other hand, the tolerance dose is much lower and serious complications occur with doses above 5000 rads.

Figure 2 shows a removable interstitial implant for a carcinoma of the tongue extending to the tonsil. The tumor dose is approximately 10,000 rads, which again is a much higher dose than can safely be given with external irradiation. A dose of this magnitude produces a mucositis confined to the implanted area, which subsides in about 2 to 3 weeks. Late reactions are rare with implants and we have seen them only with very large volumes and extremely high doses. In contrast, with external radiation therapy, even with doses of 5000 to 6000 rads, loss of taste and dryness of the mouth with resultant tooth decay occur and the patient's condition seems to deteriorate even though the cancer is controlled.

Figure 3 shows a permanent interstitial implant for an unresectable cancer of the lung. We have carried out several hundred implants of this type during exploratory thoracotomy and in many cases doses as high as 15,000 to 30,000 rads have been delivered, depending on the size of the implanted tumor. Except for a temporary esophagitis in

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Presented at the International Symposium on Radiation Therapy, March 13–15, 1968, Memorial Hospital, New York, N.Y.

Supported in part by PHS Field Investigation grant CA-09369 and by grant CA-08748 from the National Cancer Institute, and by Contract #PH 86-66-132 from the National Center for Radiological Health of the Public Health Service, Rockville, Md.

* Assistant Attending, Department of Radiation Therapy, Memorial Hospital, New York, N.Y.; Clinical Assistant Professor of Radiology, Cornell University Medical College, New York, N.Y.

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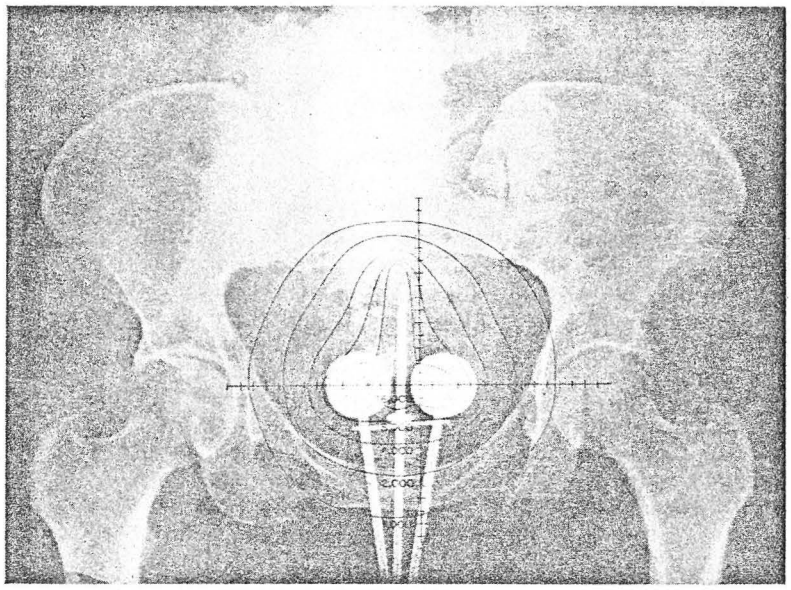

FIG. 1. Intracavitary application for a carcinoma of the uterine cervix.

cases where the implanted tumor was close to the esophagus, we did not observe any early or late symptoms from such high-dose implants, even in relatively large volumes. In contrast, severe disability and even deaths from lung fibrosis were noted with doses as low as 4000 rads when external radiation was used.

Why are such high doses well tolerated with interstital and intracavitary radiation but not with external radiation therapy?

Two factors account for this in our opin-

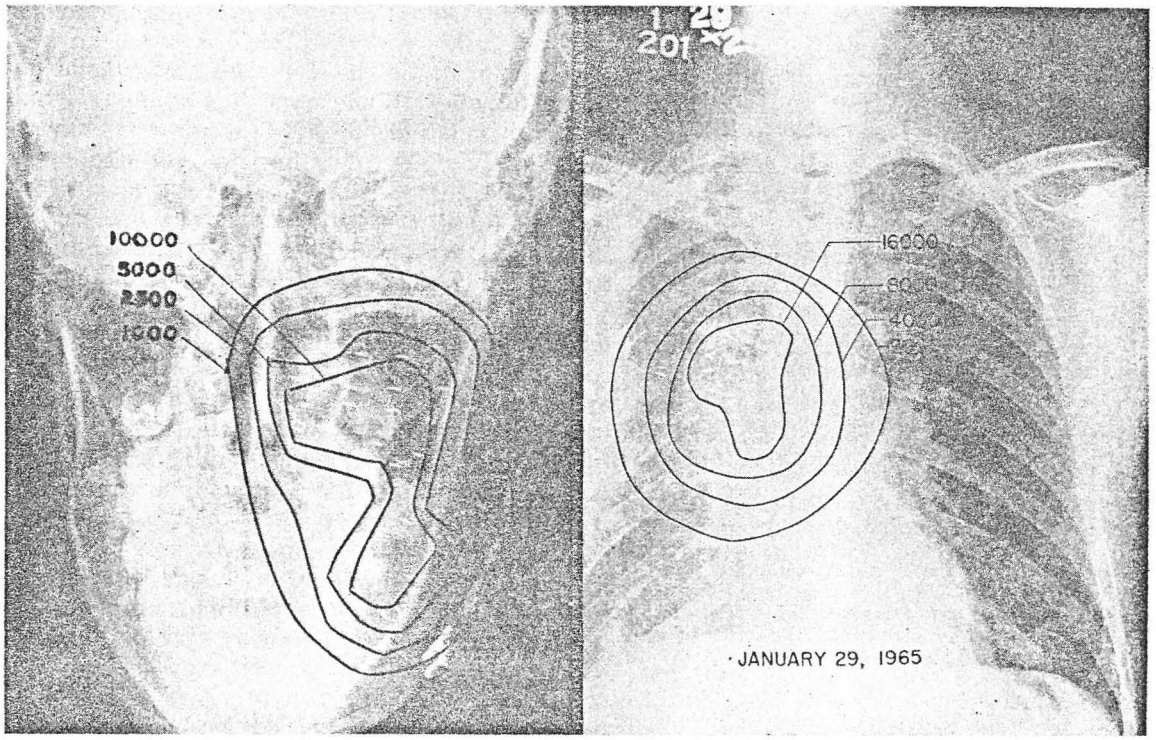

FIG. 2. Removable interstitial implant for a carcinoma of the tongue.
FIG. 3. Permanent interstitial implant for a carcinoma of the lung.

ion. First, with interstitial and intracavitary radiation, the irradiated volumes are very small compared to the volumes which are irradiated in external radiation therapy, even with small-field techniques. Second, the small volumes tolerate much higher doses than the large volumes.

The importance of these two factors is not generally appreciated. One reason for this is that there is no quantitative method available to compare irradiated volumes in interstitial and external radiation therapy. We feel that the calculation of the "half dose volume," that is, of the volume raised to 50% of the central tumor dose, would permit a good numerical comparison. In Table 1 such "half dose volumes" are given for the three cases of brachytherapy by intracavitary and intersitial therapy, which we just presented. They are compared with the "half dose volumes" which would result from teletherapy with multiple small fields for the same tumors. As the figures show, the "half dose volumes" are for external radiation therapy more than ten times as large as for intracavitary applications and intersitial implants.

The second reason is the fact that good data for the dependency of the tissue tolerance on the irradiated volumes are available only for the relatively large volumes which occur in external x-ray therapy. However, the steep increase in the tolerance dose occurs only at smaller volumes.

TABLE 1. Comparison of the Irradiated Volumes in Brachytherapy and Teletherapy
Half Dose Volumes
(Volumes Irradiated to 50% of Central Dose)

Case	Brachytherapy	Teletherapy
1. Carcinoma of the uterine cervix	29 cm^3	330 cm^3
2. Carcinoma of the tongue	16 cm^3	80 cm^3
3. Carcinoma of the lung	20 cm^3	250 cm^3

To illustrate this, we show in Figure 4 a curve which on the vertical axis gives the estimated tissue tolerance level in rads and on the horizontal axis the "half dose volume" in cubic centimeters. For field sizes above 5 cm × 5 cm, which for external radiation therapy with commonly used factors correspond to a half dose volume of 200 cm^3 or more, the curve follows the widely accepted trend which can be found as far back as 30 years in the first edition of Paterson's textbook on radiation therapy. For smaller volumes, we

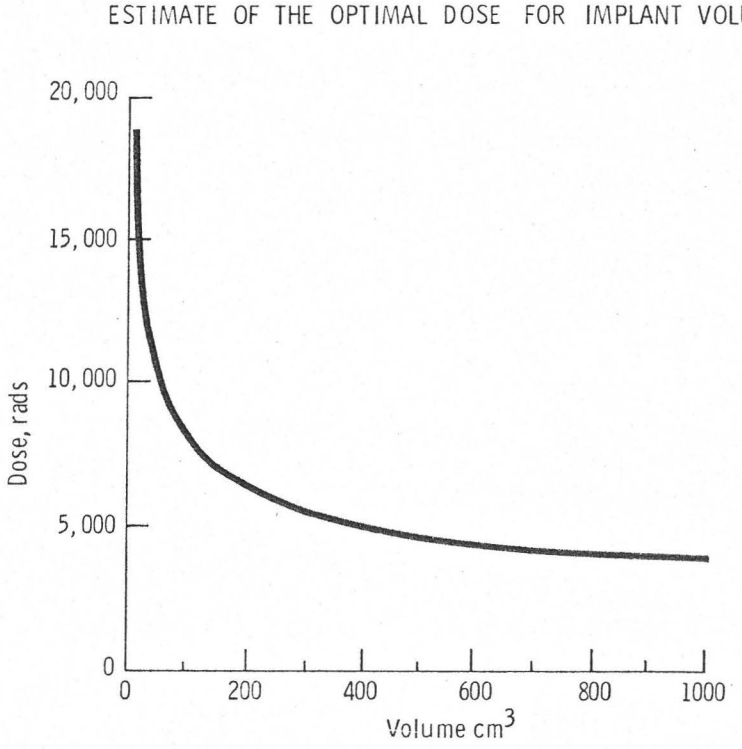

FIG. 4. Tissue tolerance vs. irradiated volume

have found no quantitative data in the literature, although it has often been stated in explaining the high tolerance doses in "grid therapy" as well as in "contact therapy" that very small volumes tolerate very high doses. The initial part of this curve is based on our clinical impressions of the tolerance doses for interstitial implants which we have used for many years as a guide to the optimal dose in interstitial implantation.

Why are high doses such as can be given safely by interstitial and intracavitary radiation important for curative radiation therapy?

The answer is that many of the most common cancers which remain localized for a long period require for a cure higher doses than 5000 to 7000 rads, which can be given with external radiation therapy. In these potentially curable tumors, interstitial and intracavitary radiation therapy becomes, in our opinion, the treatment of choice if surgical excision is not possible at all or only with severe functional loss. Therefore, intracavitary applications and interstitial implantation are best regarded and used as a supplement to external radiation therapy if the latter fails to control the local tumor growth.

What actually has been accomplished by intracavitary and interstitial radiation in curative cancer therapy?

Unfortunately, no controlled prospective clinical studies are available to answer this question with the desirable scientific accuracy. Many retrospective studies are avaliable however in the literature which point to the curative value of intracavitary applications in cancer of the uterus[9] and of interstitial implantation in intraoral cancer.[1, 8] Rather than reviewing these reports, I would like to present our results with interstitial implantation in cancer of the lung. In this most common cancer in man today, we have accumulated at Memorial Hospital a wide experience with about 500 interstitial implants during thoracotomy.

Table 2 shows data on the eight 5-year survivors among the 167 patients with primary cancer of the lung who were treated by interstitial implantation during thoracotomy from 1956 through 1961. The 5-year survival rate is nearly 5%. This may not seem impressive but it should be remembered that all these patients were judged unresectable by thoracotomy and that their prognosis was considered hopeless. All these patients except one are living and well without complications, although two of them are now more than 80 years old.

The doses given by the implants were much higher than commonly given by external radiation therapy and we feel that this is essential for the cure of the primary cancers of the lung which do not metastasize rapidly.

We also have encouraging results with interstitial implants in malignant thymoma and carcinoma of the pancreas, two other malignant tumors which have a very poor prognosis if they are unresectable.

Interstitial implants of cancers which are found unresectable during operation have besides their greater curative potential other important advantages: They usually provide good palliation by quick and prolonged tumor shrinkage, even if they fail to cure the patient. They do not require further therapy or hospital stay after the patient has recovered from the operation. Last but not least, they convert an otherwise useless operation into an effective therapeutic procedure.

If intracavitary and interstitial therapy are so valuable, why are they not used more fre-

TABLE 2. Unresectable Bronchogenic Carcinoma Five-Year Survivors of 167 Implants Memorial Hospital 1956–1961

Patient	Age	Sex	Tumor		Followup	
			Location	Dimensions		
1	78	M	RUL	4 x 3 x 3		11 years*
2	53	M	LUL	5 x 5 x 5		11 years
3	58	M	RUL	2 x 3 x 4	Living	10 years
4	39	M	RUL	4 x 3 x 3	and	8 years
5	74	M	RLL	5 x 3 x 3	well	6 years
6	52	M	LUL	5 x 4 x 3	at	6 years
7	41	M	LUL	7 x 5 x 4		6 years
8	53	M	LUL	9 x 5 x 4	Died	6 y 3 m

* Ca prostate 1967.

quently in cancer management? The answer, in our opinion, is that the methods and the radioisotopes which are commonly used in interstitial and intracavitary radiation therapy are so complicated and time consuming and so unsatisfactory from the radiation safety point of view that the preference of external radiation in the practice of radiation therapy is understandable.

Therefore, there is an urgent need for the technical improvement of interstitial and intracavitary radiation therapy. In our attempts to develop better methods at Memorial Hospital, we had a great tradition to follow. Janeway, who became the chief of the Radium Service at the old Memorial Hospital in 1915 and was joined by Dr. Failla in the same year and by Dr. Quimby in 1919, developed and applied many techniques of intracavitary and interstitial implantation which are still in use today.[1] One of their most important contributions was the development of radon seeds, which have been used at Memorial Hospital since 1916. These radon seeds initially were simple glass capillary tubes filled with radon gas and provided no absorption for the strong beta particles. Dr. Janeway himself was treated with these radon seeds for an adamantinoma of the jaw. His severe reaction following the implantation of these seeds provided a special stimulus for the development of radon seeds with an outer gold tubing, which has been in general use since 1925. Unfortunately, Dr. Janeway died at an early age in 1922 and Dr. Failla was killed in an automobile accident in 1961. Dr. Quimby, however, is among us today and a special tribute should be paid to her for the remarkable teamwork which firmly established the place of interstitial implantation in cancer management.

I would like to describe briefly two techniques which we have developed with Dr. Henschke at Memorial Hospital in recent years and which overcome most of the disadvantages of the earlier techniques.[2-5] We hope that these techniques will bring intracavitary and interstitial radiation therapy into wider use in cancer management.

Figure 5 shows a schematic drawing of the remote afterloader for intracavitary and surface applications, which has been in clinical use at the Memorial Center since July 1967. The figure illustrates its use for treatment of a cancer of the uterine cervix. First, an unloaded uterus applicator is inserted in the patient, who is then placed in a shielded room. The uterus applicator is connected with three plastic tubes to a lead-shielded safe in the wall. This safe contains three small sources of high activity, which are attached to the end of three cables. From the control panel outside the room, the sources are pushed into the uterus applicator. The two vaginal lateral sources remain stationary during the treatment while the uterine source is moved slowly back and forth by an electrical motor drive over the desired length. Since a moving source can simulate sources of any desired length and loading pattern, no additional sources are required, no special radium storage room is needed, and no transport of sources is necessary. All major causes of past radium accidents are therefore removed.

Table 3 shows out clinical experience with this remote afterloader. Between July and December 1967, 46 applications were done in 23 patients. Sixteen patients had one to two

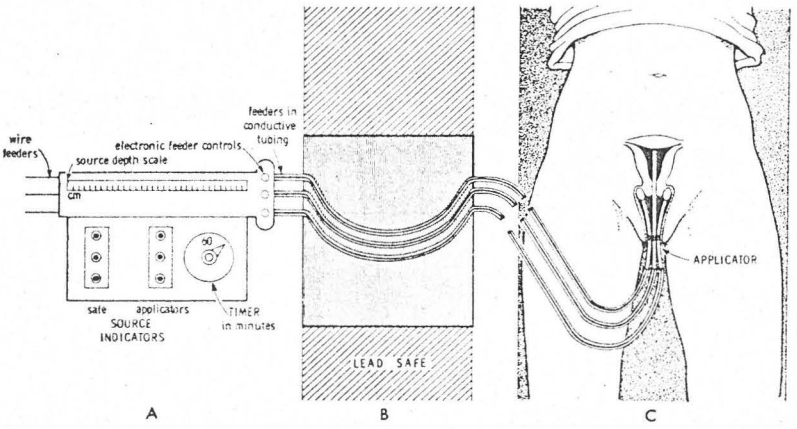

FIG. 5. Schematic drawing of remote afterloader for intracavitary and surface therapy in clinical use since July 1967.

TABLE 3. Intracavitary Radiation with Remote Afterloading Memorial Hospital 1967

Site	No. patients	No. applications
Vagina	10	22
Nasopharynx	6	9
Bladder	2	4
Cervix uteri	2	2
Corpus uteri	1	3
Max. antrum	1	3
Esophagus	1	3
TOTAL	23	46

applications with total doses on the surface of the applicator varying from 5000 to 6000 rads (500 to 1000 mghr). No reactions were noted in any of these patients. However, the therapeutic effect was the same as would have been expected with conventional applications. Of the patients who received more than two applications with total doses varying from 4000 to 14,000 rads (1100 to 3000 mghr) only two developed side reactions. Both had 4000 rads external irradiation prior to the applications.

Figure 6 shows a drawing of the type of seed we have used since 1965 and which we hope is the answer to most problems of interstitial implantation. This seed contains ^{125}I which has a half life of 60 days and a gamma radiation of only 27 kev. The ^{125}I is bound to two ion exchange resins. They are separated by a gold piece which facilitates visualization of the seeds in radiographs. The capsule consists of titanium which combines low absorption with good strength and tissue

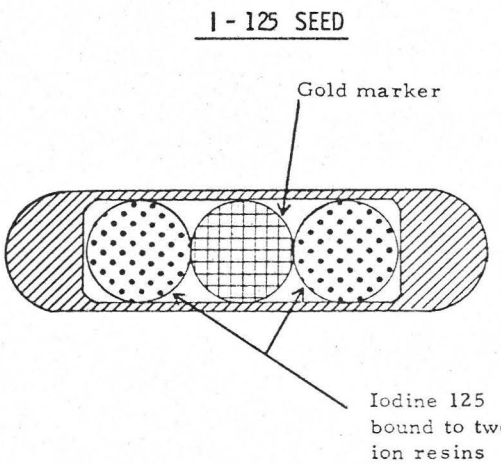

FIG. 6. ^{125}I seed (used at Memorial Hospital since December 1965 for permanent implants).

TABLE 4. Half Lives and Half Value Layers of Seeds for Permanent Implants

	Half life	Half value layer	
		Tissue	Lead
^{222}Rn	3.8 days	10 cm	12.5 mm
^{198}Au	2.7 days	6 cm	2.5 mm
^{125}I	60.0 days	2 cm	0.025 mm

tolerance and measures 4.5 mm in length and 0.7 mm in diameter.

Table 4 shows the half life and the half value layer in lead and in tissue for such an ^{125}I seed in comparison with the two most commonly used seeds for permanent implants, namely, ^{222}Rn and ^{198}Au seeds. The tissue half value layer of the ^{125}I radiation is quite sufficient for the range within which an implant is effective. However, it reduces the surface dose substantially in deeper implants, such as lung and abdominal implants. In superficial implants a thin lead foil of only 0.25 mm provides nearly complete protection.

Figure 7 shows the reduction of the radiation exposure of personnel after the use of ^{125}I implants in larger numbers. Between December 1965 and December 1967, 95 implants

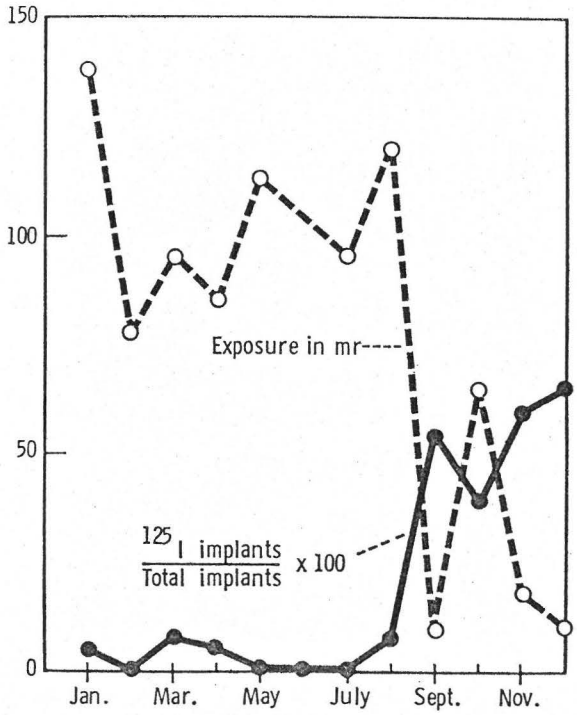

FIG. 7. Reduction of radiation exposure after use of ^{125}I seeds.

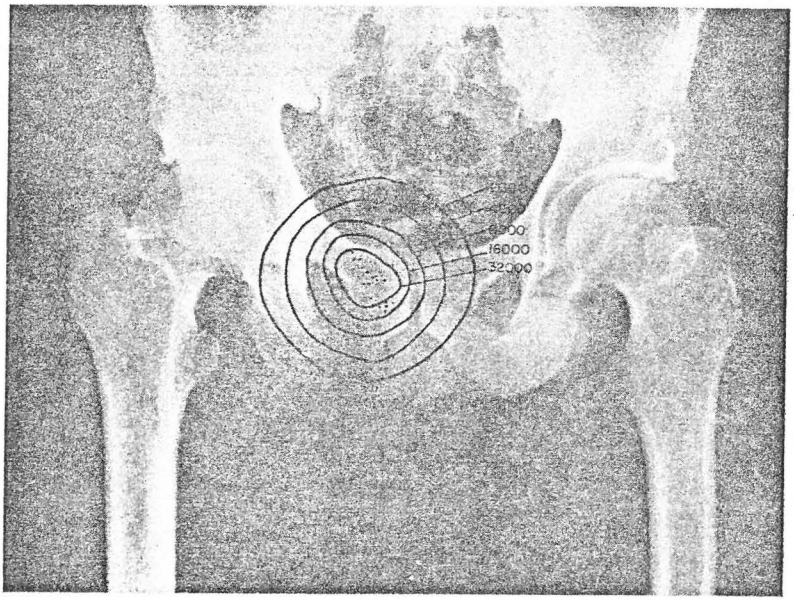

FIG. 8. Permanent interstitial implant with ^{125}I seeds for a carcinoma of the prostate.

with ^{125}I seeds were performed in 88 patients. We have observed essentially the same response and reactions as we have seen in implants with the other seeds and feel that the ^{125}I seeds provide on the whole the same therapeutic advantages as the ^{222}Rn and ^{198}Au seeds minus their practical disadvantages. Computer dose calculations were obtained in all patients. The information gathered in this way is of great help in evaluating the results from the standpoint of over- or underdose of implanted tumor.[6]

Figure 8 shows an example of an implant with ^{125}I seeds. This patient was a 45-year-old man with carcinoma of the prostate, treated previously by external radiation therapy and transurethral resection. A recurrent mass in the right lobe of the prostate measuring 4 × 2 × 2 cm was implanted on August 30, 1967 with 19 ^{125}I seeds, after exposure of the prostate through a perineal incision. Total activity was 21.6 mc and minimum tumor dose 16,000 rads, as can be seen by the superimposed computer calculated isodose curves. This patient at his last followup in March 1968 was doing well, no definite induration could be felt in the prostate, and he was asymptomatic.

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CURATIVE RADIOTHERAPY IN THE MALIGNANT LYMPHOMAS

MYRON P. NOBLER, MD*

The clinical experience and technologic improvements of the past 40 years are briefly summarized in terms of their contributions to the present optimistic and aggressive approach to the treatment of malignant lymphoma. The reasoning behind the large-field moderately high-dose technique that has evolved is reviewed and analyzed, and our treatment techniques are described in detail. Finally, the curability of malignant lymphoma is emphasized—through the use of vigorous and precisely planned irradiation of both the actual and the potential sites of lymph node involvement in either the upper or the lower trunk regions, or, in some cases, in both regions, we may now hope to produce cures or long-term survivals in a great majority of the patients treated; this results in a magnificent gain for humanity through the rescue or prolongation of many otherwise lost lives.

IN THE EARLY YEARS OF THE TWENTIETH CENtury the diagnosis of Hodgkin's disease, lymphosarcoma or reticulum cell sarcoma was tantamount to sounding the death-knell: the malignant lymphomas were thought to carry an invariably fatal prognosis. This, fortunately, has been proven false in modern radiation therapy centers where the treatment of the lymphomas may now be approached with a considerable degree of optimism that was not possible in previous years. Radiation therapy remains the treatment of choice when the intention is to achieve a cure or long-term remission, but it is now utilized in a more aggressive manner. Thus, the use of more extensive treatment fields and higher tumor doses is producing a definite improvement in survival statistics.

The present radiotherapeutic approach and the concepts on which it is based represent evolutionary rather than revolutionary changes in thought. They are based upon a wealth of clinical information obtained by extensive and exhaustive reviews of large series of patients with malignant lymphoma, the rapid technologic advances in both the equipment used in radiation therapy and in the treatment planning thereof, and much newly uncovered radiobiologic and histopathologic data. This paper is a brief review of the salient clinical evidence that has led to our present plan of treatment, an analysis of the most recent survival statistics which support this approach, and a presentation of the treatment techniques that have evolved and are now in use.

CLINICAL CONSIDERATIONS

One of the most interesting and challenging facets of the malignant lymphomas is that they often defy exact pathologic classification and have a marked tendency to transition from one pathologic type to another, as well as from one clinical phase to another. Histopathologically and clinically the lymphomas may be divided into four general categories: giant follicular lymphoblastoma, Hodgkin's disease, lymphosarcoma (or lymphoproliferative malignancy), and reticulum cell sarcoma.

In many situations a particular case of lymphoma may often fall into an exact category and behave according to a classical pattern. However, in other instances—as we have all observed—the tendency towards transition from one form of lymphoma to another manifests itself as the disease progresses or regresses. Furthermore, in many cases the pathologists are unable to differentiate microscopically between the various types of

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RAPID IMPLANTATION OF LUNG TUMORS USING I-125 SEEDS AND ABSORBABLE SPACER TECHNIQUE

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From the oldest (radon) to the newest (I-125), the implantation of permanent radioactive sources has always suffered from the difficulties of insertion, positioning, and radiation exposure of hospital personnel due to the excessive time required. A simple technique to eliminate these disadvantages has been used in our department which works with any of the radioactive seeds developed. The rapid injection method is the final refinement resulting from our experience with this absorbable spacer technique which we have used in gynecological and lung tumors without difficulties or complications and have found particularly advantageous in the latter where we are implanting a moving target.

Review of Basic Technique—Instead of being introduced individually into the tumor with a needle or gun, the seeds are introduced in a column separated one from the other by a spacer of absorbable materials such as #3 surgical gut. These spacers may vary according to the activity of the seed, e.g., 1.0 cm separation for seeds 0.5 mc or over and 0.5 separation for seeds less than 0.5 mc. The seeds and spacers are lined up alternately within a #17 gauge nylon tube forming a cartridge which is gas sterilized with #19 gauge hypodermic needles inserted in its ends to retain the seeds and spacers yet allow the gas to enter. Prior to implantation, these hypodermic needles may be removed and replaced with small plugs of sterile bone wax. The column is transferred with a stylet into the bore of a #17 gauge needle implanted within the tumor. The stylet is then introduced into the needle until it encounters the column in the distal end of the needle at which point it is stabilized with one hand while the needle is retracted back over it with the other. In so doing, a trail of seeds and spacers is deposited behind in the tumor while those remaining in the needle are later reloaded in new cartridges. Thus all unused seeds are reloaded with none wasted—and they are expensive. As the seeds decrease in activity, they are loaded in columns with shorter spacers and again none wasted. Variations in dosimetry are possible by adjusting the spacers or using seeds of different activities, i.e., dumbbell loading. Inactive gaps may be left in the tract of the implanted needle by increasing the length of the spacers.

There are several methods of loading the needle, and in the case of easily accessible tumors, the needle can be preloaded prior to implantation using (radium needle) forceps. Thus one should develop a technique which takes advantage of speed, distance, and proficiency. We generally use a standard loading of a 5 cm column of 4 seeds which seems to accommodate the "average" tumor dimensions. If the needle is inserted more than 5 cm into the tumor, additional seeds are added into the needle from a new cartridge by first expelling the unwanted seeds. If the needle is inserted less than 5 cm, fewer seeds are initially loaded (again by expelling unwanted seeds from the cartridge). With a surplus of seeds, one could have several

cartridges of different loadings or else one could load the required number of seeds into the needle from a cartridge of infinite length.

Rapid Injection Technique—Once the needle is implanted and loaded, the method of injection is the same for all types of sources. Since the last spacer in the column is just below tumor surface, we can design a C-shaped instrument with one arm (stylet) for advancing the seeds to the distal end of the needle and the other arm (stabilizer) for checking this advance as its blunt end reaches the tumor surface where and when the needle is retracted with the aid of a sliding sleeve-bolt leaving the column of seeds and spacers behind in the tumor. It is possible to expedite the procedure further by eliminating the tube technique and loading the needle directly, implanting it with the aid of radium needle forceps, and injecting the column of seeds and spacers. If these cannot be loaded using a sterile technique, they still can be gas sterilized.

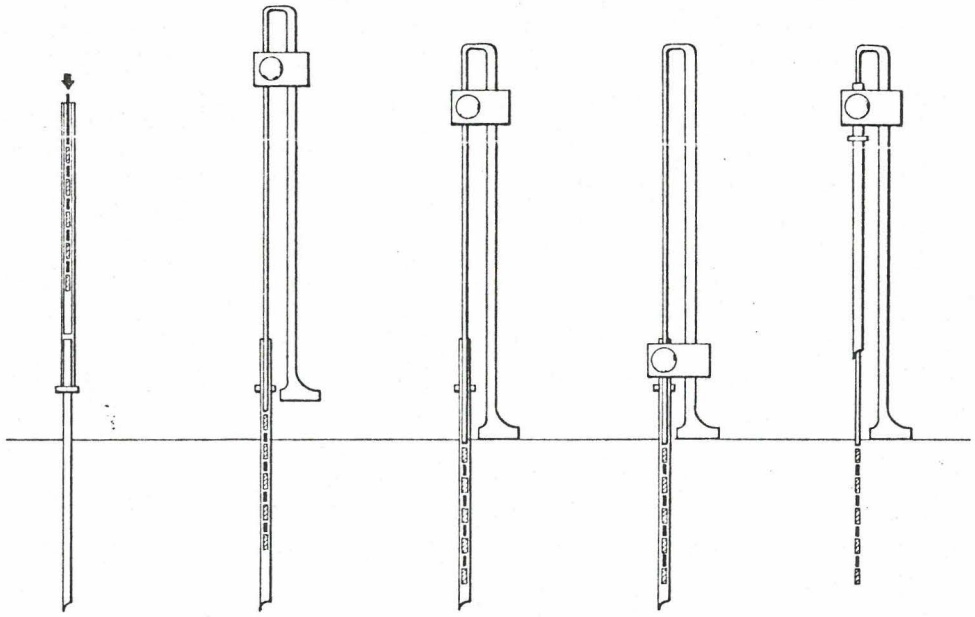

Fig. 1a. Empty needle within tumor ready to receive column of seeds and spacers from nylon tube (cartridge). b. Column of seeds and spacers within needle and Rapid Injector consisting of a stylet for transferring this column to the distal end of needle, a stabilizer for checking the advance of the stylet and insuring its stability as the needle is retracted, and a sliding sleeve-bolt for retracting the needle. c. Rapid Injector has transferred the column to the distal end of the needle and the sleeve-bolt has been slipped forward to engage the needle for retraction. d. Empty needle has been retracted leaving a column of seeds and absorbable spacers in the tumor.

Figure 1 shows the schematics of this technique and Figure 2 illustrates the Rapid Injector.

A simple formula for estimating tumor dose is easily calculated by averaging the three tumor diameters and multiplying by 10, e.g. a tumor measuring

$$\frac{3\text{ cm} + 4\text{ cm} + 5\text{ cm}}{3} \times \text{[illegible]} = \text{[illegible]}\text{ millicuries}$$

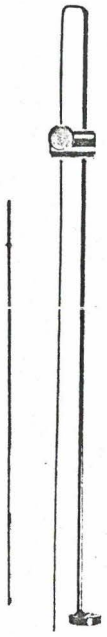

Fig. 2. Photographs(s) of Rapid Injector and needle.

Summary—The absorbable spacer technique is a simple and rapid method for permanently implanting lung tumors. I-125 with its long shelf life (60 day half life) and safer energy (28 Kev) appears to be one of the best sources now available.

39 FR 2384

Radical Radiation Therapy of Cancer of the Prostate: A New Approach Using Interstitial and External Sources*

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RADIATION THERAPY IN CANCER OF the prostate was used for the first time in the form of an intraurethral radium capsule by Pasteau and Degrais[1] in 1909 in Paris. Interstitial implants with radium 226 needles inserted into the prostate were used in 1915 by Barringer[2] at Memorial Hospital, New York.

Occasional reports describing various external radiation techniques appeared in later years (Bumpus[3], Deming[4], Hultberg[5], Widman[6]). However, the prevailing opinion was that although prostatic cancer did show some response to radiation, it could not be adequately treated in this way, mainly because of the irritative effects on the bowel at the high dose required for control.

It was not until 1951 that renewed interest in radiation therapy was aroused by the interstitial injection of colloidal solution of radioactive gold into the prostate by Flocks[7]. Momentum was gained in the 1960's following the reports of George[8], Bagshaw[9], del Regato[10], and Bennett[11], who used supervoltage radiation therapy. Bagshaw's report, in particular, demonstrated that radiation therapy can be curative in this disease by delivering high doses of radiation uniformly throughout the prostatic gland.

The value of the various ablative surgical procedures has been discussed extensively by one of the present authors[12]. Operative mortality increases from a range of 1-5% with radical prostatectomy to approximately 20% with pelvic exenteration. All of these procedures invariably produce loss of sexual function as well as the added hazards and inconvenience of urinary incontinence.

The initial enthusiasm for hormonal therapy (orchiectomy or administration of estrogens) has recently given way to a more critical appraisal. In a controlled clinical study carried out in 14 VA hospitals[13], it was concluded that "therapy by estrogen or by orchiectomy should be withheld until the symptoms are so severe that they require relief. Treatment earlier in the course of the disease is not likely to help, and it may cause considerable damage."

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Prostatic carcinoma, which has a very slow growth rate and remains localized for long periods, seemed an appropriate tumor for interstitial implantation.

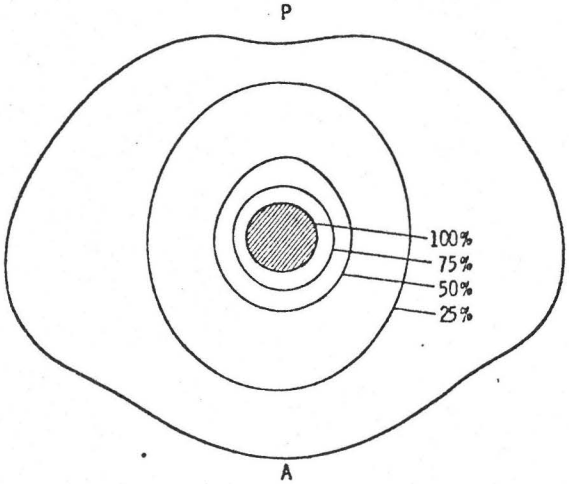
Interstitial implantation of encapsulated sources has distinct advantages over external radiation therapy in the treatment of this malignancy (Figures 1 and 2). The two cross sections of the pelvis at the level of the prostate show the same primary prostatic cancer. Figure 1 is an example of an optimum set-up with external radiation therapy. Using the linear accelerator and a 360° rotation, it is possible to deliver 100% of the planned dose to the tumor bearing area in about 6 weeks. The adjacent rectum and bladder will receive a dose in the range of 65 to 70% of the maximum dose within this same period of time. Figure 2 is an example of the dose distribution for an interstitial implant with iodine 125 seeds in the same situation. It should be kept in mind that the total planned dose (100%) to the tumor bearing area will be delivered in about one year. Comparison of these isodose curves shows that: a) localization is more precise and the dose distribution can be adapted to an irregular tumor shape, b) the dose received by the bladder and rectum is 25-30% of that delivered to the tumor, and c) treatment time is much shorter. A permanent implant requires only a single procedure; when external radiation therapy is used, a 6-7 week treatment course is usually necessary.

A preliminary study was carried out at this institution in the late 1950's and the early part of 1960 together with Dr. Henschke. Interstitial afterloading radiation techniques were used, applying high gamma energy isotopes (radon 222 and iridium 192). Some of the problems encountered at that time are illustrated in the following examples:

Case I

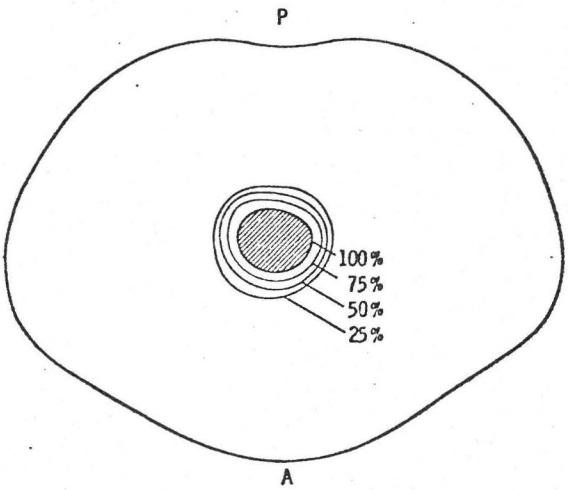
Figure 3 is a pelvic roentgenogram of a 62-year-old patient with an adenocarcinoma of the right lobe of the prostate, involving the right seminal vesicle (Stage C). On October 2, 1964, an interstitial implant, using 25 radon 222 seeds, was performed via a retropubic approach. The total activity was 16 mCi. Computerized calculations[14,15] showed the minimum dose within the implanted volume to be in the range of 6,000 rads (see isodose curve encircling most of the radon seeds). The tumor itself, which measured 1.5 cm in its greatest dimension, is within the 8,000 isodose curve. The right seminal vesicle is partly within the 6,000 isodose curve and partly within the 8,000 isodose curve. The left lobe has received only a fraction of the above doses. A retroperitoneal pelvic node dissection showed the lymph nodes to be free of cancer. The postoperative course was smooth and the patient was discharged on the 8th postoperative day. He remained essentially asymptomatic except for occasional back pain. In May 1970, blastic lesions were noted in the pelvic bones, and the acid serum phosphatase value became elevated for the first time. The left lobe of the prostate was found to be enlarged, and biopsy in September

Figure 1.



6 MEV Linac (360°, 6 x 6 cm)

Figure 2.



Iodine 125 Implant

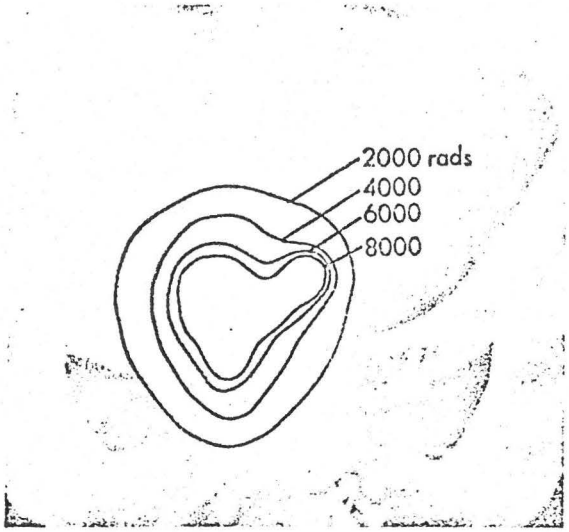


Figure 3.

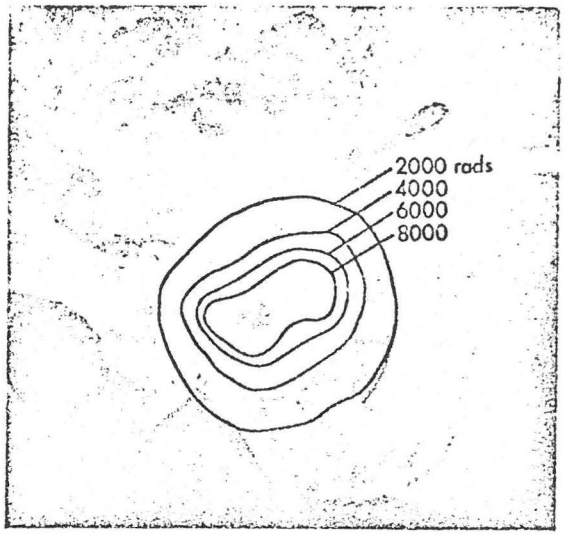


Figure 4.

1970 revealed recurrent carcinoma in the bladder neck and left lobe of the prostate. The patient was placed on estrogen. When last seen in May 1972, he had no urinary symptoms, the prostate was unchanged in size, the acid serum phosphatase value remained elevated, and the blastic changes in the bones had progressed. Retrospective analysis of the radiation distribution in this implant shows that the recurrent tumor is in the region of the prostate that received a low dose, whereas the regions that received more than 6,000 rads remained controlled. It may be argued that implantation of both lobes could have prevented the recurrence.

Case II

Figure 4 is the pelvic roentgenogram of a 63-year-old patient with an adenocarcinoma of the right lobe of the prostate, Grade 3. The tumor measured 2 x 1 x 1 cm, and there was an induration extending to the right seminal vesicle (Stage C). On September 23, 1964, 23 radon seeds were implanted, using a retropubic approach. The total activity was 19 mCi. Computerized calculations showed that the minimum dose within the implanted volume was 8,000 rads; the right seminal vesicle is within this dose level. The left lobe received only a small fraction of the radiation. A retropubic node dissection showed no nodal involvement. The patient was discharged on the 10th postoperative day, having had an uncomplicated postoperative course. He is alive without evidence of disease at present, 8 years after implantation. Retrospective analysis of the dose distribution shows it to have been uniform throughout the known disease area at the time of the implant, and in the range of 8,000 rads. This is considered the optimal dose for this tumor if radon seeds are used [16,17].

Case III

Figure 5 is a roentgenogram of a 59-year-old patient with an adenocarcinoma of the prostate. In the fall of 1955, a nodule was felt in the prostate but the patient was asymptomatic. On May 1, 1956, a TUR and bilateral orchiectomy were performed because of the onset of urinary symptoms. The patient was then placed on estrogen therapy. His symptoms were alleviated for about 2½ months and then recurred. On August 21, 1956, an exploratory laparotomy was performed and an ileal bladder constructed. The prostate cancer was hard, fixed and invading the anterior rectal wall. There was a mass in the right corpus cavernosum at the base of the penis. Large metastatic pelvic nodes were found. An interstitial implant using 24 radon seeds was performed for a total activity of 32.5 mCi. The minimum dose (isodose curve encircling all seeds) was calculated to be 8,000 rads.

In August 1957, the patient developed bone metastases for which he received several courses of external radiation therapy. He expired on November 15, 1957, 15 months after implantation of the prostatic gland. At autopsy, widespread metastases involving bladder, pelvic nodes, liver, bones and thyroid were found. There was no tumor in the prostate. Retrospective analysis of the radiation dose distribution shows that it was in the recommended range of

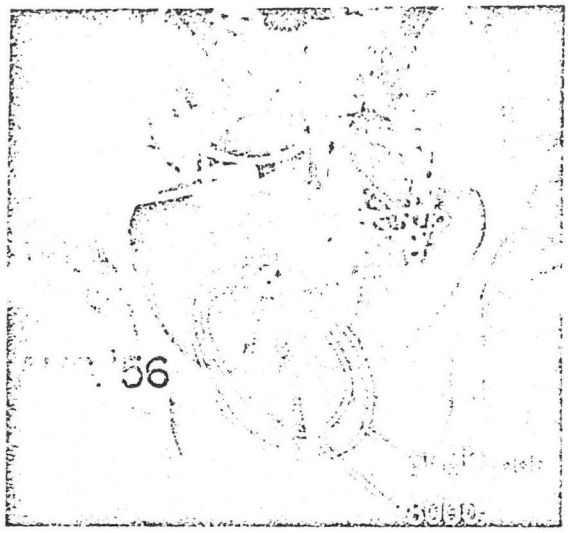


Figure 5.

8,000 rads, uniformly covering the prostatic gland and resulting in eradication of the implanted tumor.

Experience with these first few patients indicated that uniform radiation dose distribution throughout the prostate gland is necessary and can result in satisfactory local control of the tumor. Complications are negligible, since radiation reactions are limited to the implanted area. In 1965, development of iodine seeds and their application in cancer management at Memorial Hospital proved to be of great value. Radiation exposure, a drawback of interstitial implantation, was reduced to such a degree that no significant radiation is now recorded on film badges worn by the surgeons or other operating room and floor personnel caring for these patients.

TREATMENT TECHNIQUE UNDER STUDY AT MEMORIAL HOSPITAL

In the last 4 years, we have used the retropubic approach exclusively for interstitial implantation of the prostate. This approach, particularly when the tumor extends laterally, offers many advantages (Figure 6). The prostate can be completely defined, permitting more accurate determination of the extent of tumor. The regional lymph nodes can be inspected and an extraperitoneal node dissection performed, ensuring a more accurate staging of the tumor and facilitating exposure for the implantation. The insertion of the needles is easier because the prostate is directly exposed. The prostate can be defined with greater precision by having a catheter in the bladder outlining the urethra and by digital rectal palpation of the prostate. The retropubic approach has a lower morbidity than the suprapubic approach.

Patients with Stage B or Stage C (clinically manifest) cancer of the prostate[18] are selected for treatment. After appropriate evaluation to rule out distant metastases, the operation is carried out under general or spinal anesthesia. The patient is placed in a modified lithotomy position and an indwelling Foley catheter is placed in the urethra. Through a midline incision extending from the symphysis to the umbilicus, a bilateral extraperitoneal pelvic lymph node dissection is carried out. At the completion of the dissection, the implantation with iodine seeds is performed. This is done in 2 steps. First, empty needles are inserted into the prostate gland; they are pushed until their tips can be sensed in the rectum by the index finger of an assistant. Care is taken to ensure that they are not pushed through the rectal wall. The needles are spaced approximately one cm apart. The second step is to determine the number of iodine seeds required and to insert them through the needles into the gland. This is done by measuring the 3 dimensions of the implanted volume, finding the average dimension[17,19], and multiplying this figure by a factor predetermined for the specific isotope used (for iodine seeds = 5). The resulting figure indicates the amount of iodine required to deliver the effective dose within the implanted volume. This amount divided by the activity per seed yields the number of seeds required. After completion of the implant, the surgical incision is closed, leaving a Penrose drain in the retropubic area.

Figure 6.

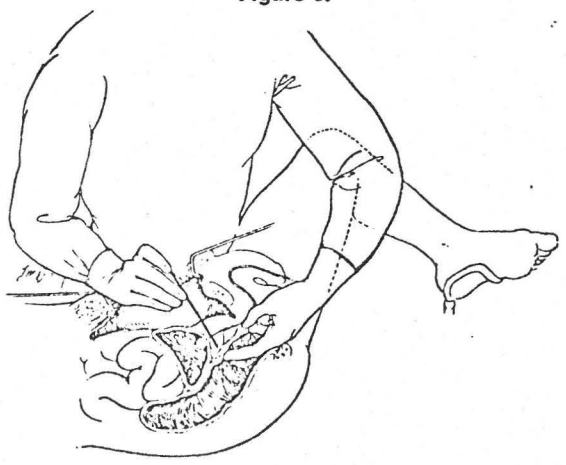


Figure 7 shows an example of such an implant. The radioactive iodine seeds (light-colored dots) indicate the implanted volume and are utilized to determine the target volume. The isodose curve encircling these seeds is 16,000 rads (minimum tumor dose), as recommended by the average dimension system, given to 22 cc of tissue in this instance. The dose falls off more rapidly than with radon seeds, becoming approximately 4,000 rads at the level of the rectum.

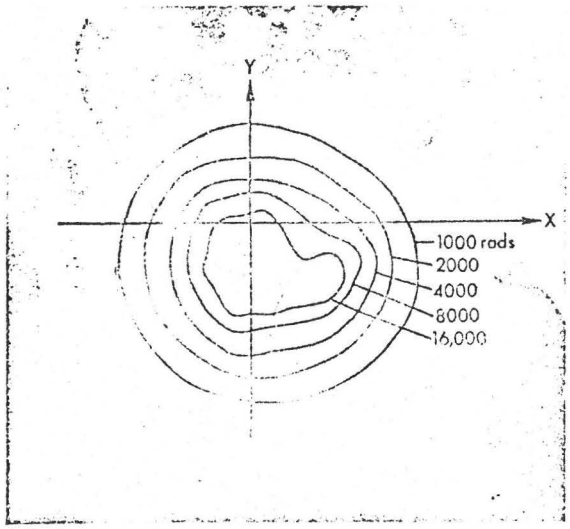


Figure 7.

Interstitial radiation is used extensively at Memorial Hospital. The treatment protocol presently under study is to use interstitial radiation with iodine seeds alone or in combination with external radiation. If there is nodal involvement, supplementary external radiation is applied, using inverted Y-shaped fields that include the regional nodes. The linear accelerator is used and doses of 4,500 rads in 4½ weeks are given. Inverted T-shaped fields are used to include the primary site whenever the primary tumor is very large and moderate doses of external radiation (4,500 rads in 4½ weeks) are employed. No severe complications have been encountered when these regimens have been followed.

Since their introduction, approximately 50 patients have been treated with iodine 125 seeds. Of these, 26 patients are available for at least a one-year evaluation. The longest survivor is a patient who is now close to 5 years from time of implantation and is without evidence of disease. Although not enough time has elapsed to judge the final outcome, it is worthy of note that, based on digital examination, size and/or induration of the prostate has been reduced in 17 patients following implantation, remained unchanged in 6, worsened in 1 and cannot be evaluated in 2.

Postoperative complications have been minimal; 19 patients had none, 5 had minor degrees of suprapubic wound infection, one had transient urinary retention which responded to conservative management and one had prolonged suprapubic urinary drainage, presumably related to a complete transurethral resection of the prostate one week prior to the implantation of iodine 125 seeds. Radiation complications were encountered in 2 patients. These consisted of transient rectal burning which subsided within 3 months in one patient, and severe tenesmus in the other. This latter patient had received 7,000 rads in 8 weeks to the prostate prior to the implantation of iodine seeds.

Eight patients had Stage B lesions. Two of them were found to have bilaterally positive lymph nodes on pelvic node dissection. Eighteen patients had Stage C lesions; on pelvic lymph node dissection, 5 had bilaterally positive lymph nodes and 5 had unilaterally positive lymph nodes.

SUMMARY

A new regimen is presently being investigated at Memorial Hospital for the treatment of patients with Stage B and C cancer of the prostate.

This approach consists of a retropubic exploration, extraperitoneal node dissection and interstitial implantation of the prostate with iodine 125 seeds. Postoperative external irradiation of the regional lymph nodes is added if there is histologic evidence of nodal involvement.

This new approach increases accuracy of staging, carries low morbidity and no mortality; it requires short hospitalization and reduces the treatment time. Information on sexual potency is still limited, but suggests that a high degree of preservation of this function when it was present preoperatively is possible.

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39 FR 2384

DESIGN REQUIREMENTS FOR I-125 SEEDS

1.) COMPLETE CONTAINMENT FOR I-125

2.) NON-TOXIC IN HUMAN TISSUES

3.) HIGH TRANSMISSION FOR 30 KEV X-RAYS (LOW "Z")

4.) "VISUALIZABLE" BY STANDARD X-RAY PROCEDURES (HIGH "Z")

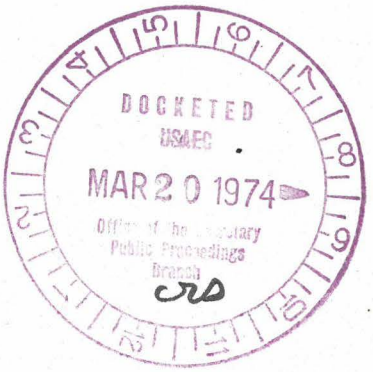
5.) HIGH STRUCTURAL INTEGRITY - STERILIZATION BY AUTOCLAVE

6.) INJECTABLE THROUGH #18 HYPODERMIC NEEDLE

7.) ADAPTABLE TO PRESENT SYSTEMS

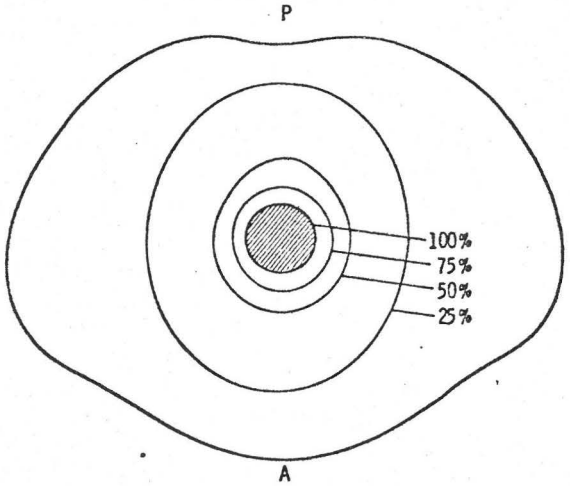
8.) ECONOMICAL PRODUCTION

9.) UNIFORM DOSE DISTRIBUTION

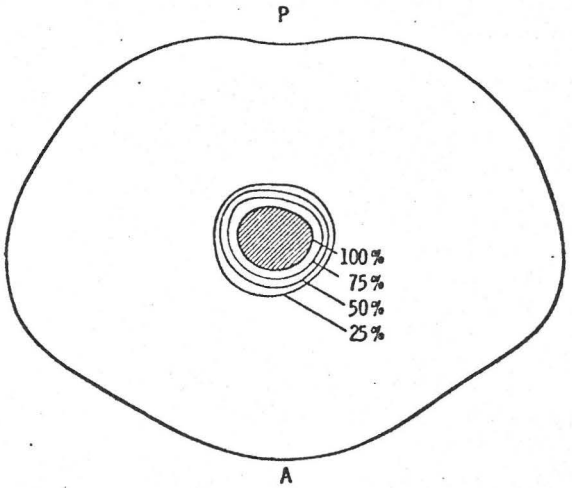


ADVANTAGES OF SOFT X-RAY "SEEDS"

1. ELIMINATION OF THERAPIST EXPOSURE.
2. SIMPLIFIED SHIPPING AND HANDLING.
3. IMPROVED TUMOR DOSE DISTRIBUTION.
4. ROUTINE IMPLANT THERAPY OF LARGE TUMORS INCLUDING LUNG.
5. THIN METALLIC FOILS PROTECT NEARBY TISSUES.
6. SIMPLE OUTPATIENT TREATMENT.
7. COULD BE USED IN REMOTE UNDERDEVELOPED AREAS.
8. SMALL DIRECTIONAL BEAM APPLICATORS CAN BE MADE.
9. COMPLETE PROTECTION OF PATIENTS, ASSOCIATES, AND NURSES.



6 MEV Linac (360°, 6 x 6 cm)

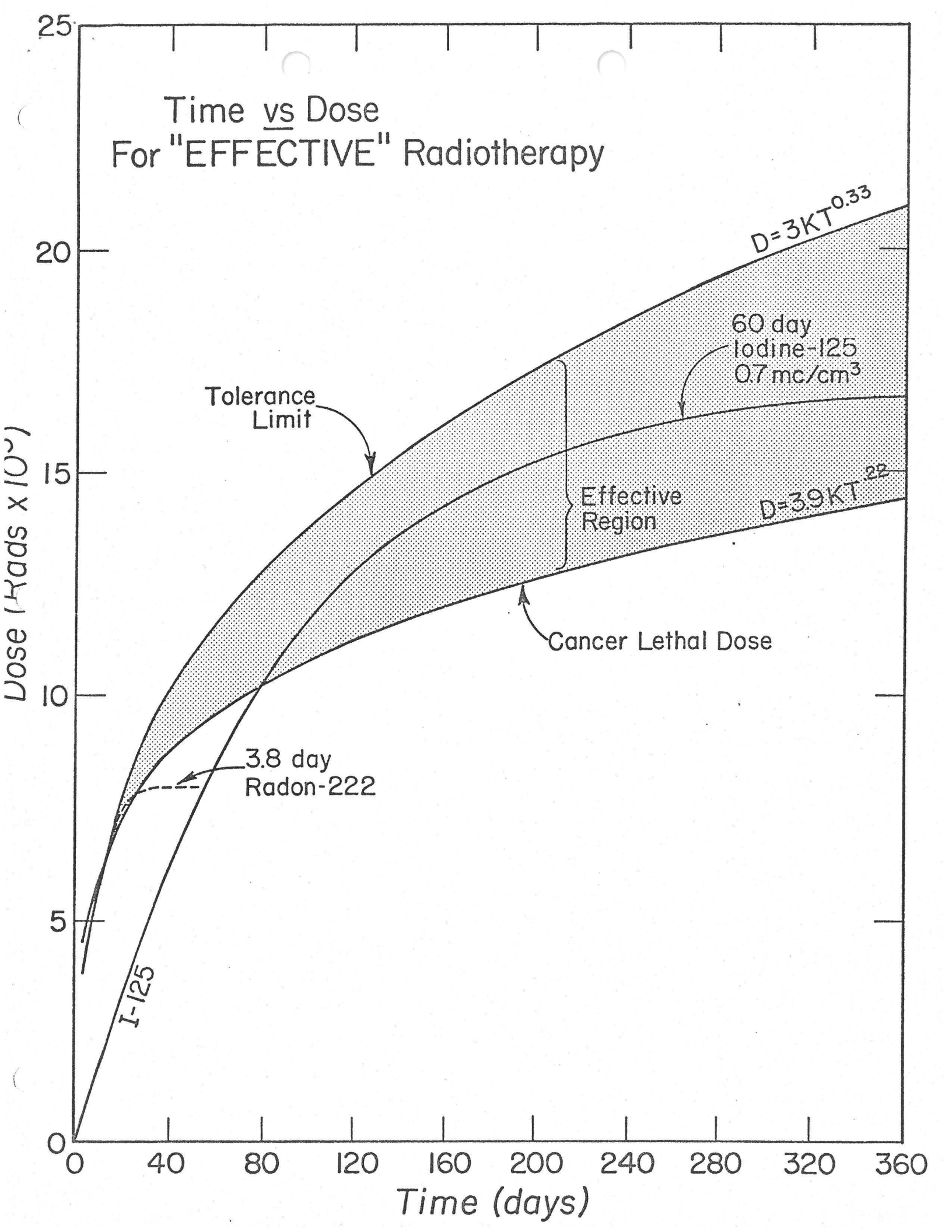


Iodine 125 Implant

TABLE I

RADIOISOTOPES FOR PERMANENT IMPLANTS

RADIOISOTOPE	HALF LIFE	GAMMA RADIATIONS	OTHER	HALF VALUE LAYER Pb	HALF VALUE LAYER H_2O (Tissue)
Au^{198}	2.7 days	0.411 & .680 Mev	.97 Mev β	.13 inch	≃ 7 cm
Rn^{222}	3.8 days	0.24 - 2.43 Mev (many)	Alpha (2) & 0.65 Mev β	0.53 inch	≃ 9 cm
Ir^{192}	74.2 days	0.2 - 1.1 Mev (many)	0.54 & 0.67 Mev β	0.14 inch	≃ 7 cm
I^{125}	60 days	28 & 35 Kev	None	0.001 inch	≃ 2.1 cm
Cs^{131}	9.7 days	29.4 Kev	None	0.001 inch	≃ 2.1 cm
Xe^{133}	5.3 days	32 and 80 Kev	0.35 Mev β	≃0.01 inch	≃ 5 cm


Time vs Dose
For "EFFECTIVE" Radiotherapy
D=3KT^0.33
60 day
Iodine-125
0.7 mc/cm³
Tolerance
Limit
Effective
Region
D=3.9KT^.22
Cancer Lethal Dose
3.8 day
Radon-222
I-125
Dose (Rads x 10³)
Time (days)
0
5
10
15
20
25
0
40
80
120
160
200
240
280
320
360

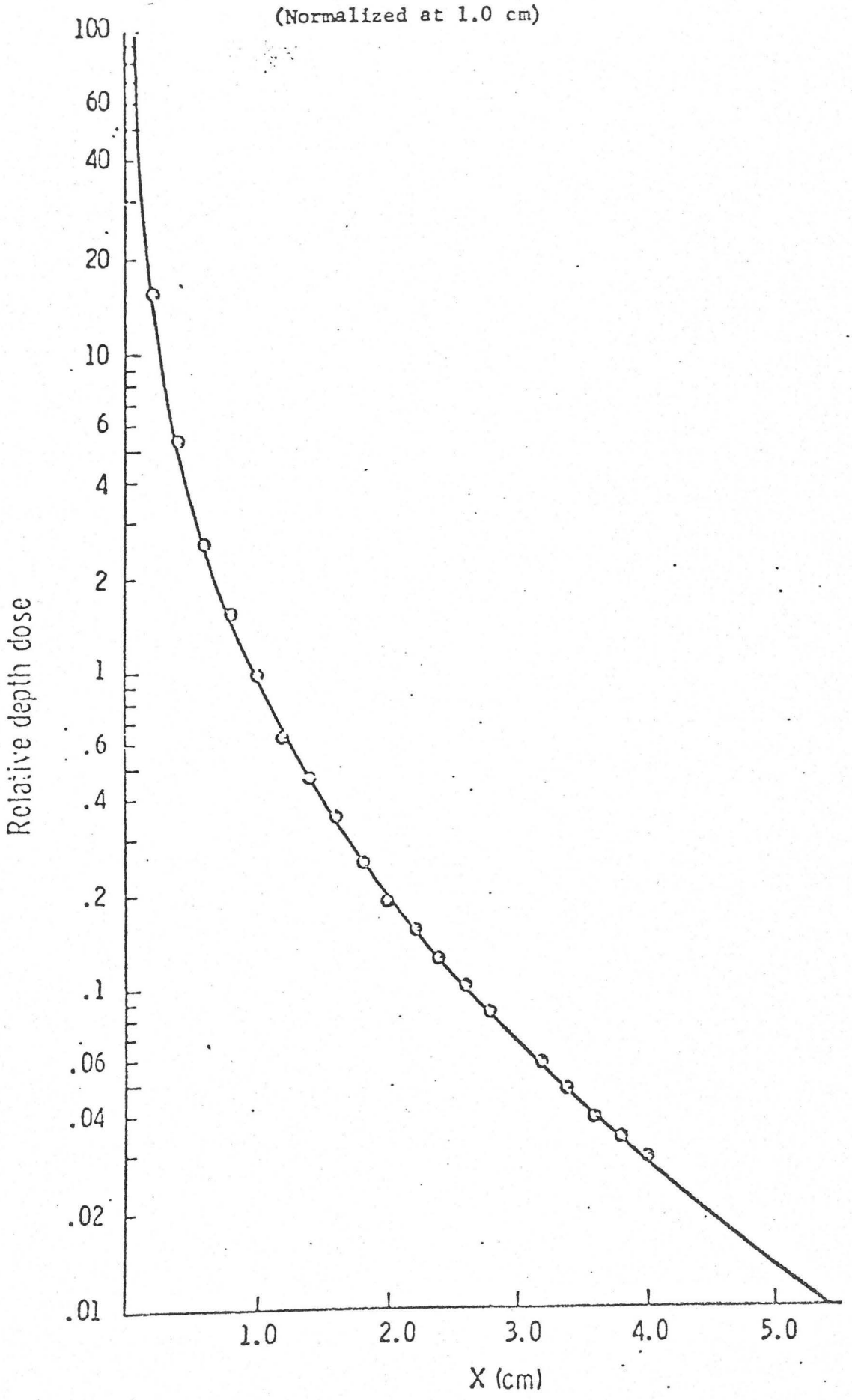
Biological Dosage Factors for Permanent Implants of Available X-ray Emitting Radioactive Sources

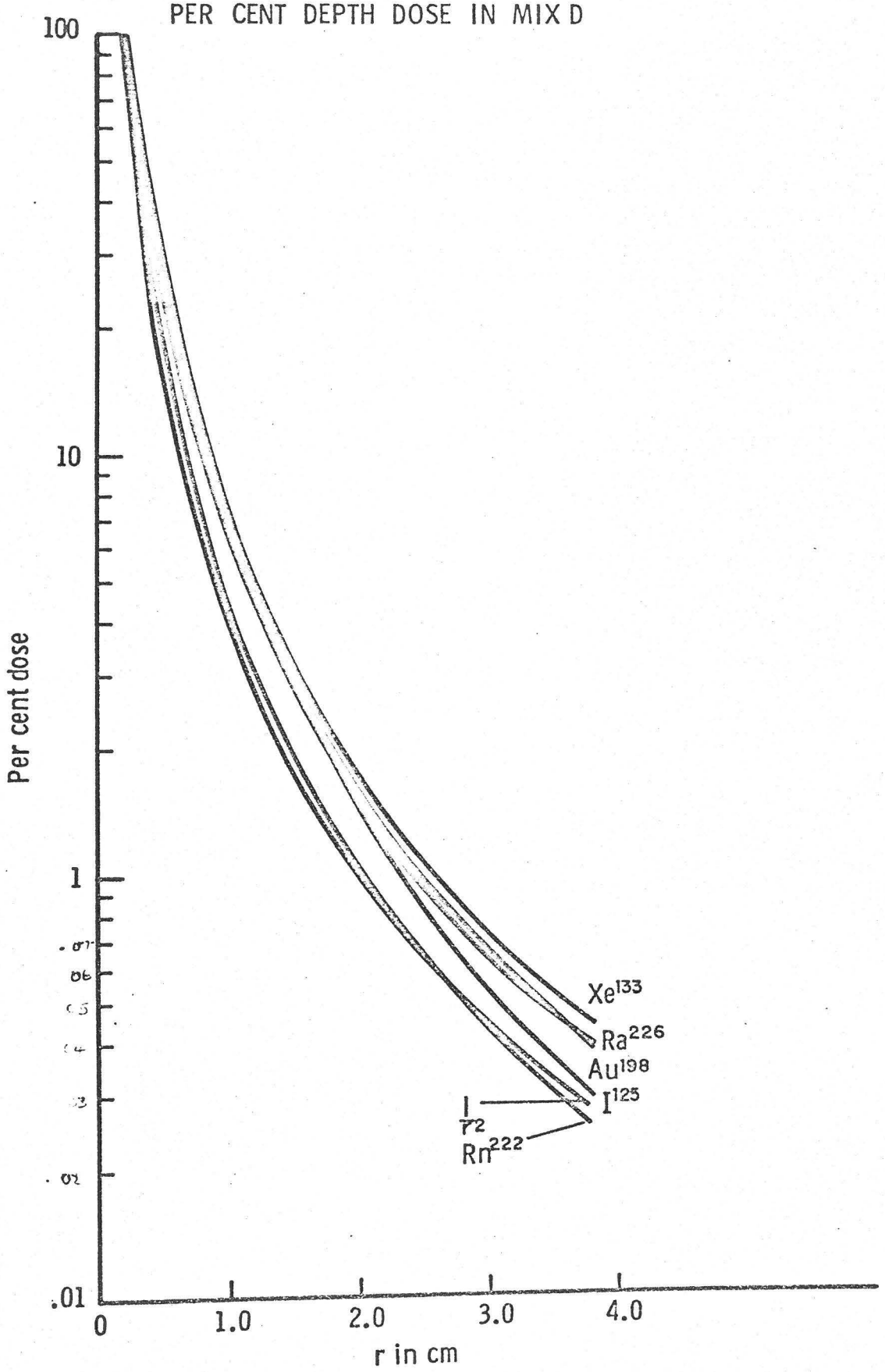
Technical data	Formula*	^{198}Au	^{222}Rn	^{131}Cs	^{51}Cr	^{125}I	^{192}Ir	^{182}Ta
Half-life (days)	a	2.69	3.83	9.7	26.5	60	74	111
Mean x-ray energy (MeV)	b	0.4	1.0	.03	0.3	0.03	0.4	1.1
Ionization factor (r/mc hr at 1 cm)	c	2.4	8.4	0.6?	0.2	1.4	2.7	6.1
Clinical life (days)	$T=2.75a$	7.4	10.5	26.7	73	165	203	305
Relative biological efficiency (Ra(x)=1, 10 ions/micron)	$\eta=\phi(b)$	1.2	1.0	1.2?	1.2	1.2?	1.2	1.0
Cancerocidal dose, Sq.Ca-LD (r at complete decay)	$D_t=1.18(E_t)T^{0.22}/\eta$	6000	7600	8170	10000	11800	12000	16000
Tolerance dose for a 10 cm skin field (r at complete decay)	$D_s=1.18(E_s)T^{0.33}/\eta$	5800	7800	8740	12500	15900	17500	24000
Largest field tolerating full cancerocidal dose (cm) with a heterogeneity factor of 1.2	$L=10\left(\frac{D_s}{1.2D_t}\right)^3$	5	6	7.9	11	14.2	17	20
Optimal initial dose-rate for a 10 cm field (r/hr)	$d=\frac{D_s+D_t}{68.6a}$	64	60	25.4	12.4	6.72	6.0	5.2
Optimal initial activity biologically equivalent to 1 mc radon in standard dosage tables (mg radium equiv.)	$e=d/60$	1.07	1.00	0.424	0.20	0.112	0.10	0.09
Optimal initial grain strength (mc), or optimal mc/cm	$f=\frac{8.4e}{c}$	3.35	1.00	6.0	8.40	0.67	0.31	0.12
Therapeutic Ratio	$\frac{D_t}{D_s}$	0.97	1.025	1.07	1.25	1.35	1.46	1.5

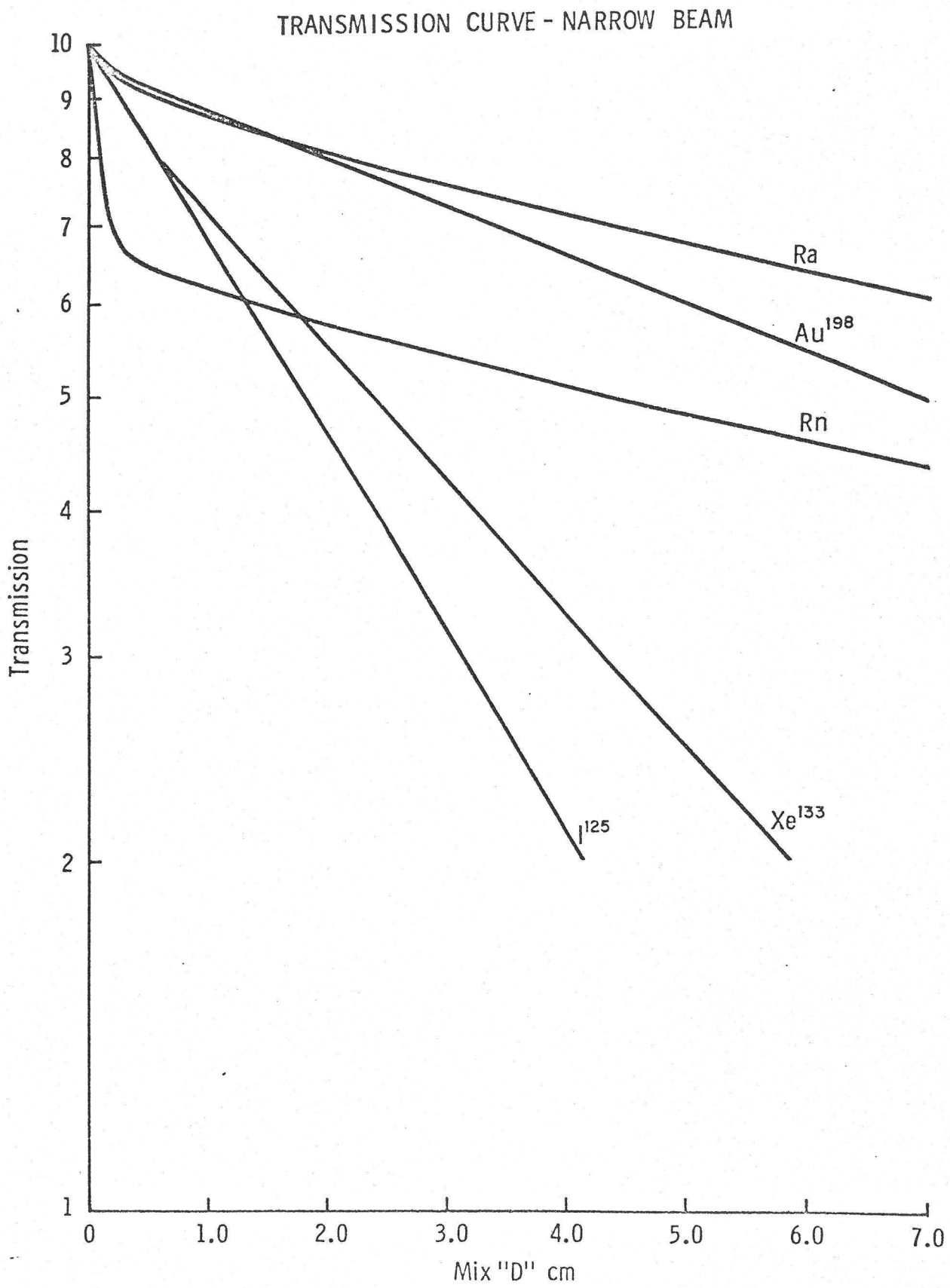
*Adapted from Cohen PB&M 2:229 (1958).

?=unconfirmed values.

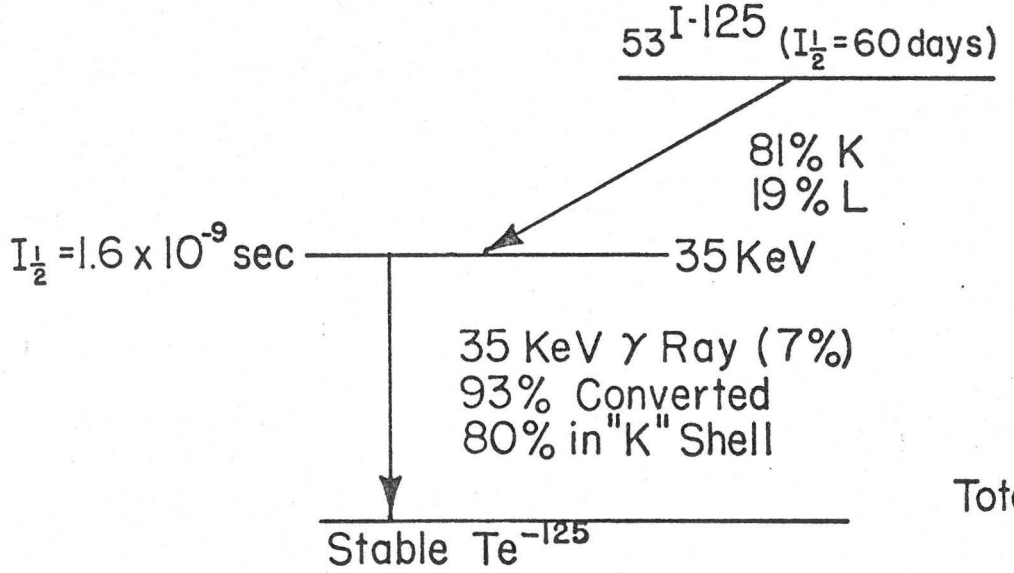
RELA[illegible]VE DEPTH DOSE FROM A POINT OF [illegible]25
(Normalized at 1.0 cm)




PER CENT DEPTH DOSE IN MIX D
100
10
1
.01
Per cent dose
0
1.0
2.0
3.0
4.0
r in cm
Xe133
Ra226
Au198
I125
I
72
Rn222


TRANSMISSION CURVE - NARROW BEAM
Transmission
10
9
8
7
6
5
4
3
2
1
Ra
Au198
Rn
I125
Xe133
0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
Mix "D" cm

IODINE-125 DECAY SCHEME



"Useable" Photons

→ 0.69 @ 27.4 KeV

→ 0.07 @ 35.4 KeV

→ 0.68 @ 27.4 KeV

Total "useable" Photons = 1.44 per Disintegration

No Higher X, γ, or β Radiations
Auger Electrons of 2.8 to 35 KeV do not escape capsule wall

Γ = 1.4 R−cm²/mc−hr

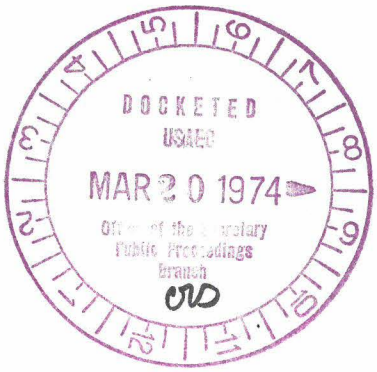
39 FR 2384

Lawrence Soft Ray Corporation

251 WEST EVELYN
MOUNTAIN VIEW, CALIFORNIA 94040
PHONE: (415) 967-2861

One mCi Equivalent I-125 Seed

Half life: 60.2 days K factor: 1.7 r/mCi/hr at 1 cm.

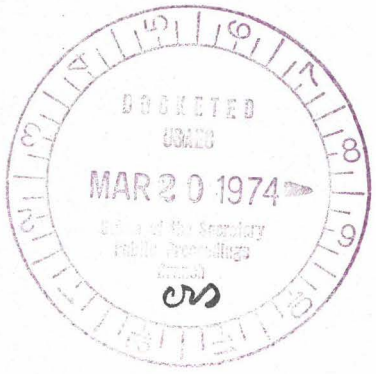


Days after assay	Decay factor	Dose rate at 1 cm.(rads/hr.)
0	1.000	1.700
2	0.977	1.661
4	0.955	1.623
6	0.933	1.587
8	0.912	1.550
10	0.891	1.515
12	0.871	1.481
14	0.851	1.447
16	0.832	1.414
18	0.813	1.382
20	0.794	1.350
22	0.776	1.320
24	0.759	1.290
26	0.741	1.260
28	0.724	1.232
30	0.708	1.204
32	0.692	1.176
34	0.676	1.149
36	0.661	1.123
38	0.646	1.098
40	0.631	1.073
42	0.617	1.048
44	0.603	1.024
46	0.589	1.001
48	0.575	0.978
50	0.562	0.956
52	0.550	0.934
54	0.537	0.913
56	0.525	0.892
58	0.513	0.872
60	0.501	0.852
62	0.490	0.833
64	0.479	0.814
66	0.468	0.795
68	0.457	0.777
70	0.447	0.759
72	0.437	0.742
74	0.427	0.725
76	0.417	0.709
78	0.407	0.693
80	0.398	0.677
82	0.389	0.661
84	0.380	0.646
86	0.372	0.632
88	0.363	0.617

Mark Smith Nuclear Instruments, Inc.

1470 Outlook Avenue Bronx, N.Y. 10465

39 FR 2384



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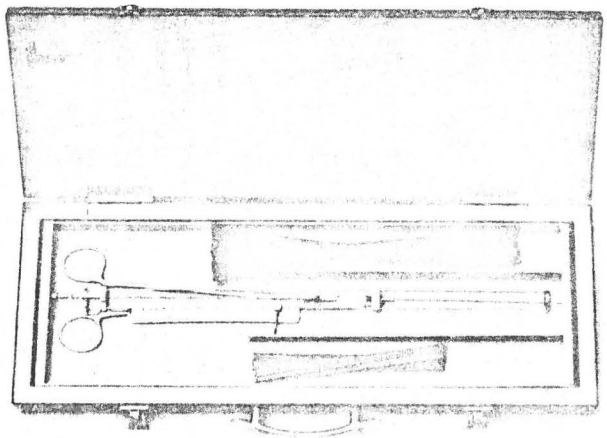
1470 Outlook Avenue Bronx, N.Y. 10465

Permanent Interstitial Implant Set

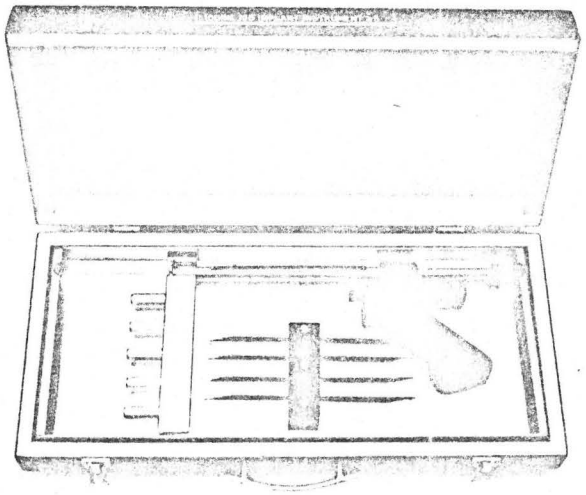


Permanent implants have in the past found their principal indication in palliative cancer treatment. However, with the improved implantation techniques and new radioisotope sources, they are being used more and more for curative therapy as well.

As the first step, unloaded, hollow 17-gauge needles, each 15 cm long, are inserted in and around the tumor. If feasible, the tumor should be so exposed that one hand can be placed under it. By measuring the length of the needles outside the tumor, the shape and size of the implanted volume can be determined. The number of sources required to give the desired dose is then calculated.

As the second step, an instrument with a depth gauge is attached to each needle in turn. Through it the required number of radioisotope sources are introduced one by one into the tissue and implanted at the desired depth.

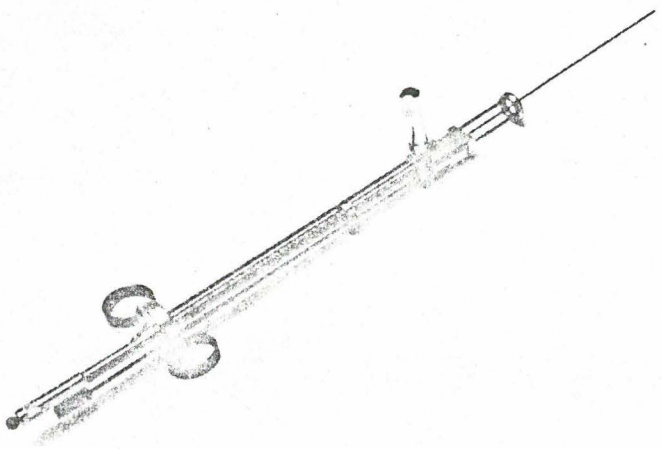
I^{125} Permanent Implant Gun



The instrument utilized most recently for implantation of Iodine 125 seeds is the Hilaris/Mahan Permanent Implant Gun, developed in 1969 at Memorial Hospital in New York.

While the afterloading principle is retained, the instrument has a magazine which permits the introduction of a number of seeds in succession through the same needle. A depth gauge attached to the gun permits accurate depth determination. No radiation exposure is incurred with the use of low energy seeds such as Iodine 125. In addition to the gun, the complete interstitial implantation kit includes a set of 32 hollow 17-gauge stainless steel needles, which are used during the first step of afterloading; 5 magazines, each with a capacity of 10 low energy Iodine 125 seeds. These magazines are mounted on a removable stainless steel tray, which can be taken out of the wooden container, autoclaved and kept sterile prior to implantation.

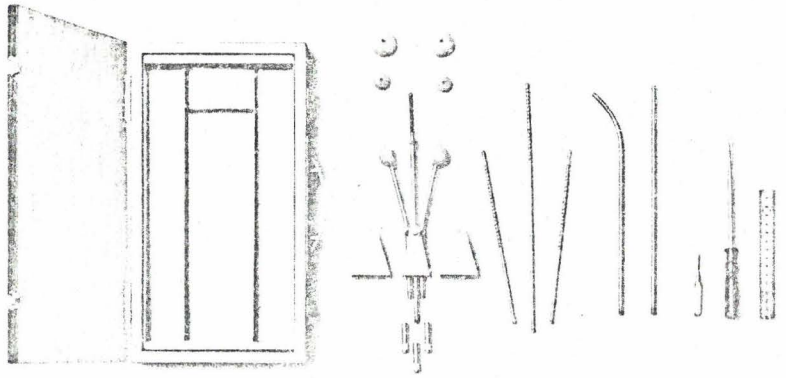
Mick Applicator



The Mick Applicator is based on the same afterloading principle as the Henschke Implant Instrument and the Hilaris/Mahan Gun. These instruments are provided with a ratched mechanism assuring accurate placement of seeds at any desired depth up to 12 cm. Needles can be withdrawn at 5 mm steps and seeds are manually transferred by means of a stylett into the tumor.

After the needle is insered into the tumor, the tissue ring is pulled back to the funnel in the needle holding device. The needle is fed into the funnel and securely fastened. The tissue ring then is brought forward to the surface of the skin or tumor and on the scale located on the main shaft, the depth of the needle is directly determined. A preloaded magazine with a capacity of 10 Iodine 125 seeds is inserted into the applicator and by pushing the stylet, seeds are transferred into the 17 gauge needle and, consequently, into the tumor.

Henschke Afterloading Cervix Applicator



The applicator is made of stainless steel and consists of a central (uterine) tube and two lateral (vaginal) tubes, which attach to the central tube by a connector. Each lateral tube ends in a spacing hemisphere of nylon. By adjustments and accessories, the applicator can be adapted to different anatomical conditions.

For the afterloading, new stainless steel source carriers have been designed with a spring type plunger, which holds any number of sources securely in place.

Central Uterine Tube ("Tandem") - Three intra-uterine tubes of different curvatures are supplied with one cervical stop which can be moved to correspond to the length of the uterine cavity.

Lateral Vaginal Tubes ("Colpostat") - Two tubes, each ending in a hemisphere which comes in three different sizes (2 cm, 2.5 cm, 3 cm) and can be moved along the tubes to adjust to different anatomical and cancer configuration.

Each lateral tube is also supplied with a locker, which is movable along the tube to adjust to different depths of the vaginal vault. These locks are then attached and secured to the central tube by a connector.

The stainless steel connector serves two purposes: A. Prevention of dislocation or rotation of uterine tube. This is achieved by a pointed thumbscrew that fits into a groove, located on top of the uterine tube. B. Attachment of vaginal tubes to central uterine tube.

Afterloading - The new type source carriers are made entirely of stainless steel. They are especially designed for flexibility to adjust to the various curvatures in lateral and uterine tubes. The spring plunger adjusts to any length and number of sources and attaches firmly to the carrier by a screw.

The spreading of the vaginal sources is maintained by a set of metal brackets (4 cm, 5 cm, 6 cm) which easily attaches to the connector outside of the patient.

Threaded caps are provided to cover each afterloaded tube. All adjustments are made by the same allenwrench.

39 FR 2384

FINAL REPORT

Project No. EC-00113

CANCER THERAPY BY INTERSTITIAL AND INTRACAVITARY RADIATION

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Public Health Service Grant EC-00113 (formerly RH-00521), Bureau of Radiological Health, Rockville, Maryland, May 1, 1968 to April 30, 1971

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Part I

INTRODUCTION

The biomedical program undertaken with the support of the Bureau of Radiological Health of the Public Health Service (May 1, 1968 through April 30, 1971) to study "Cancer Therapy by Interstitial and Intracavitary Radiation" was divided into three identifiable areas:

a. Radiation exposure
b. Radiation dosimetry
c. Clinical trials

The specific aims of this study were for the most part satisfactorily concluded. Economic production of iodine seeds for permanent implantation became possible largely because of automation and increased production of the seeds by the manufacturers. The cost was thus brought down to $5.00 a seed, compared to $12.50 a seed, which was the cost at the initiation of this project. No other isotopes were investigated, however, for permanent implantation because of the prohibitive cost of production (e.g., cesium-131 seeds are in the order of $50.00 per seed). Because of the ready availability of the iodine seeds and their acceptance by the clinical services at Memorial Hospital, they were adopted as the only radioactive sources for permanent implantation at Memorial Hospital since September 1969. The design of a special source inserter (gun) with a suitable magazine for inserting low energy sources has improved and simplified the technique of permanent interstitial implantation (Part IV. A).

Special attention was given to the problem of radiation exposure and dosimetry, although the severe cuts in the budget obliged us to limit some of our activities. The use of iodine-125 seeds and the clinical application of remote afterloading for some of the intracavitary applications has brought a dramatic reduction in radiation exposure to the extent that the exposure recorded on the personnel film badges is negligible, in contrast to earlier years when radon-222, gold-198, iridium-192, and radium-226 were used (Part II). Extensive studies on seed calibration, localization and dose distribution were conducted by our Medical Physics Department. Methods of dosimetry were developed which are adequate for using the iodine-125 seeds in clinical applications. This will be elaborated on in Part III.

Determining the proper dose with iodine seeds presented a problem for some time but was satisfactorily solved by associating the dose to the implanted volume, and referring to the previous experience with high energy gamma emitters, radon-222, gold-198, and iridium-192 (Part IV. A).

In intracavitary radiation, the Remote Afterloader was put into clinical use during the period of Grant EC 00113. New intracavitary

applicators were designed and constructed for cancer of the nasopharynx, endometrium, and intraoral lesions. Several technical refinements were achieved, but the chief obstacle, the automatic retrieval of the sources, remained (see Part IV. B).

An atlas of isodose distributions was prepared for different source excursions, but was not published owing to lack of funds. Part of the clinical experience and descriptions of the various techniques, however, were reported in a manual, which, according to the response from various sources, appears to serve a useful purpose.

The establishment of the new techniques related to low energy seeds and the Remote Afterloader has raised many new questions which must be resolved before these new techniques can be applied on an extensive basis.

Thus, with the introduction of the computer into medicine, it appears essential to computerize all work pertinent to the Remote Afterloader and iodine seed implantation, permitting:

1. Automatic control of the remote afterloader for intracavitary radiation.

2. Monitoring of the patient during the intracavitary treatment.

3. A concise practical system of dosimetry for interstitial radiation.

4. Automatic processing and final display of the dosimetry in intracavitary and interstitial therapy.

The final aim should be the gradual automation of the decision-making process for interstitial and intracavitary radiation therapy.

Part II

RADIATION PROTECTION CONSIDERATIONS IN THE USE OF IODINE-125 FOR INTERSTITIAL IMPLANTS

Jean St. Germain, M.S.*

One of the chief advantages in the use of iodine-125 is the reduction in exposure to personnel, patients and their families which is achieved by substituting iodine-125 for other hard gamma emitters in interstitial implants, especially radon-222. This section will deal only with the problems and benefits of the use of iodine-125 as far as radiation protection is concerned.

Shielding and Storage

Table 1 (Pg. 7) summarizes the properties of iodine-125 and some of the other isotopes used as seeds for implantation. As is obvious from inspection of this data, shielding for iodine-125 is something easily constructed and lightweight. In contrast, shielding for radon-222 and gold-198 usually requires at least several inches of lead and this means that carriers used to transport the materials within the hospital premises are bulky and require large amounts of storage space. A carrier used at Memorial Hospital for iodine-125 is shown in Figure 1 (Pg. 10). These carriers require little storage space and are easily carried from point to point. Activities up to 50 mCi can be easily loaded into this carrier while external exposure rates on the carrier surface remain at 0.1 mR/h or less. If for any reason it is deemed desirable to shield the area of the iodine-125 implant on the patient, this can be done with lead vinyl strips which generally cause no patient discomfort and significantly reduce external exposure levels. Lead "pigs" such as those commonly supplied by isotope manufacturers can be used for storage of iodine-125 seeds provided one has ascertained that the pig is not initially contaminated.

General Hospital Population

It has been our experience that exposures to the general hospital population (nurses, nurses aides, etc.) is considerably reduced with the replacement of iodine-125 for hard gamma emitters in interstitial implants. One of the chief advantages of iodine-125 is the attenuation of the radiation which is achieved in tissue. With the use of this isotope, patients can generally be assigned to multiple occupancy units. The decision as to whether a patient is assigned to a single or multiple occupancy unit is made only after direct measurements are made on the patient. Exposure rates are measured directly over the area of the implant and at a distance of 1 meter from the implant. Table 2 (Pg. 8) shows measurements made on a random sampling of nine iodine-125 cases.

*Assistant Physicist, Radiation Safety Service, Department of Medical Physics, Memorial Hospital, New York, N.Y.

The distance of 35 cm was arbitrarily chosen to represent the point of closest approach of the attendant's body to the area of the implant. Unit assignments are made based on these measurements. As is evident from the sample cases shown in Table 2, exposure rates can vary considerably depending on the depth of the implant. Generally patients with deep-seated implants (i.e., seeds implanted at a depth of 5 cm or more) can be assigned to multiple occupancy units. Table 3 (Pg. 9) shows a random sampling of nine radon-222 cases. It is obvious by examination of these figures that there is less attenuation in tissue and that reduction in intensity is virtually dependent on inverse square law above the surface of the implant. Most patients implanted with radon-222 would require a single room regardless of the area of the implant. We, however, would emphasize the importance of individual measurements being made on all implanted patients.

Our experience has shown that for nurses giving general nursing care to iodine-125 patients the exposures are generally minimal (viz., less than 10 mR/mo). The reduction in exposure which can be achieved is perhaps best demonstrated in the case of the private duty nurse. Using the conservative assumption of constant occupancy of the nurse at a distance of 35 cm from the patient and the values for deep-seated iodine-125 implants shown in Table 2, the maximum exposure to a nurse during an eight hour shift would be in the range of 10-15 mR. Using an assumption of constant occupancy of the nurse at a distance of 1 meter from the patient and using the values for radon-222 shown in Table 3, exposure to a nurse during an eight hour shift would be in the range of 12-96 mR. These assumptions can be verified by examination of personnel monitoring records of private duty nurses. Our records indicate that exposures up to several hundred milliroentgen can be accumulated by a private duty nurse giving special care to a patient implanted with 20 mCi or more of radon-222 in one 8 hour shift. Private duty nurses caring for iodine-125 cases have generally received minimal exposures (10 mR or less).

Operating Room Personnel

The use of iodine-125 has also considerably reduced the exposure to operating room personnel during implant procedures. The range of iodine-125 is such that the exposure to anesthetists, scrub nurses and other persons at a distance of 1 meter or greater from the patient is generally negligible. The most probable accident which may occur in operating rooms is the loss of seeds during the procedure. Although this occurs infrequently, it can pose problems. In this regard iodine-125 has some definite disadvantages. Radon-222 and gold-198 have a gold color which is easily visualized on most surfaces. Additionally the energy of these materials is such that the general positions of the seeds is easily localized. Iodine-125 seeds have a grey color which is virtually invisible on a black or marble surface. The energy of the iodine-125 seeds is such that the searchers must be very close to their location before the seed can be seen. The autoclaving process remains the same for iodine-125 as for other seeds.

Radiation Therapy Personnel

For the radiotherapist and his aides, iodine-125 has obvious radiation protection advantages. Usually the techniques of interstitial work are so specialized that the use of these implants on a large scale is confined to a few individuals in a department of radiation therapy. Figure 2 (Pg.11) shows the variation in exposures over a five year period for these personnel in Memorial Hospital. One other important fact, however, must be added in a discussion of this graph. Concomitant with the introduction of the use of iodine-125 at Memorial was the development of remote afterloading techniques. This development would be expected to further decrease exposures from ionizing radiations. The graph does present an example of the magnitude of the reductions which are possible.

One of the chief concerns to physicians working with interstitial sources has been hand and finger exposures. Here too iodine-125 has obvious advantages. Examination of the physical data alone in Table 1 would show that for the same given activity point source, a reduction in radiation exposure by a factor of approximately 6 is possible by substituting iodine-125 for radon-222.

General Public

In this section, we will confine our discussion to the patient's families and friends. Within the hospital environs, iodine-125 is almost an ideal isotope with regard to visitors since generally no restrictions are necessary regarding visiting hours although some recommendations may be made regarding distance from the patient based on individual measurements. With regard to its half-life, however, iodine-125 is far from ideal. Due to the length of time required for one half-life, one can assume that most patients will be discharged while containing approximately the same amount of material with which they were initially implanted.

The difficulties involved in releasing such patients into the general public are not insurmountable, but they do call for cooperation between the radiotherapist and the physicist. In our institution, all patients receiving iodine-125 implants are interviewed before discharge by a member of the radiation safety staff. In order to accomplish this, nuring personnel must alert the Radiation Safety Service as to the discharge date and the attending physician must be willing to allow the physicist to interview the patient. It has been our experience that cooperation on both these points is fairly easy to obtain but that occasional reminders are necessary for floor personnel. Figure 3 (Pg.12) shows the interview summary sheet which is given to the patient to take with him. Section 5 of this sheet is especially important for persons with superficial lesions in which loss of seeds is possible as the tumor regresses. Explanation of this phenomenon to the patient and his family will considerably reduce any fear should such a loss of seeds occur. Section 6 of this sheet is also extremely important since this is

the area in which most of the questions on the part of the patient's family arise. The type and depth of the interview is dependent on the patient's home situation. Figure 4 (Pg. 13) shows a sheet which can be used as a check list when interviews are conducted.

If it is determined that special problems can arise due to the exposure rate from an implant, shields can be constructed of either lead foil wrapped in gauze (average thickness 0.5 mm Pb) or lead vinyl rubber. The patient is instructed to wear these shields whenever he goes out into the general public or even in the home should the situation warrant it. Because of their light weight, these instructions are usually obeyed by patients.

We have attempted in our discussion to appraise the advantages and disadvantages in the uses of iodine-125. For the most part, the radiation protection advantages inherent in the use of this isotope outweigh the disadvantages; and these advantages are one of the strongest arguments for its wider acceptance.

TABLE 1

ISOTOPE	HALF-LIFE (da.)	SPECIFIC GAMMA CONSTANT, Γ R/mCi-h at 1 cm	HALF-VALUE LAYER (cm Pb)
^{198}Au	2.7	2.3	0.3
^{125}I	60	1.4	<.001
^{222}Rn*	3.8	8.25	1.4

* In equilibrium with short-lived daughters and filtered by 0.5 mm Pt equivalent.

TABLE 2

RANDOM SAMPLING OF NINE IODINE-125 CASES

Site of Implant	Date of Implant	Activity Implanted (mCi)	Exposure Rates (mR/hr) Surface	at 35 cm	at 1 m	mR/mCi at Surface
Upper Lobe-Lung	7/8/69	13	4	0.8	0.25	0.3
Right Lung	11/27/70	21.7	15	1.0	0.25	0.7
Lung	3/12/71	26.6	18	1.5	0.2	0.7
Pelvis	2/18/70	29.4	10	1.0	0.25	0.3
Pelvis	3/2/71	16	3	0.4	0.1	0.2
Prostate	4/8/71	14.4	1.5	0.3	<0.1	0.1
Right Tonsil	12/31/69	21	300	15	1.6	14.3
Left Neck	1/7/70	9.5	300	16	1.6	31.6
Right Neck	4/9/71	6	60	2.3	0.3	10.0

TABLE 3

RANDOM SAMPLING OF NINE RADON-222 CASES

Site of Implant	Date of Implant	Activity Implanted (mCi)	Exposure Rates (mR/hr) Surface	at 1 m	mR/mCi at Surface
Right Lung	6/6/69	4.2	50	1.5	11.9
Right Lung	9/5/69	7.6	350	3	46.1
Chest	7/8/70	7.0	200	3	28.6
Pelvis	8/14/69	10.3	300	4.5	29.1
Abdomen	9/1/70	15	600	6	40.0
Vagina	9/22/70	24.8	400	12	16.1
Right Neck	12/19/69	7.5	1200	5	160.0
Right Tonsil	8/17/70	13.0	1000	10	76.9
Left Axilla	9/8/70	11.9	1500	10	126.1

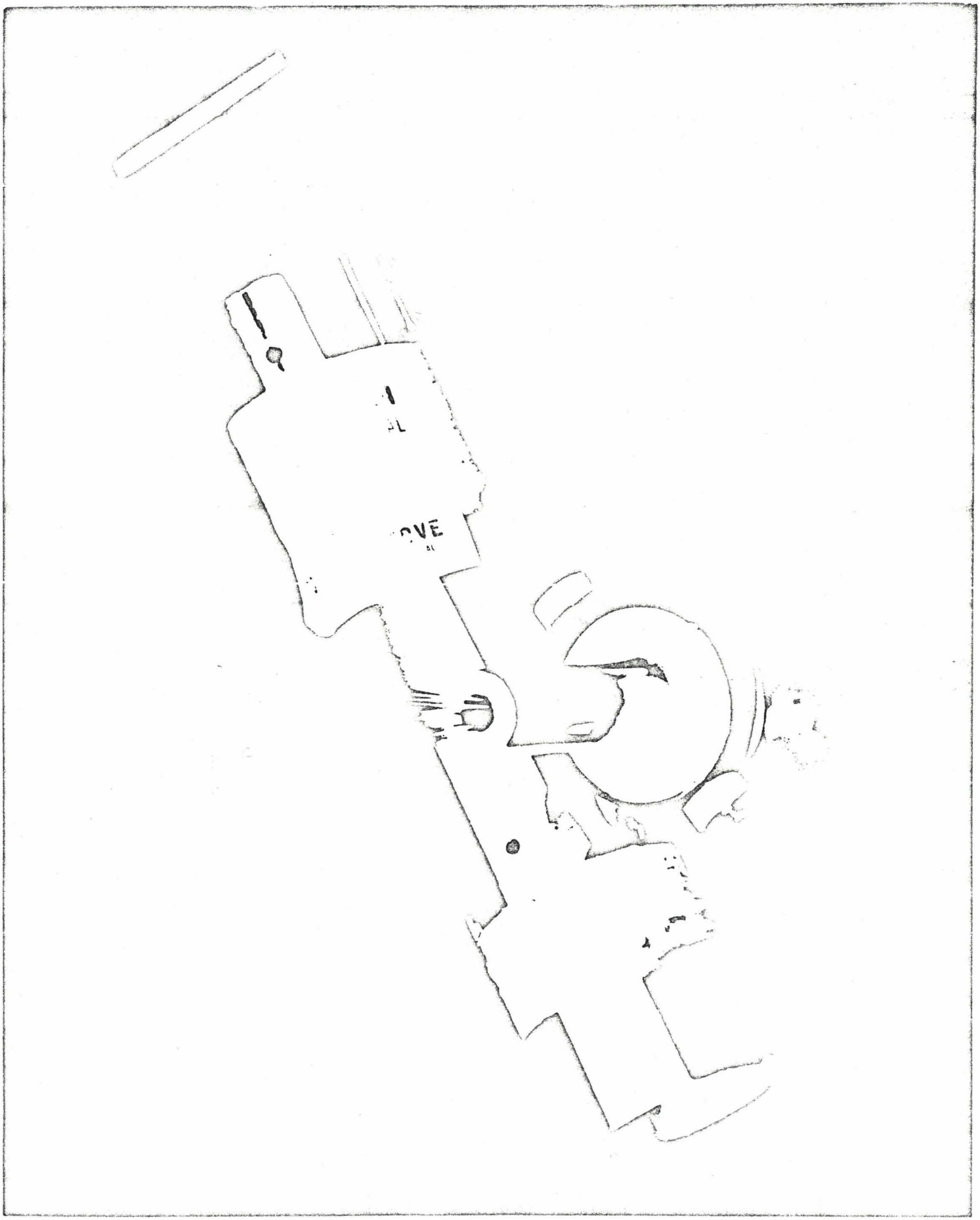


Figure 1

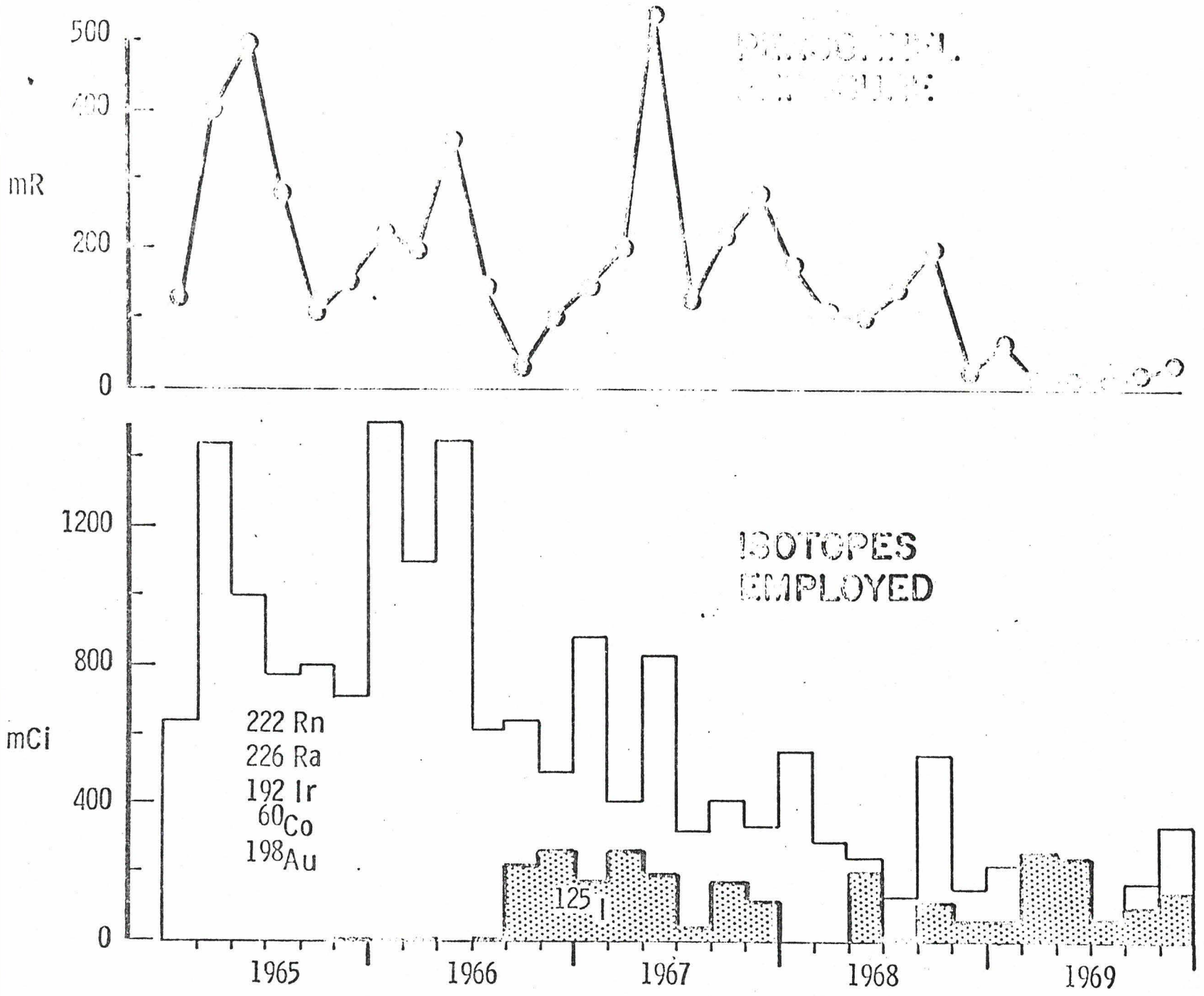

500
400
mR
200
0
PERSONNEL
EXPOSURE
1200
800
mCi
400
0
ISOTOPES
EMPLOYED
222 Rn
226 Ra
192 Ir
60Co
198Au
125I
1965
1966
1967
1968
1969
REMOTE AFTERLOADER

FIGURE 2

FIGURE 3

MEMORIAL CENTER, 444 EAST 68th STREET, NEW YORK 10021, NEW YORK

RECOMMENDATIONS FOR PERSONS NEAR PATIENT WITH RADIOACTIVE IODINE IMPLANTS

1. _____ was treated on _____, 19___ by a permanent implant with radioactive iodine (I-125) of _____ mCi.

2. No special precautions are required for the spouse or anyone else who takes care of the patient, if he or she does not expect to have any more children and is not engaged professionally in radiation work.

3. Other persons under 45 years can stay 6 feet or more from patient for ___ hours per month for the first 3 months (_____, 19___ till _____, 19___); ___ hours per month for the subsequent 9 months (_____, 19___ till _____, 19___).

4. No special precautions are necessary after (_____, 19___).

5. If you have been treated for a superficial lesion, i.e., one near the surface of the skin, it is possible that one or more iodine seeds might slough off or become detached as the tumor regresses or becomes smaller. Under these circumstances, any bandages or linens which come into contact with the site of implant should be scrutinized for small metallic iodine seeds which are about 1/3 to 1/4 of an inch long and are as thick as a straight pin, similar to the "dummy" seed shown to you. Whenever they are found they should be picked up in a spoon and placed in a jar or any other container and placed in an inaccessible area somewhere in the home. These seeds should not be handled by the fingers or hands. The Physics Department at Memorial Center should be notified of this as soon as is convenient.

6. Under other circumstances, there are no contamination problems. For example, linens, clothing, tableware, dishes, toilet facilities may be used by other persons without any special precautions. Touching the patient does not contaminate anyone. Shaking hands or kissing the patient is perfectly permissible provided that the time recommendations listed above are complied with.

7. In some cases, it is recommended that the patient sleep alone in his own room. This will depend on several factors and will be discussed with you by the Radiation Safety Officer or Deputy.

8. For any additional information or oral instructions please do not hesitate to call us as indicated below. The Radiation Safety Officer (or Deputy) should be notified if the patient is hospitalized, or if death should occur.

9. Please show this form to every physician whom you consult.

RADIATION SAFETY SERVICE
DEPARTMENT OF MEDICAL PHYSICS
MEMORIAL CENTER
879-3000
Extension 3333 or 2991

FIGURE 4

RADIATION SAFETY INTERVIEW CHECK LIST

Name of Patient: Age: Date:

Address: Tele. No.

Name of Person Interviewed:

Description of dwelling:

Household: Names, Relationship, Ages:

Regular visitors to dwelling:

Persons regularly visited by patient outside dwelling:

Explanation given:

Handling of extruded source
Importance of separate beds
Importance of distance
Importance of special care in regard to young persons
Film badges issued
Identification card, or wristband issued

Radiation Safety Officer
(or Deputy)

RSO-5/59
REV 11/61

Part III

DOSIMETRIC CONSIDERATIONS IN THE INTERSTITIAL USE OF ENCAPSULATED IODINE-125 SOURCES AND IN THE INTRACAVITARY USE OF HIGH INTENSITY ENCAPSULATED SOURCES BY REMOTE AFTERLOADING

G. Holt

A. Interstitial Use of Encapsulated Iodine-125 Sources.*

In the past 10 years, a number of radioactive nuclides were used at Memorial Hospital for interstitial implants in cancer patients. Most of these were high energy gamma ray emitting radionuclides, which included radon-222, gold-198, iridium-192, cesium-137 and cobalt-60. Since 1966, an effort was made to develop an encapsulated low energy gamma-ray emitting radionuclide as a substitute in interstitial therapy for the high energy gamma ray emitting and potentially hazardous radionuclides.[1]

After some initial experimentation with xenon-133, which is a gas and proved to be unsuitable, and cesium-131, which met all the qualifications but proved to be economically unfeasible to develop, iodine-125 was chosen because it showed the most promise to be clinically suitable. The iodine-125 seeds, which are now available commercially according to our specifications (Lawrence Soft Ray Corp. and Isotopes, Inc.) consist of iodine-125 bound to an ion resin enclosed in a titanium capsule 4.5 mm long and 0.7 mm in diameter welded on both ends. Each titanium capsule contains two such resins with a gold marker separating them making the seeds visible for radiographic purposes. Figure 5 (Pg. 24) shows the basic construction of the iodine-125 seeds. The physical aspects of encapsulated sources of iodine-125 were investigated before clinical application of interstitial radiation therapy began. Iodine-125 decays entirely by electron capture into tellurium-125. The principal radiation emitted by iodine-125 are taken from the MIRD Supplement No. 2 and are listed in Table 4 (Pg.16). The main features of iodine-125 are the emission of low energy x- and gamma rays of the order of 30 keV. Hence, the special problems encountered by the use of this isotope in interstitial therapy may be classified into the following categories:

1. Iodine-125 seed design
2. Absolute calibration
3. Routine calibration of iodine-125 seeds
4. Seed localization

---

*This was in part presented at the Annual Meeting of the American Radium Society at Mexico City, March 1971.

5. Radiation dose distribution within patients due to interstitial implants of iodine-125 seeds
6. Personnel exposure (discussed in Part II)

1. Seed design. After considerable experimentation, titanium was chosen as an encapsulating material and a gold bead was incorporated into the design for radiographic localization. The iodine was absorbed into two Dow-X microspheres. Extensive leak tests established the integrity of the encapsulation. Radiographic visibility of the seeds was ascertained by taking radiographs of iodine-125 seeds placed in various tissue-equivalent phantoms. An attempt to localize the seeds by external scanning of radioactivity was abandoned due to lack of resolution. Autoradiographs of the seeds were taken to assess the non-isotropic distribution of radiation due to self-absorption and the presence of the gold seeds. (Figure 6, Pg. 25)

On the basis of these preliminary checks, the seed design was considered satisfactory as a first attempt although the distribution of radiation in the close vicinity of the seed is less isotropic than that obtained from a typical radon seed.

2. Absolute Calibration. The calibration of the iodine-125 seeds was accomplished by an absolute cavity ionization method using a carbon extrapolation chamber. The carbon ionization chamber was cylindrical in shape and was fitted with caps of different thicknesses to facilitate the extrapolation to zero wall thickness. The low source strength of the iodine-125 seeds (8.64×10^3 ergs/mCi-hr) dictates the use of a large ion chamber for measurement and the inside dimensions of this carbon chamber were: diameter=3.7 cm, length=3.7 cm.

The dimensions of the cavity were considered large compared to the range of the most energetic secondary electrons from the iodine-125. With the exception of a small wall correction, the energy absorption within the cavity depends entirely on the absorption properties of the cavity material, air in this case, and will be proportional to the mass energy absorption coefficient for air.

The wall correction is based on the following considerations: the mean energy of the soft x-rays from iodine-125 is 28.4 keV. At this energy, about 50% of all interactions are photoelectric and 96% of the total energy is absorbed by the photoelectric process. Since the photoelectric for low atomic number materials is nearly inversely proportional to the cube of the energy, the mean energy of the photoelectrons will certainly be less than 10 keV which is the lowest energy for which tabulated coefficients are available. The range of a 10 keV electron in air is equal to 2.89×10^{-4} grams per centimeter squared, or 0.22 cm. The mean pathlength of an electron through the carbon chamber was calculated by means of a computer program and was found to be equal to 2.47 cm. Hence, the range of the 10 keV electrons is roughly equal to 9% of the total mean pathlength through the chamber. Therefore, Bragg-Gray or Spencer-Attix theory of cavity ionization does not apply to this case. Neither does the empirical theory developed by Burlin apply to this measurement which deals with the case of cavity dimensions comparable

TABLE 4

CALCULATION FOR THE Γ FACTOR OF I-125

$$\Gamma = 195 \sum_i \left(\frac{\mu a}{\rho}\right) air_i \; h\nu \;\; (MeV) \cdot h_i \; \frac{cm^2 - R}{mCi - hr}$$

Energy (keV)	% Mean No. dis.	I	(μ_a/ρ)air	Γ(E)
35.5	6.78	2.407	.093	.04365
27.5	73.8	20.29	.193	.7636
27.2	37.8	10.28	.200	.4009
31.0	19.9	6.169	.135	.1624
31.8	4.13	1.313	.126	.0323

I_T=40.47 keV/dis Γ_T=1.403 $\frac{cm^2 - R}{mCi - hr}$

The spectrum for I-125 is taken from the MIRD Supplement No. 2; the coefficients of mass absorption are from R.D. Evans in "Radiation Dosimetry" by Attix, Roesch and Tochilin, 2nd Edition.

with electron ranges. Therefore, it was necessary to work out special corrections for this measurement.

The ratio of the mean energy absorption coefficients from carbon to air are equal to .401 indicating that the wall (carbon) contributes about 40% of the deposited energy in air and this energy is deposited over a distance equal to the range of the electrons which is 10% of the mean electron path through the chamber. The contribution of the total ionization within the cavity originating from the wall was taken to be as 40% over 10% of the volume (since the range is roughly 10% of the mean path through the volume). Therefore, in addition to the electrons produced in the gas of the cavity there will be a 4% contribution from the wall and the total ionization within the chamber was reduced by this amount.

Hence the dose to the cavity is equal to

$$D_{air}=0.869 \times \frac{Q}{V} \text{ rads.}$$

From this the exposure X may be calculated

$$X = \frac{1}{1.04} \times \frac{Q}{V} \text{ roentgen.}$$

The activity A of the iodine-125 source is equal to the product of the exposure rate and the square of the distance divided by the gamma ray mission constant Γ. A correction of 1% was applied to this to account for the attenuation of the 30 keV x-rays in air over a distance of 30 cm.

$$A=\frac{X(\text{roentgen})_x}{t(\text{hours})} \frac{D^2(cm^2)}{\Gamma} \quad \frac{cm^2\text{-}R}{mCi\text{-}hr}.$$

The experimental design utilized an iodine-125 source suspended under tension, by a monofilament line (Fig. 7, Pg.27). The source was positioned 30 cm from the carbon chamber. The source could be lowered into a safe and raised to the calibration position using a laser beam for localization. The current from the carbon chamber was measured with a Keithley 640 vibrating reed electrometer in the integrating mode. The integrated value of the current was displayed on a digital volt meter. The necessary integrating time for each data point was ten minutes. For each data point an additional carbon cylinder was added to the chamber increasing the attenuation of the beam. In all 7, carbon cylinders were used allowing the wall thickness to vary from .15 cm to 1.8 cm. From this absorption curve the measured ionization was extrapolated to a value for zero wall thickness.

The background current during the experiment was of the order of 10^{-16} amperes, and current measured due to the source was of the order 10^{-13} amperes.

The rate of increase in voltage across the integrating capacitor was found to be quite linear in time. The extrapolated ionization current for zero wall thickness was found to be 1.58×10^{-13} amperes.

The volume of the chamber was accurately measured by filling the cavity with water and making allowance for the displacement of the central electrode. The volume was determined to be 40.0 cubic cm. The activity was calculated on the basis of a specific gamma ray emission constant of 1.4 cm^2-R/mCi-hr. The emission constant Γ was calculated using the most recent data on the iodine-125 spectrum published in the MIRD supplements. The soft components of the iodine-125 spectrum were not considered in these calculations since it was assumed that the soft x-rays were absorbed by the walls of the titanium capsule.

As a check on the experiment, the mass absorption coefficient for carbon was calculated based on the experimental data. This calculation yielded a mass absorption coefficient 6.7% above the published values.

3. Routine calibration of iodine-125 therapy sources. The activity of the iodine-125 sources are routinely measured with a Victoreen 440 adapted for digital readout and a specially designed holder which facilitates the reading of the large number of sources commonly handled (Fig. 8, Pg.29). A shipment of seeds is routinely calibrated against a I-125 standard which has been calibrated by means of the carbon extrapolation chamber. Each new source is placed in the holder and its activity is read. The sources are then grouped together in .05 mCi ranges of activity. The upper and lower bounds of activity considered acceptable for therapy being .65 mCi and .4 mCi, respectively.

4. Seed localization. It was demonstrated that the iodine-125 seeds were radiographically visible within a standard phantom. The seeds implanted within patients are radiographically localized by means of orthogonal-stereo radiographs. While normally only orthogonal radiographs are required for the localization of needles and wires, an additional stereo projection is required for seed identification in case of multiple seed implant. The disadvantage of all radiographic localization methods so far is that the positive identification of the projection of the source on each radiograph is required. In case of a multi-seed implant, this is very time consuming and tedious work. More recently, a method has been developed which does not require the positive identification of seeds and will lend itself to automatic scanning methods of radiographs. This method will be described in detail elsewhere.

5. Radiation dose distribution within patients. The dosimetry of interstitial implants with iodine-125 seeds is by far the greatest problem. Since the energy absorption coefficients for photons between 0-30 Kv are critically dependent on energy, the usual methods of dosimetry do not readily apply. It is not obvious that the methods developed for the computation of dose distribution for the interstitial and/or intracavitary application of high energy gamma-ray emitters also apply for iodine-125 since the soft x-rays of iodine can be treated neither as β-particles nor high energy gamma-rays. It has long been realized at Memorial Hospital that the conventional systems which assign a single dose value to an implant do not satisfactorily describe the distribution within the patient,

nor provide a sufficient physical basis for correlation with clinical experience, and do not provide an adequate basis for subsequent additional irradiation.

To compute the actual 3-dimensional dose distribution within an implant, computerized systems of dosimetry were developed at Memorial Hospital and are used routinely to compute dose matrices in any desired plane and at any desired orientation throughout the implant.[2] These systems followed the initial application of computer methods to achieve realistic treatment planning at Memorial[3-5] in 1954 for external radiation and the initial work by Nelson and Meurk[6] for implanted sources. A complete description of the 3-dimensional dose distribution within the patient permits subsequent analysis and correlation with tissue response, and guides the accurate addition of external radiation fields to the lesion.

To compute the dose distribution within a medium from a set of distributed sources, it is first necessary to determine the point source distribution. Relative depth dose measurements were made in Mix-D phantoms around a number of encapsulated sources using lithium fluoride teflon rod dosimeters as supplied by Controls for Radiation (now Isotopes, Inc.). Because of the small size of these dosimeters it was possible to measure the dose within 2 mm of the source and to proceed at 2 mm intervals thereafter. Mix-D was chosen as the phantom material in preference to water because it is a solid and easy to machine. This makes it relatively simple to produce an accurate source-dosimeter geometry. The dosimeters were arranged within the phantom along a spiral configuration in order to avoid overlapping of the dosimeters. Two similar spirals were arranged within the phantom so that the two sets of dosimeters would be spaced at equal distances from the source. Figure 9 (Pg. 31) shows the phantom and the experimental arrangement of the dosimeters. The dosimeters were removed at times which were calculated to yield the same dose, approximately 100 rads, to each dosimeter used in the experiment. A geometrical correction factor was applied to these data which allowed for the fact that both the dosimeter and the source were linear. This correction amounts to nearly 50% at 2mm from the source and is negligible at distances greater than 1 cm (Table 5, Pg. 20)

Figure 10 (Pg.33) shows the experimental depth dose curves for a number of radionuclides normalized at 0.2 cm from the source. The difference in absorption between the various radionuclides is not startling as may be surmised from the fact that at the distances encountered, the inverse square law is by far the greatest factor affecting the depth dose. Figure 11 (Pg. 35)shows the narrow beam transmission characteristics for the same radionuclides in Mix-D. Note the presence of the soft components of the radon gamma-ray spectra which is manifested in the sharp drop in the beginning of the absorption curves.

The absorbed dose at a point as a function of distance from a point source is proportional to the relative depth dose and may be computed by

TABLE 5

DOSIMETER LENGTH CORRECTION APPLIED

TO LiF (TEFLON) RODS

Distance (cm)	Source Length 2.5 mm	3.0 mm	4.5 mm
.20	.7189	.7421	.8159
.40	.8716	.8770	.8962
.60	.9312	.9329	.9391
.80	.9582	.9588	.9612
1.00	.9721	.9724	.9735
1.20	.9802	.9803	.9809
1.40	.9852	.9853	.9856
1.60	.9886	.9886	.9888
1.80	.9909	.9909	.9911
2.00	.9926	.9926	.9927
2.20	.9939	.9939	.9939
2.40	.9948	.9948	.9949
2.60	.9956	.9956	.9956
2.80	.9962	.9962	.9962
3.00	.9966	.9967	.9967
3.20	.9970	.9971	.9971
3.40	.9974	.9974	.9974
3.60	.9976	.9977	.9977
3.80	.9979	.9979	.9979
4.00	.9981	.9981	.9981

means of the experimental depth dose curves. The tumor dose should be stated in units of absorbed dose and the dose distribution should be normalized to rads.

This relationship is expressed by the following equation:

$$D(r) = kf(r) \text{ in rads}, \qquad (1)$$

where f(r) is the dimensionless relative fractional depth dose. The normalization factor k, which expresses the absorbed dose in rads/mCi-hr at 1 cm, must be determined separately.

The absorbed dose in the absorbing body may be determined on the basis of total absorption if a detecting probe is suitably calibrated and its response is proportional to the absorbed dose. Such a calibration may be made by combining an absolute calorimetric determination of the total energy released by the source (source strength) in ergs/mCi-hr with relative dose measurements (percent depth dose) made throughout the medium. The calibration requires that relative dose measurements be made throughout a medium thickness which is sufficiently extensive to absorb all emitted energy. The theoretical source strength was computed using the spectrum taken from the MIRD Supplement[7] No. 2. The coefficients of mass absorption are taken from R.D. Evans in Radiation Dosimetry, by Attix, Roesch and Tochilin, 2nd Edition. Assuming that the low energy components of the spectrum would all be absorbed by the titanium capsule, the mean intensity was computed to be 40.47 keV per disintegration which would result in a source strength of 8.64×10^3 ergs/mCi. A theoretical value for the normalization factor k was computed by means of Eq. (2).

$$K = \frac{1}{\rho} \int_{V(\infty)} \frac{f(r)\, dV}{E_\tau} \qquad (2)$$

integrated over all space. This equation states that the total energy absorbed in an infinite medium (integral dose) must be equal to the energy emitted by the source, where E_τ is the source strength in ergs/mCi-hr, ρ is the density of the material; f(r) is the experimental relative depth dose. In order to compute the volume integral, a correction was applied to the experimental depth dose f(r) which transformed the cylindrical volume geometry into a spherical volume geometry. Figure 12 (Pg. 37) shows the computed point source distribution. An analytical expression was developed for f(r) in the form of a curve fit which consisted of four exponentials. The integration of Eq. (2) yielded a value for k of 1.68 rads/mCi-hr at 1 cm.

The computations mentioned above assume that the thermoluminescence of lithium fluoride is proportional to the absorbed dose at that point and is not a function of position from the source. Standard deviations of the thermoluminescent measurements were of the order of 5%.

With a value of k=1.7 rads/mCi-hr, the total dose delivered at 1 cm from an iodine-125 seed, which has been left in place for complete decay may be computed by the following equation:

$$D=1.44 \times 60 \times 24 \times 1.7 = 3,525 \text{ rads/mCi destroyed .} \qquad (3)$$

By comparison for radon we have

$$D=133 \times 7.89 = 1,050 \text{ rads/mCi destroyed .}$$

The ratio of the total dose produced by iodine to that for radon is therefore approximately equal to 3.4. This ratio does not take into account any difference in biological effectiveness due to the marked difference in half-life between the two radionuclides. However, one would conclude from this that the required activity per seed in an interstitial implant of iodine-125 should be less than that required if radon seeds were used.

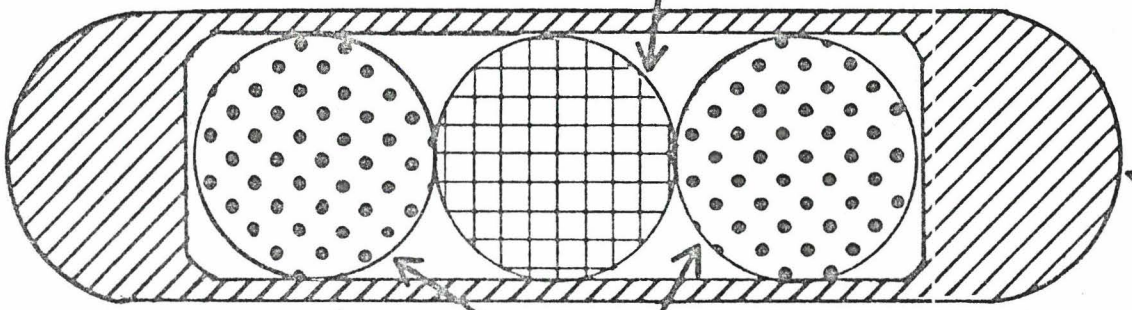
The radiation dose distribution within the implanted regions is computed by means of the Memorial MIDAS computerized dosimetry system.[8-10] These programs utilize the experimental depth dose data in the form of a table which is normalized at a distance of 1 cm from a point seed. The relative dose distribution is converted to rads by the use of the k value of 1.7 rads/mCi-hr at 1 cm from a point source of iodine-125. Complete isodose distributions are computed for all patients who receive an interstitial implant. The seeds are localized according to the Memorial orthogonal-stereo method mentioned previously.

A study was also undertaken to compare isodose distributions obtainable within lesions with iodine-125 seeds to those obtainable with radon seeds. For this purpose, two computations were made in actual patients for the same geometrical distribution of seeds assuming in one case that the seeds consisted of iodine-125 sources and in the other of radon seeds placed in the identical geometrical position. Comparison of the isodoses disclosed that by and large the distribution within the implanted region did not differ greatly between radon and iodine-125 seeds, provided the iodine-125 seeds were spaced somewhat closer within the implanted volume. Outside the implanted volume there was a marked fall-off, however, in the radiation dose when iodine-125 seeds were used (Figure 13, Pg.39 and Figure 14, Pg. 41). This is another strong argument in favor of using iodine-125 in place of high energy gamma-ray emitters in interstitial implants.

FIGURE 5

Construction of iodine-125 encapsulated interstitial seeds. These seeds are now commercially available up to 20 millicurie activity per seed.

I - 125 SEED



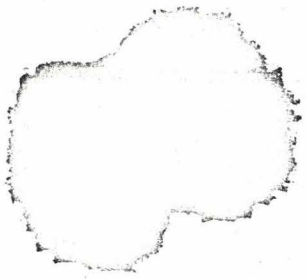
24K Gold Ball
.022" - .024" Diam.

T. I. G. Welded
Both Ends

Dowex 21 - K Spheres
.022" - .024" Diam.

Body of A - 40 Titanium Tubing
.030" Diameter x .002" Wall
Overall Length - 0.177" (4.5 mm) ± 10%

FIGURE 6



Iodine-125 seed 10 min direct exposure activity, 206 μCi.

FIGURE 7

Experimental set-up for the absolute calibration of I-125 seeds. On the right, the carbon extrapolation chamber; on the left, the electrometer. The seed may be raised remotely from the cave into the calibration position.

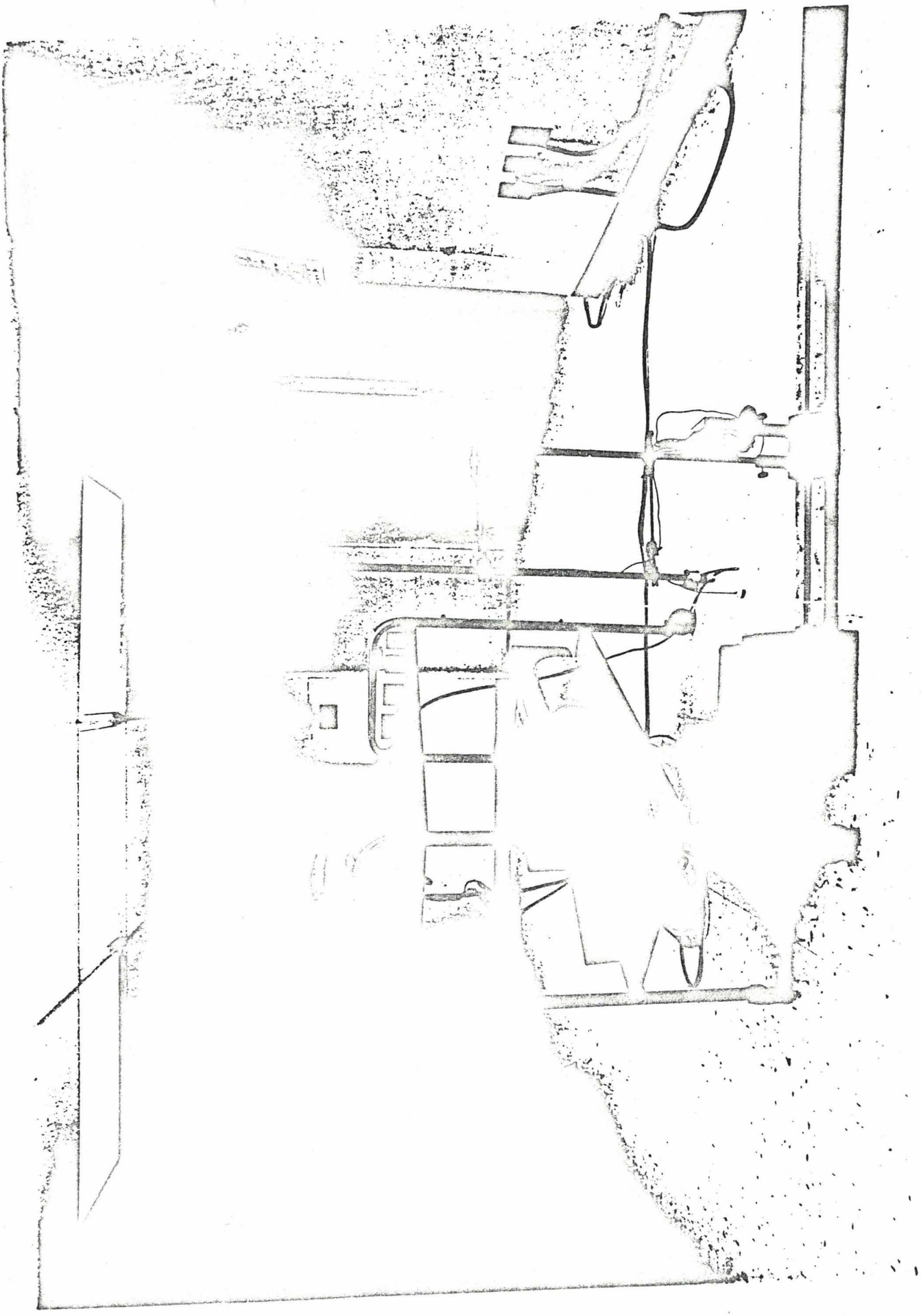


FIGURE 8

Set-up for routine calibration of iodine-125 interstitial therapy sources. The activity of the iodine-125 sources is routinely measured by a Victoreen 440 adapted for digital readout and a specially designed holder which facilitates the reading of a large number of sources commonly encountered. The activity of individual sources is determined by comparison to a laboratory standard source of known activity.

FIGURE 9

Experimental phantoms used for the depth dose measurements of iodine-125 sources. On the right is the mix-D block used and on the left is a sampling of the lithium fluoride teflon dosimeters.

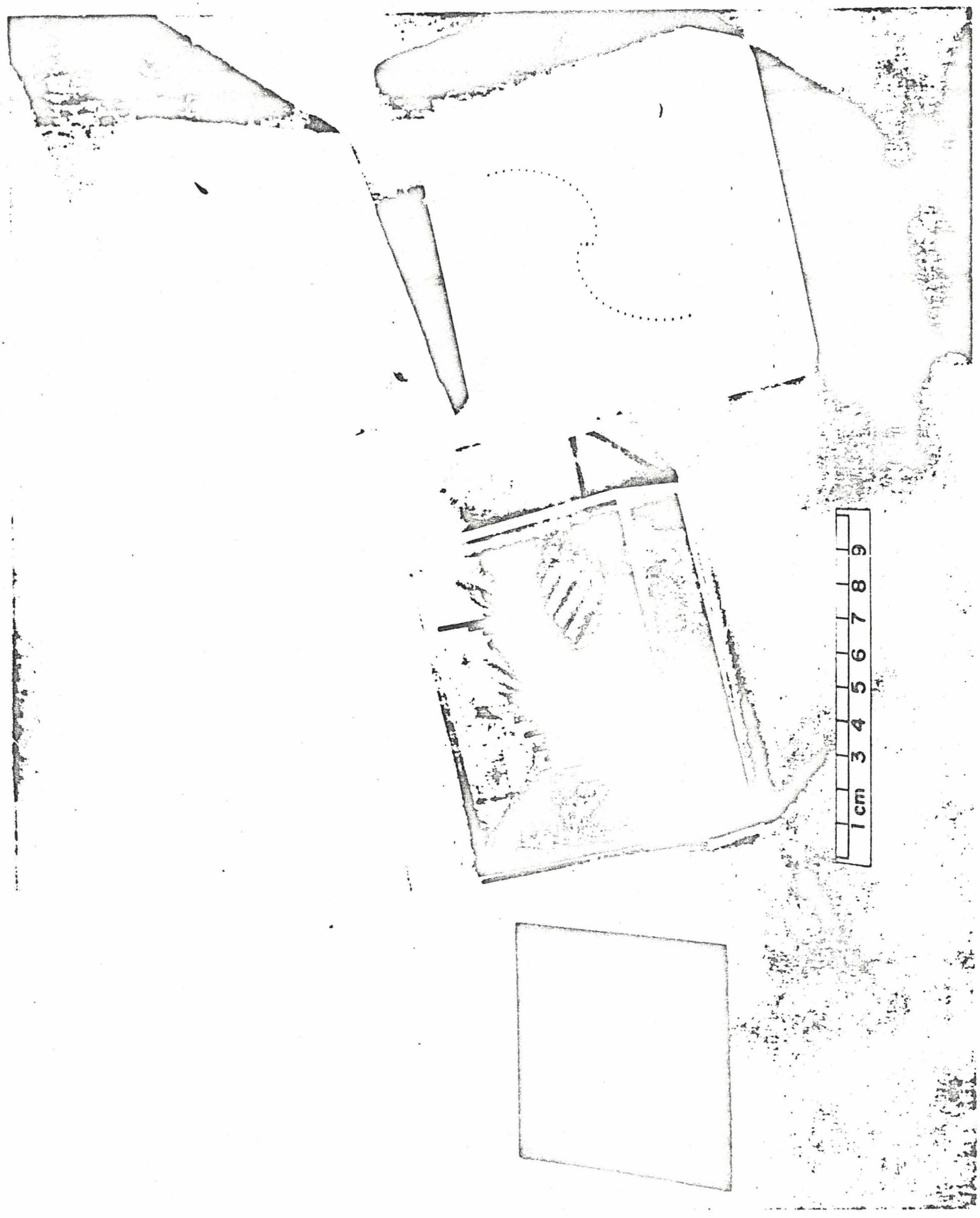

1 cm
3
4
5
6
7
8
9

FIGURE 10

Experimental depth dose curves for a number of radionuclides used in interstitial therapy. The percent depth doses were measured with lithium fluoride teflon rods in a mix-D phantom.

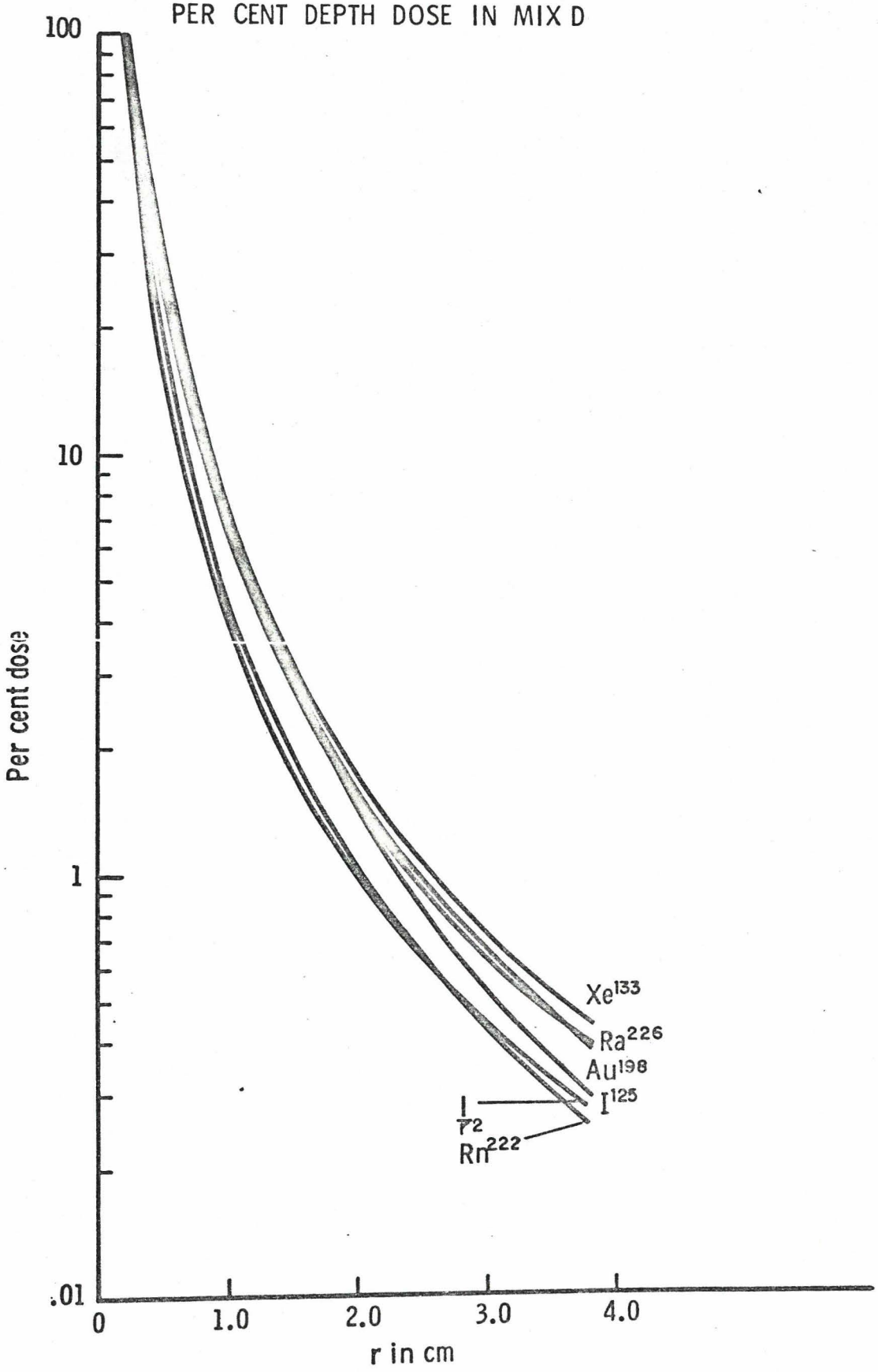

PER CENT DEPTH DOSE IN MIX D
100
10
1
.01
Per cent dose
0
1.0
2.0
3.0
4.0
r in cm
Xe133
Ra226
Au198
I125
I
T2
Rn222

FIGURE 11

Narrow beam transmission in mix-D for a number of radionuclides. Note the soft component present with radon seeds which is rapidly absorbed within the first 2 mm.

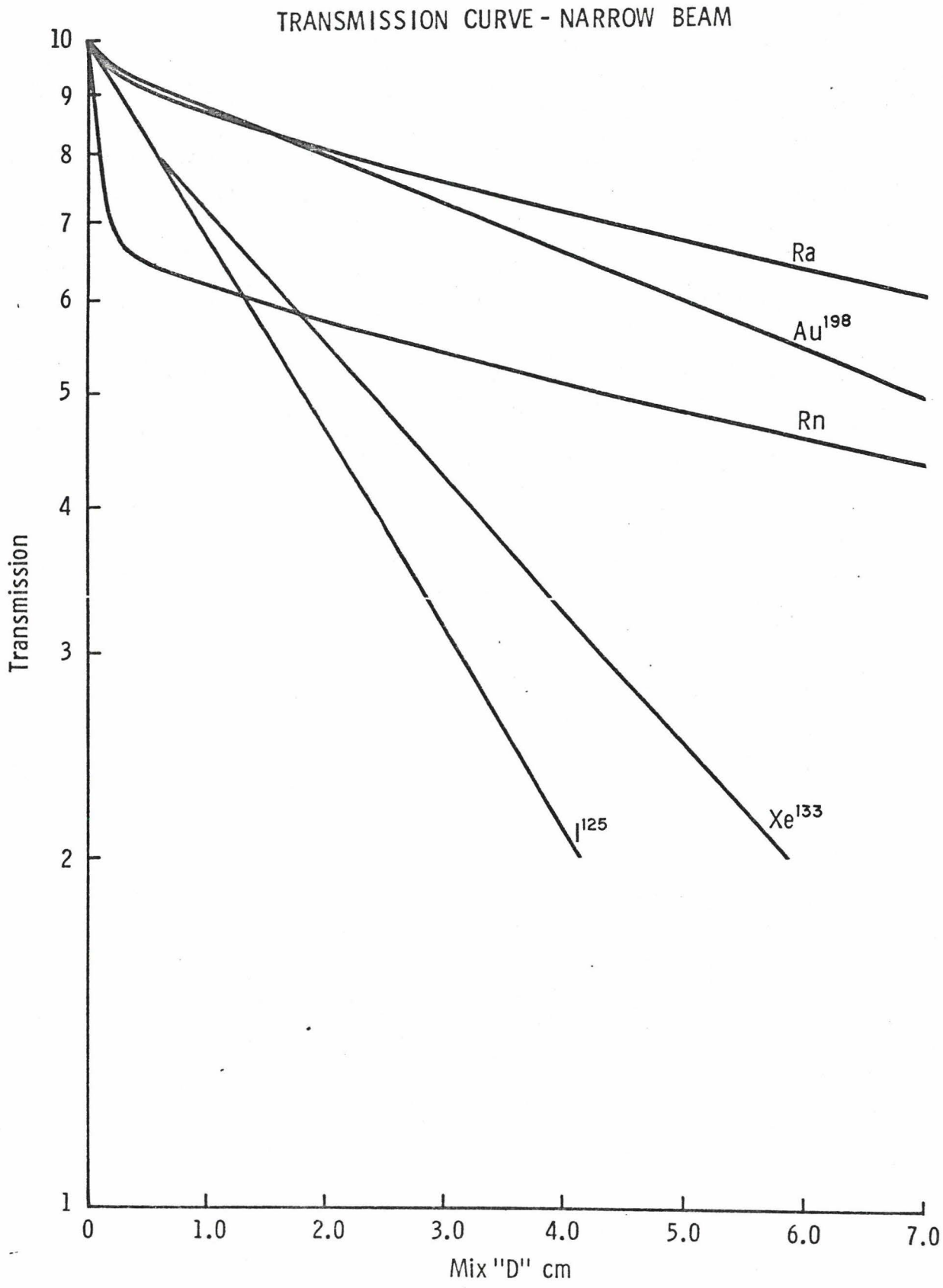

TRANSMISSION CURVE - NARROW BEAM
Transmission
10
9
8
7
6
5
4
3
2
1
0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
Mix "D" cm
Ra
Au198
Rn
I125
Xe133

FIGURE 12

Relative depth dose in water from a point source of iodine-125 normalized at 1 cm. This curve has been fitted with an analytical expression which was used for the computation of the absorbed dose constant k.

REL[illegible]TVE DEPTH DOSE FROM A POINT OF [illegible]25
(Normalized at 1.0 cm)

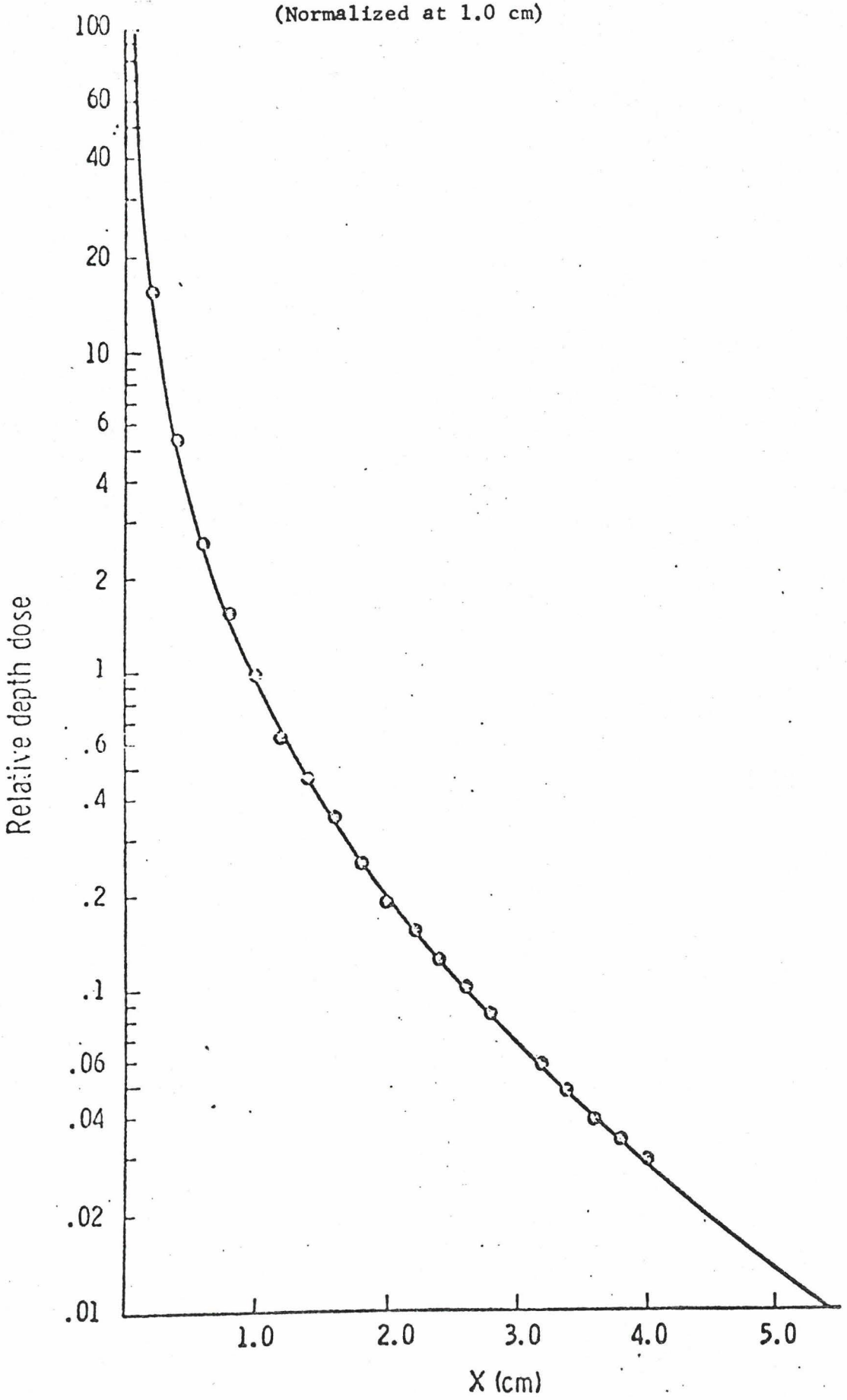
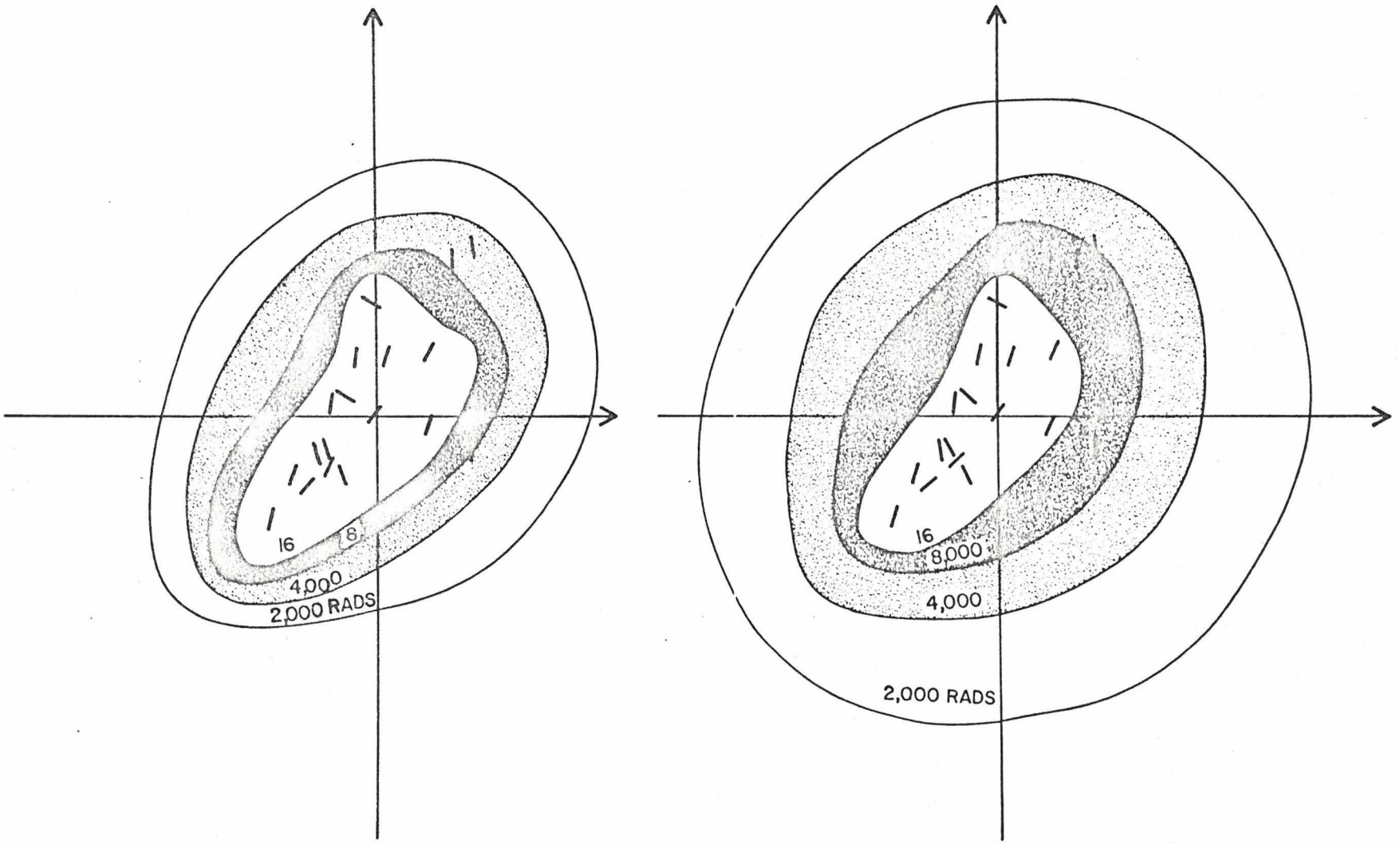


FIGURE 13

Dose distribtuions in tissue from equivalent spatial distribution for iodine-125 and radon-222. Implanted area: right neck AP projection.

DOSE DISTRIBUTION FROM EQUIVALENT SPATIAL DISTRIBUTION
FOR IODINE-125 AND RADON-222



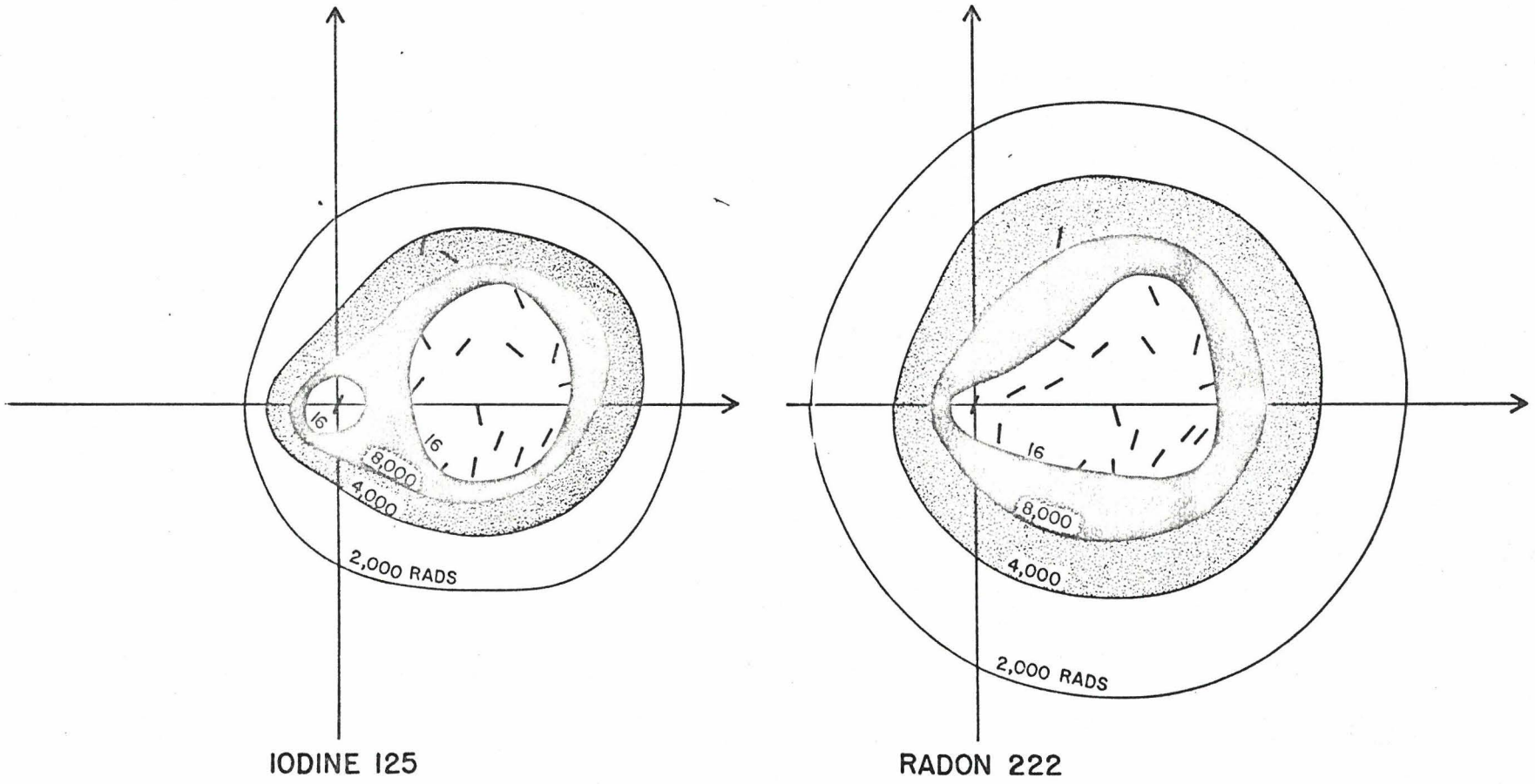
IODINE-125 RADON-222

NORMALIZATION: EQUAL DOSE AT 1 CM. PER mCi DESTROYED
IMPLANTED AREA: RT NECK - AP PROJECTION
20 SEEDS

FIGURE 14

Dose distribution in tissue from equivalent spatial distribution for iodine-125 and radon-222. Implanted area: right neck-Lateral position.

DOSE DISTRIBUTION FROM EQUIVALENT SPATIAL DISTRIBUTION
FOR IODINE-125 AND RADON-222



IODINE 125 RADON 222

NORMALIZATION: EQUAL DOSE AT 1 CM. PER mCi DESTROYED
IMPLANTED AREA: RT NECK - LATERAL PROJECTION
20 SEEDS

B. Description of Memorial Implant Dosimetry Automated System (MIDAS).*

The implant dosimetry programs and associated procedures has been given the name MIDAS: "Memorial Implant Dosimetry Automated System." The MIDAS System described below represents the latest version in a series of automated implant dosimetry systems developed at Memorial Hospital since the initiation of computer-assisted treatment planning in 1954 as a part of the effort to achieve realism in treatment planning. [11] Other implant dosimetry programs have been described in the literature. Shalek and Stovall have published several papers over the last decade [12,13] describing the development and application of implant dosimetry computations at the M.D. Anderson Hospital. They have also recently published a review of conventional and computerized implant dosimetry together with an extensive bibliography of other work. [14]

Some of the steps already described in the development of the MIDAS series include the development of a tab card system in 1957 by Nelson and Meurk [6] for the dosimetry of cubic lattice seed implants; the systemization of the planning and dosimetry of seed implants described in 1963 and [3,8] 1968; a batch processing system for the solution of clinical implants reported [9] in 1966; and the dosimetry of iodine-125 seeds. [1,15] Clinical experience with it has been reported [16] but an adequate description of the MIDAS programs has never been published and these are described in this report.

Although MIDAS was primarily developed to support the large clinical work load at Memorial Hospital, since 1967 it has been an integral component of the Memorial Dose Distribution Computation Service (MDDCS). The MDDCS system, which has been reported elsewhere [17-21] makes available to other hospitals in the United States automatic computation of treatment plans for either internally or externally applied radiation. Complexity is not a problem since the programs accommodate any known parameters including inhomogeneous structure of the irradiated region in the patient. The use of readily available teletype or facsimile units together with conventional telephone lines makes the service convenient as well as economical. As of the date of this report there are forty-seven hospitals, throughout the United States, participating in the MDDCS system.

*The material presented in this section is part of a paper in press in "Computers in Medicine and Biology": Memorial Implant Dosimetry Automated System, by G. Randall, S. Balter, J. G. Holt and John S. Laughlin

The MIDAS programs and others are kept on the user library of a commercial timesharing system, utilizing an IBM 360/67 central processer. Due to the modular construction of MIDAS it has been possible to upgrade the system continually one separate subroutine at a time, and control the release of new separate subroutines by coding in the main program. It is expected, due to the large and varied work load, that MIDAS will continue to be an evolutionary system.

Program Objectives

MIDAS' primary purpose is to provide dose distribution information for any encapsulated radionuclides implanted in an infinite homogeneous volume.

The program is designed for clinical use, therefore emphasis has been placed on the following aspects:

1. Ease of Use - The use of the program does not require programming experience. Supplied input data are in the form of words where possible, and the numerical data are in free format. Where applicable, an endeavor was made to have the program compute needed data, eliminating unnecessary input.

2. Safeguards - The program contains internal routines to check the accuracy of the input information. If there is a detectable error in the input data, specific error and diagnostic messages are printed out by the program. These aid the user in pinpointing the error for correction. For instance, the program calculates the length of each radium tube from the end coordinates, and compares this length to the length specified by the user in the input information. If these two lengths do not agree within 10%, it stops computation and prints out a diagnostic message. This message indicates the above mentioned error has occurred and specifies in which tube it occurred. The user is then able to correct either the end coordinates or the length specified.

3. Flexibility - Since the dose information needed varies from one treatment to the next, it is possible to control the range and scope of dose computations. The calculations may range from the dose at a single point, to numerous planar and volume distributions.

Planar distributions are printed out with the magnification specified by the user. This allows direct overlaying on the radiograph, or if a very large magnification is specified, micro-analysis of a particular area is obtained.

4. Readability of Output - Although the program computes three-dimensional dose distributions, the output dose information is planar and may be computed in any desired orientation. The following features have been incorporated for clarity and user convenience:

   a. All variable parameters involved with the calculation of each implant are printed as part of the output information. This accomplishes two objectives: the user can verify input information; and the user can verify the orientation of the output.
   b. Each section of output is consecutively numbered and contains the identification line supplied by the user. This identification line will usually contain the patient's name, patient number, date of implant, etc.

   c. Each section of output containing dose information, is preceded by a section describing the area or volume being investigated.

   d. Matrix output allows the user to obtain the dose at specific points of interest for any planar orientation in the patient. This information is best utilized by tabulating the points of interest vs. dose on a final report for the patient's records.

Figure 15 represents a matrix output in the Anterior-Posterior (AP) plane. In this example, the information desired is the dose at points A and B for a cervical radium application which was accomplished by computation of only one line of the matrix. The first item is the page number followed by the type of dosimetry used, the identification line as supplied by the user, the Z coordinate, i.e., the level of the plane of computation, and the magnification of the printout.

The Map and Volume dose distributions have been designed to be used directly in a final report form. The map in Figure 16 is an AP plane of the same cervix application. The first item is the page number followed

by the identification line. The program prints out the type of dosimetry used, the Z coordinate of the plane, a space for the user to supply the type of projection (e.g., A.P.), and the magnification of the map. A scale indicating the dose range of the map characters is included, and the + indicates the origin of the coordinate system and relates the map to the radiograph.

Figures 17 and 18 show the AP and lateral maps as they would appear in a final report form. The applicator and sources are traced from the radiograph, as well as anatomical structures.

The volume dose distribution is computed and utilized in the final report without any additions by the user. Figure 19 shows the Minimum Dose vs. Volume tabulation obtained for the same cervix application.

Conventions and Assumptions

1. Sources are considered to be surrounded by an infinite volume of tissue.
2. Sources are considered to be isotropic point sources or radium line sources.
   Line sources other than radium are entered as a number of point sources.
3. Dosimetry for radium line sources or inverse square law point source calculations neglects absorption and scatter due to tissue. The tissue absorption for I-125 is inherent in the stated depth dose table.
4. Inverse square law dosimetry uses an absorbed dose of 7.95 rad/mg-hr. at 1.0 cm based on a specific gamma-ray emission constant of 8.25 rad/mg-hr. and an f factor of 9.965 rad/R for water.[22] The exposure of all high energy gamma ray emitting radionuclide sources must be expressed in mg-hrs. Ra equivalent.
5. Radium line source dosimetry uses dose tables (23) for the following line sources:

	ACTIVITY	TOTAL LENGTH	ACTIVE LENGTH	DIAMETER (mm)	PLATINUM FILTER (mm)
A	Variable	Variable	Variable	1.65	0.5
B	Variable	Variable	Variable	4.05	1.0

The dose tables correct for oblique filtration due to the platinum wall and radium salt.

Coordinate Definition

1. The X, Y, Z, coordinate system is fixed with respect to the paper print out. The X-Y axes are always oriented parallel to the edges of the paper and the Z axis is directed toward the viewer.

Rotation or Translation

Any plane of arbitrary orientation may be investigated for dose information. Orientation of the plane is accomplished by defining the translation increments and angles of rotation about the X, Y and Z axis. The sources are then transformed by the program and the new source coordinates are printed out. Figure 20 demonstrates the MIDAS rotation convention.

OUTPUT

The user either specifies the range of computation to be considered for dose information or allows the program to automatically make the selection.

For AUTOMAP or AUTOMAT the program searches for the sources with the minimum or maximum X and Y coordinates, then sets the minimum and maximum coordinates of the output area 5 cm beyond these. The level chosen for the Z coordinate is the centroid of the implant, weighed with the activity of the sources. For implants of homogeneous distribution along the Z axis, the level chosen is the maximum dose plane.

For AUTOVOL the minimum and maximum X, Y and Z coordinates describing the volume are chosen to provide a 5 cm margin about all the sources.

Program Organization and Explanation

The program is divided into a number of sub-sections or sub-routines. Figure 21 depicts the logical flow of the program. The type of dosimetry to be used is first specified. The program offers the option of orthogonal or stereo shift radiographic localization. The remaining sub-routines may be called upon as required.

The following is a list of available sub-sections or sub-routines in the program with an explanation. The user may access these routines by the underlined command.

1. Type of Dosimetry - The following three types of dosimetry are presently available.

IODINE - I-125 tabulated depth dose.[1, 15]
INVSSQ - Inverse square law dosimetry for high energy gamma ray emitting radionuclides.
RADIUM - Radium line sources using dose tables.[23]

The program also offers the option of storing other depth dose tables for special dosage calculations such as Cf-252 sources.

2. Type of Demagnification Routine - Two routines presently available.

ORTHOG - Orthogonal Film Demagnification.
SSHIFT - Stereo Shift Demagnification

3. Rotation or Translation Routine

ROTRANS - Allows user to perform any desired coordinate transformation to obtain dose information in any plane or volume.

4. Output Forms - The following six sub-routines allow the user to specify three types of output: matrix, map or volume distribution.

a. DEFMAT - Defined Matrix

The user defines the area of the plane to be considered, the desired magnification and dose scale factor. The output is in matrix form. Several parallel planes can be computed with one call to this sub-routine.

b. DEFMAP - Defined Map

The user defines the area of the plane to be considered, the desired magnification and dose scale factor. The output is in map form, i.e., simulated isodose curves using typewritten characters. The origin appears as a + sign on the map. Several parallel planes can be computed with one call.

c. DEFVOL - Defined Volume

The user defines the volume to be considered, the volume increments, and dose scale factor. The output is in the form of a Minimum Dose vs. Volume Table.

The use of AUTOMAT and AUTOMAP requires that the implant be homogeneous along the Z axis. The level of the plane chosen by the program is the maximum dose plane.

d. AUTOMAT - Automatic Matrix

The user specifies only the desired magnification of the output matrix. The program determines the area to be considered, the size of the matrix and the dose scale factor. The output is in matrix form as in the DEFMAT.

e. AUTOMAP - Automatic Map

The user specifies only the desired magnification of the output map. The other parameters are set internally as in AUTOMAT. The output is in map form as in DEFMAP.

f. AUTOVOL - Automatic Volume

The size of the volume considered is symmetrically located about the implant by the program. The volume increment and the dose scale factor are also selected by the program. The output is in the form of a Minimum Dose vs. Volume Table as in DEFVOL.

Conclusion

The development of the computer system for implant dosimetry at Memorial Hospital, known as MIDAS, has been briefly reviewed. The current status of the program has been described together with features of this system and the logic of the programs.

Figure 15

MATRIX OUTPUT

3 - PAGE NUMBER
RADIUM TABLE CALCULATION - TYPE OF DOSIMETRY

CERVIX APPLICATION 3380MGHRS OF RADIUM - I.D. LINE
Z= 0.39
MAGNIFICATION =1.27

PT.B(RT)		PT.A(RT)			PT.A(LT)			PT.B(LT)	
9.6	12.9	18.4	29.9	63.1	-0.1	60.3	28.5	18.0	12.3	8.9

DOSE AT POINT A (LEFT)= (28.5) x (SCALE FACTOR) = (28.5) x (100.0) =
2850.0 RADS, ETC

CERVIX APPLICATION 3380MGHRS OF RADIUM

ROTATION DATA

4

0.0 0.0 0.0 6.500 0.0 0.0

N	X	Y	Z	S
1	-0.150	6.001	1.291	1056.340
	-0.083	4.531	0.675	
2	-0.083	4.531	0.675	422.540
	-0.042	3.051	0.190	
3	-0.042	3.051	0.190	422.540
	0.0	1.487	0.023	
4	0.0	1.487	0.023	422.540
	0.0	0.009	0.076	
5	2.417	-0.256	-0.032	528.160
	2.125	-1.774	-0.090	
6	-2.917	-0.296	-0.028	528.160
	-2.625	-1.684	-0.000	

DEFINITION OF MAP AREA

5

CERVIX APPLICATION 3380MGHRS OF RADIUM
AUTOMAP

XMIN =	-7.41	DX=	0.21	IX=	65
YMIN =	-6.35	DY=	0.35	IY=	48
ZMIN =	0.63	DZ=	1.00	IZ=	0

Figure 16

6 - PAGE NUMBER
CERVIX APPLICATION 3380MGHRS ØF RADIUM - I.D. LINE
- TYPE OF DOSIMETRY

RADIUM TABLE CALCULATIØN

Z = 0.63 - LEVEL OF PLANE

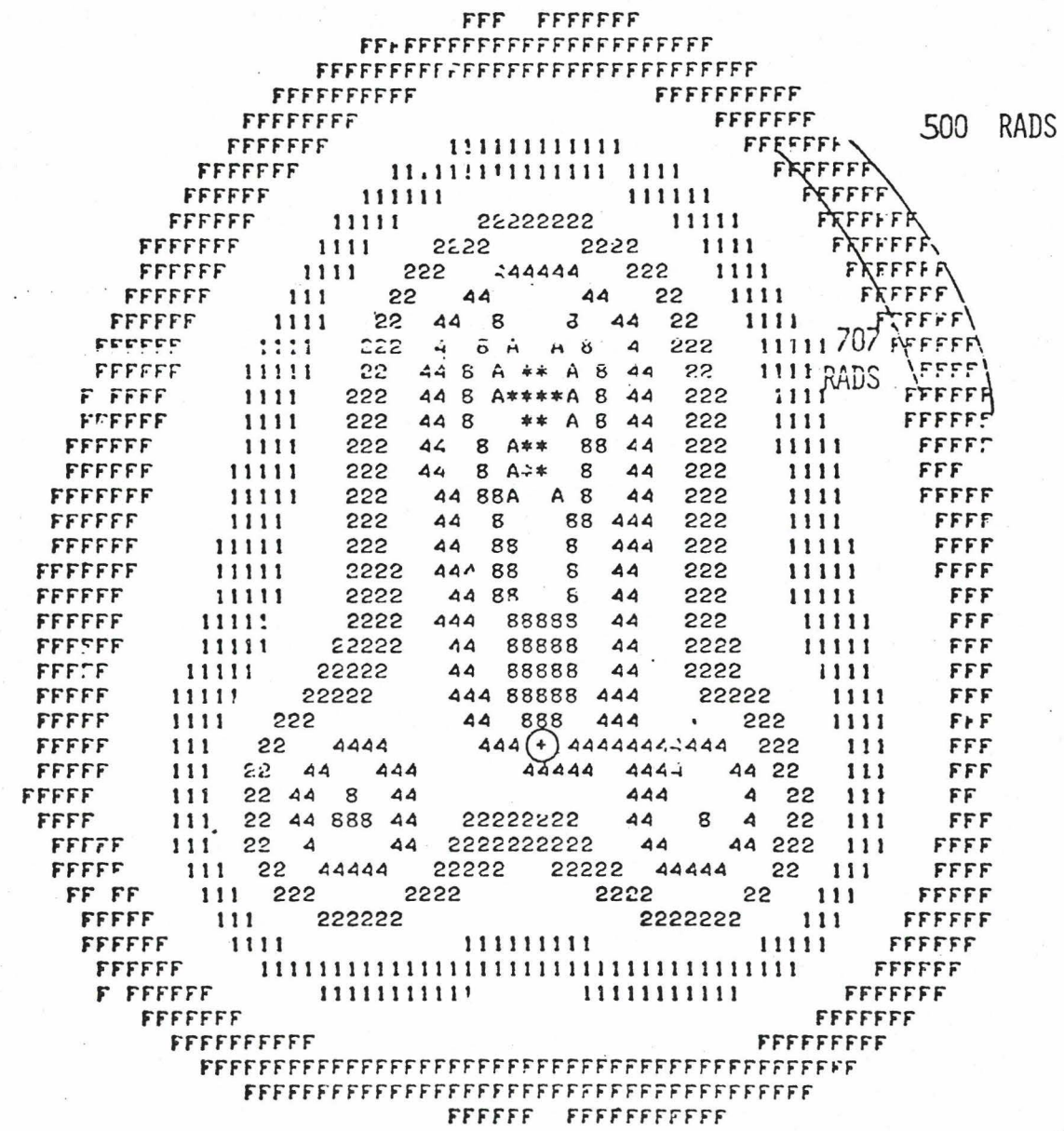
THIS SPACE IS FOR USER TO SUPPLY TYPE OF ORIENTATION (E.G., AP)

PRØJECTIØN - -

MAGNIFICATIØN = 1.20

SCALE		
SYMBØL	RADS FRØM	TØ
F	500	707
1	1000	1414
2	2000	2828
4	4000	5656
8	8000	11313
A	16000	22627
*	32000	MAXIMUM

TRACE ØUTER DIGIT FØR ISØDØSE CURVE



CIRCLED + SIGN IS THE ORIGIN OF THE COORDINATE SYSTEM.

Figure 17

6
CERVIX APPLICATIØN 3380MGHRS ØF RADIUM

RADIUM TABLE CALCULATIØN

Z = 0.63

PRØJECTIØN - - ANTERIOR-POSTERIOR

MAGNIFICATIØN = 1.20

SCALE		
SYMBØL	RADS FRØM	RADS TØ
F	500	707
1	1000	1414
2	2000	2828
4	4000	5656
8	8000	11313
A	16000	22627
*	32000	MAXIMUM

TRACE ØUTER DIGIT FØR ISØDØSE CURVE

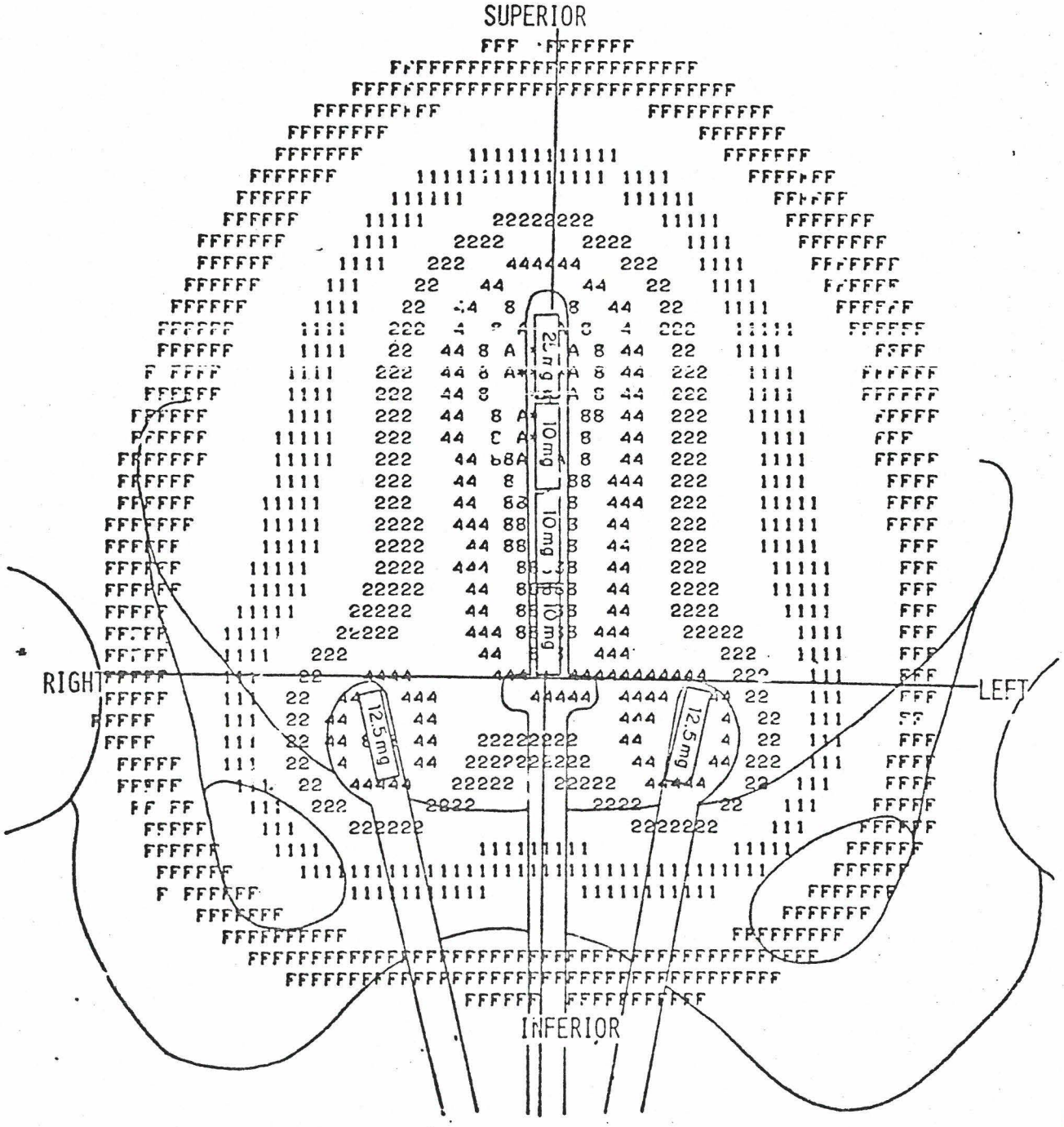


Figure 18

10
CERVIX APPLICATION 3380MGHRS OF RADIUM

RADIUM TABLE CALCULATION

Z = 0.0

PROJECTION - - RIGHT LATERAL

MAGNIFICATION = 1.31

SCALE		
SYMBOL	RADS FROM	RADS TO
F	500	707
1	1000	1414
2	2000	2828
4	4000	5656
8	8000	11313
A	16000	22627
*	32000	MAXIMUM

TRACE OUTER DIGIT FOR ISODOSE CURVE

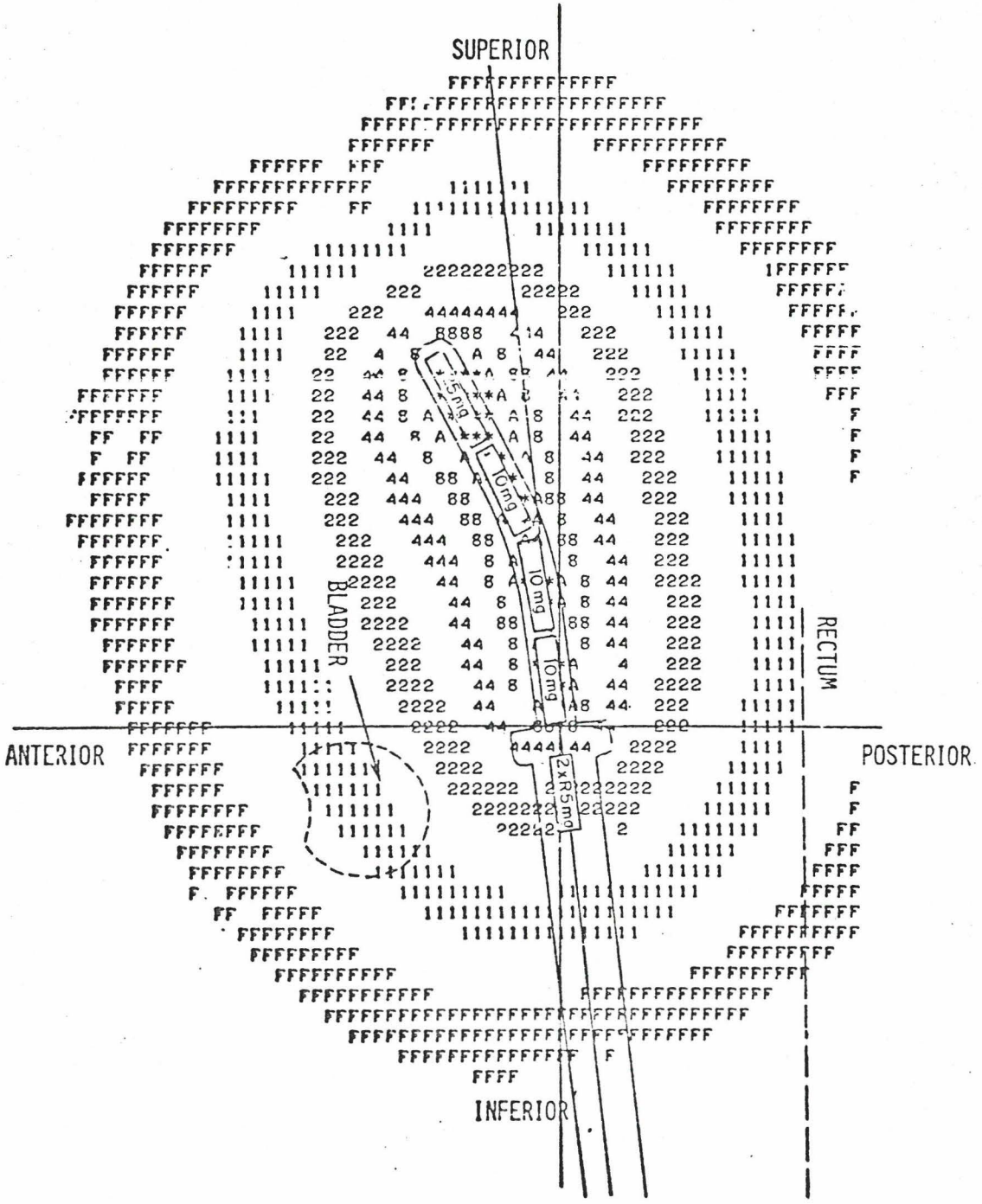


Figure 19

DEFINITION OF VOLUME

```
 11
CERVIX APPLICATIØN   3380MGHRS ØF RADIUM
AUTØVØL
XMIN =      -6.00     DX=       1.00     IX=     10
YMIN =      -6.00     DY=       1.00     IY=     16
ZMIN =      -7.00     DZ=       1.00     IZ=     13
SCALE FACTØR =    1000.00
```

DOSE VS. VOLUME

```
 12
CERVIX APPLICATIØN   3380MGHRS ØF RADIUM

          MINIMUM TØTAL DØSE WITHIN SPECIFIED VØLUME
MINIMUM
TØTAL DØSE
 RECEIVED                1     2     4     6     8    16    32
(RADS X 1000.00)

- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
VØLUME UNITS          1620   340    79    35    17     7     2
(1 VØL UNIT= 1.00 CC)
```

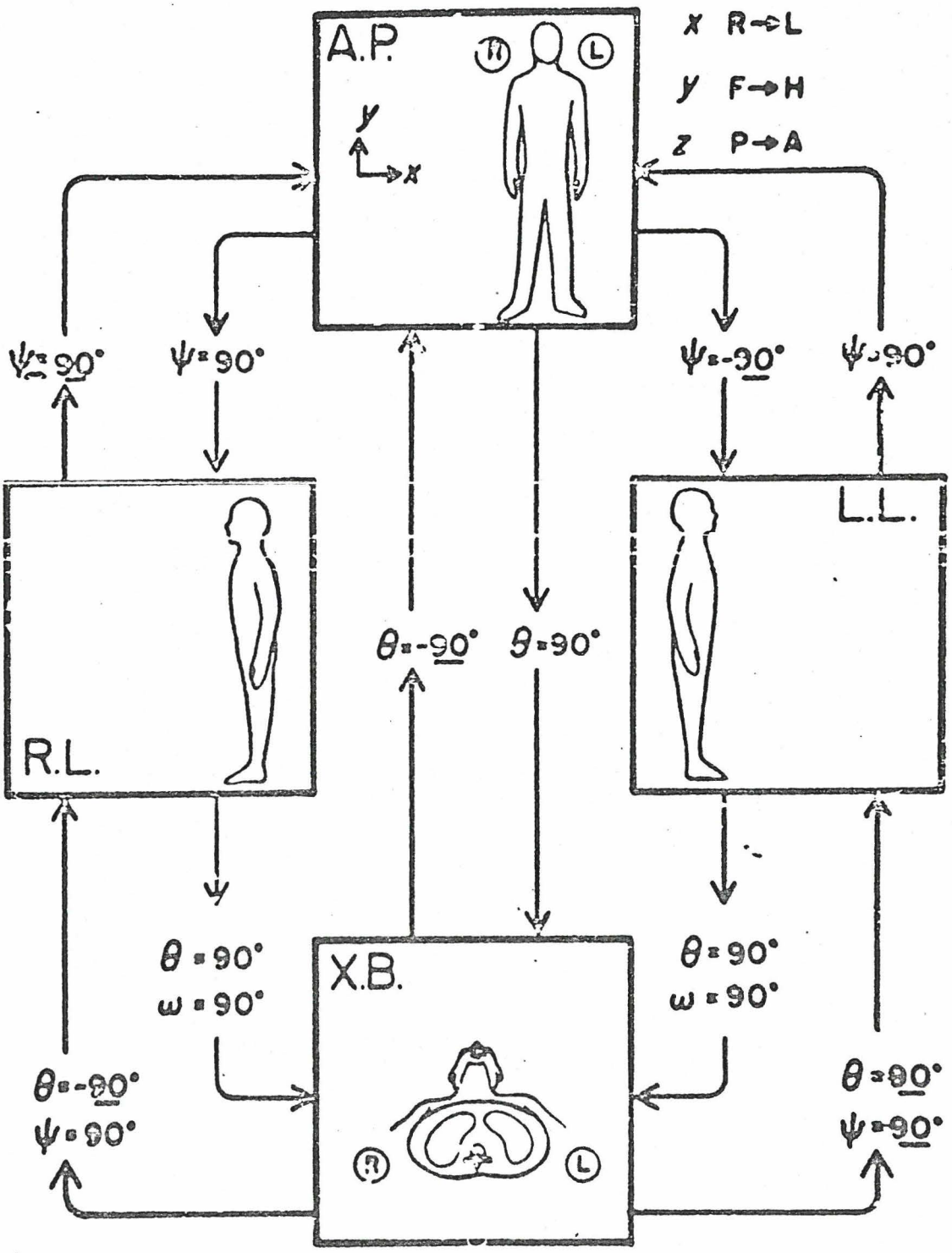
READ AS 1620 CM^3 RECEIVED AT LEAST 1000 RADS

340 CM^3 RECEIVED AT LEAST 2000 RADS

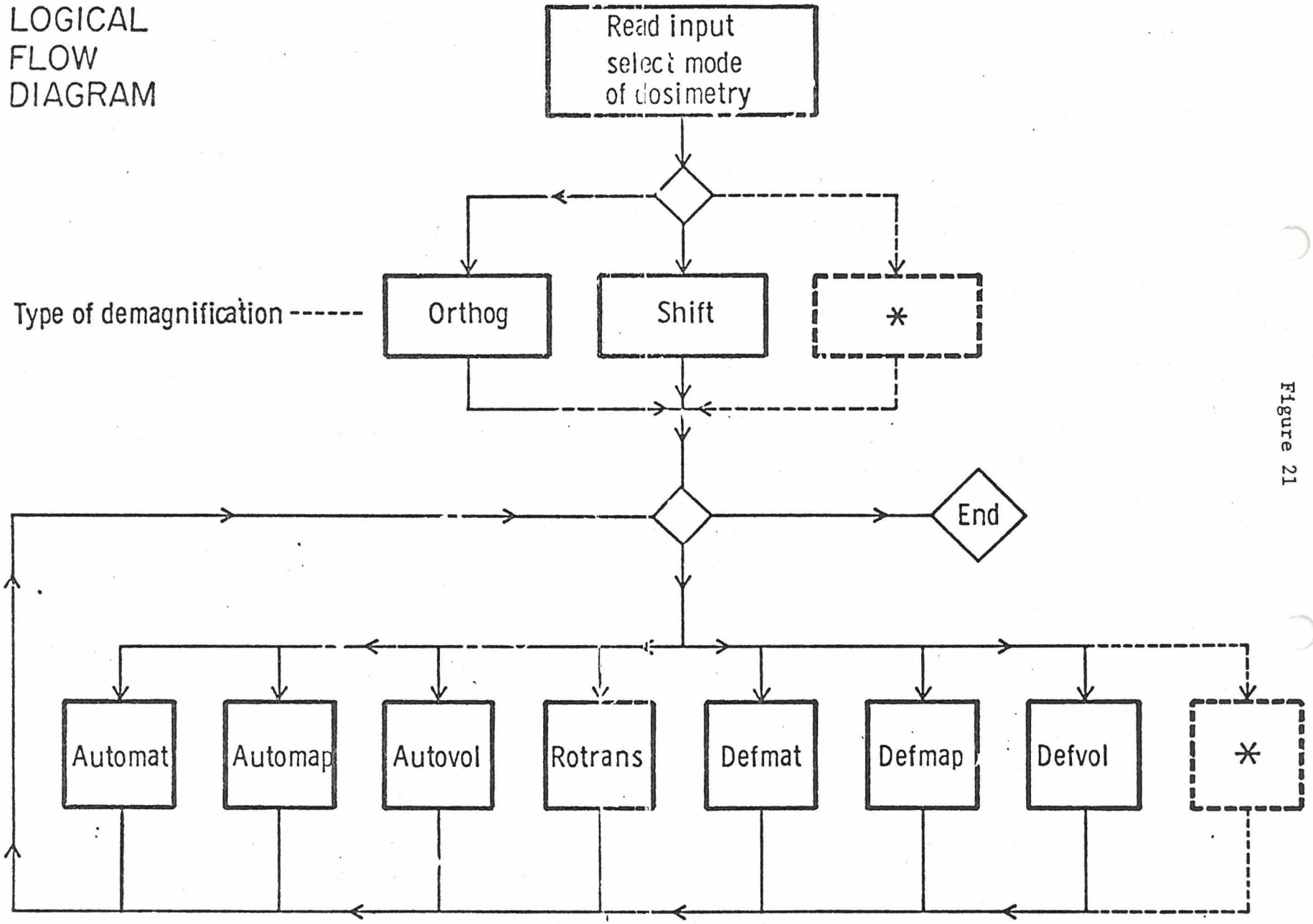
```
CALCULATIØN CØMPLETED
   06/ 30/1971      14: 35        108.520    211     RUN.
IHC0021 STØP     88
```

Figure 20

MIDAS CONVENTION



LOGICAL
FLOW
DIAGRAM



* Indicates possibility of additional subroutines

Figure 21

PART IV

CLINICAL EXPERIENCE USING IODINE-125 ENCAPSULATED SOURCES AND THE REMOTE AFTERLOADER

A. Clinical Experience with Iodine-125 Encapsulated Sources.

The first and second objectives of the biomedical program undertaken for the investigation of the iodine-125 seeds with the support of the Bureau of Radiological Health of the Public Health Service (EC 00113) are discussed in the preceding Parts II and III. The third objective, that of clinical trials, will be the main subject of this report. Figure 22 (Pg.62) is a photograph of the complete kit for permanent interstitial implantation developed specifically for iodine seeds. It includes besides the "gun" a set of 15 hollow, 17-gauge stainless steel needles, each 15 cm long, which are used during the first step of the afterloading technique of implantation[24, 25]; a stainless steel ruler subdivided into centimeters; and five magazines, each containing 10 low energy iodine-125 seeds. These components are mounted on a removable stainless steel base, which can be autoclaved and kept sterile in the operating room prior to the implantation.

One of the key problems in using the low energy iodine-125 seeds was the determination of the proper dose. In 1968, after reviewing the implants with iodine-125 done up to that time, we arrived at an estimate of this dose for permanent implant volumes and presented this in the form of a curve.[26, 27] Figure 23 (Pg. 63) shows the recommended doses for iodine-125 implants (dotted line) plotted against the implanted volume.

In this curve, a minimum dose of 16,000 rads given over a period of approximately one year is at present the minimum recommended dose for medium-sized implants only. For smaller volumes, much higher doses are considered safe. On the other hand, for large volumes, the minimum recommended dose falls below 16,000 rads. There are other factors , of course, that influence this dose, such as previous radiation, radiosensitivity of the tumor, oxygenation, etc., for which certain allowances should be made.

Additional radiation therapy, if possible, is recommended in all patients with a tumor size of less than 4 cm who received less than 8000 rads during the first half-life of the isotope, or less than 16,000 rads to total decay. Our practice has been to supplement as much external radiation therapy as is required to bring the combined dose from the implant and external radiation to 8000 rads during the first half-life. We usually add this supplementary radiation 3 to 4 weeks after each implantation.

The calculation of the required activity for each implant is determined by the "average dimension" system, which we have been using at Memorial Hospital for the past 10 years in determining the activity for implants with high energy gamma emitters.[28, 29] Figure 24 (Pg. 64) illustrates the principle of this system. The three dimensions of the implanted volume must first be determined. This should be done after the insertion of the needles. Two dimensions can be measured directly with a ruler. The third dimension is also easily obtained since all needles are 15 cm long. Let us assume that the three dimensions are 5, 4, and 3 cm. The average dimension is the $\frac{5+4+3=12}{3} = 4$ cm. This is simply multiplied by an empirical factor of 5 for iodine-125 seeds.* This gives 20, which is the recommended activity of iodine-125 in millicuries for this implant and results in the dose obtained according to the previously mentioned curve. If the implant is a single plane, the third dimension is taken as zero. This method of calculation applies to a cube or rectangular-shaped volume. If the volume is cylindrical, 10% has to be deducted; and if the volume is spherical, 20% is deducted. The number of seeds is found by dividing the total millicuries by the average activity of the seeds $\frac{20}{0.5} = 40$ seeds. A detailed mathematical analysis of this study was published by Henschke and Cevc in 1968[28].

The major anatomic sites in which permanent implants with iodine-125 seeds were used are listed in Table 6 (Pg. 74). From May 1, 1968 through April 30, 1971, a total of 234 implants were performed in 222 patients.

Seventy per cent of the patients who had iodine-125 implants had advanced tumors which had been previously treated by surgical excision or external radiation, or a combination of the two. This group includes practically all of the patients who had intraoral and superficial implants and about one-half of the patients who had intrathoracic and intraabdominal implants. No long survivals were anticipated in this group. Tumor regression, therefore, was the only useful parameter to judge the efficacy of the treatment. Regression was not dependent on the location, size or histology of the tumor. It was dependent, however, on the total dose and proper implantation of the tumor.

Figure 25 (Pg. 65) shows an example of a permanent implant in a patient with metastatic neck nodes, previously treated with 4000 rads, using the cobalt teletherapy unit. Two residual nodes in the right neck, the largest one measuring 4 x 3.5 x 1.5 cm, were implanted with iodine-125 seeds (11.7 mCi and 5 mCi, respectively). The minimum tumor dose was 16,000 rads. The graph on the left shows the pattern of regression for both nodes. Complete regression was achieved within one month after implantation. The photograph on the right shows the patient 5 months after implantation without evidence of recurrence in the neck.

Figure 26 (Pg. 66) shows an anterior posterior and a lateral planar section of the dose distribution obtained in a patient with carcinoma of the right lateral tongue implanted with iodine-125 seeds. This patient was an 85 year

---

* This was just an empirical factor and was used because it gave us, for a certain volume, half of the activity which we had utilized with the high energy isotopes, such as radon-222.

old cachetic man with a $T_3N_0M_0$ lesion. An implant was elected as the treatment of choice because of his age and poor general condition. Twenty-three iodine-125 seeds, each 0.48 mCi were implanted in a rectangular-shaped volume. The minimum tumor dose was calculated to be delivered over a period of approximately one year. The volume receiving this dose was calculated as 17 cc. The HDV (volume receiving 50% of the tumor dose - Half-Dose Volume) was 47cc.

Figure 28 (Pg. 68) shows the percent tumor regression vs. the accumulated tumor dose. Fifty percent regression was obtained at the level of 4500 rads, while complete regression was achieved at the level of 8000 rads. This patient expired 8 months after implantation. An autopsy recorded the cause of death as severe bilateral organizing bronchopneumonia complicated by acute splenitis. No evidence of carcinoma was seen in the tongue.

A more detailed analysis of these implants including response and complications is underway and will be reported when all of these data are obtained.

Permanent interstitial implants with iodine-125 seeds proved to be of particular value in cancer of the lung and prostate. These will be discussed in greater detail.

Table 7 (Pg.75) gives the number of interstitial implants at thoracotomy from 1955 through April 1970 in 305 patients with cancer of the lung proven unresectable at thoracotomy. During this period various radionuclides (including iodine-125) were implanted using afterloading techniques.[30] Since September 1969, however, only iodine-125 seeds were used for this type of implantation.

shows the percent survival by year according to the Berkson-Gage method for the patients who were implanted. For purposes of comparison, the patients are divided into three groups. In one group radionuclides with high energy and short half-life were used (radon-222 and gold-198). A total of 211 patients had implants in this category from 1955 through 1968. Gold seeds were used only during the years 1962 and 1963. The second group includes 68 patients in whom radionuclides with high energy and long half-life were used (irridium-192). These implants were carried out from 1956 through 1961. Finally, the third group includes 26 patients implanted with radionuclides of low energy and long half-life (iodine-125) from 1966 through April 1970.

The corresponding 5-year survival is 5%, 2.8% and 9%. There is no statistically significant difference in these figures. Iodine-125 emerges, therefore as a radionuclide with definite advantages for permanent implants because of its

low energy, resulting in negligible exposure to the personnel involved and lack of any need for precautions and restrictions to the patient following implantation. If there is any selective effect on the cancer cells due to the low dose rate of the iodine-125, it is not evident yet. Any such effect, if present, will require larger samples of patients than the ones available at present to be detected.

Figure 29 (Pg. 69) shows an x-ray of the chest of a 61 year-old man. A mass was found in the left upper lobe. Sputum cytology was positive for carcinoma. The patient received 4000 rads external radiation therapy; no appreciable response was evident. Exploratory thoracotomy was carried out in November 1968, at which time a 4 x 5 x 3 cm mass was found in the left upper lobe. Because of the patient's age and location of the tumor, a surgical resection was not feasible. Instead, an interstitial implant was performed using iodine-125 seeds; 45 seeds were inserted into the tumor for a total activity of 16 mCi. The computerized dose distribution is superimposed on this figure. The minimum tumor dose was calculated to be 16,000 rads. The radiation dose decreased rapidly and at a distance of 2 cm became rather insignificant.

Figure 30 (Pg. 69) shows an x-ray of the same patient two months later, at which time 50% of the calculated dose had been delivered. The patient was asymptomatic at this time. The tumor mass had regressed to 50% of the pre-implantation size.

Figure 31 (Pg. 70) is an x-ray of the same patient 18 months later. The tumor appears to be under control. This patient is alive and asymptomatic, almost three years after implantation.

The second group of patients in whom interstitial implantation appeared to be of value using the low energy radionuclides is cancer of the prostate. Interstitial implantation of encapsulated sources has distinct advantages when compared with external radiation therapy in the treatment of this malig-nancy, as illustrated in the following Figures 32 and 33 (Pg.71). The two cross sections of the pelvis at the level of the prostate show the same primary prostatic cancer. Figure 32 (Pg.71) is an example of an optimum setup with external radiation therapy. Using the linear accelerator and 360° rotation, it is possible to deliver 100% of the planned dose to the tumor-bearing area in about 6 weeks. The adjacent rectum and bladder will receive a dose in the range of 65% to 70% of the maximum within this period of 6 weeks. Figure 33 (Pg.71) is an example of the dose distribution for an interstitial implant with 125 seeds in the same situation. It should be kept in mind that the 100% of the planned dose to the tumor bearing area will be delivered in about one year. Comparison of these isodose curves shows that

- The localization is more precise and the dose distribution can be adapted to an irregular tumor shape.

- The dose to the bladder and rectum is in the range of 25-30% of the tumor dose.

Finally, interstitial irradiation requires a single procedure, while external radiation therapy extends over a period of 6 to 7 weeks.

Figure 34 (Pg.72) illustrates the retropubic approach utilized presently at Memorial Hospital for interstitial implantation of the prostate. This approach is preferred because it permits the complete mobilization of the prostate allowing more accurate determination of the tumor extent, especially laterally. The nodes can be inspected, and an extraperitoneal node dissection can be performed. More adequate manipulation is afforded by having a catheter in the bladder outlining the urethra and by inserting a finger of the operator's hand into the rectum. Figure 35 (Pg. 73)shows an example of such an implant. The radioactive seeds (light colored dots) indicate the implanted volume and are utilized to determine the target area. The isodose curve encircling these seeds on the left radiograph is the minimum tumor dose. In this example, it is 16,000 rads (darker line) as recommended by the average dimension system, given to 22 cc of tissue. The dose falls off rapidly becoming approximately 4000 rads at the level of the rectum. The radiograph on the right belongs to the same patient and was taken 6 months later. The radioactive seeds are closer together indicating regression of the tumor.

During this period of the report approximately 40 patients were implanted with iodine-125 seeds. Of these, 19 have a one-year follow up. The longest survival after implantation is now four years without evidence of disease. The remaining are all living and well with the exception of two patients; one developed inguinal nodes and the other had a biopsy showing persistent disease in the prostate 9 months after implantation. This was treated by external radiation. No unusual reactions were noted in any of these patients. In contrast to radical surgical resection, sexual function was maintained in all of these patients. Not enough time has elapsed, however, to judge the final outcome.

Conclusions

From the experience gained during the period of the grant, using iodine-125 seeds for interstitial implants, it is fair to say that iodine-125 seems to be a satisfactory substitute for high energy emitters used in interstitial radiation. The convenience of having long lived isotope seeds stocked in the hospital makes interstitial radiation available on short notice, extending its scope and simplifying the problem of availability.

In reviewing the clinical experience accumulated during this period, the following preliminary conclusions can be formed:

The optimal activity of radioactive sources is between 0.4 and 0.6 mCi; the optimal spacing of the seeds is 1 to 1.5 cm, the greater distance being used for the seeds in the center of the implanted volume.

A minimum tumor dose of about 16,000 rads is required for optimal effect for the average size implant (15 to 65 cc or 2.5 to 4 cm average dimension). This dose in general has been well tolerated without undesirable early side effects. Further follow up is desirable, however, to record the late effects, if any.

Implanted tumors receiving a tumor dose of about 16,000 rads will show at least 50% regression by the fourth week after implantation (approximately a tumor dose of 4000 rads).

These tumors have usually completely regressed by the end of the first half-life of the iodine-125 (60 days). Morphologically intact cancer cells, however, may be identified histologically for at least another two half-lives (180 days). Clinical experience indicates that these cells are apparently non-reproductively viable in that late recurrence has been rare in patients of this category. Biopsy is thus not recommended until 6 to 8 months after implantation, provided there is no evidence of activity of the tumor.

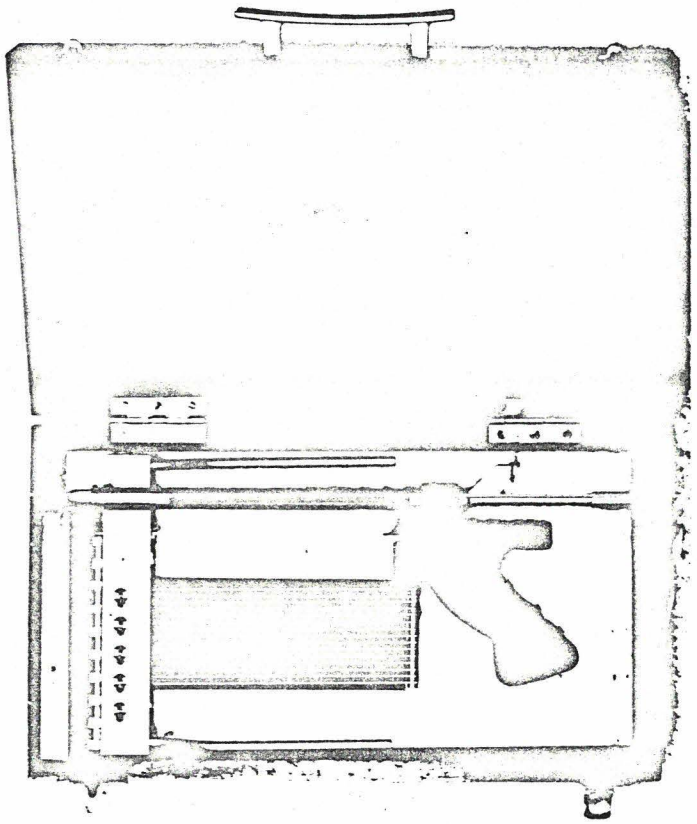
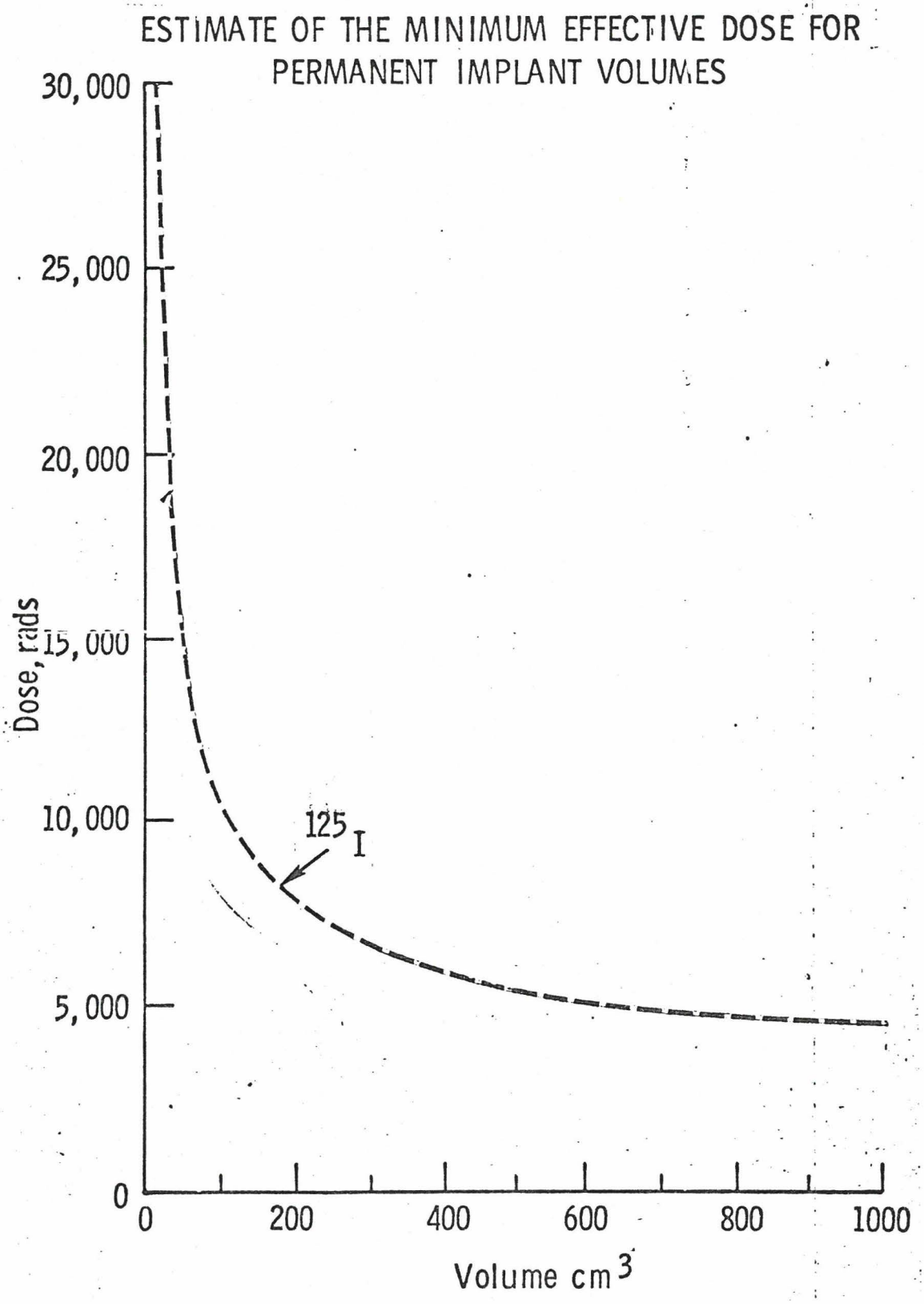


Figure 22

Figure 23


ESTIMATE OF THE MINIMUM EFFECTIVE DOSE FOR PERMANENT IMPLANT VOLUMES
30,000
25,000
20,000
15,000
10,000
5,000
0
Dose, rads
125 I
0
200
400
600
800
1000
Volume cm 3

CALCULATION OF IODINE-125 ACTIVITY

$$\text{Average Dimension} = \frac{5+4+3}{3} = 4\,\text{cm}$$

$$\text{mCi Iodine-125} = 4 \times 5 = 20$$

$$\text{Number of Seeds} = \frac{20}{0.5} = 40$$

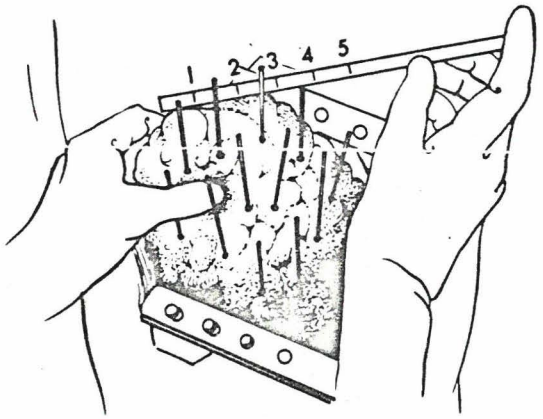


Figure 24

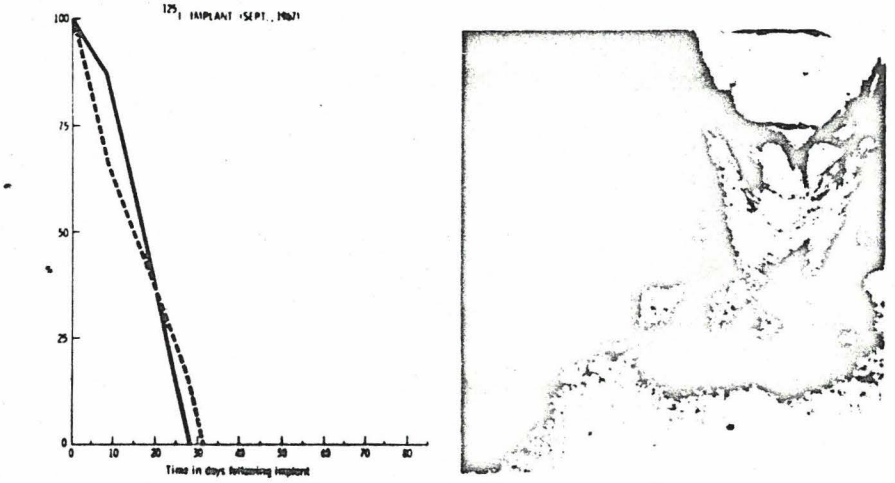

100
75
50
25
0
0
10
20
30
40
50
60
70
80
Time in days following implant

Figure 25

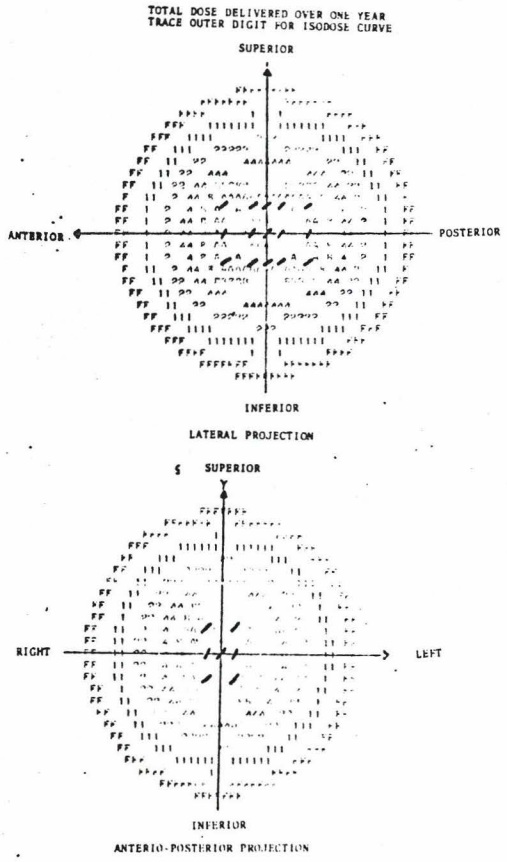

TOTAL DOSE DELIVERED OVER ONE YEAR
TRACE OUTER DIGIT FOR ISODOSE CURVE
SUPERIOR
ANTERIOR
POSTERIOR
INFERIOR
LATERAL PROJECTION
SUPERIOR
RIGHT
LEFT
INFERIOR
ANTERIO-POSTERIOR PROJECTION

Figure 26

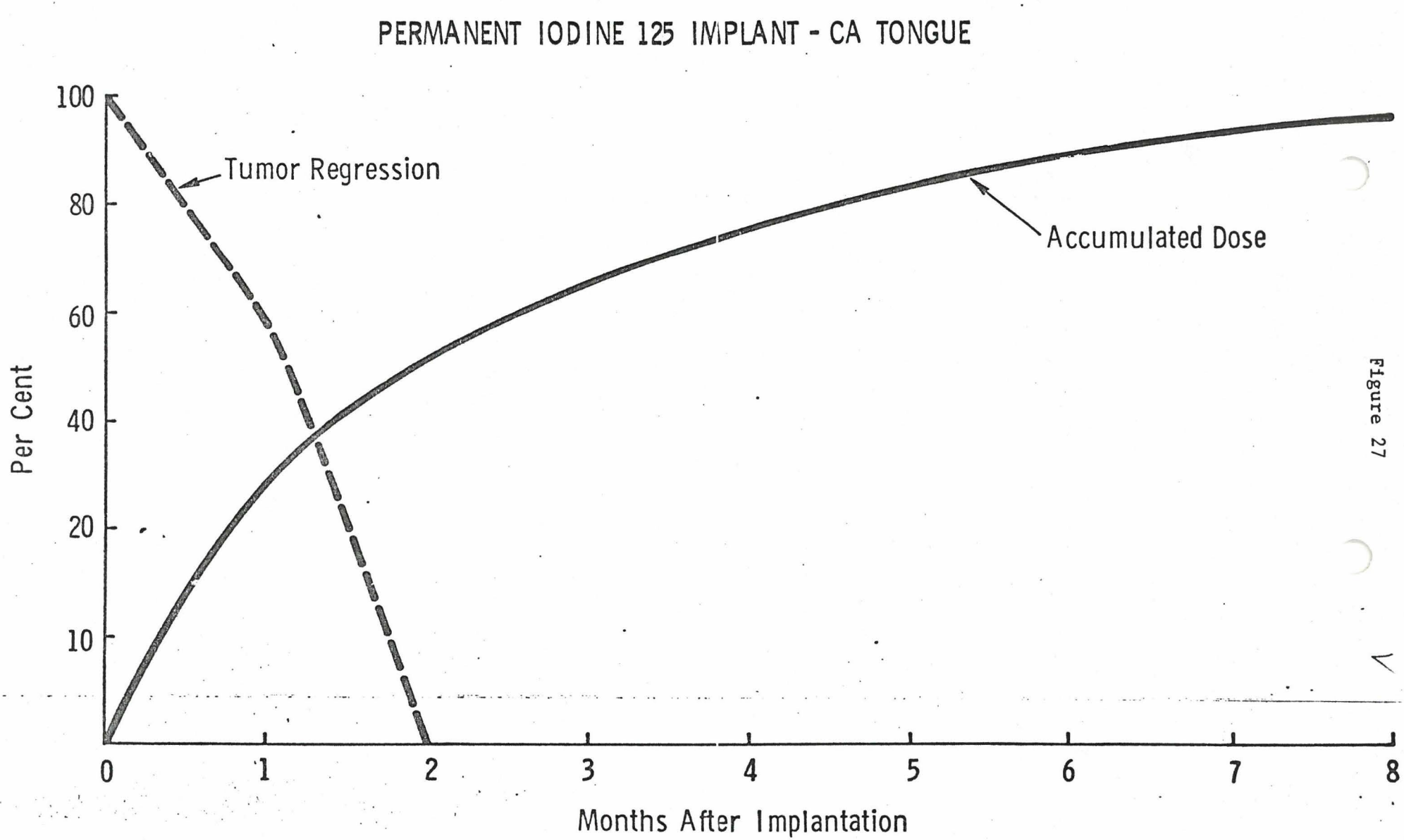
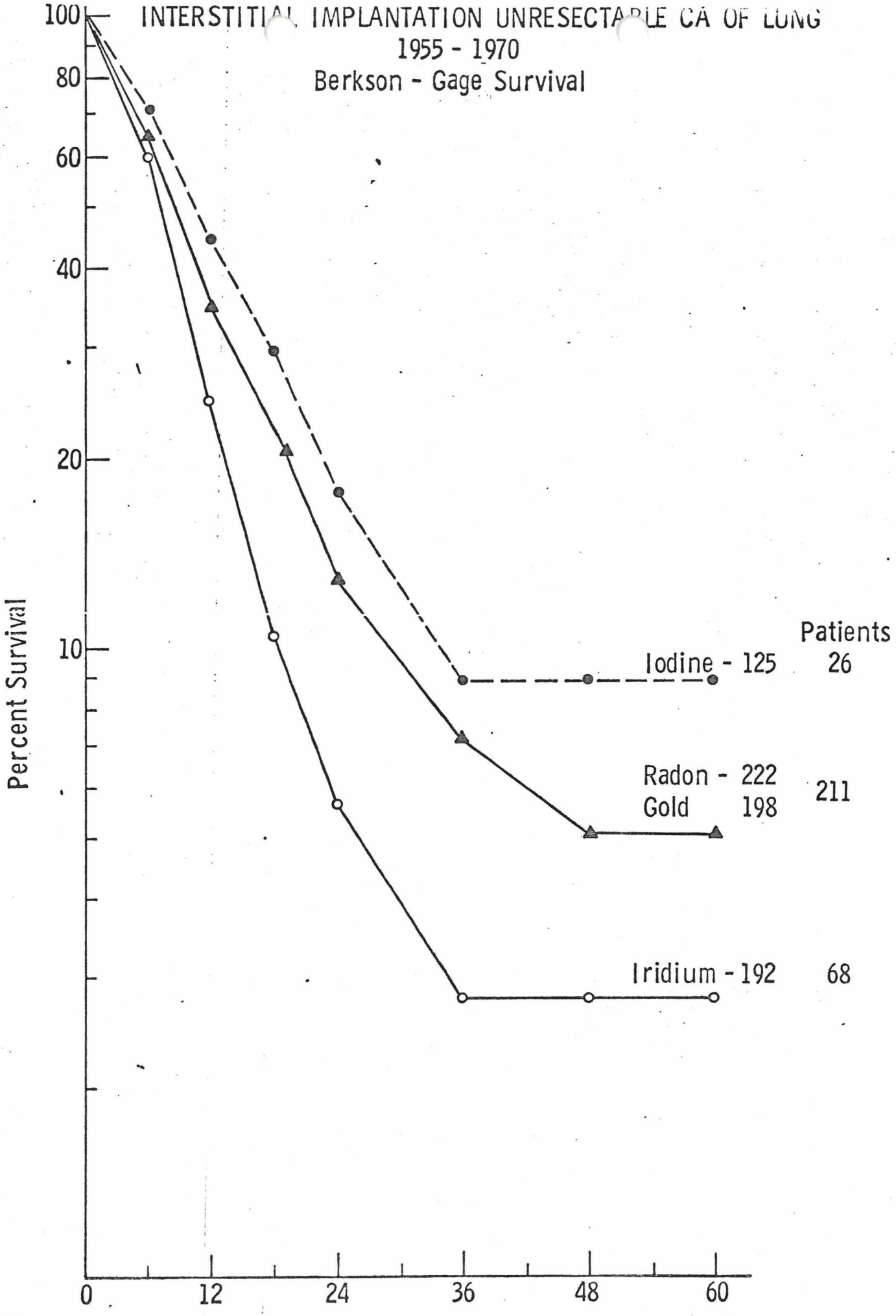

PERMANENT IODINE 125 IMPLANT - CA TONGUE
100
80
60
40
20
10
Per Cent
Tumor Regression
Accumulated Dose
0
1
2
3
4
5
6
7
8
Months After Implantation

Figure 27

Figure 28


INTERSTITIAL IMPLANTATION UNRESECTABLE CA OF LUNG
1955 - 1970
Berkson - Gage Survival
Percent Survival
100
80
60
40
20
10
0
12
24
36
48
60
Patients
Iodine - 125 26
Radon - 222
Gold 198 211
Iridium - 192 68

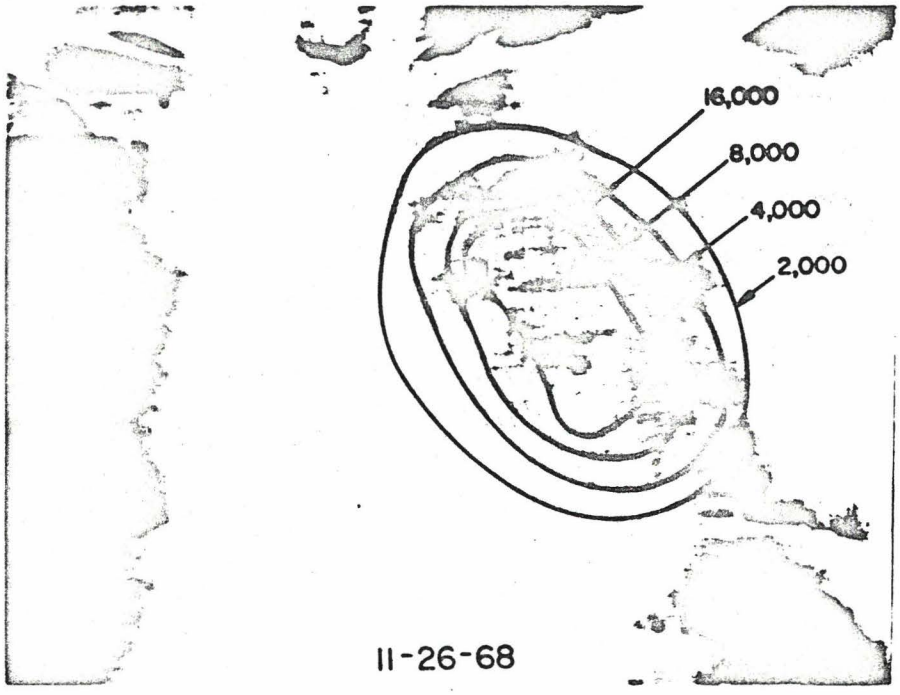


Figure 29

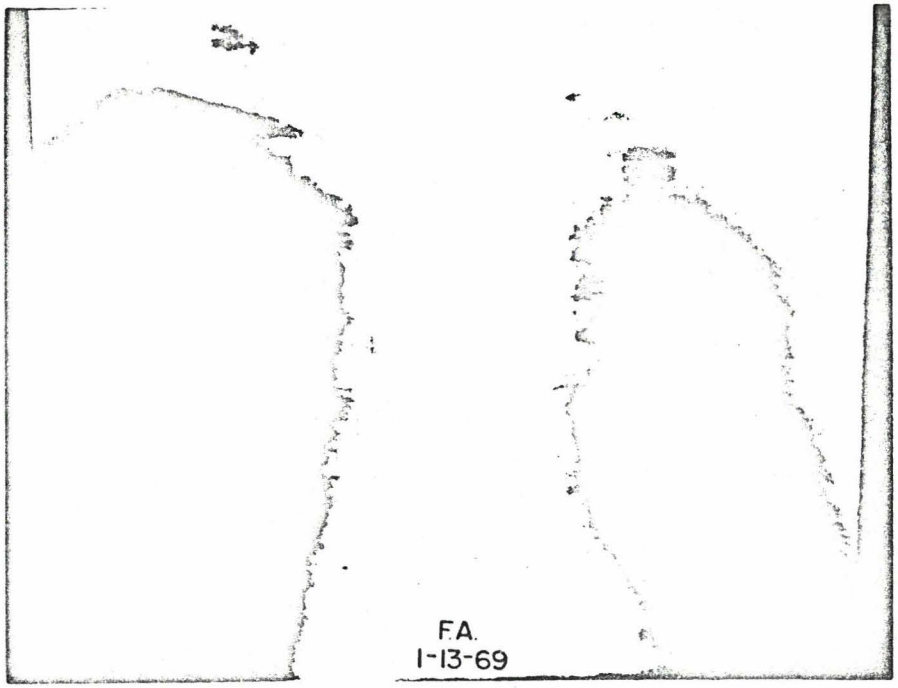


Figure 30

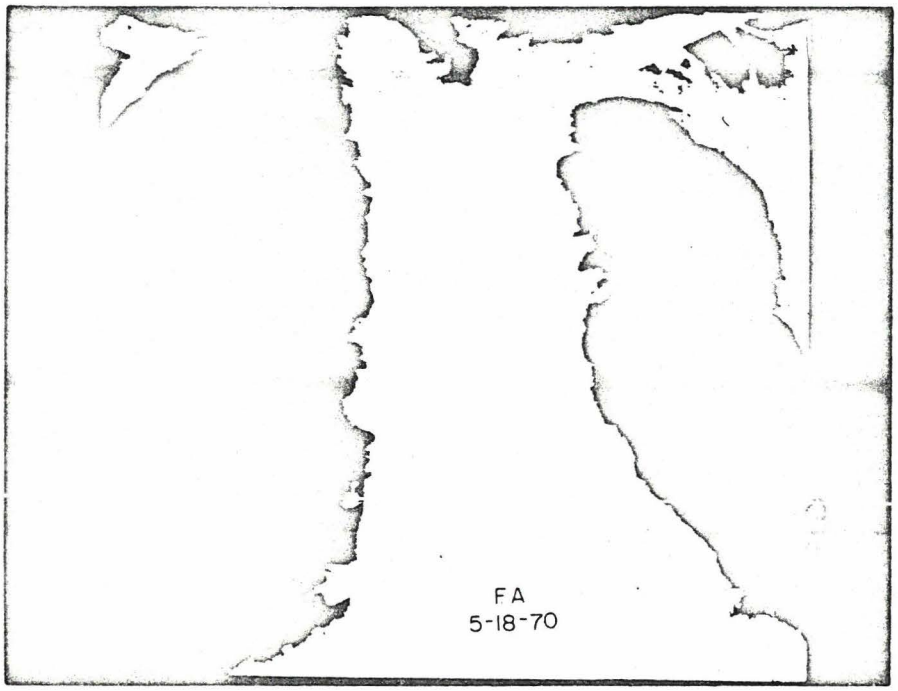
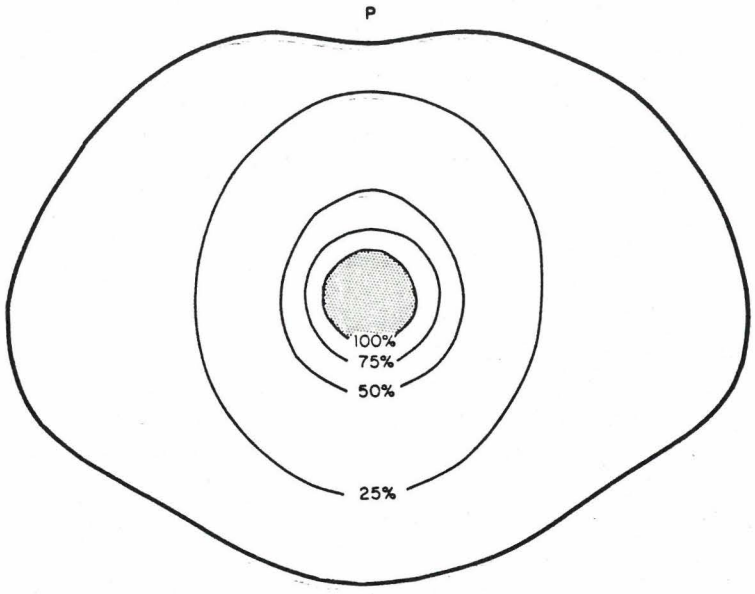
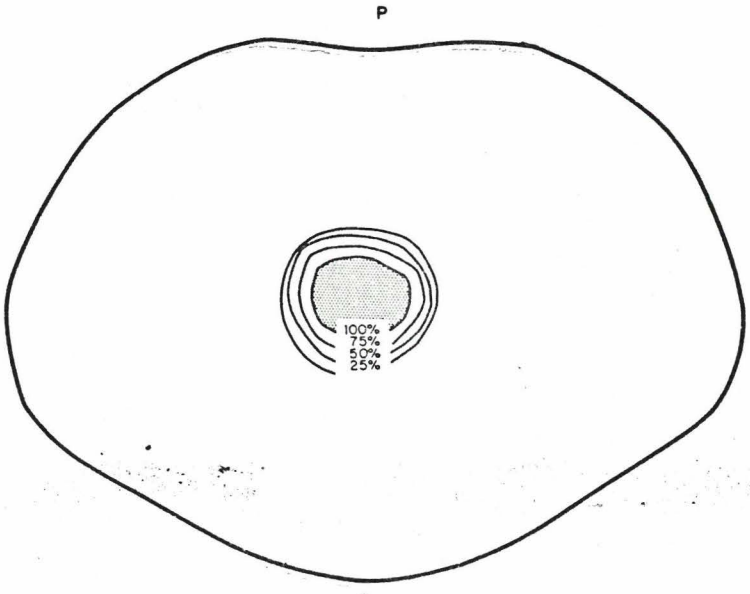


Figure 31



6MEV Linac (360°, 6 x 6cm)

Figure 32



Iodine 125 implant

Figure 33

Figure 34

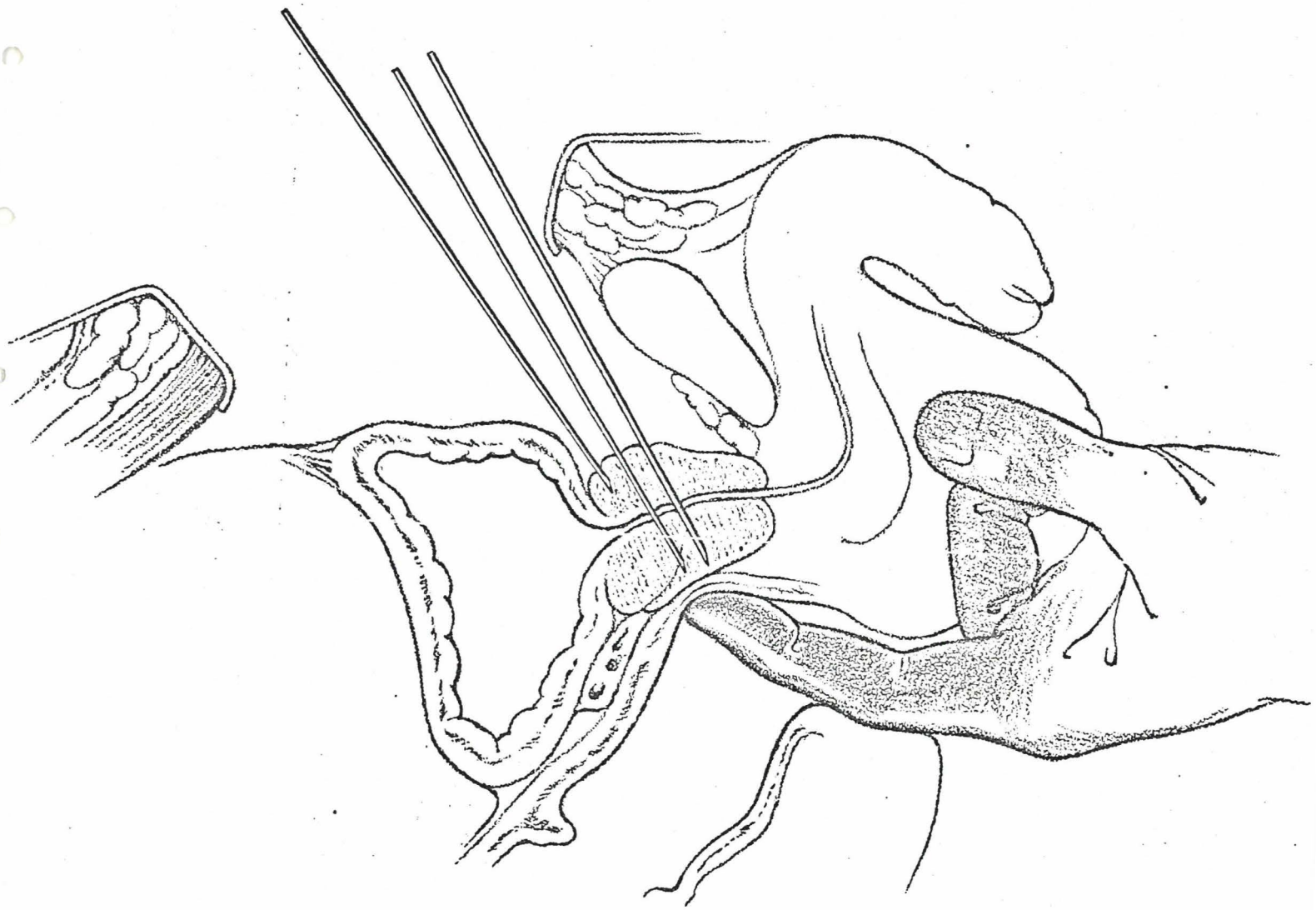


Figure 35

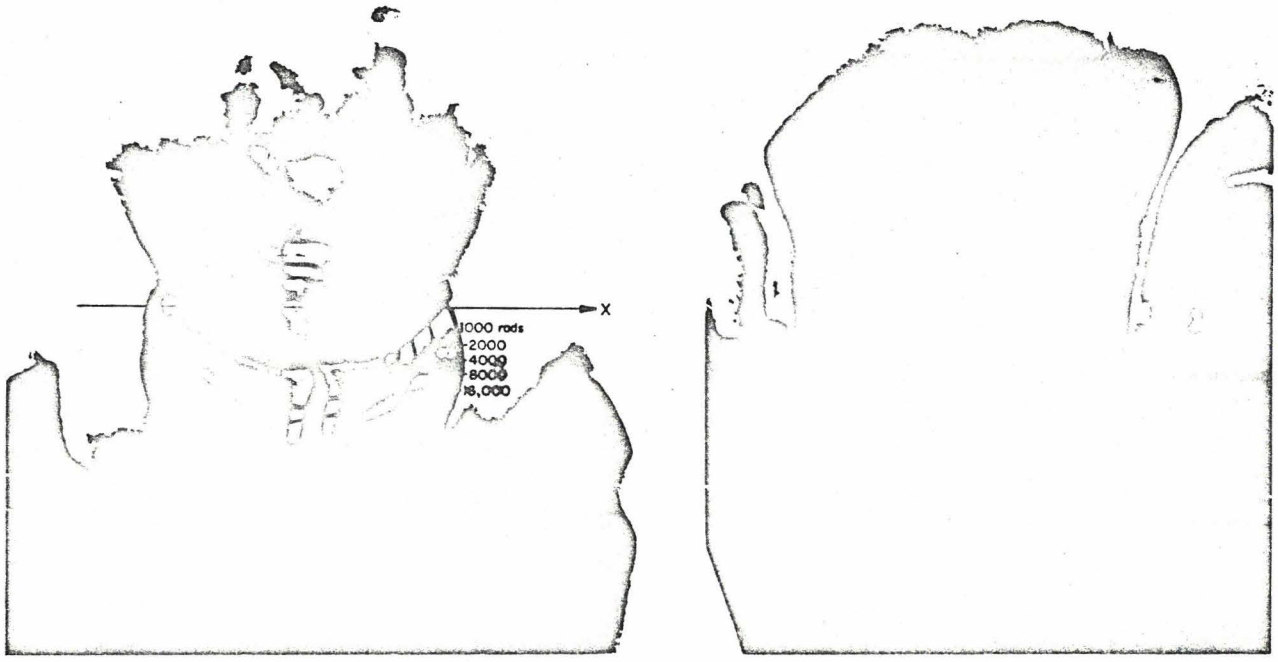


TABLE 6

PERMANENT INTERSTITIAL IMPLANTS WITH IODINE-125 SOURCES
MAY 1, 1968 THROUGH APRIL 30, 1971

	NO. IMPLANTS	NO. PATIENTS
INTRAORAL	22	21
SUPERFICIAL	77	68
INTRATHORACIC	68	68
INTRAABDOMINAL	67	67
TOTAL	234	222*

*2 patients had implants in both intraoral and superficial sites.

TABLE 7

INTERSTITIAL IMPLANTATION AT THORACOTOMY
UNRESECTABLE CANCER OF THE LUNG
1955-1970

RADIONUCLIDE	NO. PATIENTS
RADON-222	197
GOLD-198	14
IRIDIUM-192	68
IODINE-125	26
TOTAL	305

B. Clinical Experience with the Remote Afterloader.

Remote afterloading of intracavitary applicators using high intensity cycling sources was proposed a few years ago as a solution to the problem of radiation exposure to personnel.[31,32] On July 1, 1967, the first Remote Afterloader with cycling sources was installed for clinical use at Memorial Hospital. In this report we will present the experience which has been accumulated during the period of support under Grant EC 00113 from May 1, 1968 through April 30, 1971.

Figure 36 (Pg.84) shows a schematic drawing of the Remote Afterloader, the first of its type in the U.S.A. It consists of a lead safe installed in the wall of the treatment room, which contains three small cobalt sources of high activity. After the door of the treatment room has been closed, the sources, which are attached to the ends of long cables, are advanced to their treatment positions in the applicator by means of a mechanism in the control panel.

Figure 37 (Pg. 85) shows a schematic drawing of one of these cobalt-60 sources. These sources were purchased from the Atomic Energy of Canada, Ltd. and were encapsulated in the U.S.A. by the Union Carbide Company. Each source is cylindrical in shape and measures 1 x 1 mm. It is enclosed in a stainless steel capsule which measures 10 x 1.7 mm. Each capsule is attached to a stainless steel cable which passes from the treatment room to the control panel.

The remote afterloader control panel consists of the following control devices:

Patient control - This is achieved by means of a closed circuit television monitor and a camera which scans the patient during the treatment. In addition, an intercom permits us to listen to the patient and to talk with him during the procedure.

Source position control - The precise position of each of the three sources can be determined with the following devices:

1) Rate Meter, which goes off scale as soon as even one source emerges from the safe into the treatment room.

2) Green and red lights. The green light indicates that the source is in its proper position within the lead safe. The red light indicates

that the source is at its utmost forward position and has made appropriate contact with the tip of the applicator.

3) The trailing end of the cable runs in a transparent tube and is clearly visualized in the control panel. As the source is advanced, the trailing end advances exactly the same distance. By simple ruler measurement, one can therefore measure precisely how far outside the safe each source has advanced. When the sources are cycled, the trailing end advances and retreats in parallel fashion.

Source cycling control - This regulates the advancement and retraction of the sources. The cables are sufficiently exposed at this point in the control panel so that the operation can be performed manually, if necessary. For routine use, however, the sources are advanced and retracted by means of "push buttons," which activate two friction-type rollers between which each cable is moved back and forth. When the sources have been advanced to their furthermost point (red light goes on), the cable can be locked to a scaled oscillating device. The length of the cycle or oscillation is easily set on a centimeter rule on the face of the device. The sources can be cycled, or oscillated, through a distance of 18 cm. If, for instance, treatment of the whole uterine cavity is desired, the central source can be cycled over a length of 7 cm by appropriate setting of the lever.

The Remote Afterloader is designed to be used principally with high activity sources.[33] Thus, the total treatment time may amount to minutes rather than days. This in itself presents a radical departure from the traditional methods, introducing controversial radiobiological questions on dose-time relationships, total dose and fractionation.

The multiplicity of biological factors involved in the differential radiation response of normal and neoplastic tissues, e.g., intracellular repair of potentially lethal damage, cellular kinetics and anoxia - reoxygenation of tumor cells, contribute to the difficulties in arriving at the optimal dose-time relationships. To our knowledge, no laboratory investigations have been published on dose-time relationships of isotopes used in Brachytherapy.

However, at the clinical level, some information in regard to intracavitary radiation with high intensity sources in humans was available

at Memorial Hospital and the Pack Medical Group in a group of patients treated by an intravaginal applicator loaded with up to 1000 mgRa and known as the "vaginal bomb." In 1946, Focht et al. reported that in small lesions total doses of 8000 to 9000 rads at the surface of the applicator (vaginal mucosa) given in two applications, one to two weeks apart were well tolerated without permanent radiation necrosis.[34]

In an effort to estimate tolerance levels and optimal doses, in 1966 with the cooperation of Dr. G. Pack and Dr. U. K. Kenschke, we carried out a review of the records of 23 patients treated with these high intensity intracavitary sources during the period 1944 to 1953. No late reactions are recorded in any of these patients, some of them with follow up ranging up to more than 20 years. The immediate reactions were not more severe than those observed with standard radium applications. However, in one patient who received two applications on successive days of 1750 mghr and 3300 mghr, respectively, a severe vaginal mucositis developed, which persisted for about 7 months. This patient was free of disease and asymptomatic 14 years later.

A total of 402 applications were performed in 196 patients during the period May 1, 1968 through April 30, 1971. Vaginal applications accounted for 40% of the 402 applications; uterine applications 32%, nasopharyngeal applications 12%; and other applications 16% (esophageal, bladder, palate, antrum, floor of mouth, thoracic and abdominal cavities. According to the generally accepted criteria in cancer treatment (5-year cure or survival rate), insufficient time has elapsed in most of these patients to judge the efficacy of this type of irradiation. Some preliminary information, however, will be reported in the following pages.

Nasopharyngeal Irradiation

Figure 38 (Pg.86) shows the type of applicator used for the supplementary radiation of the nasopharynx after completion of external radiation (5000 to 6000 rads in 5 to 6 weeks). The insertion of the applicator is carried out under local anesthesia on an outpatient basis. A short inflatable balloon is attached to the tip of the applicator and inflated to fill the nasopharyngeal cavity. Details of the insertion are listed on attached "Instruction Sheet" (Appendix, Pg. 98). A single high intensity source approximately 1 curie is utilized after the application is connected to the Remote Afterloader (Figure 39) (Pg.86). Two applications, 500 mghr-Raeq each, are performed to deliver 2000 to 2500 rads at the surface of

the applicator. This dose is given over a period of 25 to 30 minutes. The applications are spaced two weeks apart and are done at the termination of the external radiation therapy. Complete isodose curves are obtained at various planes. Figure 40 (Pg.87) shows an x-ray of the applicator in place prior to its loading.

Figure 41 (Pg.87) shows an isodose curve for 500 mghrRaeq superimposed on a lateral localization x-ray film, which was taken prior to the loading with the radioactive sources.

Table 8 (Pg.88) gives the number of patients with primary cancer of the nasopharynx having local control of their disease at the end of the first year after radiation. For comparison purposes, in addition to the patients treated with the Remote Afterloader, the patients treated in a similar fashion but at a slower rate are also listed. No statistically significant differences are noted. The radiation was well tolerated without severe mucosal reactions in all groups of patients.

A detailed analysis and intercomparison of these patients with cancer of the nasopharynx treated by radiation (including intracavitary) since 1960 is presently underway.

Vaginal Irradiation

Figure 42 (Pg.89) shows an example of a cylindrical vaginal applicator developed specifically for intracavitary radiation by remote afterloading of the sources. Similar applicators but of various diameters and lengths have also been constructed. The dose at the surface of these applicators varies from 2500 to 3000 rads for a total of 1500 mghrRaeq. This dose was delivered in either two or three applications, each one spaced two weeks apart. Figure 43 (Pg.89) shows an example of the computerized dosimetry for the most commonly used applicator for 500 mghrRaeq. Additional examples are listed in the Appendix (Pgs. 98-106) Table 9 (Pg. 90) lists the number of applications and the various primary sites.

The patients who underwent vaginal irradiation can be divided into three groups: (1) patients who received radiation as an adjunct to surgery to prevent vaginal recurrences (preoperative and postoperative); (2) patients who had vaginal irradiation after they received the tolerance dose by external irradiation in an attempt to eradicate residual disease; and (3) patients who had advanced uncontrolled disease or recurrence after surgery or radiation. The vaginal irradiation was given in the latter group in an attempt to stop severe bleeding and/or pain Table 10 (Pg.91).

Table 11 (Pg.92) lists some preliminary information available at the time of this report. The table contains the total number of patients, according to the primary site, and the reason for which vaginal irradiation was administered. In addition, the present status of the patients is recorded.

A minimum follow up of 6 months is available in all of these patients at this time. This is of course not sufficient to judge either the therapeutic effect on the tumor or the late effect on the normal tissues. Such detailed analysis is at present underway and will be reported as soon as adequate follow up time has elapsed

The conclusions which can be drawn are the following:

Fractionated insertions seem to preserve a better vaginal function, producing less fibrosis and obliteration of the vaginal mucosa.

A single insertion of 3000 rads in 45 minutes calculated at the surface of the applicator results not only in severe early bladder, rectal and vaginal mucosal reactions but also in severe late atrophy, fibrosis and vaginal stenosis.

A dose of 1500 rads in 22.5 minutes calculated at the surface of the applicator in each of two insertions spaced two weeks apart is better tolerated but still produces moderate early and late reactions.

A dose of 1000 rads in 15 minutes calculated at the surface of the applicator given in each of three insertions in about three to four week's time for a total of 3000 rads is well tolerated without any early reactions. No late effects were noted in these patients up to a year after treatment.

In general, irradiation of the entire length of the vagina seems to be well tolerated providing that care is taken not to extend the sources beyond the vaginal orifice.

Dr. Kim of Memorial Sloan-Kettering Cancer Center attempted to estimate the NSD (nominal standard dose) using Ellis' formula and compare the high dose rate regimens of treatment of the vagina using the Remote Afterloader with the standard radium techniques.

For comparing the continuous irradiation with acute fractionation irradiation, the NSD for the standard technique proposed by Paterson

(6000 rads in 168 hours) was assumed to be 2000 ret (using Liversage's formula to convert the protracted radiation to an equivalent fractionation).

The results can be seen in the Appendix (Pg.98). The results obtained in this way can be questioned as to their value, because Ellis' formula ordinarily applies to higher fractionation (more than 4) and the smaller fractional dose (less than 1000 rads) than the one which has been utilized in intracavitary radiation. In view of the lack of any other information, however, this seemed to be the only presently available way of comparison. We hope that in the future, information obtained from in vivo studies at our Sloan-Kettering Institute (Dr. Hahn) will provide a more meaningful method of comparison.

Uterine Irradiation

Preoperative intracavitary uterine irradiation was used in 23 patients with cancer of the corpus. All of these patients' tumors were classified as Stage I or II according to the system proposed by the International Federation of the Gynecologists (FIGO). Figure 44 (Pg. 93) shows the components of the applicator, which was developed and used for this purpose.[35] It consists of two curved, long stainless steel tubes with a small slit at the open end of each tube corresponding to the curved portion; one straight stainless steel tube and several aluminum cylinders of various lengths used for the irradiation of the vagina. All stainless steel tubes are 25 cm long so that they protrude from the vagina after their insertion into the uterine cavity. The assembled applicator is shown on the left of the same figure. Each curved lateral tube is inserted into one of the cornuas of the uterus, while the straight tube is in the center to improve the dose distribution in the fundus. All three tubes are connected with the vaginal component, which is placed against the cervix. The tubes are kept in place by a locking device at the protruding end of the vaginal cylinder.

Figure 45 (Pg. 93) shows the assembled applicator in place within a uterine surgical specimen superimposed on the patient's pelvic x-ray. In this example, 5000 rads were delivered to the endometrial surface; the serosal surface received 2500 rads. One such application corresponds approximately to 3000 to 3500 mghrRaeq and is given in about one hour. Hysterectomy was performed 4 weeks later. The gross effects on the uterine specimen were similar to the effects obtained with radium given at a slower rate. Microscopic examination, however, showed a more severe reaction than with standard techniques. Figures 46-50 (Pgs. 94-96) illustrate these observations.

Figure 46 (Pg.94) shows the uterus removed 6 weeks after irradiation. There is no evidence of disease and no unusual reactions are noted. Figure 47 (Pg.95) is a low-power view of endometrium and underlying myometrium in the same patient. The surface of the endometrium is ulcerated, partly covered by debris. The endometrium only contains a few scattered glands surrounded by chronic inflammatory cells.

Figure 48 (Pg.95) is a higher magnification of the endometrium in the same patient. The atrophic and atypical glands barely lined by a few degenerating epithelial cells are embedded in a cellular dense fibrous stroma.

Figure 49 (Pg.96) shows a low magnification of the endometrium of a patient who received the same dose but using radium at slower dose rates. Although the surface is still ulcerated, the glands are more numerous and have a close resemblance to normal endometrial glands. The stroma contains only a few lymphocytes and histocytes.

Figure 50 (Pg.96) shows a high power view of endometrial gland from the same patient. Note the very close similarity to normal endometrial glands.

Intracavitary uterine applications were also performed in 44 patients with cancer of the cervix. Most of these patients' lesions were classified as Stage IIb and III. External radiation therapy was given in all of these patients. The intracavitary radiation was given by the afterloading applicator developed by Dr. Henschke (Ref. 36). Detailed instructions for the insertion of this applicator are listed in Appendix (Pg. 105-106).

Figure 51 (Pg.97) is a schematic drawing showing the patient during the treatment. The unloaded applicator has been inserted into the uterus and vagina. The patient has been placed on a bed in the treatment room, and the applicator has been connected by three plastic tubes to the lead safe in the wall.

The radiation dose to point A as well as complete isodose curves were obtained by the computer at various planes, as described in Part III of the present report. In addition, direct measurements were made in the rectum.

A detailed analysis of the clinical results obtained in the patients with cancer of the corpus and cancer of the cervix is presently underway. These results will then be compared with those of patients in whom standard radium techniques were utilized. The clinical experience thus far suggests that there are important differences in the reactions produced with the high intensity time regimens. Although the time elapsed since the treatment is not adequate for arriving at final conclusions, the clinical findings suggest that in order for the remote afterloading intracavitary techniques

of this kind to supplant standard radium techniques, further information is needed regarding the biological effects of these time-dose relationships.

Conclusions

The development of the Remote Afterloader for intracavitary radiation achieved one of the objectives of this study; namely, the elimination of the radiation exposure to the medical personnel. Several other practical advantages became evident during its application. These advantages are presented below without any attempt to attach special significance to the order of listing:

- Continuous audio and visual monitoring of the patient during the treatment.
- Continuous check of the position of the sources within the applicator.
- Continuous monitoring of the dose rate in the rectum and bladder.
- More flexibility in adjusting the loading of the various applicators than with radium sources.
- Easier adjustment of the desired dose distribution within the treated area.
- Hospitalization is not required during the treatment.
- Patients experience less discomfort because of the short treatment time
- No additional sources are required, no special radium room is needed, and no transport of sources is necessary. The major causes of past radium accidents are therefore eliminated.

It is more difficult to answer the question of therapeutic effectiveness. One should be cautious in interpreting the preliminary results reported here. The multiplicity of biological factors involved in the differential radiation response of normal and neoplastic tissues, e.g., intracellular repair of potentially lethal damage, cellular kinetics and anoxia-reoxygenation of tumor cells, contribute to the difficulties in arriving at the optimal dose-time relationships.

Several in vivo studies in animals are being carried out in cooperation with Dr. Hahn at The Memorial Sloan-Kettering Cancer Center, under the project title "Time-Dose Relationships in Brachytherapy." The isotopes studied are radon-222, iodine-125, iridium-192, radium-226 and high activity cobalt-60 sources. These studies are designed to establish isoeffect lines relative to these radionuclides. We hope that in the near future we will have enough data of this nature so that in employing barchytherapy we will be able to select the most suitable dose-time regimen for optimal treatment of the patient with cancer.

Figure 36

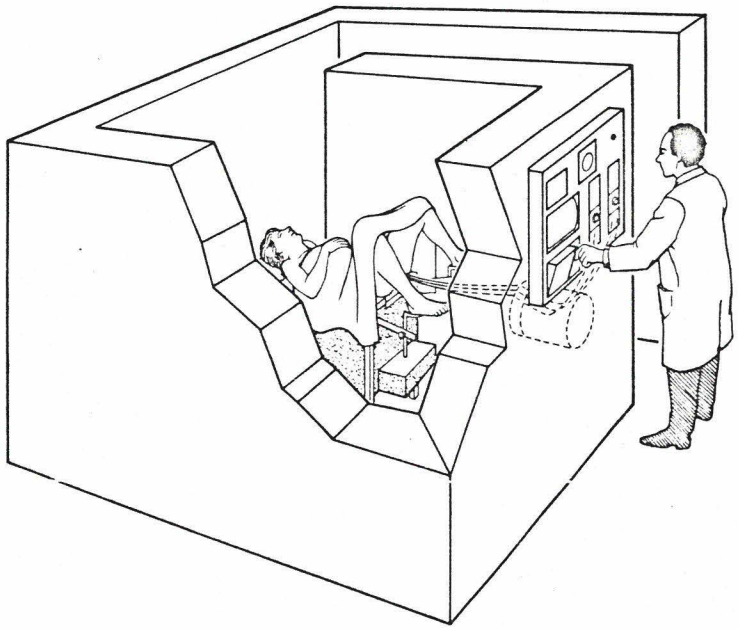
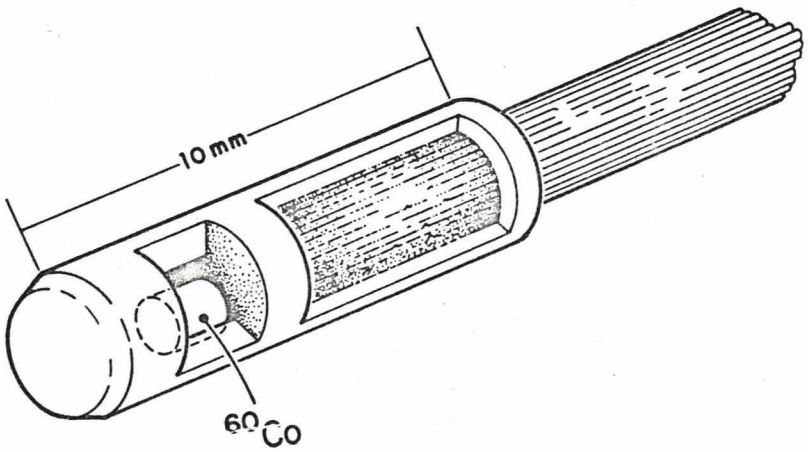


Figure 37



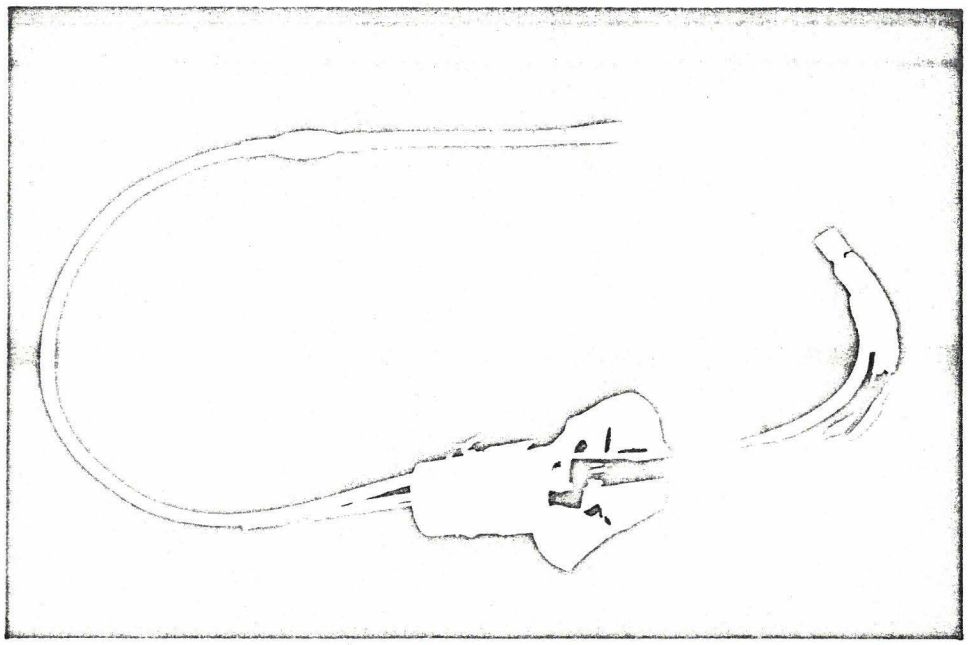


Figure 38

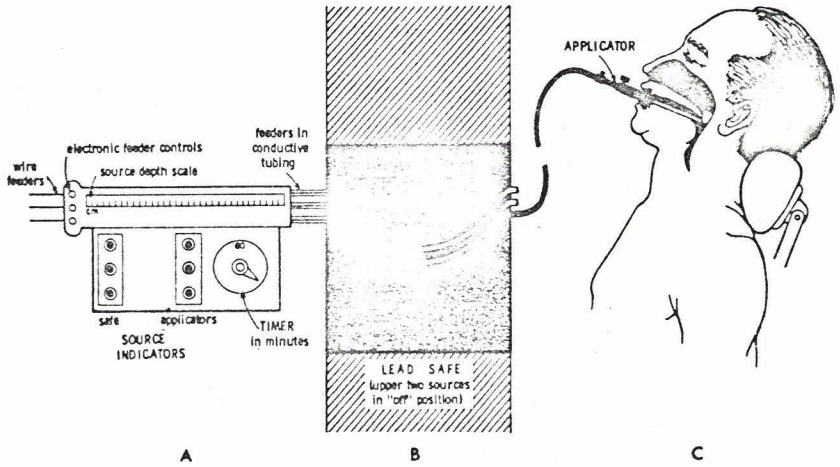


Figure 39

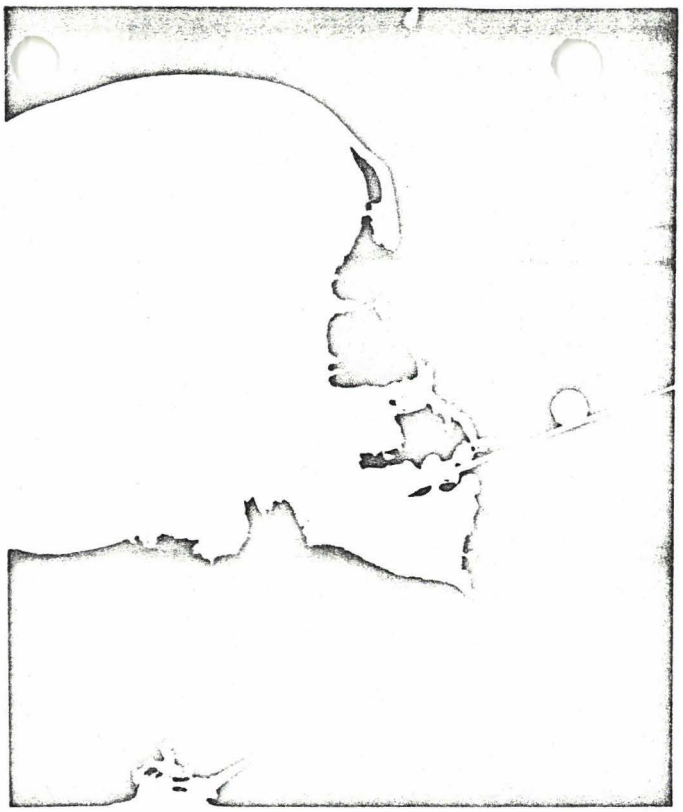


Figure 40

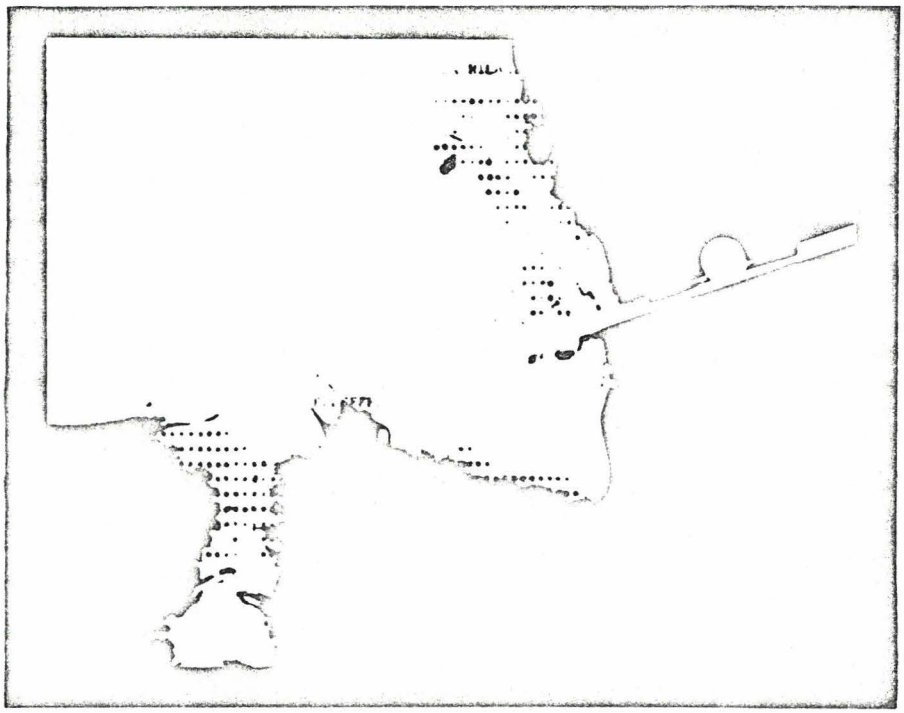


Figure 41

TABLE 8

CA NASOPHARYNX
INTRACAVITARY RADIATION

PERIOD	TIME FOR 1000 mghr	LOCAL CONTROL
1960-1963	8-10 hr	35/39 (89%)
1964-1966	2-3 hr	18/21 (86%)
1967-1970	0.5-1 hr	19/22 (88%)

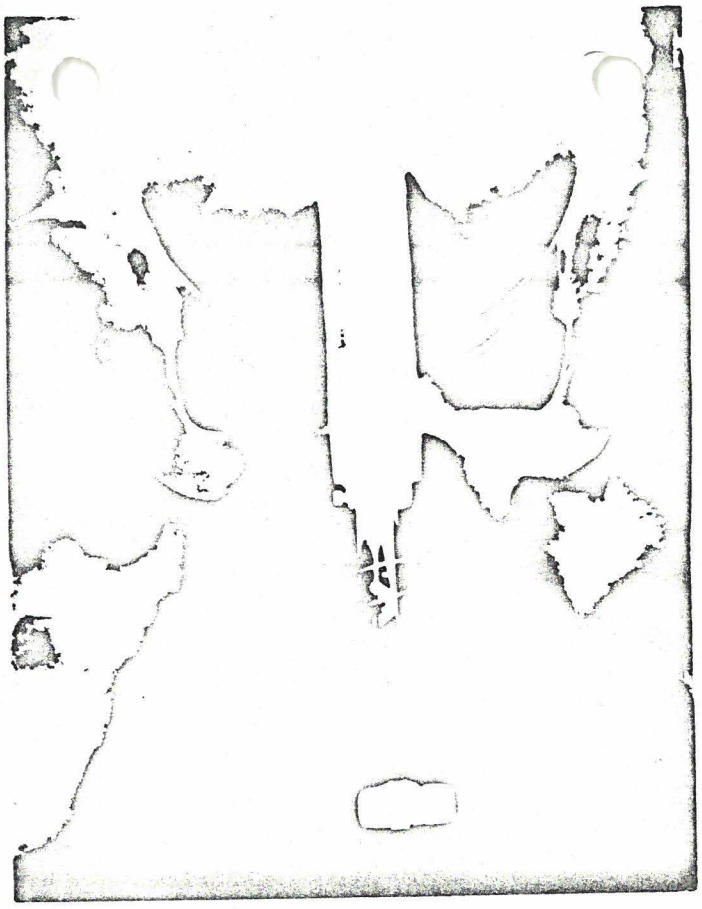


Figure 42

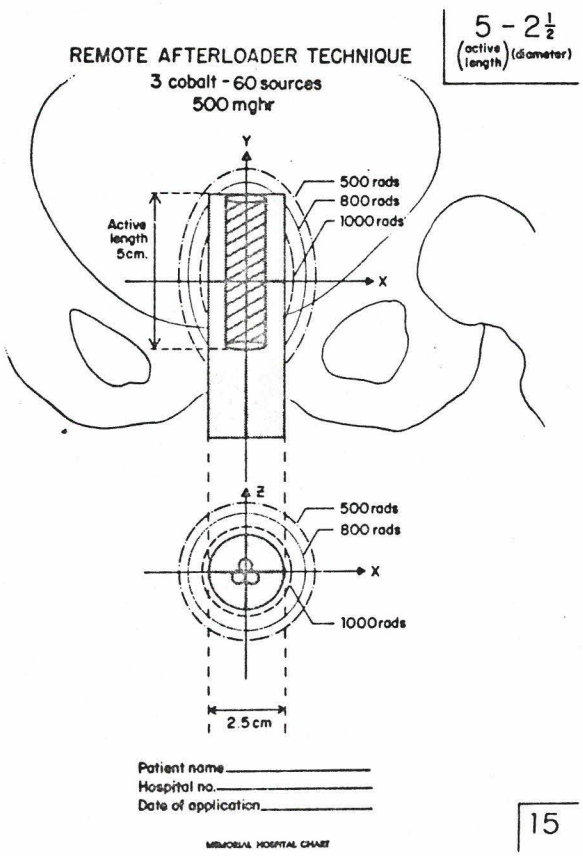


Figure 43

TABLE 9

VAGINAL IRRADIATION BY REMOTE AFTERLOADING

PRIMARY SITE	NO. OF PATIENTS	NO. OF APPLICATIONS
CA CORPUS	49	103
CA CERVIX	20	38
CA VAGINA	6	12
OTHER	6	14
TOTAL	81	167

TABLE 10

VAGINAL IRRADIATION BY REMOTE AFTERLOADING

	NO. OF PATIENTS
ADJUVANT TO SURGERY	35
ADJUVANT TO EXTERNAL RADIATION (CURATIVE)	16
PALLIATIVE	30
TOTAL	81

TABLE 11

EVALUATION OF VAGINAL DISEASE AFTER RADIATION
BY REMOTE AFTERLOADING

Primary Site	Reason for Treatment	No. Pts.	Alive		Dead	
			NED	Disease	NED	Disease
CA Corpus	Adjuvant to surgery	35	35 (6-27m)	-	-	-
	Recurrence after surgery	14	9 (6-40m)	1	2	2
	Adjuvant to ERT	10	5 (12-26m)	1	1	3
Ca Cervix	Recurrence after RT	5	2	-	1	2
	Recurrence after surgery	5	2	1	-	2
CA Vagina	Adjuvant to ERT	6	3 (16-38m)	1	1	1
Other	Recurrence	6	1	-	-	5
TOTAL		81	57	4	5	15

Note: Figures in brackets indicate range of follow up in months.

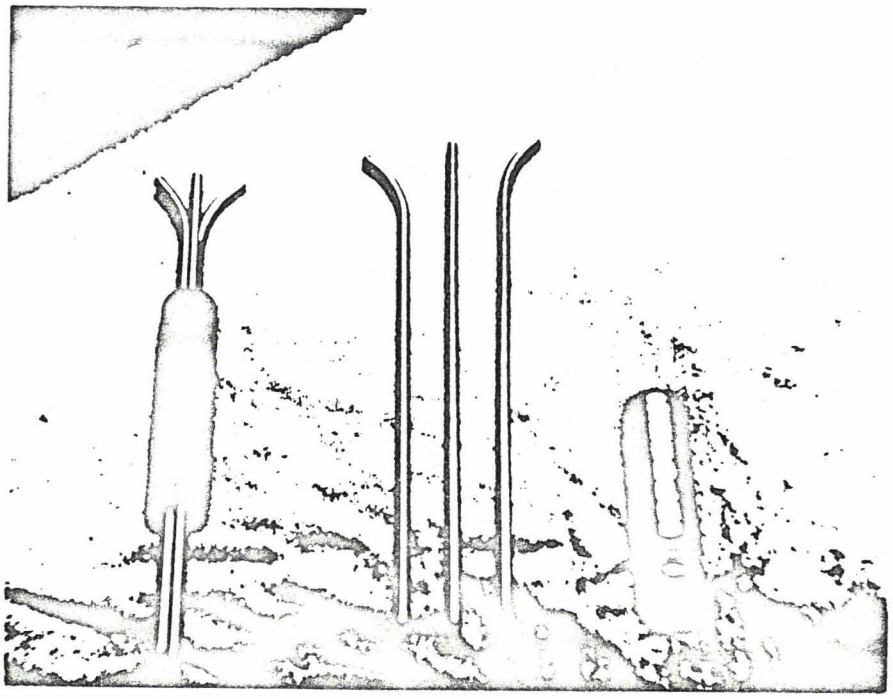


Figure 44

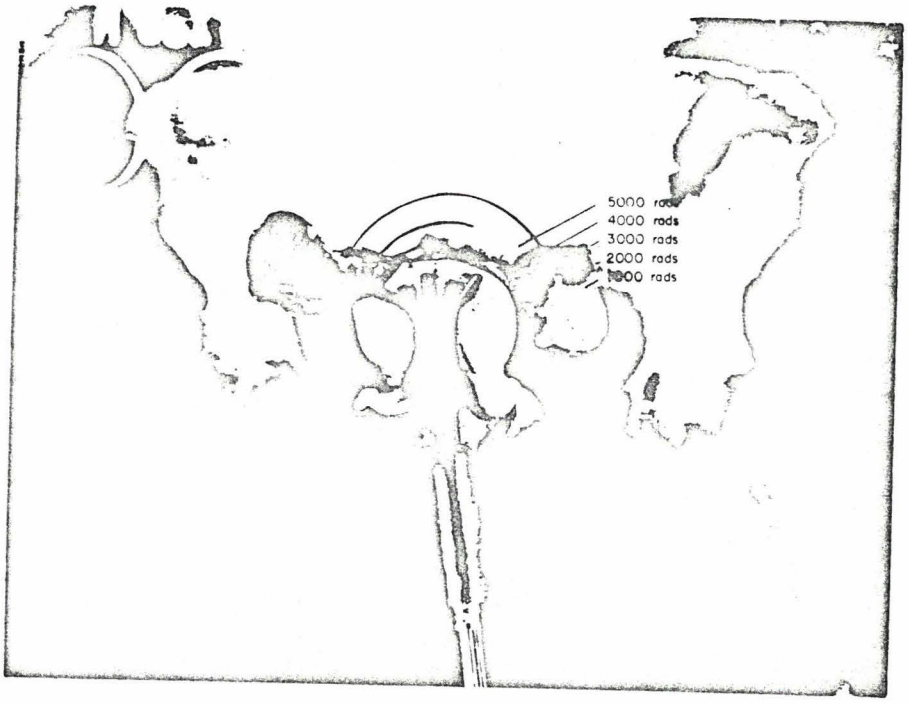


Figure 45

Figure 46

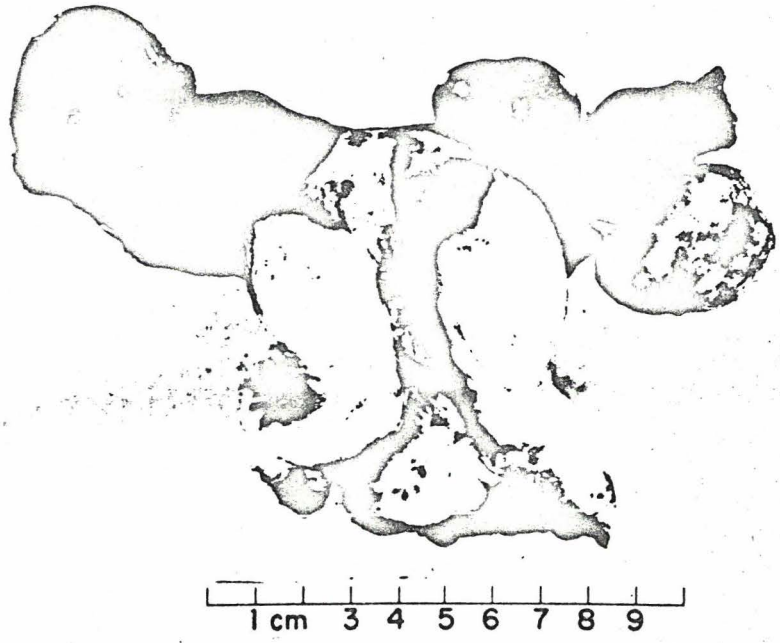


Figure 47

Figure 48

Figure 49

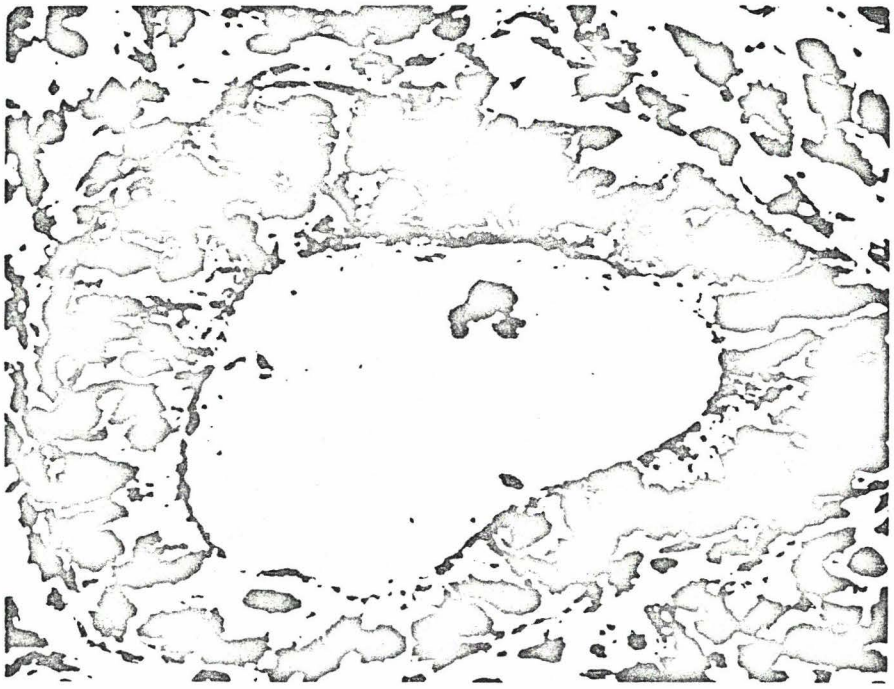
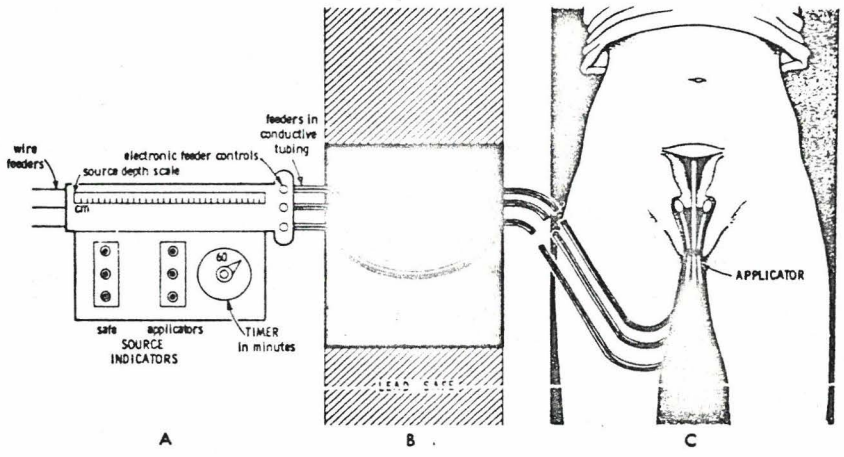


Figure 50

Figure 51


wire feeders
electronic feeder controls
source depth scale
cm
feeders in conductive tubing
60
safe
applicators
SOURCE INDICATORS
TIMER in minutes
LEAD SAFE
APPLICATOR
A
B
C

A P P E N D I X

INTRACAVITARY RADIATION BY REMOTE AFTERLOADING IN CANCER OF THE NASOPHARYNX

A. A kit is available through commercial sources made up of:

1. Case
2. Five applicators with various curves
3. Five plexiglass locking devices with knurled locking screw
4. Disposable items (which can be replaced after each use)
   a. McKesson disposable mouthpiece - adult size (32160)
   b. Short inflatable cuff with pilot balloon (5.0 mm) 2057 K (Rusch)

B. Instructions for insertion of nasopharynx applicator.

1. Anesthetize the patient with Cyclaine 2% (local spray). Make sure that in addition to the oral mucosa, the uvula, hypopharynx and nasopharynx are well anesthetized.
2. Measure the length of the nasopharyngeal cavity and the curvature necessary to enter it through the mouth, using the "uterine sound."
3. Select the appropriate nasopharynx applicator.
4. Attach the short inflatable cuff with the pilot balloon to the applicator. Make sure it is at the tip of the curve. Test the balloon with 10 cc. of air. This should result in a balloon of 2.5 cm. diameter. Inflate the ballon.
5. Adjust the McKesson disposable mouthpiece to the proper distance.
6. Turn the applicator to the side and push it behind the uvula; rotate it and position it in the middle of the nasopharynx.
7. Instruct the patient to bite lightly on the mouthpiece.
8. Inflate the balloon with 10 cc. of air. Clamp the catheter to hold the air in.
9. Secure the clamp to the patient (shoulder).
10. Take localization films with a dummy source.
11. Bring the patient to the afterloader and connect the applicator with one of the three nylon tubes(for dose, see computerized dose distribution example).
12. After the treatment, deflate the balloon and remove applicator.

C. Nasopharynx applicator dosimetry

A radioactive source, 1 cm. in length, attached to the end of a stainless steel wire, is introduced into the metallic tube. High intensity cobalt-60 sources are used if the Remote Afterloader is utilized. However, these applicators can be loaded with other artificial radioisotopes if so desired, such as iridium 192 or cesium 137.

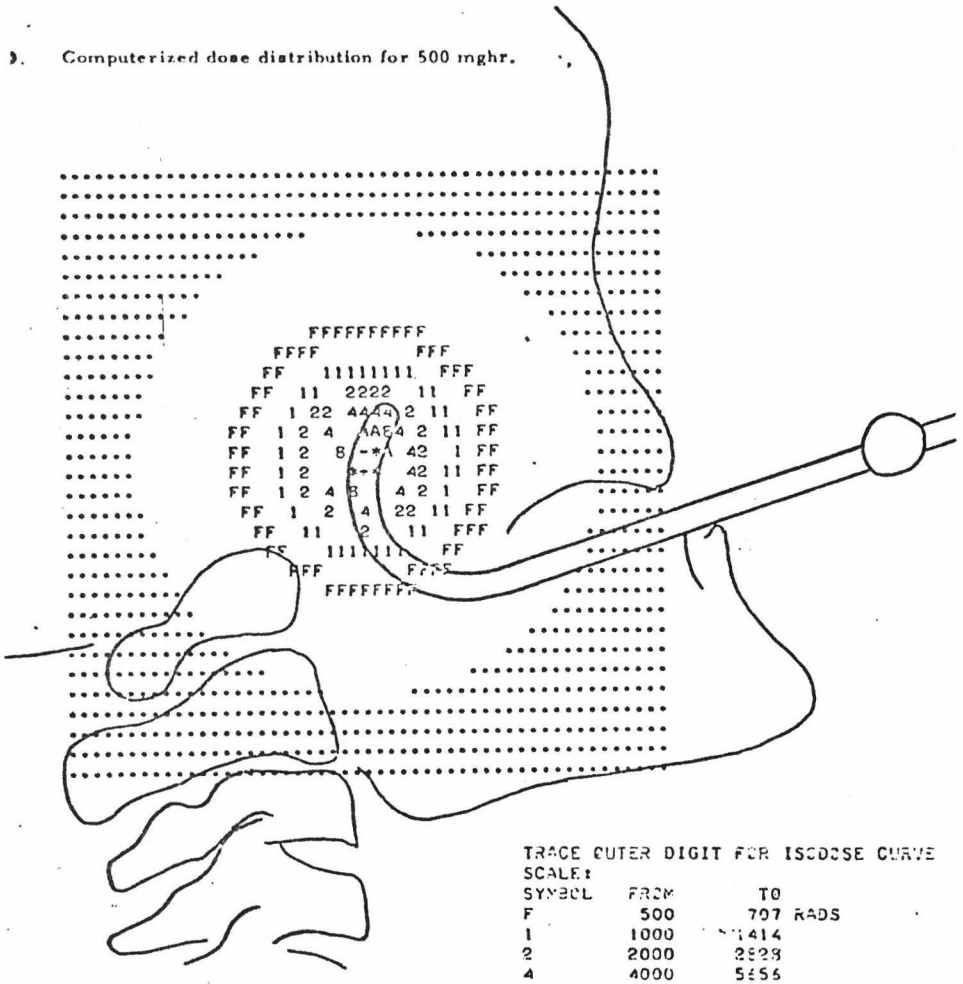
A total of 1000 mghr is given. The dose on the surface of the applicator and at different distances from it is calculated by the inverse square law, since the sources have a predetermined position in the ball. If the pilot balloon of the inflatable cuff is fill with 10 cc of air, it will have a diameter of 2.5 cm.

The resulting dose is strictly correct only if the applicator is surrounded by air. However, the error at least to a depth of 5 cm. with the previously mentioned isotopes is not that great, since the loss by absorption is compensated for by the addition of the scatter as in external therapy. For greater distances, the loss by absorption is greater than the gain by scatter,and a correction should be applied.

Since the introduction of the computer in medicine, complete isodose curves can be calculated at various planes. Because the applicators are standardized, it is possible to use precalculated sets of isodose curves for a specific application. (see drawing illustrating computerized dose distribution, for 500 mghr).

* This work was supported in part by PHS grant # EC 00113, Bureau of Radiological Health, Rockville, Md.

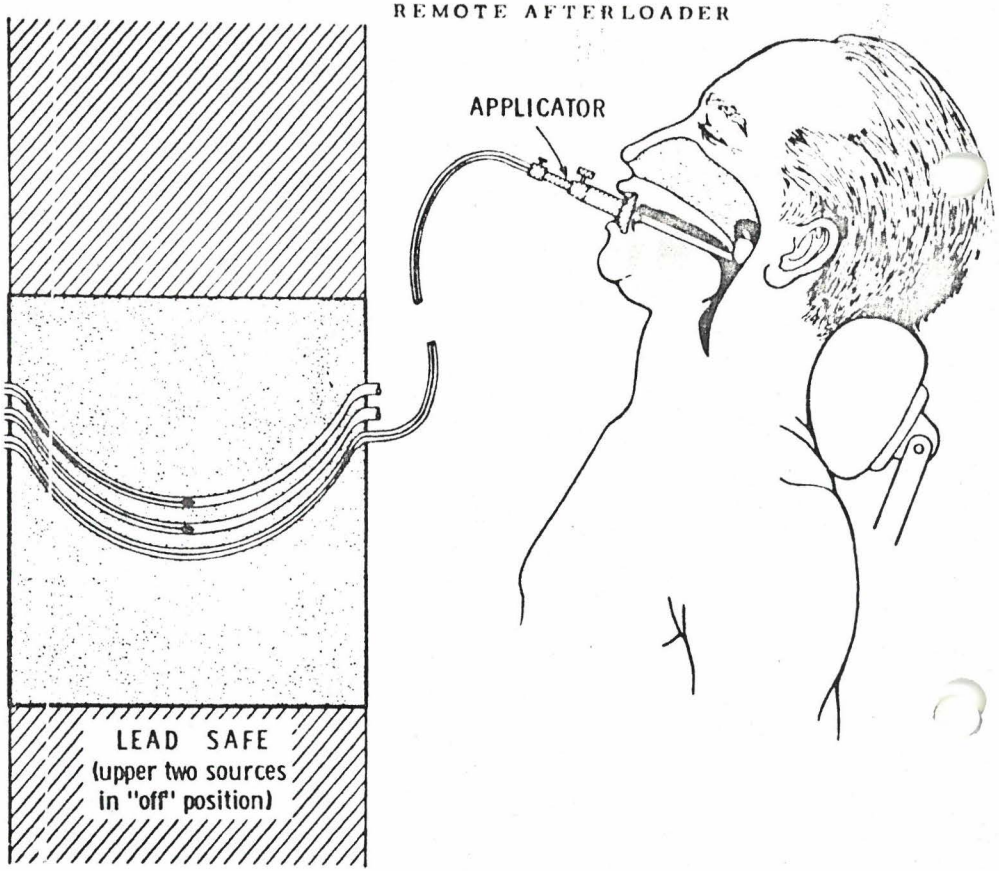
Computerized dose distribution for 500 mghr.



TRACE OUTER DIGIT FOR ISODOSE CURVE

SCALE: SYMBOL	FROM	TO
F	500	707 RADS
1	1000	1414
2	2000	2828
4	4000	5656
8	8000	11313
A	16000	22627
*	32000	MAXIMUM

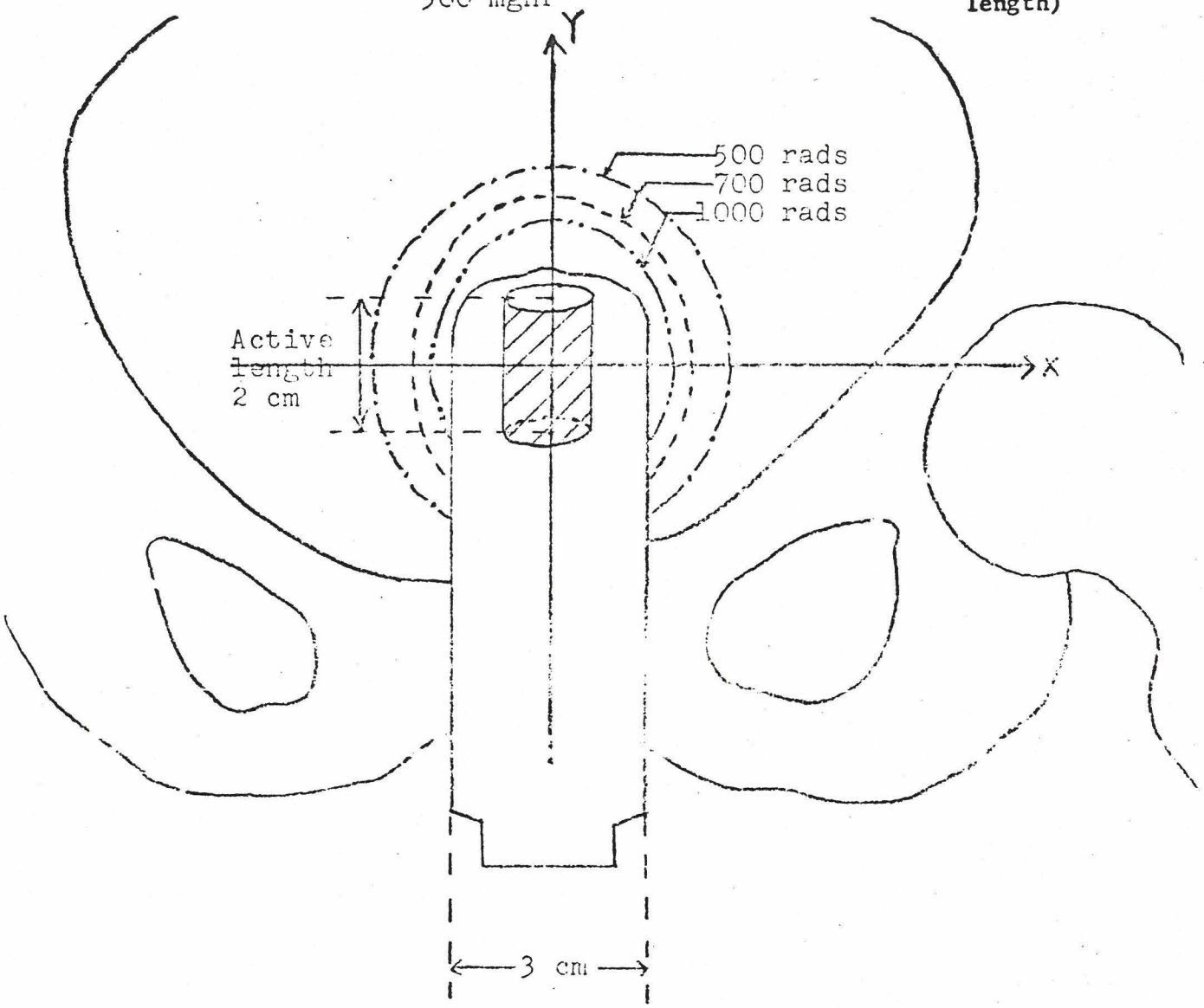
REMOTE AFTERLOADER



3 Co-60 Sources

500 mghr

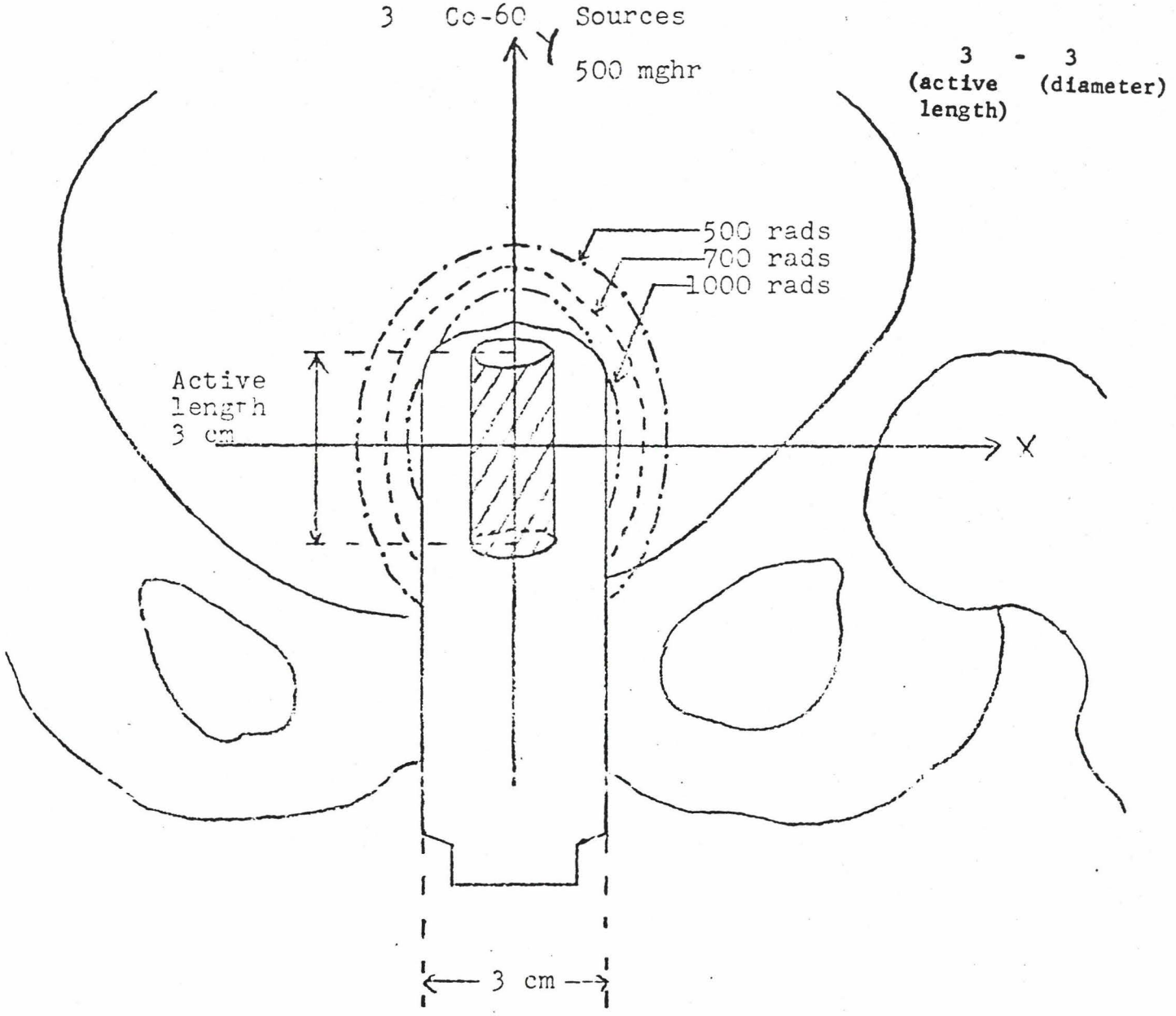
2 - 3
(active length) (diameter)



The isodose curves have been corrected under the pre-calculated and measured result of 12.4 % decrease in source strength due to absorption.

Date: 10/20/71

By: S. T. Chen



The isodose curves have been corrected under the pre-calculated and measured result of 12.4 % decrease in source strength due to absorption.

Date: 10/20/71

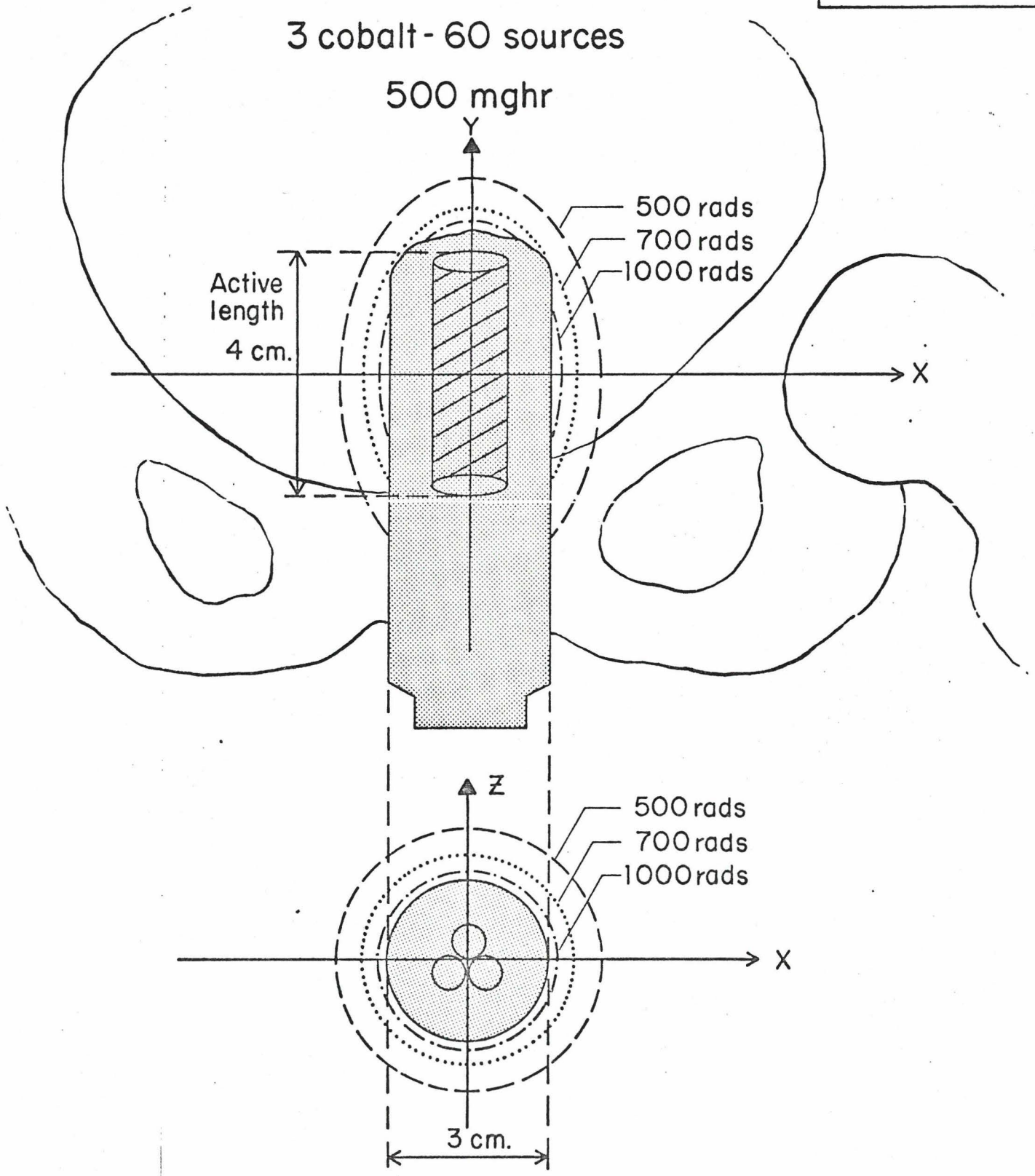
By: S. T. Chen

4 – 3
(active length)(diameter)

REMOTE AFTERLOADER TECHNIQUE

3 cobalt-60 sources

500 mghr



Patient name _____

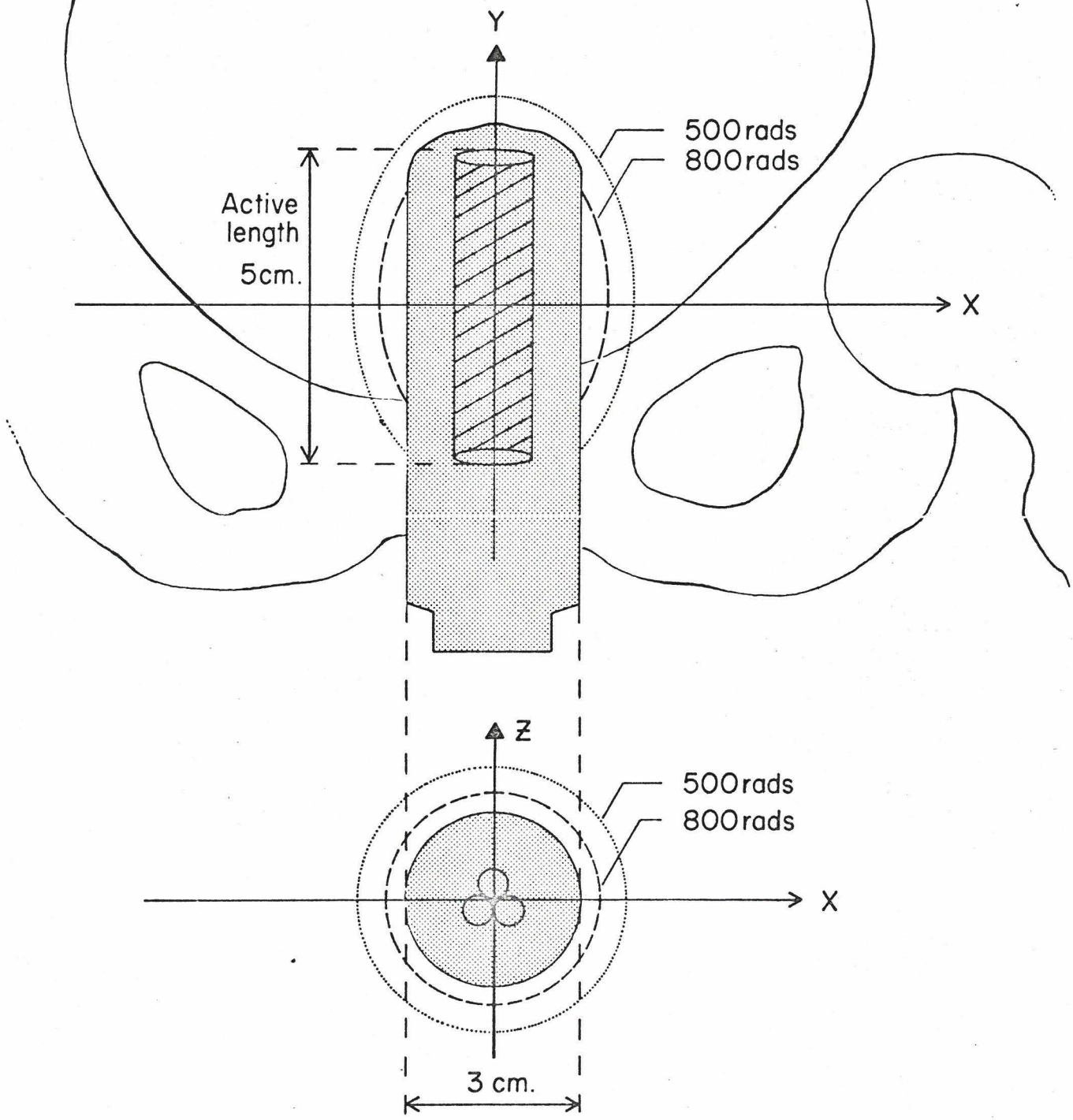
Hospital no _____

REMOTE AFTERLOADER TECHNIQUE

5 – 3
(active length)(diameter)

3 cobalt - 60 sources

500 mghr



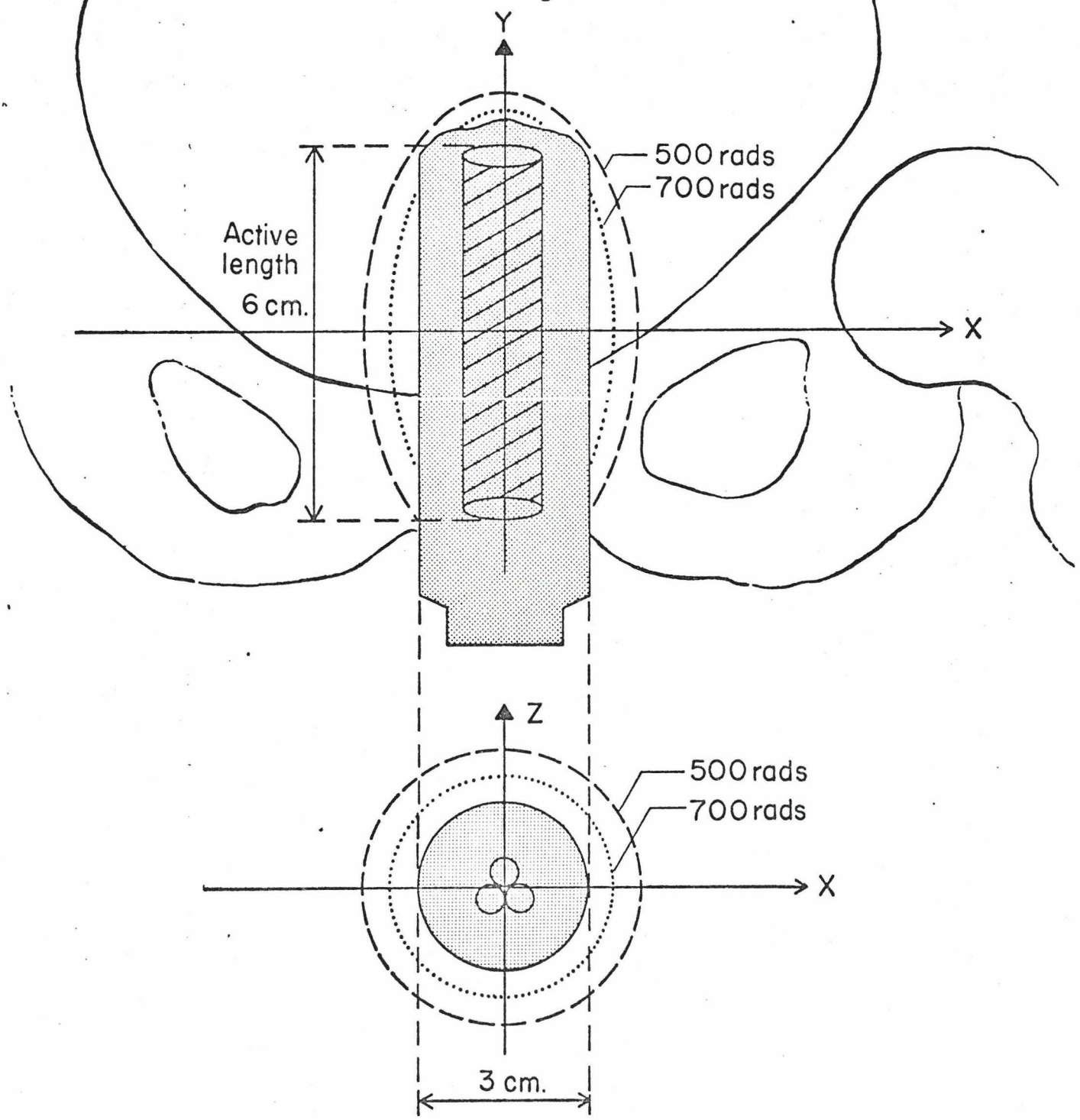
Patient name _____
Hospital no. _____
Date of application _____

6 - 3
(active length)(diameter)

REMOTE AFTERLOADER TECHNIQUE

3 cobalt-60 sources

500 mghr



Patient name _____

Appendix

1) Calculations carried out by Dr. J. Kim of Memorial Sloan-Kettering Cancer Center:

Baseline: 6000 rads continuous radiation in 168 hours is assumed to be the maximum normal tissue tolerance dose; it is equivalent to an NSD of 2000 rets.

2) Dr. Fletcher's technique for vaginal radiation at MD Anderson.

A dose of 6000 rads in 72 hours is equivalent to an NSD of 2695 rets.

3) Vaginal radiation using Remote Afterloader technique at Memorial Hospital

a. A total dose of 3000 rads given in two fractions of 1500 rads each separated by 2 week interval is equivalent to an NSD of 1900 rets.

b. A total dose of 3000 rads given in three fractions separated by 2 week intervals is equivalent to an NSD of 1600 rets.

Remarks

The formula used for calculation of the NSD was proposed by Ellis and is as follows (Modern Trends in Radiotherapy, Series 1, 34, 1967, Butterworth, London):

$$TD = NSD(N)^{\cdot 24}(T)^{\cdot 11}$$

TD = Total dose
N = Fractions
T = Total elapsed time in days
NSD = Nominal standard dose

INSTRUCTIONS FOR INSERTION OF UTERO-VAGINAL APPLICATOR

A PREOPERATIVE ORDERS

1. Schedule insertion with OR
2. Preoperative medication (ordered by anesthesia dept.): atropine sulphate, gr. 1/150; demerol, 50-75 mg
3. Perineal preparation
4. SSE night and a.m. of surgery
5. Nothing by mouth after midnight

B POSTOPERATIVE ORDERS

1. Note on the chart
2. Dictate note in OR
3. Notify radiation safety
4. Order localization films (PA + lateral stereos)
5. Separate room for patient (if standard techniques are used)
6. Bed rest, low residue diet, paregoric 4 cc tid, gantricin 1.0 mg bid x 3, codeine gr 1/2 q. 4-6 hr. prn and ASA gr 10 for pain, connect Foley catheter to bottle.
7. Fill out No. 15 sheet

C POST REMOVAL OF SOURCES (ORDERS)

1. Discontinue radioactive precautions
2. Discontinue paregoric
3. Regular diet
4. Douches with $KMnO_4$ twice daily (1:5000)

D CHECK LIST FOR AFTERLOADING APPLICATOR (Henschke Model)

1. Three central stainless steel uterine tubes each 21 cm long and each having a different curve
2. Two plastic vaginal spacers (2.5 cm diameter hemispheres) each at the end of a stainless steel tube (same diameter and length as No. 1)
3. No. 16 gauge Foley catheter with 5 cc bag (to be inserted into bladder)
4. 5 cc radiopaque material (Hypaque) and 2 cc of methylene blue (to be diluted in 10 cc of saline)

E INSERTION OF APPLICATOR IN OPERATING ROOM

1. After bimanual examination, expose cervix, take biopsies and probe the uterine cavity for position and length. Dilate cervix to take a No. 5 Hegar dilator. Cystoscopy and proctoscopy and D&C are done together with members of GYN Service, only if not done previously.
2. Slide cervical ring down to a distance approximating the measured length of the uterine canal.
3. Insert central tube of applicator into the uterine canal, then the two lateral tubes with the spacers, one after the other, into the right and left vaginal fornices. Attach each of the lateral tubes to the central tube and spread as far apart as possible.
4. Insert 16 gauge Foley catheter with 5 cc bag into bladder.
5. Check by rectal examination proper position of applicator.
6. Pack vagina with 1" inch gauze embedded in betadyne. Push gauze between posterior wall of vagina and ovoids. Repeat anteriorly.
7. Secure position of applicator by T-shaped male binder. In unreliable patients, secure applicator by two matress sutures through the labia majora, one above the applicator and one below.

F DICTATION OF POSTOPERATIVE NOTE. SHOULD INCLUDE A DESCRIPTION OF THE FOLLOWING:

FINDINGS:

1. Appearance of cervix (ulcerated, atrophic, etc.)
2. Size, shape, and position of uterus
3. Extent of tumor; specify whether or not extension to fornices or lower vagina; whether or not extension to parametrium, and how far.
4. Condition of recto-vaginal septum, and anterior extension to bladder, if present.
5. International stage

PROCEDURE:

1. Sound depth of uterine canal
2. Dilation, if done, size of largest dilator used
3. Curettings: character, and from where obtained
4. Biopsy, if taken, and from what point or points
5. Bladder catheter (No. 16 Foley with 5 cc balloon)
6. Insertion of the two vaginal spacers, attachment to the central tube, and degree of spread in centimeters

G X-RAY LOCALIZATION STUDIES

1. Order:
   a. AP stereo of pelvis
   b. Lateral pelvis with patient lying on the side on Bucky table
2. Before taking above films:
   a. In bladder: inject 20 cc of aqueous Dionosil 50 cc of saline
   b. In rectum: insert the special graduated (in centimeter) rectal tube
   c. In central and lateral uterine tubes: insert dummy (inactive) sources

H INSERTION OF RADIOACTIVE SOURCES

IN REMOTE AFTERLOADING ROOM:

1. Bring patient in bed to remote afterloading room and position bed for ease of insertion
2. Connect each lateral tube and the central tube with the plastic tubes of remote afterloader

IN PATIENT'S ROOM (if radium sources are to be used):

Insert the sources, enclosed in one end of a plastic tube. The choice of length and activity depends on the length of the uterine tube and on the desired radiation distribution.

I DOSE MEASUREMENTS

1. Insert measuring probe into rectum and press crystal gently on the anterior wall (do not use extreme pressure). Move probe along anterior rectal wall and watch the instrument indicator at the same time. Determine maximum reading and localization in centimeters from the rectal sphincter; in addition, determine length in centimeters over which you read up to 50% of the maximum dose.
2. Bladder measurements will not be done routinely. If they are desired in a special case, the Foley catheter has to be removed. Bladder measurements should be done before the rectal measurements to avoid contamination of the bladder.
3. If the Remote Afterloader is used, follow instructions for the special probe.

J REMOVAL OF APPLICATOR AND RADIOACTIVE SOURCES

The following steps apply to both the remote afterloading applicator and the ordinary application with radium 226 sources:

1. Remove active sources from the central and the two lateral tubes and put them into the safe.
2. Deflate the Foley catheter of the applicator
3. Rotate applicator 45 , and pull it out gently. If the introitus is very narrow, remove each piece of the applicator separately.
4. Examine patient for bleeding, lacerations, etc.
5. Check parts of applicator and make sure that everything has been removed.
6. Clean applicator.

K RECORDING DATA

For each application, the following data should be recorded:

1. Length and activity of active source(s) in uterus
2. Length and activity of active source in vaginal balls
3. Time of application
4. Time of removal
5. Total application time in hours
6. Total mghrs
7. Dose to point A
8. Dose to point B
9. Dose to primary site (cervix)
10. Maximum dose to rectum and the depth at which it occurred

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DOCKET NUMBER
PROPOSED RULE PR-31,32&35
Medical Uses
(39 FR 2384)

ACNP American College of Nuclear Physicians

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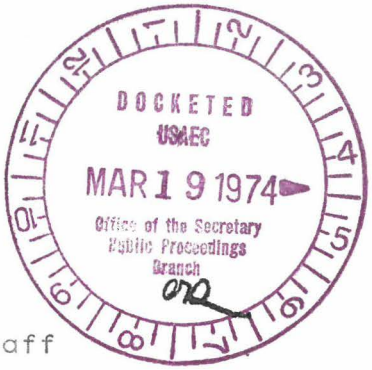
Speaker of the House of Delegates
Richard C. Reba, M.D.
Washington, D.C.

March 14, 1974

Acknowledged 3-19-74, cmz



Secretary of the Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545

Attention: Chief, Public Proceedings Staff

Reference: FR Doc. 74-1678, 10 CFR Parts 31, 32 and 35

Dear Sir:

I have reviewed the above-mentioned publications of proposed rulemaking in the Federal Register, Vol. 39, No. 14, pages 2384-2388, January 21, 1974.

The repeated references to effective New Drug Application (NDA), Notice of Claimed Investigational Exemption for a New Drug (IND) and Biologic Product License from FDA are entirely appropriate for inclusion in this Proposed Rule, which concerns only specific licenses for certain groups of medical uses of byproduct material.

However, since the Proposed Rule also notes the intent of the FDA to terminate the existing exemption for radiopharmaceuticals for investigational use "at an early date", the continued existence of Specific Licenses of Broad Scope appears in jeopardy. It must be emphasized that the original need for the broad license concept with its inherent institutional peer review remains unchanged.

A complete review of FDA regulations relating to New Drugs (21 CFR 130) fails to identify a mechanism equivalent to the AEC broad license. Without such a mechanism, the advances in nuclear medicine, clinical and research, under the guidance and supervision of AEC and Agreement States will be severely curtailed.

It is, therefore, strongly recommended that the Commission take all necessary steps to insure that necessary action is taken to protect public health and safety without unduly

P.O. Box 1245 / Berkley, Michigan 48072

inhibiting the use of radioactive materials in medicine and to assure no disruption in the supply of these drugs, which are of vital importance in many medical applications. I respectfully submit that without the appropriate changes in regulations to permit a continuation of the broad license concept, there will occur a serious impediment in the delivery of nuclear medicine as currently practiced. Equally important, there will be a disruption in the investigational aspects of the development of nuclear medicine in this nation.

Sincerely yours,

Oscar M. Powell, M.D.
President
3135 Webster Street
Oakland, California 94609

OMP/kd

DOCKET NUMBER
PROPOSED RULE PR-31, 32 & 35 (39 FR 2384)
Medical Uses

MEMORIAL SLOAN-KETTERING CANCER CENTER
1275 YORK AVENUE, NEW YORK, NEW YORK 10021
(212) 879-3000

Acknowledged
3-19-74, ERA

March 13, 1974

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USAEC
MAR 19 1974
Office of the Secretary
Public Proceedings
Branch
ERA

Secretary of the Commission
U.S. Atomic Energy Commission
Washington,D.C. 20545

Attn: Chief, Public Proceedings Staff

Dear Sir:

We are responding to the proposed rules 10-CFR, parts 31, 32, and 35, entitled, Group Licensing for Certain Medical Uses, published in the Federal Register, Monday, January 21, 1974. The comment particularly applies to paragraph 35.14, subparagraph b, subheading (7) which states, "For group IV, any licensee who possesses and uses radiopharmaceuticals for therapy shall assure that patients containing more than 8 mCi of iodine-131 for the treatment of thyroid carcinoma or patients containing more than 23 mCi gold-198 shall be hospitalized".

As physicians with fifteen to twenty years experience in treating patients with thyroid cancer with radioiodine, we believe that this rule is too restrictive. The previous rule permitted discharge of patients containing 30 mCi of I-131, although procedures within the hospital required segregation of patients containing levels above 7 or 8 mCi of I-131. Thus, it has been the practice among us using radioiodine to treat thyroid cancer to release patients containing between 8 and 30 mCi to their homes during convalescence from therapy. We estimate that an additional two weeks of hospitalization would be required in the patients receiving I-131 therapy for thyroid cancer. This will add an estimated $3,000 of expense to the therapy, in addition to requiring isolation of the patient within the hospital for that period of time. The isolation already required is oppressive to many patients with this malignant disease.

In regard to the treatment of thyroid cancer with I-131, we now regard this as a routine therapy, no longer subject to governmental support as a research effort and being paid for by patients themselves or their insurance. We also believe that this is an established therapy applicable to a certain small percentage of all patients with thyroid cancer, and of proven effectiveness. We believe that this new regulation will be unduly restrictive and prohibit the application of this effective therapy to some patients with malignant disease who could benefit therefrom. We would request that you look at the integral dose delivered throughout the quarter of the year rather than directing your attention to the 2 mR/hour at 1 meter which is emitted from a patient who contains 8 mCi.

OFFICE OF THE SECRETARY
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Memorial Hospital for Cancer and Allied Diseases
Sloan-Kettering Institute for Cancer Research
Sloan-Kettering Division, Graduate School of Medical Sciences, Cornell University

Secretary of the Commission

It has been our custom to caution patients leaving the hospital with these levels of radiation, that is, between 8 and 30 mCi, to keep their distance from young people, to sleep alone, and to avoid exposure of others unduly. We believe that this conforms to public health safety and does not result in the exposure of the general public to harmful levels of radiation.

We respectfully request that this portion of the proposed rule-making be reconsidered.

Sincerely yours,

Richard S. Benua,M.D.
Chief, Nuclear Medicine Service

Robert D. Leeper,M.D.
Associate Attending
Endocrinology Service

RSB/jcf
copies to:
C. Jules Rominger,M.D.
Philip Johnson, M.D.

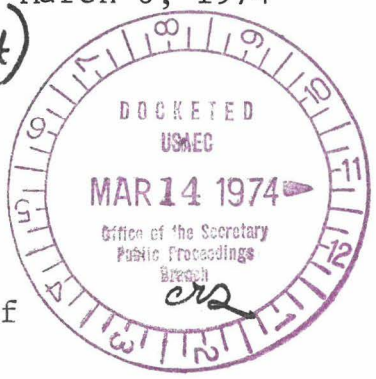
UNIVERSITY HOSPITAL
EDWARD J. CONNORS, DIRECTOR
ANN ARBOR, MICHIGAN 48104

THE UNIVERSITY OF MICHIGAN MEDICAL CENTER

Nuclear Pharmacy

March 6, 1974

DOCKET NUMBER
PROPOSED RULE PR-31,32+35 (39 FR 2384)
Medical Uses



Secretary of the Commission
U.S.A.E C
Washington D.C. 20545

Attention: Chief, Public Proceeding Staff

Gentlemen:

I have reviewed the proposed regulations concerning group licensing for certain medical uses, Fed. Reg. 39, #14, Monday, January 21, 1974.

Upon examinatin of the proposed regulations I note they are directed at actual users of radiopharmaceuticals, and manufactures and distributors to actual users. The question arises do you mean manufactures and distributors in the traditional sense of drug nomenclature, i.e., those who have a manufactures or distributors license issued by State Boards of Pharmacy? Then the proposed regulations are satisfactory as compounding pharmacies are not licensed manufacturers or distributors but are separate from manufacturers and distributors. If this is the intent of the AEC, then clarification of intent could be easily established by using the format contained in Section 510 (g) (1) of the Federal Food Drug and Cosmetic Act.

Furthermore, the exclusion of compounding pharmacies would bring the proposed regulations into conformance with:

1. The intent of Congress in writing Section 510 (g) (1) of the Federal, Food Drug and Cosmetic Act.

2. The regulations now enforced by your sister agency, the Food and Drug Administration.

3. Applicable state laws that provide for the health and safety of patients receiving pharmaceutical s from a licensed pharmacy and a registered pharmacist.

The proposed regulations seem to be a part of the broader question whether the AEC has the regulatory authority over the practice of pharmacy. Please see the attached letter to James Malaro that identifies the problem and suggests a possible answer.

In essence I support the regulations on any entity (Manufacturers, distributors or pharmacies having manufacturing

or distributors licenses) that is suppling in multidose containers radiopharmaceuticals. In this case, individual patients are not identified. However, the proposed regulations, Fed Reg 39 #14, Monday January 21, 1974 should not in any way interfer with the practice of pharmacy, i.e, the compounding of prescriptions for radiopharmaceuticals wherein a prescription for a particular patient is received from a licensed physician.

The best medical care for a patient, involving a pharmaceutical, comes from a close physician-pharmacist relationship where the prescription is optimized for a specific patient. To assume that manufacturers, distributors and pharmacies are synonomous assumes that a particular dosage form is good for everyone regardless of age, disease and physical condition. The exemption of Compounding pharmacies from your proposed regulations is the only way in which the individual health care can be maximized.

Your truly

Rodney D. Ice Ph.D
Associate Professor
College of Pharmacy

RDI:elp

UNIVERSITY HOSPITAL

January 31, 1974

James C. Malaro, Chief
Materials Branch
Directorate of Licensing
United States Atomic Energy Commission
Washington, D.C. 20545

Dear Mr. Malaro:

Our regional nuclear pharmacy is receiving requests for radiopharmaceuticals from nuclear medicine physicians licensed in the State of Michigan. To date, we have only supplied products to physicians who are under the scope of "broad" specific AEC licenses where approval authorization has been made locally. The question arises, what is the AEC policy for dispensing radiopharmaceuticals by pharmacists, on a physicians prescription, where the physician has only a specific AEC license?

Pharmacy represents a profession devoted to the assurance of pharmaceuticals to all patients. This assurance involves availability, quality control and proper patient utilization. Pharmacists who have met established state standards for education, internship, and examination are licensed and registered by the states. A pharmacists professional role is under surveillance by pharmacy organizations where peer review procedures are utilized. Failure to meet established legal regulations can result in loss of license. Patients have recourse to any pharmacist's actions through malpractice action.

Regional nuclear pharmacies represent a method through which the pharmaceutical quality of radioactive materials may be routinely assessed by qualified personnel. Under the aegis of the University of Michigan "broad" specific license, a regional nuclear pharmacy was established at the University of Michigan Medical Center in 1971. The nuclear pharmacy is licensed by The Michigan State Board of Pharmacy and all radiopharmaceuticals are dispensed on prescription only by Michigan State Registered Pharmacists (see attached letter from the Michigan State Board of Pharmacy). Since our nuclear pharmacy is in conformance with applicable local laws, we are exempt from registration and inspection by the FDA (See attached letter from the FDA). The radiation protection aspects of our nuclear pharmacy were presented at the Third International Congress on Radiation Protection, Washington, D.C., September 11-14, 1973. (A preprint is enclosed.)

I recognize the need for adequate regulations regarding radi-

ation protection. However, I would object to any AEC regulations or guidelines that define my professional role of assessing pharmaceutical quality of any product. Pharmacies serve a unique purpose within the health care system, i.e., they can individualize the product for the patient.

Our pharmacy meets all state requirements. I am a board certified health physicist and registered pharmacist. If a licensed physician prescribes a radiopharmaceutical, the manner in which I compound the product for the particular patient represents my professional capabilities. These products are not being manufactured for distribution. We deal with an individual prescription written for a specific patient.

I have examined this matter with counsel and have been informed that, while the AEC may possess statutory authority to regulate in the area, there appears to be no specific rules aimed at nuclear pharmacies. This being the case, I would like to know the exact extent to which the AEC regulates such pharmacies and the authority and rules it specifically relies upon and applies.

Assuming the AEC does, in fact, exercise jurisdiction over nuclear pharmacies, I would like you to consider a separation of regulations for radiation protection for occupational exposed personnel from the practice of pharmacy. Pharmacy practice should be exempted in light of the control exercised by the Michigan State Board of Pharmacy, as was done in connection with the FDA.

Any continued overlapping of jurisdiction can only present possible conflicts, so that it would be better to leave the regulation of a nuclear pharmacy to the control of an expert state body designed specifically to regulate such. The AEC should continue seeking evidence of pharmaceutical quality where radiopharmaceuticals are not obtained from licensed pharmacies having qualified nuclear pharmacists.

The AEC should also consider the possibility of requiring a qualified nuclear pharmacist (as a health physicist is required for radiation protection) on staff or in consultation to staff where not well-established products are being used in lieu of requiring detailed product specifications, quality control, compounding procedures, etc.

Fifteen Universities are currently training nuclear pharmacists. I enclose a preprint describing the Purdue and Michigan Programs. Recognition of Nuclear Pharmacists as specialists is presently being considered by the American Pharmaceutical Association. Nuclear pharmacies are being initiated in several states.

Your assistance in clarifying the status of our pharmacy and the potential nuclear pharmacies operated by my students will be a first step in improving health care delivery in this new area of

of medicine and pharmacy.

Yours truly,

Rodney D. Ice, Ph.D.
Assoc. Prof. of Pharmacy
Director,
Radiopharmaceutical Services
Nuclear Pharmacy

c.c. Don Van Farowe, Chief
Michigan Division of Radiation Health
R.R. Eldredge, Executive Secretary
Board of Pharmacy, State of Michigan

RDI/co

UNIVERSITY OF COLORADO
MEDICAL CENTER
4200 EAST NINTH AVENUE
DENVER, COLORADO 80220

COLORADO GENERAL HOSPITAL
COLORADO PSYCHIATRIC HOSPITAL
CHILDREN'S DIAGNOSTIC CENTER
SCHOOL OF MEDICINE
SCHOOL OF NURSING
SCHOOL OF DENTISTRY

DOCKET NUMBER
PROPOSED RULE PR-31,32+35
Medical Uses
(39 FR 2384)

25 February 1974

Acknowledged 3-14-74, ers

G. Wayne Kerr, Acting Chief
Agreements and Exports Branch
Directorate of Licensing
United States A.E.C.
Washington, D.C. 20545

Dear Mr. Kerr:

At the request of the Colorado Department of Health, I have reviewed The A.E.C.'s proposed amendment to 10 CFR Parts 31, 32 and 35 pertaining to group licensing for certain medical uses. In order to avoid delay, I am sending my comments to you directly. I strongly oppose adoption of these amendments without incorporation of many changes including the following:

1. Section 35.14 paragraph b(7) "8 millicuries of iodine 131" is unrealistic as a limit above wich patients may not leave the hospital. The limit should remain at least as high as 30 millicuries. The limit should apply equally to treatment of hyperthyroidism as well as carcinoma of the thyroid. Patients with hyperthyroidism are often treated with doses of I-131 between 8 and 30 millicuries. It creates an unnecessary financial burden and added discomfort for patients to require hospitalization. It is inappropriate to separate treatment of carcinoma of the thyroid from treatment of hyperthyroidism for purposes of radiation protection. If anything, patients with hyperthyroidism remain highly radioactive longer than patients with carcinoma of the thyroid. In the case of Gold-198 in the same paragraph, this limit should remain as it was in the past but as noted below, this can no longer be considered a "routine" form of therapy. It should be replaced by colloidal chromic phosphorus P-32 except for experimental purposes.

2. The proposed section 35.100 of 10 CFR part 35 as amended contains a number of uses which can not be considered routine because they are now obsolete. Their use should be restricted to experimental situations. Just as you propose to make additions to the groups from time to time, you should be just as ready to make deletions. Otherwise your regulations will only tend to promote the use of suboptimal diagnostic and therapeutic procedures. Specifically, I would recommend

deletion of group I, items 11 and 12, Co-58 and Co-60 labeled cyanocobalamine. In group I, I also recommend substitution of Cr-51 chromic chloroid for Cr-51 labeled human serum albumin, in item 14, since the Cr-51 as albumin has been shown to move to transferrin and use of ionic Cr-51 avoids administration of foreign protein, but achieves the same results. Group II's items (4) and (5) I-131 macroaggregated and microaggretated albumin, (11) Cr-51 albumin for placental localization, (12) Au-198 for liver imaging, (14) Hg-203 chlormerodrin for brain imaging, (16) Sr-85 for bone imaging and Group IV, items 1 and 2 Au-198 colloid for malignancy should all be deleted.

Sincerely yours,

Donald W. Brown

Donald W. Brown, M.D.
Head
Division of Nuclear Medicine

cc: William R. Hendee, Ph.D.
Mr. Robert Siek

THE SOCIETY OF NUCLEAR MEDICINE

305 EAST 45th STREET
NEW YORK, N.Y. 10017
PHONE: 212 • 889-0717

March 8, 1974 DOCKET NUMBER PR-31,32+35 (39 FR 2384)
PROPOSED RULE
Medical Uses

Mr. Gordon M. Grant
Acting Secretary
United States Atomic
Energy Commission
Germantown, Maryland 20545

Dear Mr. Grant:

I would like to express some brief comments in connection with the proposed amendments to 10 CFR, Parts 31, 32, and 35 as published in the Federal Register for January 21, 1974.

In 35.14, part 7, page 2386, it states that patients containing more than eight millicuries of ^{131}Iodine for thyroid carcinoma must be hospitalized. This change from the existing level of thirty millicuries certainly would add considerably to the extreme cost of hospitalization which must be borne by such patients, and would seem to allow therapy doses greater than eight millicuries on an outpatient basis in conditions other than carcinoma (e.g. Plummer's Disease). While I understand and agree completely with the principle of diminishing environmental contamination, I would suggest that this new regulation would seem to elevate the risk far out of proportion to the economic problems which are created.

Sincerely,

John A. Burdine, M.D.
Chairman, Scientific Affairs and
Research Committee

JAB:lw

Acknowledged 3-14-74, ers

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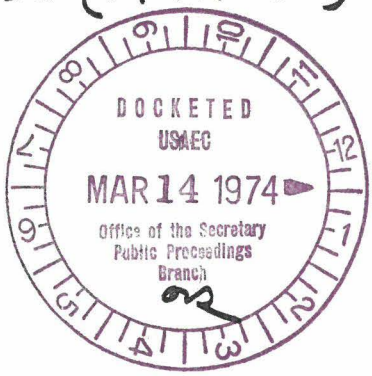
GENERAL ELECTRIC

NUCLEAR ENERGY DIVISION

GENERAL ELECTRIC COMPANY, VALLECITOS NUCLEAR CENTER, VALLECITOS ROAD
PLEASANTON, CALIFORNIA 94566, Phone (415) 862-2211

March 7, 1974

DOCKET NUMBER
PROPOSED RULE PR-31,32+35 (39 FR 2384)
Medical Uses



Secretary of the Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545

Att: Chief, Public Proceedings Branch

Gentlemen:

On January 21, 1974, the AEC published proposed changes in 10CFR Parts 31, 32, and 33 (38FR2384) concerning the licensing of users and manufacturers of radiopharmaceuticals, and requested comments from interested parties. The General Electric Company, Vallecitos Nuclear Center, has reviewed the proposals and has the following comments and/or questions concerning these proposed regulations:

1. The proposed regulations are unclear as to whether specific licenses will be granted under 10CFR35.11, 35.12, or 35.13 for the medical use of byproduct materials not specifically covered under 10CFR35.100. In addition, would such licenses be granted for materials listed 10CFR35.100 but of a different chemical form, dose unit, or application than specified in 10CFR35.100? We believe this should be clarified.

2. 10CFR35.100, Groups I and II, specify that Xe-133 may be received as "prepackaged individual doses only." We are unclear as to why this restriction is placed only on Xe-133 and not other diagnostic radionuclides. A conflict could ensue if the FDA grants a New Drug Application (NDA) for the manufacture and delivery of Xe-133 in bulk. Such an NDA would correctly imply an inherent low risk in permitting the receiving licensee to establish the dose unit. (Please note that conflicts between the NDA required in 10CFR32.72(b) and the provisions of 10CFR35.14 could arise for other byproduct materials.) Again, we are unclear as to why under the proposed regulations dose establishment by the receiving licensee should be permitted for other byproduct materials but not for Xe-133. We recommend that this restriction on Xe-133 be removed.

3. Byproduct material for radiopharmaceutical users is produced by such AEC contractors as National Laboratories as well as private industry, i.e., licensees. We believe that a serious conflict of interest could arise if private licensees are required to meet the provisions of 10CFR32.72(b) for the manufacture, labeling, and packaging of the byproduct materials under an accepted NDA or IND while AEC contractors were exempted. We request clarification of this matter.

Sincerely,

Acknowledged 3-14-74, CRR

G. E. Cunningham
Administrator - Licensing

gw

DOCKET NUMBER
PROPOSED RULE PR-31,32+35 (39 FR 2384)

Mercy Hospital CONDUCTED BY SISTERS OF MERCY
TWELFTH AND NORTH WALKER • OKLAHOMA CITY, OKLAHOMA 73103 • (405) 232-9171

DOCKETED
USAEC
MAR 14 1974
Office of the Secretary
Public Proceedings
Branch

February 27, 1974

Acknowledged

3-14-74, ERA

United States Atomic Energy Commission
Washington D.C. 20545

Re: Proposed AEC Rules 2384-1

Gentlemen:

I have reviewed your proposed new rules published in the Federal Register Volume 39 #14, Monday January 21, 1974. This appears to be a move to simplify licensing and perhaps reduce the volume of paper work necessary to maintain a Nuclear Medicine Department and reduce the volume of paper work necessary by your organization. I therefore encourage you to institute these rules and further modify them to reduce or simplify the paper work involved.

Our goals must be to reduce the paper work volume which is growing steadily day by day. If the holder of a license is competent to use certain agents, new agents which have been approved should be easily added to their license without requiring additional applications. You will have already determined the proven safety of certain products and could therefore simply advise us of their addition to the list of approved materials.

Thank you.

Sincerely yours,

David G. Rogers

David G. Rogers, M.D.
Chairman of the Isotope Committee
Mercy Health Center
Oklahoma City, Oklahoma 73103

HARVARD MEDICAL SCHOOL ◆ MASSACHUSETTS GENERAL HOSPITAL

DEPARTMENT OF RADIOLOGY
Division of Radiological
Sciences and Technology

Mailing Address:
Massachusetts General Hospital
Boston, Massachusetts 02114
(617) 726-8326
if no answer: 726-3033

March 4, 1974

Secretary of the Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545

DOCKET NUMBER
PROPOSED RULE PR-31,32&35 (39 FR 2384)

Attn: Chief, Public Proceedings Staff. Medical Uses

Gentlemen:

Pursuant to the proposed amendments to 10CFR35 published in Federal Register, Volume 39, No. 14 on Monday, January 21, 1974, the Committee on Nuclear Medicine of the New England Radiological Physics Organization and the Standards Committee of the New England Chapter of the Society of Nuclear Medicine (serving jointly) expresses its concern for the limited calibration and reference source allowance covered under 35.14(d).

The experience gained by the above joint committee over the past three years in a regional effort at interhospital calibration and standardization of nuclear medicine equipment has convinced us that the requirements for calibration and reference sources in a well-run nuclear medicine department that might be licensed under one of the groups in 35.100 would not be satisfied by the long-lived standard allowance proposed under 35.14(d). We therefore suggest that the total possession limit for materials of half life greater than seven days be increased to three millicuries, of which up to one millicurie may be in the form of calibration and reference standards, no single source of which may exceed 200 microcuries in strength, and up to two millicuries may be in the form of a large area, uniformly dispersed "flood" source for analysis of gamma camera performance (e.g., employing Cobalt-57).

The joint committee feels strongly that the above recommended standards requirements are minimal in the operation of a basic Nuclear Medicine Program and that the increase in possession allowance suggested will not significantly increase the radiation hazards associated with the overall proposal.

Yours truly, E.W. Webster

N.E.R.P.O., Committee on Nuclear Medici
S.N.M., N.E. Chapter, Standards Committe
J.C. Brantley, Ph.D.,
J.A. Cardarelli, M.S.,
F.P. Castronovo, Jr., Ph.D.,
H. Chandler, M.D.,
S. Genna, Ph.D.,
F. Masse, M.S.,
H. Shore, B.S.,
R.E. Zimmerman, M.S.,
E.W. Webster, Ph.D. -- Chairman.

Acknowledged 3-14-74, ors

E.W. Webster, Ph.D.
IF NOT DELIVERED IN FIVE DAYS RETURN TO
MASSACHUSETTS GENERAL HOSPITAL
FRUIT STREET
BOSTON, MASS. 02114

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USAEC ors
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THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL SCHOOL AT DALLAS
FREDERICK J. BONTE, M.D., DEAN

DOCKET NUMBER
PROPOSED RULE PR-31,32+35 (39 FR 2384)
Medical Uses

March 4, 1974

Dr. Gordon M. Grant
Acting Secretary
United States Atomic Energy Commission
Germantown, Maryland 20545

Acknowledged 3-14-74, ERD

Dear Dr. Grant:

It is my understanding that Special Amendment 35.14, Section B(b) 7 will require hospitalization of any patient who contains more than eight (8) millicuries (mCi) of Iodine-131 activity, if this radionuclide has been administered for the treatment of thyroid carcinoma. I would like to oppose implementation of this proposed regulation for several reasons: (1) For many years, informed physicians and physicists have retained thyroid cancer patients in a hospital until their total body activity was less than 30 mCi, having found on the basis of experience and numerous observations that this was a safe level in terms of persons with whom the patient might have contact, and one which would permit the patient to leave the hospital in a reasonable period of time. Any factor which lengthens hospitalization by two or three days, such as the proposed regulation, will increase the cost of this procedure by $200 to $400. This is hardly a sensible way to manage health care costs.

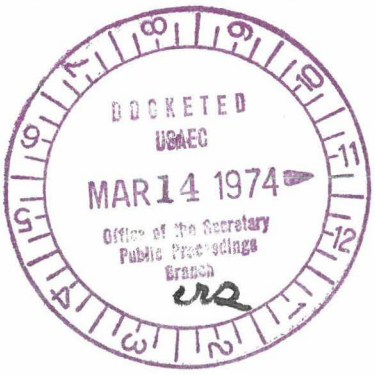
Further, (2) it is my understanding that the regulation calls for the hospitalization of patients who contain the stipulated amount of I-131 for the treatment of thyroid carcinoma, but that they do not stipulate that patients who are being treated for benign thyroid disease, whose number significantly exceeds that of patients being treated for cancer, need be hospitalized until the same body burden is achieved. This likewise does not make sense, and suggests that the entire regulation was not well thought out before publication, and that prior consultation had not been conducted with responsible physicians and radiation physicists. I therefore ask for the withdrawal of this regulation pending open hearings on the subject.

Thank you very much for your attention to this matter, and best personal wishes.

Sincerely yours,

F. J. Bonte /cc

Frederick J. Bonte, M. D.
Dean and Professor of Radiology
Founding Trustee, American Board of Nuclear Medicine
Chairman of Nuclear Medicine, American Board of Radiology



SS

5323 HARRY HINES BOULEVARD ☐ DALLAS, TEXAS 75235 ☐ TELEPHONE (214) 631-3220

DOCKET NUMBER
PROPOSED RULE PR-31,32 & 35 (39 FR 2384)
Medical Uses

March 5, 1974

Secretary of the Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545

Attention: Chief, Public Proceedings Staff

Dear Sir:

In response to your invitation for comment on AEC proposals to extend group licensing (federal register Vol. 39, #14) be noted that:

The attempted simplification of group licensing procedure of trained personnel is simply beyond the scope of your jurisdiction and in my opinion, nor are changes at present necessary.

Yours sincerely,

TRINITY MEMORIAL HOSPITAL
5900 South Lake Drive
Cudahy, Wis. 53110

J. Gimenez, M.D.
Radiologist

JG:DE

Acknowledged 3-14-74 crs

DOCKET NUMBER
PROPOSED RULE PR-31 +32 (39 FR 2384)
+35 – Medical Uses

THE SOCIETY OF NUCLEAR MEDICINE

GREATER NEW YORK AREA CHAPTER

President
C. JULES ROMINGER
Mercy Catholic Medical Center
54th and Cedar Avenues
Philadelphia, Pennsylvania 19143

Secretary
RICHARD N. PIERSON, JR., M.D.
St. Luke's Hospital
421 West 113th Street
New York, New York 10025

President Elect
LESTER M. LEVY, M.D.

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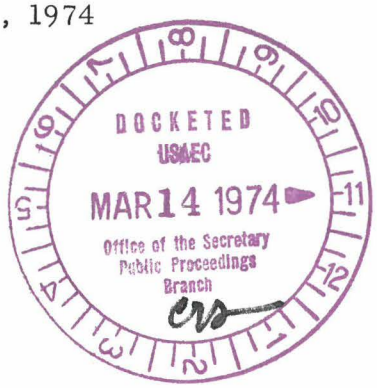
PHILIP A. BARDFELD, M.D.

Historian
SIDNEY RUBENFELD, M.D.

March 5, 1974



Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D. C. 20545

RE: AEC proposal to expand group licensing for certain medical uses of radioisotopes - released 1/21/74

Gentlemen:

I have read proposed rules 2384-1, etc. as published in the Federal Register volume 3 #14, Monday, January 21, 1974.

I am writing to render objection to paragraph 7 on page 2385-2 where there is a requirement for hospitalization for patients containing more than 8 millicuries of I 131 in treatment of thyroid carcinoma. I fail to see the reason for the change in this policy, which for years, has been left at a level of 30 millicuries. I think that to change this regulation at this time, would result in unnecessary hospitalization at a time when Utilization Committees are pushing for proper utilization of hospital beds. I am writing to render this objection as an individual as well as the President of the Greater New York Area Chapter of the Society of Nuclear Medicine.

Sincerely yours,

C. Jules Rominger, M. D

Acknowledged 3-14-74, ers

CJR:lcb

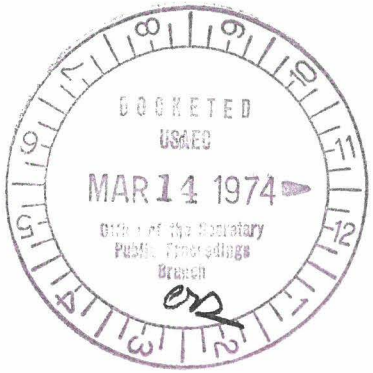
cc: Dr. R. Pierson
Dr. R. Benua

MERCY RADIATION THERAPY CENTER
C. JULES ROMINGER, M.D., DIRECTOR
5301 CEDAR AVENUE
PHILADELPHIA, PENNSYLVANIA 19143

DOCKET NUMBER
PROPOSED RULE PR-31,32,35 (39 FR 2384)
Medical Uses

STATE OF NEW YORK
DEPARTMENT OF HEALTH
ALBANY 12208

HOLLIS S. INGRAHAM, M.D.
COMMISSIONER



March 4, 1974

Acknowledged 3-14-74, ERA

Dear Mr. Grant:

The New York State Department of Health wishes to comment on the proposed regulations published in the Federal Register of January 21, 1974 which would amend 10 CFR Parts 31, 32, and 35 relating to group licensing for certain medical groups.

These proposed changes in federal regulations would help to simplify the present New York State licensing process of radioactive isotope users. Since the number of clinical radiopharmaceuticals has been steadily increasing, there exists a definite need to change the licensing procedures to handle the increasing workload.

At the present time, the New York State Department of Health licenses operators of radioactive isotope installations for a specific isotope or isotopes. If the licensee desires to use an additional isotope, he must file a new application, his training and license must be reviewed and, if approved, an amendment to his license must be processed. Under this new proposed change in the federal regulations, all radioactive isotopes will be categorized and placed in one of five different groups. Therefore, when a person is licensed in the future, he will be licensed by group and will be allowed to use any isotope listed in that group. It will avoid the filing of a new application, the unnecessary review of the licensee's training and the processing of a new license amendment.

However, the present proposals by the AEC need some further study, particularly in the areas listed as follows:

1. In the present proposal we are not sure that the proper isotopes are in the proper groups. The groups should be based upon a selection of common criteria, such as:

   a. type and energy of rays emitted,

   b. sealed or unsealed sources,

c. in-vitro or in-vivo use,

d. type of instrumentation needed for use of isotopes, and

e. degree of potential hazard of isotopes.

2. The groups, when established, should be identified by name summarizing its use rather than by number. A group for "imaging", "scanning" or "therapeutic" means more than a designation by number. In addition, since licensing of nuclear medicine technologists in the near future is a possibility, licensing technologists by the same groups would be a natural extension; but here again, the collection of isotopes going into each group must be done using a workable system.

With these few suggestions, we endorse the proposed regulations.

Sincerely yours,

Hollis S. Ingraham, M.D.
Commissioner of Health

Mr. Gordon M. Grant
Acting Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D. C. 20545

Attention Chief, Public Proceedings Staff

DOCKET NUMBER
PROPOSED RULE PR-31,32+35 (39 FR 2384)
Medical Uses

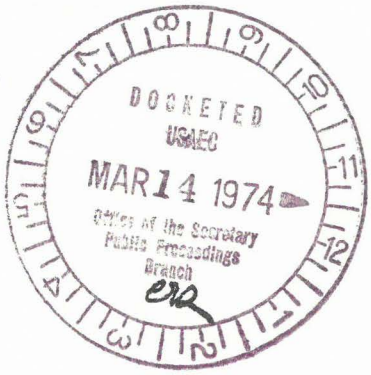
UNIVERSITY of PENNSYLVANIA

PHILADELPHIA 19104

Acknowledged
3-14-74 ers

Radiation Safety Committee

March 7, 1974



U. S. Atomic Energy Commission
Washington, D. C. 20545

Attention: Chief, Public Proceedings Staff

Dear Sir:

This is to comment upon proposed amendments to 10 CFR Parts 31, 32 and 35, "Group Licensing for Certain Medical Uses", as appearing in the Jan. 21, 1974 FEDERAL REGISTER. Our comments are directed to the proposed requirements of 35.14, b, 4, v and to the overall coordination with FDA of investigational uses of byproduct materials in humans.

We do not believe that FDA should terminate the existing exemption from IND requirements for radioactive materials used in humans for investigative purposes until suitable application procedures and criteria for approval of IND applications for radioactive substances have been formulated, discussed and duly promulgated. By extension, we do not believe that AEC should require an accepted IND as a condition for investigational uses in any license schema, group licensing or other, at this time.

AEC has for many years carried the responsibility for investigational uses of radionuclides in humans in view of the FDA exemption and has fulfilled this task with a noteworthy balance between control and undue restriction. Even recognizing the exemption from the IND requirements, the IND process has also been followed in appropriate circumstances. We believe it important that FDA not fully terminate this exemption without first establishing application procedures and approval criteria. This is particularly important in view of the special considerations associated with "radiopharmaceuticals".

Some of these considerations are:

a) In a majority of instances, "radiopharmaceuticals" are not employed as drugs, per se. They are tracers, markers, imaging agents, physiologic indicators, a means of depositing energy for therapeutic purposes, or a combination of such.

b) Investigative uses of radioactive materials in humans often are for purely research use having no direct diagnostic or therapeutic purpose or potential purpose.

c) Physical dosimetry (rads or rems) and evaluation of these considerations.

We recognize the joint AEC/FDA jurisdiction considerations in this matter. But we believe that FDA should show that it is geared to assume the special considerations

associated with radioactive materials in investigative human use without either undue restriction of such use or inadequate control of such use before the transition is effected. We do not believe that this capability can be taken for granted and urge that criteria and procedures to be employed by FDA in this regard be established and disseminated before AEC changes its current procedures in this regard.

Sincerely yours

D S Murray

Donald S. Murray, Chairman
Radiation Safety Committee

DSM/mvw

DOCKET NUMBER
PROPOSED RULE PR-31,32&35 (39 FR 2384)
Medical Uses

TRINITY MEMORIAL HOSPITAL

5900 South Lake Drive — Cudahy, Wisconsin 53110 Telephone: 414 - 769-9000

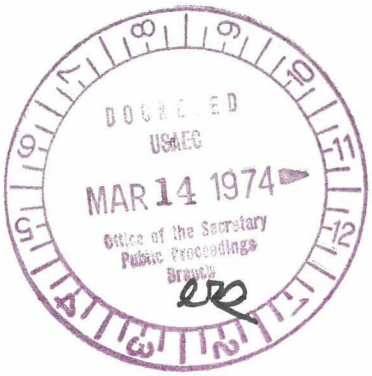
DEPARTMENT OF LABORATORY MEDICINE

Rocco Latorraca, M. D.
Director of Laboratories

Marilyn J. O'Brien, M. D.
Associate Pathologist

Antonio A. Rabor, Jr., M. D.
Associate Pathologist

Acknowledged 3-14-74, ERS



March 7, 1974

Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D.C. 20545

Attention: Chief, Public Proceedings Staff

Dear Sir:

This letter is in reference to the proposed rules in the Federal Registry dated Monday, January 21, 1974 (Vol. 39, #14).

I would be opposed to any change in the existing rules and regulations concerning the medical uses of the Radioisotopes and particularly as proposed in the aforementioned release. The necessity of additional subdivision eludes me, as does the rigidity of the proposed grouping and method of approval. The intention to evaluate the Paramedical personnel is something new.

The latter can only impede further our abilities to both satisfy all governmental requirements and at the same time deliver medical care at a reasonable cost.

Yours truly,

R. Latorraca

R. LATORRACA, M.D.
Director of Laboratories

ea

DOCKET NUMBER
PROPOSED RULE PR-31,32,35 (39 FR 2384)
Medical Uses

State of New York
ATOMIC ENERGY COUNCIL
Department of Commerce
99 Washington Avenue
Albany, New York 12210

CHAIRMAN
NEAL L. MOYLAN
COMMISSIONER OF COMMERCE

STAFF COORDINATOR
DR. WILLIAM E. SEYMOUR
DEPUTY COMMISSIONER
DIV. OF INDUSTRIAL SCIENCES
AND TECHNOLOGIES

Acknowledged 3-14-74, ers

March 6, 1974

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Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D. C. 20545

ATTN: Chief, Public Proceedings Staff

Dear Sir:

The New York State Atomic Energy Council's Committee on Licensing has reviewed the U. S. AEC's proposed amendments to 10 CFR Parts 31, 32 and 35 pertaining to "Group Licenses for Certain Medical Uses."

Since the proposed amendments, which were published in the Federal Register on January 21, 1974, are essentially the same as the draft proposed amendments of October 4, 1973, the Committee has concluded that the comments submitted to the U. S. AEC on November 21, 1973 should be restated.

The Committee generally agrees with the proposal to extend the present group license approach to include generators, reagent kits, therapy with radiopharmaceuticals, and sources and devices. However, the Committee feels that the group licensing procedure should be restricted to routine, well-established medical uses of radioactive materials and that any investigational drugs or procedures should not be included.

The specific comments of the New York City Department of Health are contained in the enclosure.

We appreciate the opportunity you have provided for comment on this proposal.

Sincerely,

T. K. DeBoer, Director
Technological Development Programs

Enc.
cc: Committee on Licensing
TKD/HDB:prp

DEPARTMENT OF HEALTH
OFFICE OF RADIATION CONTROL
[illegible] BROADWAY, NEW YORK, N.Y. 10007
Telephone (212) 566- 7750

Committee on Licensing
RECEIVED
NOV 13 1973
New York State
Department of Commerce
ATOMIC ENERGY COUNCIL

November 9, 1973

TO: Fred Strnisa, Committee on Licensing

FROM: Saul J. Harris, Director, Office of Radiation Control

SUBJECT: Comments on AEC Proposed Amendments to 10 CFR 31, 32 and 35, on Group Licenses for Certain Medical Uses

Since the number of FDA-approved Phase III clinical radiopharmaceuticals has been steadily increasing, there exists a definite need to change the licensing procedures to handle the increasing workload. However, the AEC proposal could result in a loss of radiation control over many uses of radioactive materials.

We have no objection to the concept of licensing radioactive materials by groups for certain in vitro or laboratory uses. However, the use of the "general licensing" approach would be confusing. We also feel that the proposals by the AEC need much further review and comment before they reached the stage that they seem to be in already. Before the proposals were reduced to legal language, as proposed amendments to specific provisions in AEC regulations, they should have been reviewed at some length with the agreement states as a concept.

Our specific comments on the two large documents are:

1. The classification of radioactive materials should be done based upon a careful selection of common criteria, such as:

   a. Type and energy of emitter

   b. Sealed or un-sealed use

   c. Human or non-human use

   d. Type of facilities or instrumentation needed to use

   e. Degree of hazard if completely misused

   f. Whether compliance inspection would be needed, whether labeling would be needed

I am not sure that the groups proposed are properly collected together.

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2. The use of the term "General License" should be avoided, absolutely. I would even suggest that the use of the term in 31.11 for in vitro kits be rescinded. The "certificate of registration" for inbetween quantities of Iodine-125 cannot fit the AEC definition of "General License," as we old-timers know it. I would urge the AEC to retract 31.11 and issue a "Registration License" if they are reluctant to issue specific licenses.

3. I would suggest that the groups, when established, be easily identified by a work or two as well as by a number or a letter. A group for "imaging" or for "teletherapy" means more than designating these by Group II or Group XIX, or Group B or Group L. Why add more "jargon" to the licensing process?

4. Licensing of users should focus on his ability to use one or more groups safely. We could still issue broad, human use or non-human use license, which would permit the institution to issue group authorizations. We could insist that these institutions grant these authorizations on the same criteria (whatever they are) that we would use. This is why the "jargon" should be simplified or eliminated.

5. When and if further control of nuclear medicine technicians is proposed or established, the technicians might be licensed using the same groups. Again, the identification of the groups, assuming the classification has been done with a system of criteria easily understood by technicians, is important.

6. It should be obvious that the new classifications for licensing will have some effect upon compliance inspections. The AEC's new "Categories of Violations" should where possible be reflected in the new categories of licenses. Our chief concern with the use of "General License" terminology for the inbetween in vitro kits is the assumption that such kits never need to be inspected by anyone. If the AEC finds, and deems, certain uses of radioactive materials to be so inherantly safe that no inspections are needed. or that inspections need be made only every five or ten years, then the uses and materials should be classified as "exempt". Can we assume that the simplified group licensing will result in simplified compliance inspection?

7. Where a program has established licensing fees, (such as ours, the AEC's, New Jersey's, etc.) a study of the cost of licensing and compliance inspection by groups should be started. A system of fees for each group might be feasible, with different fees for different costs.

8. A national catalog of classified uses will be needed, each section of which would include those products, licensing criteria, safety program criteria, required equipment and instrumentation, laboratory or office engineering features and layout, and inspection guides appropriate to the classification. The AEC could publish

these as a set for everyone's use. The AEC, FDA, and the agreement states should develop these catalogs together.

In general, as long as the AEC is considering revamping the licensing (and compliance inspection) of medical uses, why not go all the way and get everything in line at the same time. This could include: forms, filing system, computer storage of data, inspection reports, deficiency letters, penalties, etc.

Saul J. Harris

cc: B. Jim Porter (Louisiana)
Dave Lacker (Texas)

DOCKET NUMBER
PROPOSED RULE PR-31, 32, 35
Medical Uses
(39 FR 2384)

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March 5, 1974

Secretary of the Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545

Attn: Chief, Public Proceeding Staff

Dear Sir:

Acknowledged 3-11-74, ers

As regards proposed rulemaking in 10 CFR Parts 31, 32, and 35, I would like to submit the following suggestion:

With reference to 35.14.(b)(7),(requires hospitalization of patients containing more than 8 millicuries of I-131 or 23 millicuries of Au-198) I wish to point out that this requirement will in many cases cause an ambulatory radioiodine therapy patient to be hospitalized for as long as 5 days when it may not be necessary for purposes of the patient's health or the public's safety. No doubt the 8 mCi limit for I-131 was drawn from NCRP Report No.37, but it is also true that Section 4 of that report provides for exceptions to this limit (release with less than 80 mCi if all persons in household are over 45, release with less than 50 mCi if some members of household are under 45) provided that "circumstances leading to the decision to make an exception, the evaluation of the exposure conditions, and the means of controlling individual exposures shall be documented", and that "the local health authorities shall be notified of the action". Certain restrictive procedures are required in Sec. 4.1.2(d).

Furthermore, in the case of patients who have received radioiodine following previous thyroidectomy surgery from which they have recovered, there is no reason for them to be hospitalized as far as their own care is concerned. If the rationale for hospitalization is to control radiation exposure of others, it is worth noting that the population density in the typical hospital ward or suite is much greater than in the typical home. The population exposure, in terms of person-rems, is likely to be lower if such a patient is released under restrictive procedures, rather than hospitalized. There is nothing "magical" about hospitalization.

I note that 35.14.(b)(7) does not apply to patients treated for hyperthyroidism, some of whom receive 8-10 mCi. Was this purposeful? Why apply the rule to thyroid carcinoma patients only?

Is it not possible to reword* 35.14(b)(7) to allow for release of patients according to Table 4 of NCRP No.37? This would reduce unnecessary hospitalization and still provide for protection of the public.

Sincerely,

Roland A. Finston

ROLAND A. FINSTON, Ph.D.
Sr. Health Physicist

RAF/eh
Attachment: Section 4 of NCRP No.37

*for example, by setting a standard for release from hospitalization based upon imposition of restrictions such that no member of the family or public is exposed to more than 0.5 rem.

4. Release from Hospital of Patients Containing Radioactive Material

The Atomic Energy Commission has usually required that patients receiving radioactive materials be hospitalized until their content of radioactivity is less than 30 mCi.[7] Since the exposure rates and half-lives of various radionuclides differ greatly, a more meaningful basis for release from the hospital is the possible exposure to other individuals with whom the patients are likely to associate.

There may be some relatively rare and unusual situations where it would be necessary, or highly desirable, to send a patient home in spite of his carrying a burden that could result in a dose to other persons in excess of 0.5 rem. Such cases may be permitted, *as exceptions,* provided in general that

(1) No person under the age of 45 years *shall* be permitted to receive a dose in excess of 0.5 rem in a year.
(2) No person over the age of 45 years *shall* be permitted to receive a dose in excess of 5 rems in a year.
(3) The circumstances leading to the decision to make an exception, the evaluation of the exposure conditions, and the means of controlling individual exposures *shall* be documented.
(4) The local health authorities *shall* be notified of the action.

The division at the age of 45 is suggested by that made in NCRP Report No. 17 [1] which permits weekly doses twice as high for the individual over 45 as for those under that age. A higher permissible dose as an exception for the older group is recommended here for the probably small number of exceptional patients to be sent home. The alternative would be to declare someone in the household a radiation

[7] Exceptions to this requirement are provided when it appears likely that the release of the patient will not result in radiation exposure to members of the household, or others, greater than that permitted for members of the general public. In this report it is recommended that exposure rate rather than activity constitute the basis for patient release.

TABLE 4—*Radioactivity levels for discharge of radioactive patients from hospital*

Radionuclide	No Restrictions		All Persons in Household Over 45 Years of Age. Restriction as in Section 4.1.2(d)[a]		Some Members of Household Under 45 Years of Age. Restrictions as in Section 4.1.2 (d)[b]	
	Exposure Rate at 1 Meter	Activity at Discharge	Exposure Rate at 1 Meter	Activity at Discharge	Exposure Rate at 1 Meter	Activity at Discharge
	mR/h	mCi	mR/h	mCi	mR/h	mCi
Cr-51	0.5	35	5	350	1.5	100
Au-198	5.3	23	53	230	16	70
I-125	0.2	8–80[c]	2	20–800[c]	0.6	25–250[c]
I-131	1.8	8	18	80	11	50
Rn-222	3.8	4.6	38	46	15	18
Ir-192	0.2	0.4	2	4	0.6	1.2
Ta-182	0.1	0.2	1	2	0.3	0.6

[a] These levels are in general higher than any likely to be encountered.

[b] These values are rather arbitrarily selected on a basis of the probability of the situation. They represent complete integrated doses of between 1.5 and 2.5 R.

[c] These values cover a large range, due to the variable attenuation of the 35 keV x rays in the patient.

worker, and to institute the necessary system of supervision and monitoring.

Table 2 presents data for total integrated exposure from specific therapeutic doses of several radionuclides. Based on this information, further tables for permissible exposure times for the two levels assigned to persons under and over 45 years of age have been developed (see Table 4 and Section 4.1). It is recognized that as far as people in the household are concerned, exposures taken from these tables will be approximate, since it is certain that specified distances will not be maintained for specified periods. The object here is to present reasonable limits. Longer distances and shorter times will lead to smaller exposures and need cause no concern. But shorter distances and longer times lead to higher exposures and are to be avoided.

On the basis of Table 4, it is seen that in some cases a 30-millicurie limit for discharge of the patient from the hospital is unnecessarily restrictive, especially when treatment has been with short-lived radionuclides. On the other hand, adequate protection for other individuals is not necessarily assured by a 30-millicurie limit when long-lived nuclides are used. The following recommendations have been formulated to correlate discharge from hospitals with possible exposure to persons in patients' homes.

4.1 Discharge of Radioactive Patients from the Hospital

4.1.1 *Patients Containing Radioactive Nuclides with Half-lives Greater than 125 Days.* It is recommended that for therapeutic procedures involving the use of gamma-ray emitting nuclides with half-lives greater than 125 days, the patients *shall* be hospitalized for the duration of the treatment. Radium-226, cobalt-60, and cesium-137 are nuclides in this category; these sources *shall* be removed before discharge of the patient. Exposures to other patients can be calculated as discussed in Section 3.5 and the provisions of that Section *shall* be observed. Such a situation has been analyzed in Section 3.7.

4.1.2 *Patients Containing Radioactive Nuclides with Half-lives Less than 125 Days.*

(a) It is recommended that in the case of iodine-125, iodine-131, chromium-51, and radon, patients may be released without restrictions when their radioactive content does not exceed the amount listed in Table 2. The physician, with the concurrence of the Radiation Protection Supervisor, *shall* be permitted to increase these values slightly for the short-lived nuclides. However, it is suggested that rather than making any substantial increase he *should* make use of one of the restrictive procedures discussed in Section 4.1.2 (d)

(b) It is recommended that hospitalization be required for at least 48 hours following the intraperitoneal or intrapleural administration of colloidal gold-198. Accidental loss of colloidal gold occurs usually via the insertion site and a period of at least 48 hours permits observation of the progress of healing of the puncture wound. After this period release can be in accordance with Section 4.1.2 (a)

(c) Patients treated with the long-lived tantalum-182 or iridium-192 need special consideration (see 4.1.2 (e) below)

(d) Following hospitalization, as recommended in (a) and (b) above, discharge of all patients who have received therapeutic amounts of any radioactive nuclide *shall* be governed by the following provisions.

(1) A patient *shall not* be discharged from the hospital if the maximum integrated exposure, at a distance of one meter from the patient, for continuous exposure, exceeds 5 R in one year.

The initial exposure rates at one meter, or the activities which will result in an integrated exposure (for continuous exposure) of approximately 5 R in one year, can be obtained from the last two columns of Table 2, by multiplying the values there given by a factor of 10.

(2) If the initial exposure rate at one meter, or the activity remaining in the patient, indicates by the above application of values in

the last two columns of Table 2, that the integrated exposure will not exceed 5 R in one year, provision for release from the hospital *shall* be made for one of two different situations, as follows:

(i) In the event that all persons in the household of the radioactive patient, and hence all those persons with whom the patient will have appreciable contact, are *over the age of 45 years:*

—The patient *should* be instructed to remain at distances greater than 3 feet from other people, except for brief periods for necessary procedures.

—Babies and young people (*of ages less than 45 years*) *should not* visit the patient, but if they do, the visits *should* be brief, and a distance of at least 9 feet from the patient *should* be maintained.

(ii) In the event that a person *under the age of 45 years* lives in the household of the patient:

—Stricter precautions *shall* be observed than when all contacts are with persons over 45 years of age.

—Children and persons under 45 years of age *shall not* be allowed in the same room, nor at a distance of less than 9 feet, for more than a few minutes a day. Observance of these conditions will insure that persons under 45 years of age will not be exposed to more than 0.5 R per year from the radioactive individual.

—Other restrictions may be specified by the physician.

All restrictions may be removed when the activity reaches that listed in Table 2. The Radiation Protection Supervisor *shall* determine this time, and give the necessary instructions. The instructions *should* be printed or typewritten. A form similar to that given in Appendix IV, or at least the pertinent parts thereof, may be used.

These conditions for release are summarized in Table 4.

(e) Permanent implants with the relatively long-lived iridium-192 and tantalum-182 constitute more serious problems than arise with the shorter-lived nuclides. It is difficult to maintain precautions for a year or more. Accordingly, permanent implants with these nuclides *should* be limited. A patient with such an implant *should* be discharged only when it is reasonably certain that precautions will be observed. The precautions *shall* be given in detail by the physician or the Radiation Protection Supervisor to the responsible persons in the household.

For doses of these long-lived nuclides such as might be encountered, and also for larger doses of short-lived nuclides, for households containing young people (under 45 years of age), more detailed data may be useful to the physician and the Radiation Protection Supervisor. Accordingly, Table 5 has been developed for this purpose.

Three categories of contact with the patient are used in Table 5: "no

TABLE 5—*Approximate times for permissible exposures (for persons under 45 years of age) at indicated distances from patients with indicated exposure rates at 1 meter, or indicated radionuclide content, at time of hospital discharge*

[These rates at the time of discharge from the hospital are arbitrarily selected on the basis of probability of the situation.]

Radioactive Nuclide	Exposure Rate at 1 Meter at Time of Discharge from Hospital	Approximate Activity at Time of Discharge	Category of Contact with the Patient		
			"No Contact" (Greater than 2 Meters Distance)	½ Hour/Day at 1 Meter Plus 2 Hours/Day at 2 Meters	4 Hours/day at 1 Meter
I	II	III	IV	V	VI
	mR/h	mCi	weeks following discharge	weeks following discharge	weeks following discharge
Chromium-51	1.5	100	(see column V)	1st, 2nd & 3rd	4th, 5th & 6th
Gold-198	16	70	1st	2nd & 3rd	no restrictions
Iodine-125	0.6	75	1st thru 4th[a]	5th thru 10th[a]	11th thru 18th[a]
Iodine-131	11	50	1st	2nd, 3rd & 4th	5th thru 8th
Radon	15	18	1st	2nd & 3rd	4th, 5th & 6th
Iridium-192	8.0	15	1st thru 24th	25th thru 35th	36th thru 45th[b]
Tantalum-182	5.0	17	1st thru 27th	28th thru 44th	45th thru 60th[b]

[a] For the very unpenetrating radiation from this nuclide, a fluoroscopic type leaded rubber apron should provide good protection. On the advice of the Radiation Protection Supervisor, such a garment may be used to permit spending more time near the patient.

[b] It is recognized that these conditions are extremely difficult to maintain. Accordingly, use of permanent implants of these nuclides *should* be limited. The activities given are much greater than ten times the values of Table 2. They represent, however, clinically possible situations.

contact", "½ hour per day at 1 meter (3 feet) plus 2 hours per day at 2 meters", and "4 hours per day at 1 meter". These obviously do not meet all practical situations; they serve, rather, as practical guides.

(i) There *should* be "no contact" with the patient after discharge from the hospital for the period specified in column IV, Table 5. By "no contact" is meant that the distance between the patient and an individual under 45 years of age *should* be greater than 2 meters (6 feet). In practice it *should* be considerably greater most of the time.

(ii) For the period listed in column V, Table 5, the individual under 45 years of age may spend half an hour a day at 1 meter, and 2 more hours per day at 2 meters. For the remainder of the time he *should* be farther away.

(iii) At the expiration of the period listed in column V, Table 5,

restrictions can be considerably relaxed, but the conditions listed in column VI should be observed—not more than 4 hours a day at 1 meter.

(iv) Holding of infants by the patient *should not* be allowed until the period listed in column VI has passed, and then only for a brief period each day.

(v) Brief periods of closer contact, such as shaking hands, may be permitted.

(vi) Following the period in column VI, Table 5, definite restrictions are removed, but prolonged close association with the patient *should* be limited.

For somewhat smaller initial exposure rates, observation of the same times will result in a larger margin of safety, and this is probably simpler than trying to make adjustments in the table. If the initial rates are as little as half those tabulated, the times per day in each category can be doubled or distances reduced to ¾ of those tabulated.

For initial exposure rates exceeding those tabulated by more than 15 percent, corresponding reductions *should* be made in the permissible times. Thus for a patient with 30 mCi of radon (25 mR/h at onset), the time at one meter in the second week *should* be reduced to 40 minutes per day. The appropriate instructions *should* be given to the responsible family member at the time of discharge. This may well be in the form of a typewritten memorandum embodying the times for the two specified "contacts". A suggested form for such instructions is given in Appendix IV.

When such a patient is sent home, it will be noted on his chart. A specific statement concerning instructions given the family is desirable. A suitable form for insertion in the history is given in Appendix III.

TABLE 6—*Approximate activity which will produce an exposure rate of 0.25 R/h at 25 cm*[a]

Radionuclide	Approximate Activity
	mCi
Gold-198	70
Iodine-131	70
Iridium-192	30
Radon-222[b]	20
Tantalum-182	20

[a] Values for Cr-51 and I-125 are not given in this table because the amounts required to produce this exposure rate are not ordinarily used in clinical practice.

[b] In equilibrium with short-lived daughters and filtered by 0.5 mm Pt.

4.2 Return of Patient to Work

The patient with a permanent implant may feel well enough to return to work after a short period. In such a case there would be a possibility of his irradiating his fellow workers, or in the case of a teacher, of irradiating his students. Accordingly, any such case *should* be studied by the Radiation Protection Supervisor before permission to work is granted. The same rules *should* be followed as for individuals under 45 years of age at home. Workers who are always at least 2 meters from others would be governed by the provisions of column IV of Table 5, but those who may be closer will need to wait longer. Particularly when school children might be exposed, the patient with iridium-192 or tantalum-182 *should not* return to work for the first year without the advice of the Radiation Protection Supervisor. Exposure to "innocent bystanders" in travel to and from work by public transport must be considered and conditions set by the Radiation Protection Supervisor.

4.3 Death of Radioactive Patient at Home

It must be impressed upon the responsible family member that if the patient dies at home or in another hospital, the radiation therapist *shall* be informed *immediately*. (A statement to this effect *should* be included in the instruction sheet. See Appendix IV.) The embalmer is not to be considered a radiation worker, and hence his maximum exposure *should not* exceed 0.5 R/year. Table 6 gives the approximate millicuries which will result in one half of this total exposure in one hour (see Section 5.2). If the patient received iodine-131, gold-198, or radon, embalming can be safely performed provided the body is not opened. If there is to be an autopsy the provisions of Section 5 *shall* apply and the autopsy *shall* be performed in an institution with a Radiation Protection Supervisor.

Section 5 contains detailed information covering many contingencies for patients who die or need emergency surgery while in the hospital. Pertinent parts of this section can be applied to the patient who dies or has an emergency illness at home.

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DOCKET NUMBER
PROPOSED RULE PR-31,32+35
Medical uses

ACNP American College of Nuclear Physicians

March 8, 1974 (39 FR 2384)

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Secretary of the Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545

Attention: Chief, Public Proceedings Staff.

Acknowledged 3-11-74, ers

Dear Sir:

I send you these remarks for your consideration in connection with proposed amendments to the rules in Title 10 of the Code of Federal Regulation part 35 - in particular Section 35.14 (d) as published on page 2386 of the Federal Register, vol. 39, No. 14 of Monday, January 21, 1974.

Section 35.14 (d) reads "Any licensee who is licensed pursuant to paragraph (a) of this section for one or more of the medical use groups in 35.100 also is authorized to receive, possess and use for calibration and reference standards any byproduct material with an atomic number not higher than 83 in amounts not to exceed 15 millicuries total of materials with half lives not longer than seven days and not to exceed 200 microcuries total of materials with half lives longer than seven days."

These proposed amendments would, in my opinion, place an unnecessarily low limit on licensees in regard to calibration standards, particularly those with half lives longer than seven days.

Calibration standards soon to be sponsored by the Society of Nuclear Medicine would exceed these limits. Flood pools for imaging devices exceed these limits and are needed for day to day activity in nuclear medicine laboratories.

Licensees handle and keep safe much larger amounts of radioactive materials for other matters in medicine. It seems unnecessary to so restrict amounts of radioactivity allowed for calibration standards.

I urge that you consider less strict limits for

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calibration standards and suggest that you solicit members of your advisory committee for limits in keeping with current safe practice.

Sincerely yours,

Oscar M. Powell, M.D.
President
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OMP:rp

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DOCKET NUMBER
PROPOSED RULE PR-31,32 & 35 (39 FR 2384)
Medical Uses

March 4, 1974

Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D. C. 20545

Acknowledged 3-8-74, crs

Attention: Chief, Public Proceedings Staff

Dear Sir:

This letter is in reference to the proposed rules in the Federal Registry dated Monday, January 21, 1974 (Vol. 39, #14).

I would be opposed to any change in the existing rules and regulations concerning the medical uses of the Radioisotopes and particularly as proposed in the aformentioned release. The necessity of additional subdivision eludes me as does the rigidity of the proposed grouping and method of approval. The intention to evaluate the Paramedical personnel is something new that the commission has taken on to itself, I would suggest that it confine its attention to its present regulatory function without attempting extension of its scope. The latter can only impede further our abilities to both satisfy all governmental requirements and at the same time deliver medical care at a reasonable cost.

Yours truly,

G. J. Biedlingmaier

G. J. Biedlingmaier, M.D.
Radiologist
Director, Department of Radiology

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DOCKET NUMBER
PROPOSED RULE PR-31,32+35 (39 FR 2384)
Medical Uses

Roy E. Woodard, Jr., R.T. (NM)
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Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D. C. 20545
ATTN: Chief, Public Proceedings Staff

Acknowledged 3-8-74, ERP

Dear Sir:

Having read the AEC Notice of Proposed Rules Change, Dated 21 Jan. 74, Relating to Expansion of Group Licensing for Certain Medical Uses of Radioisotopes, it appears that the provisions of this expansion do indeed represent one of the most significant advances in simplification of the burden of licensing procedures that has been made in years. It is a laudable achievement, particularly with respect to paragraph 35.100.

There is however a section of paragraph 35.14 (section 7) that leaves much to be desired in terms of clarity. The specification reads to the effect that 'any licensee who possesses and uses radiopharmaceuticals for therapy shall assure that patients containing more than 8 millicuries of iodine 131 for the treatment of thyroid carcinoma or patients containing more than 23 millicuries of gold 198 shall be hospitalized'. It appears from the wording of this section that although hospitalization is necessary for all thyroid cancer patients containing more than 8 millicuries of iodine 131, hospitalization would be unnecessary for a hyperthyroid patient containing 25 millicuries of iodine 131 administered for the treatment of hyperthyroidism. I submit that the current wording of section 7 is inadequate since the hyperthyroid patient containing 25 millicuries of iodine 131 would certainly be much more of a radiation hazard for a much longer period of time (if all technical and physiological factors are considered) than would the thyroid cancer patient who in most cases will demonstrate a very low 24 hour retention due to the fact that most of these cancer patients will have undergone surgical thyroidectomy.

I propose that a more realistic guide would be along those lines found in NCRP 37, relating to hospitalization of the iodine 131 containing patient. In many cases hospitalization of the patient containing the 8 millicuries, or even the patient containing 25 millicuries of iodine 131 would not necessarily be hospitalized if all pertinent factors, including medical, occupational, and environmental situations were carefully considered.

I respectfully request that section 7 of paragraph 35.14 be carefully reviewed with respect to improvements in both clarity of wording, and functional practicality.

Roy E. Woodard Jr.
ROY E. WOODARD, Jr., R.T. (NM)

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AMERICAN SOCIETY OF HOSPITAL PHARMACI

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April 30, 1973

Secretary of the Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545

Attention: Chief, Public Proceedings Branch

Dear Sir:

The American Society of Hospital Pharmacists desires to comment on the proposed revision of 10 CFR Part 135 as published by the Atomic Energy Commission (AEC) on March 9, 1973, at 38 Federal Register 6399. We appreciate the extension of time granted in which to submit our comments.

The ASHP is the national specialty society of pharmacists practicing in hospitals and related institutions throughout this country. We have a natural interest in the proposed regulation since ASHP members are practicing radiopharmacy in a wide variety of institutional settings and are highly qualified professionals in the field of nuclear medicine. As a result of this involvement, ASHP has supported expansion of radiopharmacy education and practice since the development of the specialty. Committees were formed to bring radiopharmacists together and provide a forum for continuing education. The American Hospital Formulary Service, a comprehensive drug compendium published by ASHP and updated 4 times a year is a leading reference for the institutional use of radioisotopes. As an example of Section 78:00 (Radioactive Agents) from AHFS, we have attached the general statement on radiopharmaceuticals as well as a listing of the former Advisory Panel on Radiopharmaceuticals (Appendix A). ASHP's American Journal of Hospital Pharmacy, an important source of professional literature, has published articles dealing with the practice of radiopharmacy. Attached is the most recent article from AJHP, Brown, M.L.: Radioimmunoassay and Its Application in the Measurement of Triiodothyronine, Amer. J. Hosp. Pharm. 30:336 (Apr.) 1973. (Appendix B). Previous articles in this area include: Fincher, J.H. and Jones F.E. : Current Handling Procedures of Radiopharmaceuticals in U.S.

Hospitals, Amer. J. Hosp. Pharm. 27:38 (Jan.) 1970: Bowen, B.M. and Wood, D.E. : The Radiopharmacist in Nuclear Medicine - Preparation of Technetium-99m Human Serum Albumin Macroaggregates, Amer. J. Hosp. Pharm. 26:529 (Sep.) 1969 and Barnett, M. and Barletta, F. : The Pharmacist's Role in Radiological Health, Amer. J. Hosp. Pharm. 24:361 (Jul.) 1967.

Pharmacists are an integral part of the nuclear medicine team and perform specialized activities based upon education and training that were first developed in pharmacy. Pharmacists are generally responsible for selection, storage and distribution of drugs and maintaining security over drug stocks. Preparation and compounding of pharmaceuticals are traditional duties in the practice of pharmacy. More recently, pharmacists have expanded their activities to include consultation with both patients and other professionals, drug administration and education and research among peer groups and technical personnel.

Just as with physicians in the area of nuclear medicine, relatively little additional training is needed to qualify pharmacists to work with radiopharmaceuticals. Duties of radiopharmacists include:

1. Responsibility for Radiopharmacy Preparation and Administration:

   Synthesis of radiopharmaceuticals; Compounding and dispensing radiopharmaceuticals; Advising on dosage form and incompatibilities; and,

   Overseeing radiation safety procedures;
   Improving and maintaining radiosotope facilities;
   Handling radiopharmaceutical aspects of State and Federal Food and Drug laws.

2. Involvement in Research and Development:

   Improving existing preparative and dispensing techniques;
   Studying synthesis and metabolism of new radio-pharmaceuticals;
   Assisting with research involving labeled compounds.

3. Participation in Teaching:

   Educating the patient;
   Training nurses and technicians;
   Lecturing to interns and residents;
   Instructing other pharmacists in radiopharmacy.

As with all other drugs, the preparation of radiopharmaceuticals requires a knowledge of drug characteristics, chemistry and efficacy which a pharmacist is uniquely qualified to exercise. His abilities are also useful in the supervision of technical personnel.

As we understand the proposed regulations they would, in part, establish which activities must be performed by licensed physicians and which uses may be performed by other persons when making medical use of radioisotopes. However, we note the absence of any reference to the important duties performed by qualified pharmacists on a daily basis in comprehensive nuclear medicine programs. It seems appropriate that the regulations should clearly recognize the pharmacist's role in nuclear medicine. Therefore, we recommend that the following changes be made to accomplish this goal:

1. Amend §35.32(c) to read:

> Subject to the provisions of paragraphs (b), (d), (e), (f), and (g) of this section, an authorized physician or pharmacist may permit technicians and other paramedical personnel to perform the following activities: ...

2. Amend §35.32(d) to read:

> Authorized physicians or pharmacists who permit activities to be performed by technicians and other paramedical personnel pursuant to paragraph (c), of this section shall: ...

With the preceeding modifications, the proposed regulations should provide an improved approach to the control of radioisotopes for medical use. We appreciate this opportunity to provide our comments to you and would be pleased to meet with representatives of the AEC to discuss the matter further.

Yours truly,

Carl T. DeMarco, J.D.
General Counsel

CTDM:jm
Enclosure

r. J. Hosp. Pharm. 31:158–164 (Feb.) 1974

Centralized radiopharmaceutical services of the Indiana University Medical Center

Michael P. Kavula, Jr.

The facilities of a centralized radiopharmacy service are described, and the formulations of the routine radiopharmaceuticals prepared by the service are presented in detail.

The radiopharmaceuticals discussed are sodium pertechnetate used for cerebral imaging, ^{99m}Tc-sulfur colloid for reticuloendothelial system imaging, ^{99m}Tc-macroaggregated albumin for lung imaging, ^{99m}Tc-diethylenetriamenepenta acetic acid for renal imaging, ^{99m}Tc-human serum albumin for placental and blood pool imaging, and ^{99m}Tc-1-hydroxy-ethylidene-1, 1-disodium phosphonate for bone imaging.

Key words: Formulations; Pertechnetate; Pharmacy, institutional, hospital; Planning and design; Radiopharmaceuticals; Radiopharmacy; Technetium

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Radiopharmaceutical services at the Indiana University Medical Center are offered by a centralized radiopharmacy that supplies radiopharmaceutical kits and radiopharmaceutical unit doses to the Medical Center's three nuclear medicine clinics.

The current trend in Nuclear Medicine is to prepare routine diagnostic radiopharmaceuticals from kits, a "kit" being any combination of sterile, pyrogen-free, nonradioactive reagents packaged in unit-of-use or unit dose type containers. In order to prepare the needed radiopharmaceutical, one must usually just add the radioactive ingredient and follow a simplified procedure using aseptic technique.

Within the past year, nuclear medicine has witnessed a plethora of commercially available radiopharmaceutical kits. Even if the nuclear medicine clinic in a hospital relies entirely on commercially supplied kits, the pharmacist can extend his consultative services by advising the nuclear medicine physician or technologist on which kit is best for the particular study intended. The consultant role of the pharmacist in nuclear medicine is most important when one considers that radiopharmaceutical advertising is not regulated as "legend" drug advertising is; thus, the commercial suppliers have concentrated their advertising campaigns on the nuclear medicine physician and the nuclear medicine technologist, both of whom have had little or no pharmaceutical training.

It is the philosophy of our radiopharmacy service to rely as little as possible on commercial suppliers and to prepare most radiopharmaceutical kits "in-house." Our reliance on commercial suppliers is in the form of clinical investigation for manufacturers who are obtaining the necessary clinical data for FDA approval.

In 1963, Briner published an article in the *Journal* describing the methodology of preparing radioactive chemicals for human use.[1] Ten years later this article remains as the first paper a pharmacist should read prior to developing a radiopharmacy service. In an article entitled, "Radiopharmacy—The Emerging Young Speciality," published by Briner in 1968,[2] he describes the scope of radiopharmacy as consisting of: (1) formulation, (2) control, (3) research and development and (4) consultation; to this list can now be added the fifth category of education.

Before a pharmacist can perform control, research and development, consultative and educational services relating to radiopharmaceuticals, an adequate and thorough knowledge of the formulation of radiopharmaceuticals is necessary. It is the objective of this paper to present, in detail, the formulations of the routine radiophar-

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flow hood modified with a center plastic window to divide the counter lengthwise into two sections. This modification allows the use of the air system from either side of the dispensing counter. Clear plastic side windows extend down from the sides of the laminar flow hood to the dispensing counter to form a box-like structure. A lead-shielded refrigerator (B) to the right and a lead-lined storage module (C) to the left of the dispensing counter allow for quick availability of radiopharmaceuticals from either side.

A record/calculation bench (D) displays records for each radiopharmaceutical and permits calculation of doses to be done away from a radiation area. Receipt of radiopharmaceuticals from vendors is handled through a window separating the bench (D) from the check-in and distribution area (E). A door leading only to the distribution area from the traffic lane prevents unauthorized persons access into the radiopharmacy.

Counter areas (F & G) provide approximately 18 linear feet each for quality control equipment such as microscopes, chromatography apparatus and *p*H meters. Beneath each counter are drawers for miscellaneous supplies and two removable trash receptacles for nonradioactive materials. A bathroom sink and stall shower (H) are available for personnel decontamination.

A "barrier" wall separates the dispensing area from the high-level activity area (I). Radioactive gases and oral iodine solutions are stored under a chemical exhaust hood (J) and also dispensed from this area. Fixed stainless steel counters with drawers and a stainless steel sink adjacent to the exhaust hood are adequate for the iodine preparative techniques. Elutions of short-lived radionuclides from radioactive generators are also handled in this area.

A "hot" storage area (K) permits storage of filled radioactive gas spirometers and aerosol equipment. A 55-gallon drum serves as a temporary radioactive waste disposal bin within this area.

An entrance (L) allows passage from one room to the other avoiding security problems at traffic lane doors. Sliding doors at entrances within the radiopharmacy allow more space and avoid the hazards of hinged doors when radioactive materials are being transported. Extemporaneous preparations of nonradioactive materials are compounded in the manufacturing area (M). Radiopharmaceuticals that require specific equipment and long preparation times are also prepared in this area. A laminar air flow hood (N) is provided for aseptic procedures, and a portable autoclave and pyrogen oven are available for sterilization. Wall-mounted storage cabinets allow for the storage of glassware and chemicals.

The low-level counting area (O) has been located away from the high-level activity areas (J and K). For measurement of low-energy radionuclides (50–500 keV) a sodium iodide well scintillation system will adequately accommodate routine counting requirements. A lithium-drifted germanium detector sensitive to gamma radiation between 10 keV and 1.5 MeV would be desirable to measure very low energy radionuclides with better resolution.[4]

Areas P and Q are the teaching area and technician/secretary area, respectively. Since most nuclear medicine departments have radioisotope technician programs, a generous amount of space should be used for teaching aids and tape cassette/film strip for individual instruction. Radiopharmacy students and technicians, nuclear medicine resident physicians and technicians, and pharmacy students can rotate through the learning program without affecting the clinical functions of the radiopharmacy service.

The administration section (R) is the office for the supervision of radiopharmacy services and library for the drug information service. An intercommunications system within the radiopharmacy allows for conversations among the various rooms without having to handle a telephone. A separate intercommunication system allows for conversation between radiopharmacy and nuclear medicine personnel.

The climate of the radiopharmacy is regulated by central air conditioning in all areas.

Lighting is with standard fixtures strategically located over working areas.

Research

In most hospitals, animal studies are not allowed in the same areas used for patients. Although many pharmaceutical research projects and quality control procedures require the use of test animals, the clinical environment is not the place for such studies. Arrangements should be made to have a small area outside the hospital for research and animal holding quarters. Vivaria facilities are available to most investigators upon request.

Summary

The steps involved in the planning and construction of a radiopharmacy depend upon the services offered and the types of radioactive materials to be handled. A simple compounding type radiopharmacy program obviously requires only limited equipment and physical space whereas a more complex operation requires a "hot" laboratory with a variety of equipment. Although specific requirements will vary for each facility, guidance for a step-by-step development of a model radiopharmacy is outlined.

References

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3. Tubis, M. (Chief Clinical Research Biochemist, Veterans Administration Center [Wadsworth], Los Angeles, California): Personal communication.

4. Harwood, G. (Chief, Health Physics, LAC-USC Medical Center, Los Angeles, California): Personal communication.

maceuticals that are currently being used at the Indiana University Medical Center.

Physical Facilities

The radiopharmacy is an integral part of the nuclear medicine clinic at the University Hospital and is composed of four separate rooms.

Radiopharmaceutical Preparation—Hot Lab (Figure 1). In this laboratory most extemporaneous mixing of the radiopharmaceuticals is done. All the technetium-99m radiopharmaceuticals are prepared in this room. Note the "L-shield" for added personnel protection and the plastic backed absorbent paper on the bench top. Personnel who prepare the radiopharmaceuticals also wear long laboratory jackets and disposable gloves for added protection.

Chemistry and Pharmacy Laboratory (Figure 2). In this laboratory preparative chemistry and final packaging of the radiopharmaceutical kits are accomplished. All work is done using aseptic technique and presterilized equipment, and all packaging procedures are performed within a laminar flow hood. An analytical balance is used to weigh accurately the various ingredients. A chemistry exhaust hood is used for labelling procedures that involve radioactive iodine[3] and other volatile radionuclides or for chemistry procedures that require the use of an exhaust hood.[4]

Chromatography and Additional Chemistry Laboratory (Figure 3). In this laboratory we have set up our chro-

Figure 1. Radiopharmaceutical preparation—hot lab; radiopharmacy assistant preparing a radiopharmaceutical using accepted radiation safety procedures (jacket, gloves, tongs, lead shielding)

Figure 2. Chemistry and pharmacy laboratory

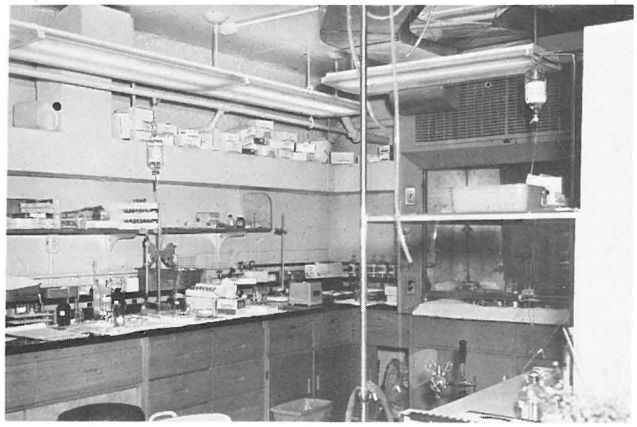


Figure 3. Chromatography and chemistry laboratory

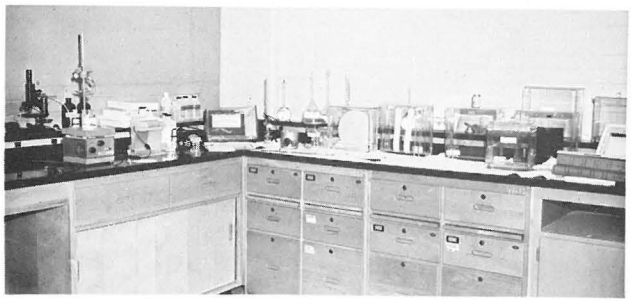
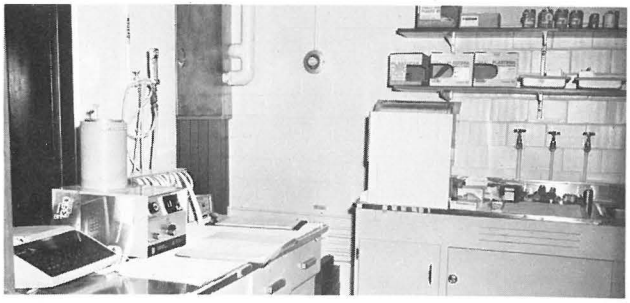


Figure 4. Dispensing radiopharmacy



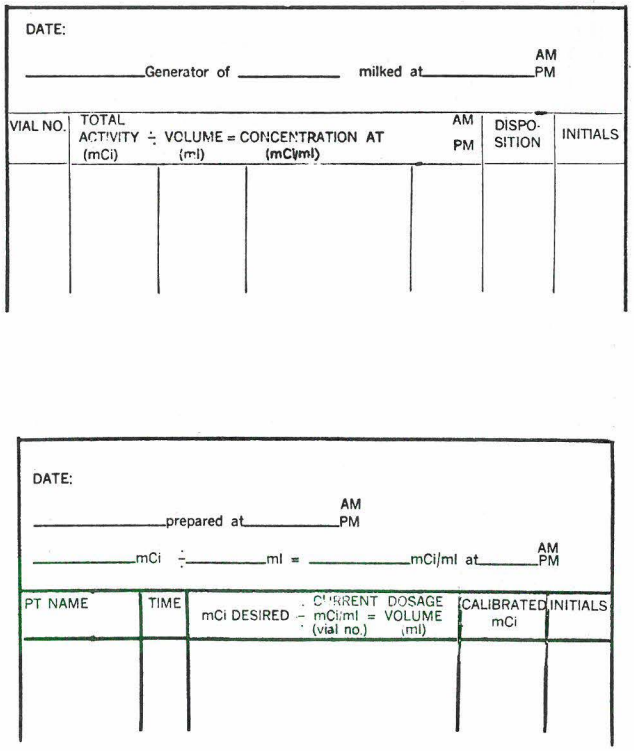
matography chambers and various chemistry procedures that do not require the exhaust hood.

Dispensing Radiopharmacy (Figure 4). The dispensing radiopharmacy is located within the clinical area of nuclear medicine. After the radiopharmaceuticals are prepared in the radiopharmaceutical hot lab (Figure 1), they are assayed in the dose calibrator, labelled and entered into the log books. Every radiopharmaceutical must be entered into a log book and each patient dose must be recorded in a manner very similar to controlled substances. We have devised a rubber stamp that simplifies the entry and calculation of doses (Figure 5).

Vials and lead containers are labeled with a special radioactive label that is in International Radiation Colors and dose syringes and syringe lead containers are labelled with Monarch labels that include the patient's name, name of the radiopharmaceutical, assay, time and date (Figure 6). After the patient has been dosed, the label on the lead container is removed and placed in the patient's record. Unit doses for the other laboratories are calculated, assayed and dispensed through this area.

Radioactive iodine-131 and iodine-123 for therapeutic and diagnostic purposes are stored in a chemistry exhaust hood in the dispensing radiopharmacy. Our source of xenon-133 gas for pulmonary ventilation studies is also stored under the hood.

Figure 5. Rubber stamps used to aid log book entries; the top stamp is used to log in generator elutions and the bottom stamp is used to log in various radiopharmaceuticals



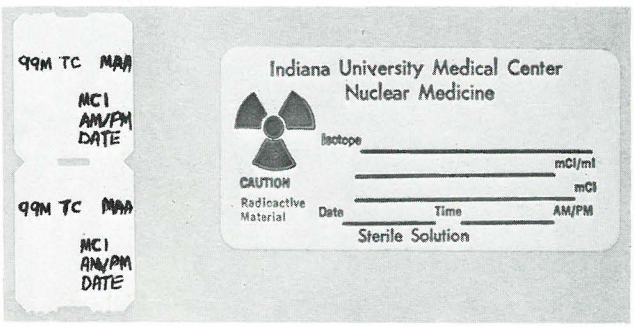
Routine Radiopharmaceuticals—Formulation Procedures

Sodium Pertechnetate, $Na^{99m}TcO_4$: Cerebral Imaging. This radiopharmaceutical is primarily used for imaging of the cerebrovascular space but has also found use in thyroid, cardiac and placental studies.[5] Sodium pertechnetate is the eluant as obtained from the commercially available molybdenum-99-technetium-99m anion exchange generators, the chemistry and physical properties of which have been adequately covered in the literature.[6-8] Suffice it to say that all molybdenum-99-technetium-99m generators are *not* alike and the pharmacist can offer consultative services to the nuclear medicine laboratory in regard to purchase of a generator. Some of the criteria I use in the selection of a generator are:

1. Compatibility of generator eluant with radiopharmaceutical kits,
2. Radiation exposure from generator,
3. Elution technique and radiation exposure during elution procedure,
4. Method of preparation of molybdenum-99,
5. Radionuclidic purity of eluant,
6. Strengths available and calibration date, and
7. Price.

^{99m}Tc-Sulfur Colloid: Reticuloendothelial System Imaging. ^{99m}Tc-sulfur colloid is the most commonly used agent for reticuloendothelial system imaging although other agents have been proposed and employed.[9,10] The

Figure 6. Radiopharmacy labels; label on right is used to label vials and outside lead containers; label on left after being filled out is placed on the dose syringe and lead syringe container



history and development of ^{99m}Tc-sulfur colloid has been covered in a recent issue of the *Journal*[11] and I shall present the formulation used at Indiana University Medical Center. Our formulation is based on the method published by Patton et al.[12] and consists of a reaction vial, hydrochloric acid vial and phosphate buffer vial.

Formulation of Kit Reagents:

A. Premix sulfide stock solution.
   1. Decant 600 ml of 0.9% NaCl from a 1500-ml Abbott Urogate container.
   2. Dissolve 1.2 g of sodium thiosulfate ($Na_2S_2O_3 \cdot 5H_2O$) and 250 mg of potassium perrhenate in the Urogate bottle.
   3. Dissolve 9 ml of benzyl alcohol in the Urogare bottle. Mix well.
   4. Using 0.9% sodium chloride for injection (i.v. container), q.s. to the 1000-ml mark. Mix well.
   5. Attach a Venotube 20-inch to the cystoscopy set, attach 0.22-μ Millipore filter and 23-gauge needle.
   6. Package 10-ml portions in precalibrated 30-ml vials.
   7. Change the Millipore filter and needle frequently throughout the packaging procedure.
   8. Autoclave for 30 minutes at 15 psi.
   9. Fill out the appropriate reagent control form and label the containers.

B. Hydrochloric acid, 1.0 N.
   1. Decant 325 ml of sterile water from a 500 ml Abbott Urogate container.
   2. Add 16.4 ml of concentrated HCl. Mix well.
   3. Using sterile water for injection (i.v. container), q.s. to 200 ml. Mix well.
   4. Attach a Venotube 20-inch to the cystoscopy set, attach a 0.22-μ Millipore filter and a 23-gauge needle.
   5. Package 1.5–2.0-ml portions in 5-ml vials.
   6. Change the Millipore filter and needle frequently throughout the packaging procedure.
   7. Autoclave for 30 minutes at 15 psi.
   8. Fill out the appropriate reagent control form and label the containers.

C. Phosphate buffer.
   1. Decant 750 ml of sterile water from a 1500-ml Abbott Urogate sterile water container.
   2. Dissolve 152.4 g of disodium phosphate ($Na_2HPO_4 \cdot 7H_2O$) and 9.2 g of monosodium phosphate (NaH_2PO_4-H_2O) in the Urogate container.
   3. Add 9.0 ml of benzyl alcohol. Mix well.
   4. Using sterile water for injection (i.v. container), q.s. to 1000 ml. Mix well.
   5. Attach a Venotube 20-inch to the cystoscopy set, attach a 0.22-μ Millipore filter and a 23-gauge needle.
   6. Package 2–3-ml portions in 5.0-ml vials.
   7. Change the Millipore filter and needle frequently throughout the procedure.
   8. Autoclave for 30 minutes at 15 psi.
   9. Fill out the appropriate reagent control form and label the containers.

D. Preparation of ^{99m}Tc-sulfur colloid.
   1. Begin heating water for boiling 5–10 minutes before continuing.
   2. Add 1–5 ml of ^{99m}Tc sodium pertechnetate to the 30-ml reaction vial containing 10 ml of the premix sulfide solution.
   3. Add 1.0 ml of 1.0 N HCl to the 30-ml sterile vial and equip the vial with a vent needle (e.g., 23-gauge).
   4. Heat the reaction vial in the boiling water bath for 4–5 minutes.
   5. Remove the reaction vial from the water bath and allow to cool to room temperature (about 10–15 minutes).
   6. Add 2 ml of phosphate buffer. Mix well.
   7. Compute the total volume by adding the volume of ^{99m}Tc pertechnetate added to 13 ml. Divide the total volume into the final assay figure (mCi) in order to obtain mCi/ml.
   8. Label properly and enter in log book.
   9. Shake well before removing dose.

E. Discussion of formulation: Sulfur colloid preparations have a tendency to settle and aggregate upon standing and for this reason various stabilizers have been utilized to prevent this aggregation and eventual lung uptake upon injection. Gelatin,[13] mannitol[14] and PVP[15] have been reported in the literature as possible stabilizers for sulfur colloid preparations. Most commercially available sulfur colloid kits employ gelatin as the stabilizer.

A stabilizer is not used in our preparation because we feel that the majority of adverse reactions that have been attributed to colloidal prepartions are due to the stabilizer.[16] Potassium perrhenate, a homologue of technetium, is used as a carrier and stabilizer in our preparation and apparently prevents the technetium-labelled sulfur colloid particles from hydrolyzing into free technetium.[17] Our preparation will aggregate and in order to prevent this, it is necessary to shake the vial well prior to withdrawing a dose.

Quality control chromatography is performed on this radiopharmaceutical using Whatman 3MM paper and 85% methanol.

^{99m}Tc-Macroaggregated Albumin (MAA): Lung Imaging. We recently reported on the formulation for this radiopharmaceutical which consists of one reaction vial containing all the ingredients.[18]

Formulation of Kit Reagents:

A. Hydrochloric acid, 0.25N.
   Transfer 2.1 ml of concentrated HCl, ACS reagent, to a sterilized 100-ml volumetric flask. Add water for injection (no preservative) to the 100-ml mark. Mix well. Filter through a 0.22-μ Millipore filter into 2.0-ml sterile vials. Store in the refrigerator. Fill out the appropriate control form and label.

B. Stock macroaggregated albumin (MAA) suspension, 3 mg/ml.
   1. Add 1 ml of 5% human serum albumin (salt-poor) to a 30-ml sterile vial.
   2. Add 15 ml of 0.9% NaCl solution (no preservative).
   3. Add 6 drops of 0.25 N HCl (use 1-ml syringe with 18-gauge needle).
   4. Autoclave at 250 F for 15 minutes.
   5. Allow to cool to room temperature.
   6. Mix gently and centrifuge at 190–200G for 2 minutes.
   7. Draw off the supernate and reconstitute with the same volume of 0.9% NaCl (no preservative).
   8. Resuspend and package 3-ml portions in 10-ml sterile vials.

C. Stock tin solution: 15.0 mg $SnCl_2 \cdot 2H_2O$/100 ml.
   1. Weigh 15.0 mg of stannous chloride ($SnCl_2 \cdot 2H_2O$) and place in a 100-ml volumetric flask.
   2. Add 0.25 ml of concentrated HCl and dissolve the stannous chloride with heat.
   3. Add sterile water (no preservative) that has been previously purged with sterile N_2 gas up to the 100-ml mark. Mix well.
   4. Filter through a 0.22-μ Millipore filter and package 1.0-ml portions in the vial containing the MAA suspension.

D. Phosphate buffer: 0.8 M $NaH_2PO_4 \cdot H_2O$.
   1. Weigh out 11.04 g of NaH_2PO_4 and place in a 100-ml volumetric flask.
   2. Add sterile water (no preservative) to the 100-ml mark. Mix well.
   3. Pass the solution through a 0.22-μ Millipore filter.
   4. Package 0.15 ml of the solution in the 10-ml sterile vial containing the MAA suspension and stock tin solution.

E. Processing of 10-ml reaction vial.

1. Purge the atmosphere of the vial containing the MAA suspension, tin solution and buffer with sterile nitrogen for 5 minutes.
2. Remove the vent needle and leave a positive pressure of sterile nitrogen in the vial.
3. Label properly and include a two-week expiration date.

F. Preparation of ^{99m}Tc-MAA.
1. Remove the positive pressure within the reaction vial with a 25-gauge needle.
2. Gently add 5 ml of $Na^{99m}TcO_4$ to the reaction vial.
3. If less than 5.0 ml of $Na^{99m}TcO_4$ is used, bring the volume up to 5 ml with 0.9% sodium chloride injection.
4. With forcep, swirl the vial for 1 minute (do not shake vigorously).
5. Centrifuge the reaction vial at 190–200G for 2 minutes.
6. Remove the supernate and resuspend the particles with 8.0 ml of 0.9% sodium chloride (10-ml syringe with 20-gauge needle).
7. The final product has a volume of 9.15 ml.
8. Assay in the dose calibrator and determine the concentration (mCi/ml).
9. Label properly.
10. Shake the vial *gently* before withdrawing a dose.

G. Discussion of formulation: A longer shelf life than two weeks can probably be obtained by packaging the three ingredients separately and then adding all three to a vial at the time of preparation. However, we feel that by including all ingredients in one vial there is less chance of error, and emergency lung procedures are also expediated by having a single vial that needs only minimal manipulation in order to prepare the radiopharmaceutical.

Reagent preparation is rather straight forward with the following exceptions:

(1) Macroaggregated albumin suspension: It is important to use a 1-ml syringe with an 25-gauge needle in order to obtain the proper pH for coagulation (~5.5). In the packaging of the MAA suspension in the 10-ml vials, a 5-ml syringe with a 20-gauge × 1½-inch needle is used. This size needle homogenizes the albumin particles to the proper size needed for lung imaging (20–30 μ).

(2) Stock tin solution: Care must be taken in the preparation of this solution in order to insure that the tin used is all in the Sn(II) state. Reagent grade stannous chloride ($SnCl_2 \cdot 2H_2O$) from any reputable chemical firm is adequate. Start with a clean lump of the salt and not the powder on the bottom of the reagent bottle (oxidation products), triturate in a sterilized mortar and pestle and then weigh out the required amount. Add the concentrated hydrochloric acid with a sterile, glass pipet or a Teflon catheter. Do *not* use an aluminum hub needle!

The heating of the stannous chloride-hydrochloric acid solution is critical. If too much heat is applied, the Sn(II) will be oxidized to Sn(IV) and reduction of pertechnetate to the lower valence state necessary for labelling will not be obtained. I place the volumetric flask about one inch above a hot plate (on hottest setting) and heat the flask until it is warm to the touch.

Sterile nitrogen gas is necessary in all formulations that utilize tin as the reducing agent. An inert atmosphere must be maintained in order to keep the tin in the (II) state.

Quality control chromatography on this radiopharmaceutical is performed with Whatmann-3MM paper and 85% methanol.

^{99m}Tc-Diethylenetriamenepenta Acetic Acid (DTPA): Renal Imaging. Three formulations for ^{99m}Tc-DTPA have been proposed and an evaluation of the three preparations has been published.[19] We employ the formulation proposed by Eckelman and Richards in 1970.[20] ^{99m}Tc-DTPA prepared by this method is suitable for static renal imaging and also dynamic renal imaging because it is solely excreted by glomerular filtration.

The kit is composed of one reaction vial which requires the addition of the pertechnetate solution and mixing for one minute.

Formulation of Kit Reagents:

A. Hydrochloric acid, 0.25 N.
Transfer 2.1 ml of concentrated HCl, ACS reagent, to a sterilized 100-ml volumetric flask. Add water for injection (no preservative) to the 100-ml mark. Mix well. Filter through a 0.22-μ Millipore filter into 2.0-ml sterile vials. Store in a refrigerator.

B. $CaNa_3$ DTPA solution: 100 mg/ml.
1. Aseptically weigh a desired amount of $CaNa_3$ DTPA powder into a tared sterile 10-ml vial.
2. Add sufficient sterile water to produce a 100 mg/ml solution.
3. Tare the final container to determine the exact amount of sterile water added.
4. Purge the solution with sterile N_2 for 5 minutes and leave a positive pressure of N_2 in the vial.
5. Label properly.

C. $CaNa_3$ DTPA–$SnCl_2 \cdot 2H_2O$ stock solution.
1. Aseptically weigh out 5.0 mg of powdered $SnCl_2 \cdot 2H_2O$ into a 30-ml sterile vial.
2. Add 1-ml of the $CaNa_3$ DTPA (or that volume of the solution that contains 100 mg of the salt) to the sterile vial containing the $SnCl_2 \cdot 2H_2O$.
3. Purge the vial with sterile N_2 for 10 minutes and leave a positive pressure of N_2 in the vial.
4. Place in the autoclave and heat at 100 C for 15 minutes. Let cool to room temperature.
5. Add 17.0 ml of sterile water and mix well.
6. Adjust the *p*H to 4.0 with 0.25 N HCl (usually about 1.3 ml)—check with *p*H paper (2 ranges).
7. Add sufficient sterile water to bring the final volume to 20 ml. Mix well.
8. Purge the final solution with sterile N_2 for 15 minutes.
9. Package 1.0-ml portions into 5-ml sterile vials through a 0.22-μ Millipore filter.
10. Purge the atmosphere of each vial with sterile N_2 and leave a positive pressure within the vial.
11. Label properly and include a one-week expiration date (7 days from day of preparation).

D. Preparation of $CaNa_3$ DTPA: U.S. Patent 3,062,719, Ruben & Dexter.
1. Slurry 78.6 g of DTPA powder in 400 ml sterile water.
2. Add 20 g of calcium carbonate.
3. Heat to reflux with stirring and slowly add 24 g of sodium hydroxide and 100 ml of sterile water for injection.
4. Concentrate in vacuum on a steam bath to a volume of approximately 250 ml. Cool.
5. Precipitate the $CaNa_3$ DTPA by adding 625 ml of ethyl alcohol.
6. Filter on a Buchner funnel and dry.

E. Radiochemical purity check.
1. Prepare a sample with a dilute solution of $Na^{99m}TcO_4$ as described in section F.
2. Assay on a Sephadex G-25M column using N_2-purged 0.9% NaCl as the eluting fluid.
3. Collect 5.0 ml void volume.
4. Collect 25 × 2-ml samples. ^{99m}Tc-DTPA(Sn) will be in the 12–20-ml portion of the eluant and $^{99m}TcO_4^-$ will be in the 38–46-ml portion.
5. Apply approximately 2.0 ml of hydrogen peroxide (0.1%) to the column and collect 25 × 2-ml samples.
6. Hydrolyzed technetium (TcO_2) originally adsorbed on the column will be eluted as $^{99m}TcO_4^-$ in the

38–46-ml portion.
7. Combine the ^{99m}Tc-DTPA(Sn) and $^{99m}TcO_4^-$ portions from the first elution with the $^{99m}TcO_4^-$ portion from the second elution (corrected for decay) and determine the percent of each species. Typical formulations will contain greater than 98% ^{99m}Tc-DTPA(Sn), 1–2% hydrolyzed and usually no free pertechnetate (from first elution).

F. Preparation of ^{99m}Tc-DTPA.
1. Remove the positive pressure within the vial with a vent needle.
2. To the reaction vial containing the $CaNa_3$ DTPA-Sn solution add 3 ml of $Na^{99m}TcO_4$.
3. Swirl the vial gently for 1 minute using forcep.
4. Assay in the dose calibrator and determine the concentration (mCi/ml). Final volume of preparation is 4.0 ml.
5. Label and enter in the log book.
6. *Use the preparation within 4 hours from the time of preparation.*

G. Discussion of formulation: Of all the preparations presented, the DTPA formulation is by far the most critical in regard to time and temperature. The procedure must be followed religiously in order to obtain activity greater that 98% of labelled amount. A poorly labelled product (e.g., unlabelled $^{99m}TcO_4^-$ or $^{99m}TcO_2$) will produce clinically unacceptable static and dynamic images that may be interpreted as poorly functioning kidneys.

The major problem in the formulation of this kit is that the calcium, trisodium salt of DTPA is not available commercially and must be manufactured by following the U.S. Patent procedure as described in D.[21] This is a simple procedure and all pharmacists have sufficient chemistry background to prepare this chelate. One reaction can produce enough $CaNa_3$ DTPA powder to last a few years.

Sephadex Gel Filtration using G-25M gel and 0.9% sodium chloride purged with nitrogen is the only method currently available to assay this radiopharmaceutical. Gel chromatography, to say the least, is difficult and the only suggestion I can give is: practice makes perfect. Eckelman and Richards have adequately described gel chromatography[22] and this article is required reading before anyone undertakes the preparation of DTPA kits. The theory, techniques and problems encountered in gel chromatography are adequately covered in Pharmacia's booklet.[23]

^{99m}Tc-Human Serum Albumin (HSA): Placental and Blood Pool Imaging. This radiopharmaceutical is primarily employed for placental and blood pool imaging although other uses such as radioisotope cisternography and brain imaging have been described.[24,25] Our method of preparation is based on the method published by Eckelman et al.[26] and consists of a reaction vial to which is added three other ingredients.

Formulation of Kit Reagents:

A. Tin solution: $SnCl_2 \cdot 2H_2O$.
1. Aseptically weigh 12.5 mg of stannous chloride to a tared 30.0-ml vial.
2. Add 0.25 ml of concentrated hydrochloric acid and dissolve the stannous chloride.
3. Heat on hot plate for a few minutes. Let cool to room temperature.
4. Dilute to 25 ml with sterile water (no preservative) that has been previously purged with sterile nitrogen gas.
5. Pass through a 0.22-μ Millipore filter and package 0.5-ml portions into 10-ml sterile vials.
6. Purge the atmosphere in the vial with sterile nitrogen gas and leave a positive pressure within the vial.
7. Label and place a two-week expiration date on the label.

B. Phosphate buffer: 0.8 M $NaH_2PO_4 \cdot H_2O$.
1. Weigh out 11.04 g of $NaH_2PO_4 \cdot H_2O$ and place in a 100-ml volumetric flask.
2. Add Sterile Water, USP (no preservative) to the 100-ml mark. Mix well.
3. Pass the solution through a 0.22-μ Millipore filter.
4. Package 1.0-ml portions in 1.0-ml sterile vials.
5. Label properly.

C. Preparation of ^{99m}Tc-HSA.
1. Remove the positive pressure within the HSA kit vial with a 23-gauge needle.
2. Add 0.1 ml of 250 mg/ml of human serum albumin (salt-poor) to the HSA kit vial.
3. Add 0.1–2.0 ml of $Na^{99m}TcO_4$. If 2.0 ml of $Na^{99m}TcO_4$ is not used, add sufficient sodium chloride 0.9% (no bacteriostat or preservative) in order to bring the total volume added up to 2.0 ml.
4. Mix for 30 minutes on a Vortex mixer.
5. Remove from Vortex mixer and add 0.15 ml of phosphate buffer.
6. The final volume of the preparation is 2.75 ml.
7. Assay in the dose calibrator and determine the concentration (mCi/ml).
8. Label and enter in the log book.

D. Discussion of formulation: The precautions used in handling the tin solution as described in the section on ^{99m}Tc-macroaggregated albumin above also hold true for this kit. Radiochemical purity, ideally, should be performed using Sephadex Gel Filtration in the manner described in the section on ^{99m}Tc-DTPA. ^{99m}Tc-HSA filters out immediately after the void volume and the $^{99m}TcO_4^-$ and TcO_2 fractions filter out as described above.

^{99m}Tc-1-hydroxy-ethylidene-1, 1-disodium phosphonate (EHDP): Bone Imaging. In April 1971, Subramanian et al.[27] introduced a ^{99m}Tc-Sn-tripolyphosphate for bone imaging procedures. This complex is characterized by a P-O-P bond and is labelled with technetium by using Sn(II) as the reducing agent. One problem that has been experienced clinically with this preparation is that the P-O-P bond is apparently broken down in vivo by phosphatase enzymes thus increasing the soft tissue uptake.[28]

During 1972, condensed linear polyphosphate polymers were introduced for bone imaging again using Sn(II) to reduce the technetium.[29] Soft tissue uptake is also experienced with this preparation due to the enzyme degradation, as mentioned above, and depolymerization of one or two phosphate units per month.

Another inorganic phosphate compound, sodium pyrophosphate, has been labelled with technetium-99m using Sn(II) as the reducing agent. This compound has been reported to produce skeletal images of the same quality as ^{99m}Tc-EHDP.[30]

^{99m}Tc-EHDP is an organic phosphate characterized by a P-C-P bond which apparently does not undergo enzyme degradation. We are currently evaluating a kit for the preparation of ^{99m}Tc-EHDP (supplied by Proctor & Gamble, Cincinnati, Ohio) which employs the Sn(II) method of reduction.[31] Castronovo[4] and Subramanian[28] have reported methods used to prepare this compound.

Conclusion

Upon completion of a batch of kits, the radiopharmaceutical must be tested in an animal (e.g., rabbit) prior to initial clinical use. This is done routinely in our laboratory on new batches of kits when the formulation is being developed. Once the method of kit preparation has been established, I find it necessary to only spot check routine batches. Sterility and pyrogen tests must be performed prior to initial clinical use to prove that the methods and techniques used produce a radiopharmaceutical suitable for intravenous administration. The short shelf-life of some of the kit reagents and the short physical half-life of technetium-99m prevent the performance of USP sterility and pyrogen tests prior to clinical use of these radiopharmaceuticals. After the initial studies during the developmental stages of a kit, these tests are performed post facto.

The formulations presented in this paper are currently being used by our radiopharmacy with excellect clinical results.

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Planning a radiopharmacy

Tom Kawada, Walter Wolf and **Stanley Seibert**

A radiopharmacy planning guide featuring operational planning as well as architectural planning is discussed to assist hospital pharmacists in their planning of a radiopharmacy either in existing construction or blueprint models.

Operational planning factors such as "radiopharmaceutical type" and "service contribution" are discussed to show their influence on architectural planning requirements. Space requirements are discussed in detail and a model for an ideal radiopharmacy facility is explained.

Key words: Pharmacy, institutional, hospital; Planning and design; Radiopharmaceuticals; Radiopharmacy

Every hospital pharmacy at some time or another will be faced with the task of planning a new pharmacy facility. With the current emphasis on pharmacy specialities such as clinical pharmacy and radiopharmacy, the key to avoiding early obsolescence of a "new" pharmacy facility is to incorporate space for these specialities. The purpose of this paper is to assist hospital pharmacists in their planning for a radiopharmacy either in existing facilities or blueprint models.

A Planning Guide

Most facilities designed for the use of radiopharmaceuticals must cope with the same basic problems. Protection of personnel from internal and external radiation exposure, elimination of interferences on radiation detection systems and safe disposal of radioactive materials are special problems arising because a pharmaceutical emits radiation.[1] However, all likenesses among radiopharmacys end here. Before one is able to design a radiopharmacy, it is necessary to establish a planning guide.[2] This planning guide may be divided into two parts: operational planning and architectural planning. Operational planning determines current roles and provisions for future growth and change, while architectural planning translates these into physical space, fixtures and instrumentation.

Operational planning for a radiopharmacy can be divided into two major parts: radiopharmaceutical type and service category. Service category can be subdivided into three parts:

1. Compounding service (Category I)—radiopharmaceuticals are prepared in the radiopharmacy and delivered to the requesting department (nuclear medicine) for storage.
2. Bulk distribution service (Category II)—radiopharmaceuticals are prepared, stored and dispensed *in toto* as requested.
3. Unit dose distribution service (Category III)—radiopharmaceuticals are prepared, stored, dispensed and delivered in unit dose packages (individual patients) at specified times.

Radiopharmaceutical type can be subdivided into three types:

1. Liquids,
2. Powders, and
3. Gases.

These types may be further classified into light-sensitive, volatile, cool-refrigerated and humidity control.

Operational planning factors definitely influence architectural planning requirements. If the radiopharmacy plans to provide only a compounding service for specific radiopharmaceuticals, a large radiochemical type laboratory would not be indicated. On the other hand, if the service functions as a unit dose distribution service, a

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larger facility to accommodate the storage of items in addition to increased equipment will be required. The space requirements depend primarily on the type of services to be rendered, the type of radiopharmaceuticals to be handled and the number of personnel required to perform all tasks.

Radiopharmacy Design

With the trend toward low-energy, short-lived radionuclides, facilities for compounding radio-pharmaceuticals (Category I) can be as small as a 12 × 12-foot room. With the appropriate use of minimal shielding, background radiation can be maintained at a very low level and radiation exposure reduced. A small radiopharmacy (Category I with Type I and II radiopharmaceuticals) can be conservatively equipped with the following fixtures:

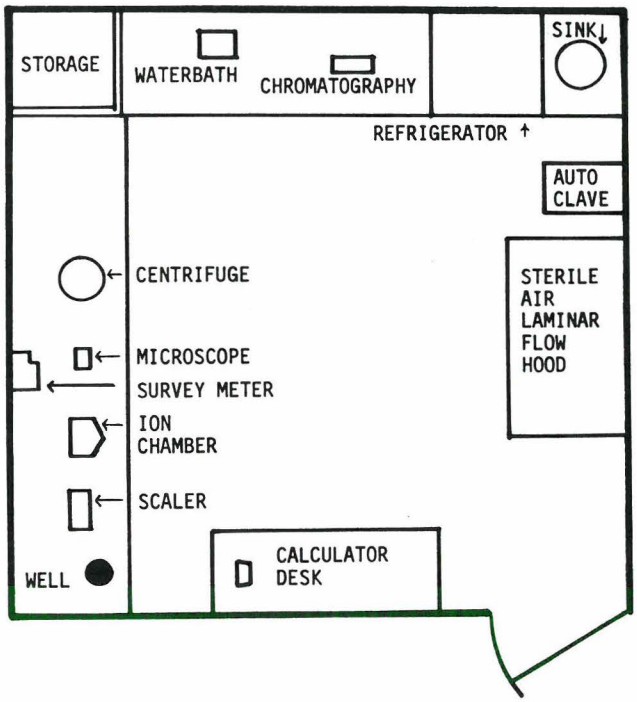
1. Fixed workbenches (Formica or stainless top) placed along two walls.
2. Foot-operated stainless steel sink.
3. Multiple electrical outlets for both 110-V and 220-V currents from two different circuits strategically placed along the work bench. Two circuits will reduce overloading of circuitry.

Sterile, nonradioactive solutions can be prepared in the main pharmacy manufacturing facility; therefore, duplication of pharmacy equipment is avoided. Equipment required in the radiopharmacy (Category I) include the following (see Figure 1):

A. Assay
   1. Scaler and scintillation well counter
   2. Dose calibrator ionization chamber
   3. Radiation survey meter
   4. Multi-channel analyzer (optional)
B. Quality control
   1. Microscope with $\frac{1}{10}$ mm deep hemocytometer (laboratory type)
   2. Chromatography apparatus (instant thin layer sandwich type)
   3. Radiochromatogram scanner (optional)
C. Manufacturing/compounding
   1. Laminar air flow hood (mini-bench)
   2. Electric heating element for water bath
   3. Refrigerator (under counter)
   4. Portable autoclave
   5. Centrifuge (bench model)
   6. Remote handling tongs
D. Inventory control
   1. Record books
   2. Calculator

The radiopharmacy will be operational only during the time of radiopharmaceutical compounding and preparation. After all procedures are completed, the radioactive materials (syringes, vials) are stored in a corner surrounded by 2 × 4 × 8-inch lead bricks to physically decay to nonradioactive states. Since most hospitals have a designated area for radioactive waste disposal to be shared by all departments, the radiopharmacy's radioactive waste can be disposed on a daily basis if desired. The daily disposal of radioactive waste to a central area eliminates high levels of radiation in the radiopharmacy. The compounded radiopharmaceuticals are immediately delivered in lead containers to the requesting department.

Figure 1. Schematic drawing of Category I radiopharmacy with basic equipment



If the radiopharmacy remains as a Category I, Radiopharmaceutical Type I and II facility, future work load for the department has been identified. It should be kept in mind that an increase in work load in the nuclear medicine service does not necessarily mean an increase in radiopharmacy work load. The same number and types of radiopharmaceuticals are prepared in exactly the identical manner; only the quantity of radionuclide (radioactivity of radiopharmaceuticals) need be increased to provide more patient doses per item.

As the radiopharmacy expands to a bulk distribution service (Category II), the physical size of the facility increases. Since radioactive materials are now to be stored in the facility, the compounding area must be separated from the storage area by distance or partitioning. One might assume that another small room will solve this problem; however, it is a common mistake in planning to always think about additional small rooms. Too many "little cubicles" produce built-in inflexibility. There also

Figure 2. Schematic drawing of Category II radiopharmacy in a single room

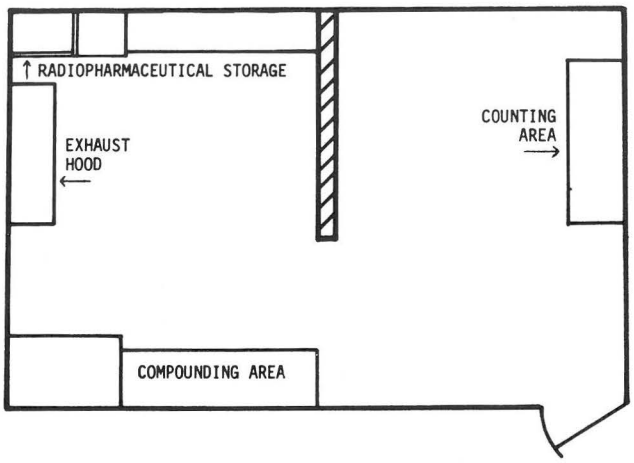
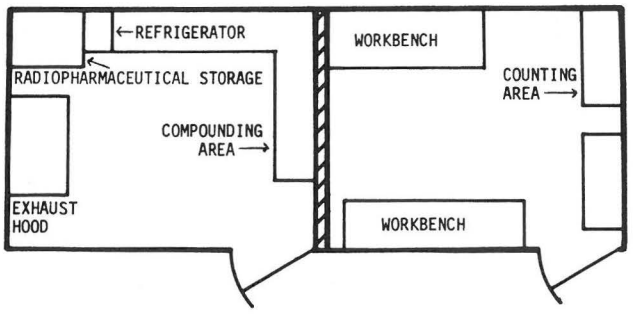


Figure 3. Schematic drawing of Category II radiopharmacy in multiple rooms



exists a problem in work flow. The radiopharmaceutical must be transferred from one room to another then back again. The work pattern should be as uninterrupted as possible.

The radiopharmacy expansion dictates a larger room (900 square feet) (Figure 2) or two rooms of approximately the same dimensions (450 square feet each) (Figure 3). A small portion of the room should be reserved for storage of radiopharmaceuticals. Small wall storage cabinets can be lined with $\frac{1}{8}$–$\frac{1}{4}$-inch flat lead or lead cylinders ($\frac{1}{4}$–$\frac{3}{8}$-inch) can enclose individual radiopharmaceuticals. If cabinets are not available, a metal box with lead shielding ($\frac{3}{8}$-inch) can be placed on a sturdy table. The metal box should be about 18 × 30 inches inside dimension with a lid capable of being locked.[3] Any accidental spills will be confined to the metal box and removed from the area *in toto*. Those items requiring refrigeration can be handled in the same manner. Lead cylinders ($\frac{1}{4}$-inch) around each radiopharmaceutical do not present a weight problem for ordinary home-type refrigerators. The remaining area of the radiopharmacy is used in the same manner as in a Category I facility.

With the introduction of volatile and gaseous radiopharmaceuticals (Radiopharmaceutical Type III) to the radiopharmacy drug formulary, problems of ventilation become of concern. Although all gases are confined in glass ampoules or rubber stoppered vials, the possibility of escaping radioactive gas should be examined. Volatile radiopharmaceuticals should be stored in an area where escaping vapors do not pose a hazard to the personnel. The obvious remedy to these situations is to install a constant flow type radiochemical fume exhaust hood capable of removing air at a rate of 500–700 cubic feet per minute. Rapid removal of escaping vapors and gases and prevention of backflow into the radiopharmacy can be achieved at this air flow rate. The ventilation pattern of air flow in the radiopharmacy exhausts exclusively by way of the radiochemical hood if undisturbed by forced air. Air conditioners forcing air directly toward the radiochemical hood have been known to create turbulence and interrupt air flow causing considerable backflow.

With an increase in physical space, movable work benches can be used to rearrange the equipment. Instruments for radiation detection and measurements can be relocated to an area farthest away from the "hot" storage area and designated as the counting room/area. Since most radiation detection systems utilize shielding to minimize background radiation, measurements are not grossly affected by extraneous low level radioactivity. However, it should be emphasized that precise measuring equipment should be separated from instruments used in the measurement of moderate- to high-level radioactivity. For example, a sodium iodide scintillation detection system should not be used near an ionization chamber dose calibration system. Caution must be exercised to limit the radioactivity level for a designated area and to the appropriate instrumentation.

Up to this point, this article has discussed a radiopharmacy located within the main pharmacy area. Ra-

diopharmaceuticals have been delivered or picked up by the various departments in shielded containers. Transportation of these few items through the hospital was not a problem.

As the radiopharmacy service expands to a total radioisotope service and a unit dose distribution service (Category III), the radiopharmacy must be closely coordinated with the operations of the nuclear medicine department. Although not always necessary, it is advantageous to have the radiopharmacy immediately next to or on the same floor as the nuclear medicine department. Such an arrangement permits easy distribution of radiopharmaceuticals on a scheduled basis and more important, in nonroutine emergency situations. However, caution should be exercised in that accessibility to this area by patients should not be overlooked. Areas of uncontrolled traffic can present a problem and should be avoided. Since the radiopharmacy is removed from the central pharmacy area, it becomes necessary to identify the staff and the work area each member will occupy during a normal workday. Each individual should have an adequate working space and a desk for recording information. The total physical size of the radiopharmacy now increases to multiple rooms to accommodate the required personnel. An ideal arrangement of space includes the following (Figure 5):

1. Office area—administrative activities.
2. Counting area—low-level activity for identification or measurement purposes.
3. Dispensing area—equipped with a laminar air flow mini-bench with a protective shield. Low-energy, short-lived materials that are most frequently used can be stored in the hood behind minimal shielding. Dose calibrator for measuring dose activity.
4. High-level activity storage area—storage of gases and iodine preparations under exhaust hood.
5. Compounding area (radioactive).
6. Manufacturing area (nonradioactive).
7. Decontamination/safety shower.

Note that the high-level storage area has been placed in an area farthest removed from the administrative office and dispensing area. Radioactive materials are kept away from areas where personnel spend most of their working day. Exact arrangement of the department is not pursued because each person has his own remodeling abilities.

Planning a New Facility

Let's suppose that we have been asked to design and equip a radiopharmacy for a new hospital building. Given only 1,200 square feet adjacent to the nuclear medicine department, let us theoretically design a practical model of a radiopharmacy.

The radiopharmacy extends 40 feet down the hospital traffic lane and 30 feet back for a total of 1,200 square feet. The center of work activity is a perforated stainless steel dispensing counter (see A in Figure 5) approximately 6 feet long, 4 feet wide and 3½ feet high. Directly over the dispensing counter hangs a vertical laminar air

Figure 4. Schematic drawing of Category III radiopharmacy; note that the storage area is farthest removed from the administrative area

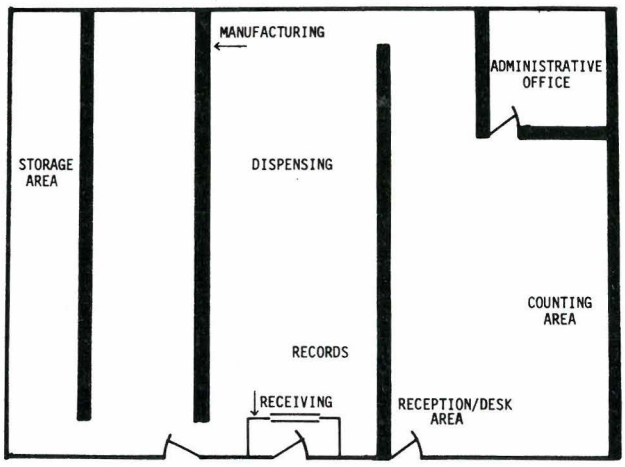
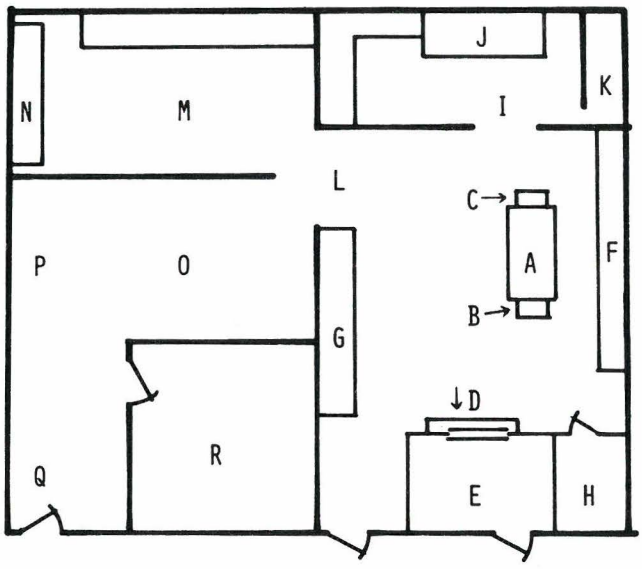


Figure 5. Practical design of a model hospital radiopharmacy (see text for explanation of letter codes)



flow hood modified with a center plastic window to divide the counter lengthwise into two sections. This modification allows the use of the air system from either side of the dispensing counter. Clear plastic side windows extend down from the sides of the laminar flow hood to the dispensing counter to form a box-like structure. A lead-shielded refrigerator (B) to the right and a lead-lined storage module (C) to the left of the dispensing counter allow for quick availability of radiopharmaceuticals from either side.

A record/calculation bench (D) displays records for each radiopharmaceutical and permits calculation of doses to be done away from a radiation area. Receipt of radiopharmaceuticals from vendors is handled through a window separating the bench (D) from the check-in and distribution area (E). A door leading only to the distribution area from the traffic lane prevents unauthorized persons access into the radiopharmacy.

Counter areas (F & G) provide approximately 18 linear feet each for quality control equipment such as microscopes, chromatography apparatus and *p*H meters. Beneath each counter are drawers for miscellaneous supplies and two removable trash receptacles for nonradioactive materials. A bathroom sink and stall shower (H) are available for personnel decontamination.

A "barrier" wall separates the dispensing area from the high-level activity area (I). Radioactive gases and oral iodine solutions are stored under a chemical exhaust hood (J) and also dispensed from this area. Fixed stainless steel counters with drawers and a stainless steel sink adjacent to the exhaust hood are adequate for the iodine preparative techniques. Elutions of short-lived radionuclides from radioactive generators are also handled in this area.

A "hot" storage area (K) permits storage of filled radioactive gas spirometers and aerosol equipment. A 55-gallon drum serves as a temporary radioactive waste disposal bin within this area.

An entrance (L) allows passage from one room to the other avoiding security problems at traffic lane doors. Sliding doors at entrances within the radiopharmacy allow more space and avoid the hazards of hinged doors when radioactive materials are being transported. Extemporaneous preparations of nonradioactive materials are compounded in the manufacturing area (M). Radiopharmaceuticals that require specific equipment and long preparation times are also prepared in this area. A laminar air flow hood (N) is provided for aseptic procedures, and a portable autoclave and pyrogen oven are available for sterilization. Wall-mounted storage cabinets allow for the storage of glassware and chemicals.

The low-level counting area (O) has been located away from the high-level activity areas (J and K). For measurement of low-energy radionuclides (50–500 keV) a sodium iodide well scintillation system will adequately accommodate routine counting requirements. A lithium-drifted germanium detector sensitive to gamma radiation between 10 keV and 1.5 MeV would be desirable to measure very low energy radionuclides with better resolution.[4]

Areas P and Q are the teaching area and technician/secretary area, respectively. Since most nuclear medicine departments have radioisotope technician programs, a generous amount of space should be used for teaching aids and tape cassette/film strip for individual instruction. Radiopharmacy students and technicians, nuclear medicine resident physicians and technicians, and pharmacy students can rotate through the learning program without affecting the clinical functions of the radiopharmacy service.

The administration section (R) is the office for the supervision of radiopharmacy services and library for the drug information service. An intercommunications system within the radiopharmacy allows for conversations among the various rooms without having to handle a telephone. A separate intercommunication system allows for conversation between radiopharmacy and nuclear medicine personnel.

The climate of the radiopharmacy is regulated by central air conditioning in all areas.

Lighting is with standard fixtures strategically located over working areas.

Research

In most hospitals, animal studies are not allowed in the same areas used for patients. Although many pharmaceutical research projects and quality control procedures require the use of test animals, the clinical environment is not the place for such studies. Arrangements should be made to have a small area outside the hospital for research and animal holding quarters. Vivaria facilities are available to most investigators upon request.

Summary

The steps involved in the planning and construction of a radiopharmacy depend upon the services offered and the types of radioactive materials to be handled. A simple compounding type radiopharmacy program obviously requires only limited equipment and physical space whereas a more complex operation requires a "hot" laboratory with a variety of equipment. Although specific requirements will vary for each facility, guidance for a step-by-step development of a model radiopharmacy is outlined.

References

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2. Barker, K.: Planning a Hospital Pharmacy Facility, *Amer. J. Hosp. Pharm.* 28:423–431 (June) 1971.

3. Tubis, M. (Chief Clinical Research Biochemist, Veterans Administration Center [Wadsworth], Los Angeles, California): Personal communication.

4. Harwood, G. (Chief, Health Physics, LAC-USC Medical Center, Los Angeles, California): Personal communication.

Amer. J. Hosp. Pharm. 31:158–164 (Feb.) 1974

Centralized radiopharmaceutical services of the Indiana University Medical Center

Michael P. Kavula, Jr.

The facilities of a centralized radiopharmacy service are described, and the formulations of the routine radiopharmaceuticals prepared by the service are presented in detail.

The radiopharmaceuticals discussed are sodium pertechnetate used for cerebral imaging, ^{99m}Tc-sulfur colloid for reticuloendothelial system imaging, ^{99m}Tc-macroaggregated albumin for lung imaging, ^{99m}Tc-diethylenetriamenepenta acetic acid for renal imaging, ^{99m}Tc-human serum albumin for placental and blood pool imaging, and ^{99m}Tc-1-hydroxy-ethylidene-1, 1-disodium phosphonate for bone imaging.

Key words: Formulations; Pertechnetate; Pharmacy, institutional, hospital; Planning and design; Radiopharmaceuticals; Radiopharmacy; Technetium

Radiopharmaceutical services at the Indiana University Medical Center are offered by a centralized radiopharmacy that supplies radiopharmaceutical kits and radiopharmaceutical unit doses to the Medical Center's three nuclear medicine clinics.

The current trend in Nuclear Medicine is to prepare routine diagnostic radiopharmaceuticals from kits, a "kit" being any combination of sterile, pyrogen-free, nonradioactive reagents packaged in unit-of-use or unit dose type containers. In order to prepare the needed radiopharmaceutical, one must usually just add the radioactive ingredient and follow a simplified procedure using aseptic technique.

Within the past year, nuclear medicine has witnessed a plethora of commercially available radiopharmaceutical kits. Even if the nuclear medicine clinic in a hospital relies entirely on commercially supplied kits, the pharmacist can extend his consultative services by advising the nuclear medicine physician or technologist on which kit is best for the particular study intended. The consultant role of the pharmacist in nuclear medicine is most important when one considers that radiopharmaceutical advertising is not regulated as "legend" drug advertising is; thus, the commercial suppliers have concentrated their advertising campaigns on the nuclear medicine physician and the nuclear medicine technologist, both of whom have had little or no pharmaceutical training.

It is the philosophy of our radiopharmacy service to rely as little as possible on commercial suppliers and to prepare most radiopharmaceutical kits "in-house." Our reliance on commercial suppliers is in the form of clinical investigation for manufacturers who are obtaining the necessary clinical data for FDA approval.

In 1963, Briner published an article in the *Journal* describing the methodology of preparing radioactive chemicals for human use.[1] Ten years later this article remains as the first paper a pharmacist should read prior to developing a radiopharmacy service. In an article entitled, "Radiopharmacy—The Emerging Young Speciality," published by Briner in 1968,[2] he describes the scope of radiopharmacy as consisting of: (1) formulation, (2) control, (3) research and development and (4) consultation; to this list can now be added the fifth category of education.

Before a pharmacist can perform control, research and development, consultative and educational services relating to radiopharmaceuticals, an adequate and thorough knowledge of the formulation of radiopharmaceuticals is necessary. It is the objective of this paper to present, in detail, the formulations of the routine radiophar-

Michael P. Kavula, Jr., Pharm.D., is a radiopharmacist and Instructor in Radiology at Indiana University School of Medicine, Indianapolis 46202.

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. J. Hosp. Pharm. 31:165–166 (Feb.) 1974

A product standards form for new radiopharmaceuticals

Ann Warbick

A model form is presented for developing standards on new radiopharmaceutical products.

The form is divided into the following sections: (1) pharmaceutical properties, (2) radioactive properties, (3) pharmaceutical chemistry and (4) pharmacology.

Key words: Forms; Radiopharmaceuticals; Standards

The increasing involvement of the pharmacist in nuclear medicine demands that he conform to the changing trends in radiopharmaceuticals used in diagnostic procedures. The radiopharmacist must use his skill and resources as a pharmacist in developing new radiopharmaceuticals as the need for such products arises.

The *United States Pharmacopeia* and the *British Pharmacopoeia* have not yet established standards for new radiopharmaceuticals on the market or in the literature. The radiopharmacist must therefore find some way to cope with the problem of establishing standards for radiopharmaceuticals which he may develop himself.

Standards and limitations for each new radiopharmaceutical should be established in a responsible and orderly manner. In the standards, a review should be made of the pharmaceutical, radioactive, chemical and pharmacological properties of the product. In addition, standards and methods of determining labelling efficiency, sterility and apyrogenicity must be devised and maintained.

The following outline may serve as a guideline for the radiopharmacist in setting up a new product standards form when developing a new radiopharmaceutical.

Ann Warbick is a radiopharmacist at The Princess Margaret Hospital, Toronto, Canada M4X 1K9.

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New Product Standards Form

Note: Fill in and check the appropriate information and attach data to substantiate.

Radiopharmaceutical: _____

I. Pharmaceutical Properties

Pharmaceutical Classification

(A) Solution— (1) Clear, particle free ..... _____
(2) Color ..... _____

(B) Colloid— (1) Clear, particle free ..... _____
(2) Color ..... _____
(3) Particle size (a) Electron microscope ..... _____
(b) Coulter counter ..... _____
(c) Other ..... _____
(4) Tyndall effect ..... _____
(5) Brownian motion ..... _____

(C) Suspension— (1) Free of contaminant particulate matter
(2) Color ..... _____
(3) Particle size (a) Light microscope ..... _____
(b) Other ..... _____

(D) Capsule— (1) Color ..... _____
(2) Appearance (a) Small amount of solid or solids ..... _____
(b) Empty ..... _____
(3) Content uniformity (a) Dissolution rate _____
(b) Other ..... _____

Stability

Note: Indicate stability range where applicable.

(A) Temperature ..... _____
(B) pH ..... _____
(C) Time ..... _____
(D) Light ..... _____
(E) Effect of radiation ..... _____

Sterility

Microbiology ..... _____

Pyrogenicity

(1) USP test ..... _____
(2) Other ..... _____

Packaging

(A) Primary package— (1) Vial _____

(2) Plastic pill container _____

(B) Secondary package—(1) Lead container _____

Storage

(A) Room temperature _____

(B) Refrigerate _____

(C) Presence of light _____

(D) Other _____

Container Labelling

Note: Indicate the following that are applicable.

(A) Solution_____; Injection_____; Capsule _____

(B) Date _____

(C) Activity _____

(D) Specific activity _____

(E) "Caution Radioactive" label _____

(F) Appropriate dispensing label (1) "Shake well" _____

(2) "Refrigerate" _____

(G) Other _____

II. Radioactive Properties

Radionuclide

(A) Physical half-life _____

(B) Energy _____

(C) Production—(1) Fission _____

(2) Fusion _____

(3) Reactor (indicate reaction) _____

(4) Generator (indicate manufacturer) _____

(D) Radioactive contaminants _____

III. Pharmaceutical Chemistry

Preparation

(A) Reagents (indicate strength) (1)_____

(2)_____

(3)_____

(4)_____

(5)_____

(6)_____

(7)_____

(8)_____

(B) Equipment (1)_____

(2)_____

(3)_____

(4)_____

(5)_____

(6)_____

(7)_____

(8)_____

Method

Carrier

Concentration (if a constant) _____

Labelling Efficiency

(A) Chromatography (1) Solvent _____

(2) ITLP type or other _____

(3) Running time _____

(4) rf. (a) Radiopharmaceutical _____

(b) Free isotope _____

(B) Electrophoresis _____

(C) Other _____

IV. Pharmacology

Indication

_____

Mechanism

(A) Hypothesis _____

(B) Organ distribution data (animal studies)

(1) Radiopharmaceutical _____

(2) Reagents or stabilizers _____

(C) Biological half-life _____

(D) Effective half-life _____

(E) Route of excretion _____

Toxicology

Toxic dose (1) Radiopharmaceutical _____

(2) Reagents or stabilizers (a)_____ _____

(b)_____ _____

(c)_____ _____

(d)_____ _____

Adverse Effects (Include possible effects of reagents or stabilizers)

(A) Allergic manifestations (1)_____

(2)_____

(3)_____

(4)_____

(5)_____

(B) Other _____

Contraindications

(A) Pregnancy _____

(B) Less than 18 years old _____

(C) Other _____

Dosage

(A) Adult _____

(B) Child _____

DOCKET NUMBER
PROPOSED RULE PR-31, 32 & 35
Medical Uses
(39 FR 2384)

AMERICAN SOCIETY OF HOSPITAL PHARMACISTS

4630 Montgomery Avenue / Washington, D. C. 20014

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USAEC
MAR 8 1974
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March 6, 1974

Acknowledged
3-8-74, ers

Secretary of the Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545

Attention: Chief, Public Proceedings Branch

Dear Sir:

On January 21, 1974, the Atomic Energy Commission published proposed rulemaking at 39 Federal Register 2384, concerning Group Licensing for Certain Medical Uses. This proposal would amend certain provisions of Title 10, Code of Federal Regulations. The American Society of Hospital Pharmacists has reviewed the proposal and wishes to comment on it.

ASHP is the national specialty organization of over 10,000 pharmacists practicing in hospitals and related institutions in this country. A significant number of our members practice in the field of radiopharmacy and have contributed to patient care and research in this specialty. Because radiopharmacy practitioners are essential members of the nuclear medicine team, we believe that the AEC should specifically recognize their activities and responsibilities within the agency regulations. In this regard, your attention is directed to the attached discussion of these issues presented in our comments on proposed rulemaking for 10 CFR Part 135, published at 38 Federal Register 6399, March 9, 1973.

In the rulemaking presently under consideration, §35.14(a)(3) establishes one of several conditions which must be met for approval of a special license application. As written, this section does not acknowledge that pharmacists have a primary responsibility in the preparation of radioactive material and training of technical personnel.

Therefore, we recommend that the section be amended to read:

> (3) The applicant or the physicians, pharmacists, technologists, radiological safety personnel and other paramedical personnel who will use the byproduct material have adequate training and experience in the handling of radioactive material appropriate to the uses included in the group or groups; (new language underlined)

Amending the proposal in the foregoing manner would accomplish two important objectives. It would recognize that pharmacy practitioners share primary responsibility for the safe and effective use of radiopharmaceuticals as with all other drugs. Secondly, the amended language would be in alignment with the changes previously suggested by ASHP for Conditions of Licenses for Medical Use of Radioisotopes at 10 CFR 35.32 (c) and (d).

The Atomic Energy Commission has developed a comprehensive proposal for group licensing for certain medical uses. The regulations discuss storage, labeling, dosages and formulations of radioactive materials, among others. We believe the effective implementation of these criteria demands supervisory, quality control and radiochemistry methodology experience within the licensed group. Radiopharmacy educators and practitioners have advised ASHP that such standards are difficult to maintain when program responsibility is divided among various disciplines and technological specialties. On the other hand, it is possible to achieve optimum standards through the direction, supervision and activities of radiopharmacy services. While we realize that not every nuclear medicine activity has the capability to employ a full-time radiopharmacist on its staff, it is still reasonable to encourage the development of radiopharmacy services within the AEC regulatory framework.

To illustrate the continuing interest of health care institutions and pharmacists in radiopharmacy facilities and procedures, we have attached copies of three recent articles from the American Journal of Hospital Pharmacy, the official publication of ASHP. Attached for your review are: Kawada, T., Wolf, W. and Seibert, S., Planning a Radiopharmacy, Amer.J.Hosp.Pharm., 31:153-157 (Feb) 1974; Kavula, M.P., Jr., Centralized Radiopharmaceutical Services of the Indiana University Medical Center, Ibid.: 158-164; Warbick, A., A Product Standards Form for New Radiopharmaceuticals, Ibid.: 165-166.

The modifications suggested in §35.14(a)(3) would be an appropriate recognition of pharmacy practice in nuclear medicine. Such changes would stimulate potential and current utilization of pharmacy services in this area. We appreciate the opportunity to provide the AEC with our views and would be pleased to meet and discuss the matter further.

Yours truly,

Carl T. DeMarco

Carl T. DeMarco, J.D.
General Counsel

CTDM/ni
Attachments

Duke University Medical Center
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27710

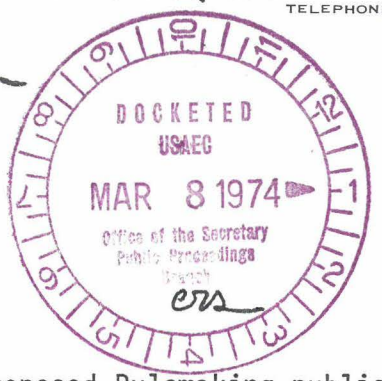
DEPARTMENT OF RADIOLOGY
DIVISION OF NUCLEAR MEDICINE

TELEPHONE 919—684—2466

DOCKET NUMBER
PROPOSED RULE PR-31,32 & 35
Medical Uses
(39 FR 2384)

4 March 1974

Acknowledged
3-8-74, crs



Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D. C. 20545

Attention: Chief, Public Proceeding Staff
Ref.: FR Doc. 74-1678, 10 CFR Parts 31, 32, and 35

Dear Sir:

I wish to comment on two portions of the Notice of Proposed Rulemaking published by the Commission in the Federal Register, Volume 39, No. 14, 21 January 1974, pages 2384-2388, which relates to Group Licensing for Certain Medical Uses.

The first of these comments relates to 35.14 (b) (7), page 2386, in which the requirement is stated that patients containing more than 8 millicuries of iodine 131 for the treatment of thyroid carcinoma shall be hospitalized. When contrasted with the current limit of 30 millicuries, it is quite obvious that it will incur considerable extra hospitalization expenses for patients undergoing this type of therapy, should this lower limit be codified. Indeed, when one considers the 7.2 day effective half-life for this radionuclide, the additional expense may approach $1000.00 or more, just to reduce the body burden from the currently acceptable limit of 30 mCi to the suggested limit of 8 mCi --- at a time when other instrumentalities of the U. S. Government are imposing controls to reduce the costs of health care delivery. The fact that the suggested limit of 8 mCi is the most restrictive value to be found in NCRP Report No. 37 (Table 4, p. 18) makes it appear to be an even more arbitrary requirement, since under certain circumstances, up to 80 mCi of iodine 131 is permitted by this same Report at the time of release of the patient from a hospital. Since, to my knowledge, there has been no demonstrable harm which has resulted from the use of the currently permissible 30 mCi body burden of iodine 131 on the day of discharge from the hospital, it is recommended that the 30 mCi limit continue to be permitted in the new regulations when finally codified.

My second comment concerns 35.14 (d), page 2386, which imposes an unnecessarily low limit on licensees with regard to the radioactivity contained in calibration standards, particularly those with half-lives longer than 7 days (a 200 microcurie limit is suggested). It is a rather questionable philosophy that assumes that a licensee is capable of handling activity levels several orders of magnitude larger than this 200 microcurie level when the licensee administers radionuclides to patients for therapeutic or diagnostic purposes, but infers that he loses that capability when handling calibration standards of usable activity levels. In addition, the Proposed Rule fails to take cognizance of the fact that calibration standards, including phantoms for imaging systems, may be obtained as essentially sealed sources, reducing even further the probability of contaminating incidents. It is therefore strongly suggested that the opinions of the AEC Advisory Committee on Medical Uses of Isotopes

(continued)

and other AEC consultants be obtained regarding practical limits on radioactivity to be contained in calibration standards prior to codification of this section. The Commission's effort to facilitate the procurement, possession, and use of calibration standards in this Proposed Rule is laudable. However, practical limits must be set, if the intent of this Rule --- that is, the proper calibration of instruments --- is to be realized.

The remainder of the Proposed Rule is satisfactory as written and represents a desirable approach to simplifying the licensing procedure without sacrifice of appropriate control.

Sincerely,

W. H. Briner

William H. Briner
Captain, USPHS, (Ret.)
Assistant Professor of Radiology
Director, Section on Radiopharmacy

WESTERN UNION INCOMING

1974 MAR 7 PM 11 24

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DOCKET NUMBER
PROPOSED RULE PR-31,32&35
Medical Uses
(39 FR 2384)

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PMS SECY OF THE COMMISSION US ATOMIC ENERGY COMMISSION

WASHDC 20545

THIS IS REGARDING NOTICE OF PROPOSED RULE MAKING CONCERNING 10 CFR PARTS 31 32 AND 35 - GROUP LICENSING FOR CERTAIN MEDICAL USES PLEASE BE ADVISED THAT THE NEBRASKA STATE HEALTH DEPARTMENT HAS PARTICULAR COMMENTS AND CONCERNS REGARDING THE IIMPACT OF THE PROPOSED RULE MAKING UPON AGREEMENT STATES. OUR DETAILED CONCERN AND OBJECTIONS WILL BE FORTHCOMING SO THAT THEY WILL BE AVILABLE FOR YOUR CONSIDERATION

HENRY D SMITH MD MPH DIRECTOR NEBR DEPT OF HEALTH

NNNN

WESTERN UNION INCOMING

MAR 7 1115P

Acknowledged 3-8-74, ers

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USAEC HQS GTWN

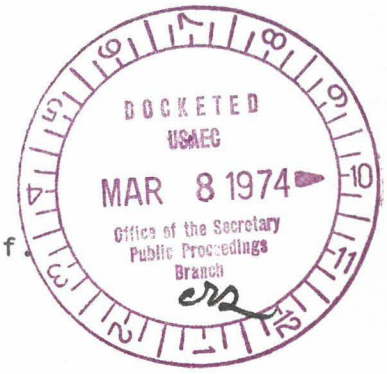
DOCKET NUMBER
PROPOSED RULE PR-31,32,35

ACNP Medical Uses (39 FR 2384)

American College of Nuclear Physicians

February 4, 1974

Acknowledged 3-8-74, crr



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Washington, D.C.

Secretary of the Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545

Attention: Chief, Public Proceedings Staff

Dear Sirs:

These comments are submitted for your consideration in connection with the proposed amendments to rules of Title 10 Code of Federal Regulations part 35 - in particular Section § 35.14 (b)(7) as published on page 2386 of the Federal Register, Vol. 39, No. 14 - Monday, January 21, 1974.

§35.14 (b)(7) reads "For Group IV, any licensee who possesses and uses radiopharmaceuticals for therapy shall assure that patients containing more than 8 millicuries of iodine 131 for treatment of thyroid carcinoma or patients containing more than 23 millicuries of gold 198 shall be hospitalized."

My first concern is to ask if the figure of 8 millicuries is what is truly intended, or may it be a typographical error? Most nuclear medicine practitioners probably would agree that 8 millicuries is a very modest dose that should not require hospitalization. 80 millicuries or even 50 millicuries probably should be a level at which hospitalization should take place, but not 8 millicuries.

Hospitalization for such small doses would add considerably to cost of therapy. Such cases require private rooms which cost in the neighborhood of $100 per day.

How long should hospitalization continue? For as long as the patient "contains" more than 8 millicuries?

Adequate sequestration of the radioiodine treated patient in the home cuts down on unnecessary radiation exposure to nursing personnel, a potentially recurrent problem. At the same time this management keeps to a minimum radiation exposure to the family

which is usually a one time occurrence.

The paragraph specifies the limit of radioiodine for treatment of thyroid carcinoma. Such cases usually have a low uptake and retention of radioiodine and consequently excrete most of the treatment dose in the first 48 hours leaving little residual radioiodine in them to produce a radiation health hazard for other persons.

It seems that these regulations will work a financial burden on patients and insurors. We urge that you consider either less stringent limits or allow an acceptable alternative such as sequestration of the patient at home.

Sincerely yours,

Oscar M. Powell, M.D.
President
3135 Webster Street
Oakland, CA 94609

OMP:rp

DOCKET NUMBER
PROPOSED RULE PR-31,32+35
Medical Uses (39 FR 2384)

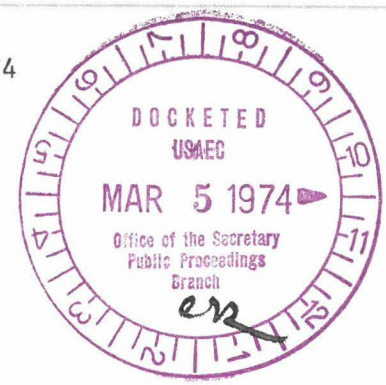
Arkansas
STATE DEPARTMENT OF HEALTH

4815 WEST MARKHAM STREET • LITTLE ROCK, ARKANSAS 72201
TELEPHONE AC 501 661-2000

J. A. HARREL, JR., M.D., M.P.H., DIRECTOR

Acknowledged 3-5-74 ERR

March 1, 1974



Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D.C. 20545

Attention: Chief, Public Proceedings Staff.

Dear Sir:

The following comments, relating to the proposed amendments to 10 CFR Parts 31, 32 and 35, entitled "Group Licensing for Certain Medical Uses," dated January 15, 1974, are submitted for consideration:

1. The proposed amendment, as presented, should be rejected because of the inclusion of Groups IV and V, which establishes group licensure for the therapeutic use of radioactive materials. Primary considerations for this rejection, as noted in my letter of November 1, 1973, are (a) the large and varying therapeutic doses used, (b) the physician's qualifications for each procedure, (c) specialized procedures peculiar to therapy, and, (d) possible inclusion, by precedence, of non-agreement materials in the Group License of Agreement States.

2. To insure compliance with the Regulations, the Department should have the opportunity to review the proposed dose schedule, the physician's qualification for each type of therapy, and the special procedures and nursing instructions peculiar to the specific therapeutic procedure. Under the proposed amendment, the individual review of each of these factors may not be possible; therefore, what administrative actions will be initiated to exclude a therapeutic procedure from the Group, based on a physician's lack of qualifications and/or equipment?

3. Please refer to the proposed Section 35.14, paragraph (a) (3). The inclusion of this requirement may be premature because the term "use" is questionable as it relates to the human use of radiopharmaceuticals by technologists, radiological safety personnel and other paramedical personnel. Additionally, has criteria been developed to evaluate the adequacy of the training and experience of technologists, radiological safety personnel and other paramedical personnel?

Continued .....

4. Under the proposed amendment, will it be necessary for non-agreement materials to be included in Group V in Agreement States programs?

Thank you for the opportunity to comment on this proposed amendment.

Sincerely yours,

David D. Smellings, Jr., Director
Division of Radiological Health
Bureau of Environmental Health Services

DDSjr:ef

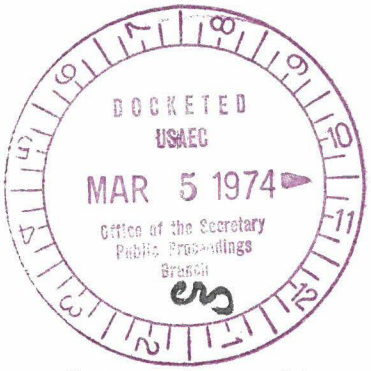
DOCKET NUMBER
PROPOSED RULE PR-31,32+35 (39 FR 2384)
Medical Uses

Saint Luke's Hospital

601 EAST NINETEENTH AVENUE • DENVER, COLORADO 80203 • PHONE (303) 292-0600

February 26, 1974

Acknowledged 3-5-74, ERS



Secretary of the Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545

ATTN: Chief, Public Proceedings Staff

Dear Sir:

We wholeheartedly concur with your proposal to streamline licensing procedures by Amending 10CFR31, 32 and 35 to allow Group Licensing for certain Medical Uses (Federal Register, January 21, 1974).

Specific comments are as follows:

1. The six month periodic leak test requirements (35.14 (b) (8) (i)) may be too frequent for the 3M-Cesium-137 ceramic microspheres encased in needles and applicator cells.
2. The quarterly physical inventory should be in addition to a "use-logbook" for recording each withdrawal and replacement to storage.
3. Par. 35.100 (a) Group I should include Cobalt-57 labeled cyanocobalamin and (12) should be Cobalt 60-----
4. Par. 35.100 (e) Group V add Iodine 125 as sealed sources for interstitial therapy of cancer.

Thank you for this opportunity to comment on a worthwhile proposal.

Sincerely,

Floyd W. Wilcox

Floyd W. Wilcox
Certified Radiation Physicist
Certified Health Physicist

FWW/naz

CONSULTANTS
IN
RADIOLOGY

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OKLAHOMA CITY, OKLAHOMA 73103

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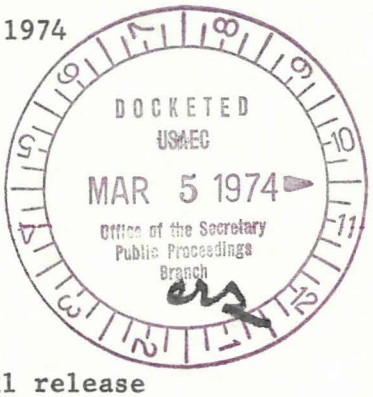
DOCKET NUMBER
PROPOSED RULE PR-31,32&35 (39 FR 2384)
Medical Issues

February 20, 1974

Acknowledged 3-5-74, ERO



Secretary of Commission
U.S. Atomic Energy Commission
Washington D.C. 20545

Attention: Chief Proceedings Staff

Re: January 21 release
Human Use Groups

Dear Sirs:

Thank you for your recent publication noting the proposed changes in license procedure.

I heartly agree with the proprosed change. This will eliminate many unnecessary man hours on the part of the physicians and physicists as well as the A.E.C.

Sincerely,

David Lowry

David C. Lowry, M.D.

DCL:jd

DOCKET NUMBER
PROPOSED RULE PR-31,32&35
Medical uses
(39 FR 2384)

WINFIELD DUNN
GOVERNOR

Eugene W. Fowinkle, M.D., M.P.H.
Commissioner

STATE OF TENNESSEE
DEPARTMENT OF PUBLIC HEALTH
NASHVILLE 37219

February 22, 1974

DOCKETED
USAEC
MAR 5 1974
Office of the Secretary
Public Proceedings
Branch

Acknowledged 3-5-74, ers

Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D.C. 20545

ATTENTION: Chief, Public Proceedings Staff

Gentlemen:

A review has been made of the proposed amendments to Parts 31, 32, and 35 of AEC regulations concerning "group licensing of certain medical use of radioisotopes" which were published in the Federal Register on January 21, 1974.

The proposed amendments appear to be a continuation of an approach to licensing initiated by the AEC some years ago. At that time, we, as an agreement state, did not believe such an approach an acceptable method for licensing medical uses of radioactive materials in this State and, therefore, did not include "group" licensing for medical use in our Regulations. It appears that expansion of the group licensing concept could result in very little benefit and possible deleterious effect to our licensing program for medical uses of radioactive materials; therefore, we are not planning to incorporate such a concept in our Regulations.

We appreciate the opportunity afforded us to review and comment on your proposal.

Sincerely yours,

Robert H. Wolle
Director
Division of Occupational and
Radiological Health

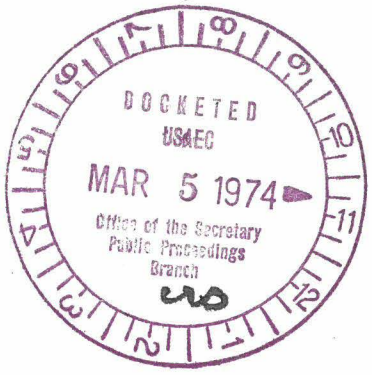
RHW:CPW:mf

dielman consultants, inc.

consultants to hospital management • *specialists in nuclear medicine*

DOCKET NUMBER
PROPOSED RULE PR-31,32+35 (39 FR 2384)
Medical Uses

February 25, 1974



Gordon M. Grant
Acting Secretary of the Commission
United States Atomic Energy Commission
Washington, D.C. 20545

REFERENCE: FR Doc. 74-1678, Filed 1-18-74; 8:45 am

Dear Mr. Grant:

In response to requests for comments concerning notice of proposed rule making: Group Licensing for Certain Medical Uses, 10 CFR Parts 31, 32 and 35, we encourage the proposed amendments to expand licensing of groups of medical uses of byproduct material; the specification of licensing requirements for the distribution of byproduct material licenses to such licensees, and the addition of new byproduct materials to general licenses for certain in vitro clinical and laboratory testing.

In our view, the proposes rules would enhance the AEC regulatory program and assist user understanding of the AEC-FDA relationship.

We urge that the Commission consider strengthening 35.14, items 1, 2, 3, 4 and 5 by development of specific education criteria to be met by physicians, technologists, radiological safety personnel, and other para-medical personnel. The physician educational protocol could follow that which is required for American Board of Nuclear Medicine eligibility; and for the technologists - that proposed and published in the Federal Register of March 9, 1973.

What is the disposition of the proposed rules published on March 9, 1973, amending 10 CFR Part 35?

Sincerely,

Ray W. Dielman

Acknowledged 3-5-74, ERB

Ray W. Dielman
President

RWD:rm

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DOCKET NUMBER
PROPOSED RULE PR-31,32+35
Medical Uses (39 FR 2384)

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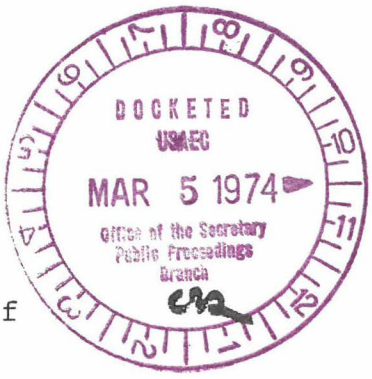
TEL. (612) 733-7454

March 1, 1974

Acknowledged 3-5-74, ers



Mr. Gordon M. Grant
Activity Secretary of the Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545

Attention: Chief Public Proceedings Staff

Dear Sir:

This letter is in response to the proposed amendments to Parts 31, 32 and 35 of AEC Regulations. In general, we find the proposed regulations acceptable and desirable, but feel very strongly that the following points should be considered and the regulations amended accordingly:

1. Section 35.14 (Paragraph b-4)

   This paragraph requires a licensee using an investigational new drug for which an IND has been filed with the FDA to also register with the AEC. The stated purpose is to identify the drug, its use, the supplier and to certify compliance with FDA requirements. This paragraph amounts to dual regulation of investigational new drugs by the AEC and FDA. It would increase the amount of forms required and also delay the investigation while the AEC waited for confirmation by the FDA that the investigator has been accepted as qualified.

   The FDA requires all of the information requested by the AEC on form AEC_____, and the FDA is quite capable of assuring that FDA requirements are complied with. It is redundant and inefficient for the AEC to require the same information as the FDA as well as to be responsible for enforcing FDA regulations.

2. Section 35.14 (Paragraph b-8i)

This paragraph states that all radioactive devices containing more than 100 microcuries of by-product material with a half life greater than 30 days be tested for leakage every six months.

This requirement is not needed for all devices. This paragraph should be amended to state that devices should be tested for leakage or contamination at intervals not to exceed 6 months unless the manufacturer has submitted adequate evidence to the AEC that a longer test period is acceptable. We would like to point out that we have supported, and the AEC has allowed, a longer test period for some of our sources. To unnecessarily require a shorter test period for all devices would be costly, unwarrented and inefficient.

3. Section 32.74 (Paragraph b-4)

This paragraph requires the applicant to furnish the radiation profile around a prototype device. The requirements of this paragraph are extremely vague. It is not clear as to whether this would pertain to individual radiation sources used in radiation therapy or to assembled applicators (which are after-loaded in an almost infinite variety of source loadings and geometries) - or both. It may be reasonable to request this information for individual sources. This information for the applicators, however, would be impossible for anyone to provide.

In addition, if this information is required for the safety of the general public for Cs-137 and Co-60 sources, it is also imperative that radium sources should meet all of the requirements listed in the entire section 35.74. Otherwise this could cause manufacturers to switch to radium for entirely the wrong reasons.

Since we feel very strongly on these points, I would welcome a chance to discuss them with you. Please contact me if any clairfication or further elaboration is needed.

Yours very truly,

Theodore F. Bolles

T. F. Bolles, Manager
Nuclear Medical Laboratory

TFB/ss

DOCKET NUMBER
PROPOSED RULE PR - 31, 32 & 35 (39 FR 2384)
Medical Uses

MEDICAL PHYSICS & ENGINEERING CENTER
DEPARTMENT OF RADIOLOGY
UNIVERSITY OF WISCONSIN MEDICAL SCHOOL
MADISON, WISCONSIN 53706
PHONE (608) 262-2170

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G. M. Chenevert, Ph.D.
P. M. DeLuca, Ph.D.
R. M. Grant, Ph.D.
C. A. Kelsey, Ph.D.
R. G. Lane, Ph.D.
M. R. Mayhugh, Ph.D.
R. B. Mazess, Ph.D.
C. A. Mistretta, Ph.D.
P. R. Moran, Ph.D.
R. J. Nickles, Ph.D.
B. R. Paliwal, Ph.D.
M. P. Siedband, M.S., P.E.
J. R. Tesmer, Ph.D.
R. P. Torti, Ph.D.
D. D. Tolbert, Ph.D.
K. L. Watkin, Ph.D.
C. R. Wilson, Ph.D.
J. A. Zagzebski, Ph.D.

Acknowledged 3-5-74, esr

February 25, 1974

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MAR 5 1974
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esr

Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D. C. 20545

Attention: Chief Public Proceedings Staff

Dear Sirs:

I would like to comment on the proposed amendments to parts 31, 32 and 35 of AEC regulations, specifically section 35.1 4-7. In the proposed change you require that any patient containing more than 8mCi of I131 shall be hospitalized. We believe this is unnecessarily restrictive and will increase the hospitalization costs for patients with no significant benefit to the public.

It is clear that 8mCi I131 will give an integrated exposure of 0.5 R at 1 meter during total decay. However, if one assumes that general exposure to the patient is no more than 8 hours daily for 7 days a week than the initial allowed activity could be increased to 24 mCi. Although the exposure in some isolated conditions may be for more than 8 hours daily it would be unlikely that the distance would be as close as 1 meter for all of this time. Thus we believe that the proposed restriction in 35.14-7 should be relaxed.

If 30 to 40 mCi of I131 is given for hyperthyroidism the proposed requirement will require an extra 10 to 20 days of hospitalization to reduce the concentration to 8 mCi. At an average cost of $100 per day this would add at least an extra $1,000 per patient for hospitalization cost. In our opinion the slight reduction in radiation exposure to a limited number of people is not worth the added hospital cost.

One alternative which should be considered is to add a qualifying sentence which says that the concentration of I131 in patients discharged from the hospital shall give an integrated exposure of less that 0.5 R during total decay for persons likely to be in contact with the patient. Alternately the limit chould be raised to a value of 20 to 30 mCi.

Thank you for the opportunity to provide these comments.

Sincerely,

Charles A. Kelsey, Ph.D., Chairman
University of Wisconsin Radiation
Safety Committee

CAK:mw

cc: Robert Radtke

DOCKET NUMBER
PROPOSED RULE PR-31,32+35 (39 FR 2384)
Medical Uses

STATE OF COLORADO DEPARTMENT OF HEALTH

4210 EAST 11TH AVENUE • DENVER, COLORADO 80220 • PHONE 388-6111

OCCUPATIONAL AND RADIOLOGICAL HEALTH DIVISION
February 26, 1974

Acknowledged 3-1-74 crs

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USAEC
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Office of the Secretary
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Branch

Secretary of the Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545

ATTENTION: Chief, Public Proceedings Staff

Gentlemen:

Please accept the following comments on your "Notice of Proposed Rulemaking" related to 10 CFR Parts 31, 32, and 35 as published in the Federal Register, Vol. 39, No. 14 on January 21, 1974.

1. Although the proposed group licensing is good in principle, there is enough disparity between items within some of the groups to cause an increase in the licensing workload rather than the intended decrease. For example:
   a) The inclusion of Xenon-133 in Groups I and II would require either (1) that each application for any item in either of those groups be evaluated to determine that adequate room size, ventilation, and exhaust-stack location are available to properly dissipate the maximum feasible spill of Xe-133, or else (2) that the resulting license include a condition excepting that nuclide from the authorized usage of those groups.

   b) Similarly, an applicant for any radiopharmaceutical in Group II would have to (1) possess a nuclear camera for use of Tc-99m as pertechnetate for placenta localization and make the usual preprequisite statements about placenta localization with Tc-99m as pertechnetate and with I-131 (IHSA), or else (2) those usages would have to be excepted by condition of licensure.

   c) Similarly, the diagnostic use of sealed sources of Am-241 or I-125 in Group V would be restricted to physicians qualified to do cancer therapy with sealed sources of Co-60, Au-198, or Ir-192 and to do treatment of superficial eye conditions with Sr-90, unless a restrictive condition were added to the license for each usage for which the applicant was unqualified. That is, the reviewer would have to consider the qualifications for each item in the group instead of perhaps two or three actually needed.

2. The registration requirement for IND investigators is good in theory, but our attempts in Colorado to get FDA confirmation of IND investigators have not functioned. Only one Colorado investigator for one radiopharmaceutical, to our knowledge, has been confirmed as an IND investigator by the FDA, and that information was made available several weeks after the investigation was authorized on the basis of our Medical Advisory Committee review. We have had to burden our Medical Advisory Committee with many non-routine protocols because of our inability to get timely FDA confirmation.

3. We have not seen evidence that the Food and Drug Administration is prepared and willing to accept the additional responsibilities that the promulgation of this proposed rule would place upon it. Although we encourage any changes that will restrict the cognizant area of our licensing staff to the health physics aspects of the licensees' programs, we would caution against excessive haste in the changes.

4. If the propsed rule is to be promulgated, we recommend addition of provisions (a) to limit the maximum quantities of radiopharmaceuticals and sealed sources contained in each group and (b) to require the users of radiopharmaceuticals, generators, kits, and sealed sources to follow the procedures recommended by the respective manufacturers unless exceptions are granted by license conditions.

5. It is obvious that proliferation of radioactive materials in medical offices and institutions will result from promulgation of this rule and will increase the workload of our compliance personnel. This may not be conducive to compliance with the comments of the GAO on control over medical licensees unless more manpowercan be made available.

Sincerely,

for A. J. Hazle
Assistant Director

AJH/ljw

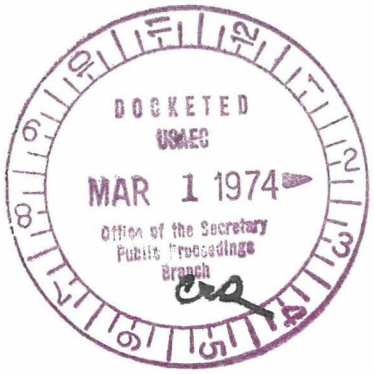
THE SOCIETY OF NUCLEAR MEDICINE

DOCKET NUMBER
PROPOSED RULE PR-31,32 & 35
Medical Uses (39 FR 2384)

305 EAST 45th STREET
NEW YORK, N.Y. 10017
PHONE: 212 • 889-0717

February 25, 1974

Acknowledged 3-1-74, cpr



Gordon M. Grant
Acting Secretary of the Commission,
Atomic Energy Commission
Washington, D.C. 20545

Dear Mr. Grant:

I am writing you in response to the proposed rule changes published by the Atomic Energy Commission in the Federal Register, Vol. 39, No. 14 on Monday, January 21, 1974. This has to do with proposed changes in relation to group licensing for certain medical uses (10, CFR, Parts 31, 32 and 35.)

I would like to comment on changes proposed under Section 35.14 of 10 CFR, Part 35 as published under Paragraph 7 on page 2385 of the Federal Register. As proposed No. 7 states that for group IV (prepared radiopharmaceuticals for therapy) any licensee who possesses and uses radiopharmaceuticals for therapy shall assure that patients containing more than 8 millicuries of ^{131}I for the treatment of thyroid carcinoma shall be hospitalized.

At the present time the AEC does not require hospitalization unless an amount of 30 millicuries of radioactive ^{131}I is contained within the body. This proposed change reducing the amount to 8 millicuries would produce an inordinate hardship on patients with thyroid carcinoma since it could greatly prolong their hospital stay. These patients frequently receive in excess of 100 millicuries of radioiodine as a theraputic dose. In the usual case, a 48 to 72-hour period of hospitalization is required to get body levels down to 30 millicuries. This hospitalization is generally only for custodial care and supervision of the radioactive disposal, and it is usually very costly. If the body level required for discharge from the hospital was reduced to 8 millicuries, this would require on the average 2 to 3 additional days of hospitalization. The terminal portion of the excretion rate is considerably slower than the initial portion and it is this last amount that is usually fixed in active tumor and is released from the body slowest of all. In certain instances, extremely prolonged (an unnecessary) hospitalization in excess

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New York, New York

of a week would be required to comply with this regulation.

I see no basis for this change and would strongly object to it primarily because of the tremendous increase cost burden for patients with cancer who are already burdened with an expensive medical care program. I see no reason to implement the change in the interest of public health and safety since these individuals can be carefully instructed and usually are exposed to very limited numbers of individuals during post-treatment period.

Moreover, I see no reason to make a distinction between those patients with thyroid carcinoma and those patients who may be receiving radioiodine therapy for hyperthyroidism for example. Thus the rule of change proposed is discriminatory against cancer patients.

I trust you will take these remarks under careful consideration. If you have any questions, I would be happy to discuss this with you personally. My telephone number is (206) 543-3538.

Most sincerely,

Wil B. Nelp

Wil B. Nelp, M.D.
President

WBN:mo

Dictated by Dr. Nelp but signed in his absence.

cc: Richard E. Cunningham, Assistant Deputy Director for Fuels and Materials, Director of Licensing, AEC
Dixy Lee Ray, Ph.D., Chairman, Atomic Energy Commission
Senator Henry M. Jackson
Senator Warren G. Magnuson

Duke University Medical Center
DURHAM, NORTH CAROLINA
27710

DEPARTMENT OF RADIOLOGY
DIVISION OF NUCLEAR MEDICINE

TELEPHONE 919—684-2466

DOCKET NUMBER
PROPOSED RULE PR-31,32 & 35 (39 FR 2384)
Medical Uses

Mr. Gordon M. Grant
Acting Secretary
U. S. Atomic Energy Commission
German Town, Maryland
February 25, 1974

Re: Proposed rule changes

Acknowledged 3-1-74, crs

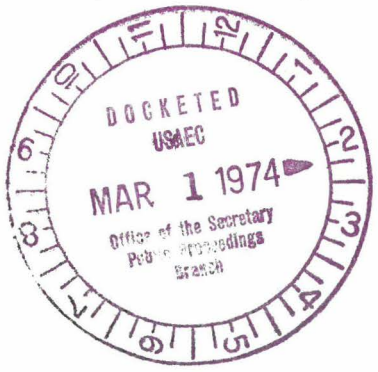
Dear Mr. Grant:

I am writing in response to the proposed rules changes regarding uses of radioisotopes which appeared in the Federal Register, January 21, 1974. My comments are in regard to the amendment 35.14, Section (b), Item #7 which reads as follows: "For Group IV, any licensee who possesses and uses radiopharmaceuticals for therapy shall assure that patients containing more than 8 millicuries of iodine-131 for treatment of thyroid carcinoma or patients containing more than 23 millicuries of gold-198 shall be hospitalized."

As a practicing nuclear medicine physician, I must protest the truly unnecessary restrictions placed on the management of thyroid carcinoma patients imposed by the 8 millicuries iodine-131 restriction noted above. The present limit of 30 millicuries is restrictive enough and has resulted in additional financial hardship to patients with thyroid cancer. To lower this limit to 8 millicuries will add a minimum of 2 and possibly 3 days to the presently required 3 to 4 days of hospitalization of thyroid cancer patients receiving I-131 therapy. At present average hospital day costs of $100.00, the added burden of $300.00 to $400.00 is truly excessive.

If 8 millicuries I-131 truly represents a radiation hazard to the general population, it certainly should not be applied only to the relatively small number of thyroid cancer patients, but also to the infinitely larger group of hyperthyroid patients.

In summary I feel that the 8 millicuries I-131 amendment to current regulations is arbitrary, discriminatory, unnecessary, and will place an undue hardship on the families of thyroid cancer patients.



Sincerely,

J. Wendell Tyson, M.D.
Division of Nuclear Medicine

WM. BENZING JR., M. D. A. PAUL COMPTON, M. D. WALTER H. GARY, M. D.

RADIOLOGY

507 WARREN PROFESSIONAL BUILDING – 6465 SOUTH YALE

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TULSA, OKLAHOMA 74135

DOCKET NUMBER PROPOSED RULE PR-31, 32 & 35 (39 FR 2384) Medical Uses

February 25, 1974

Secretary of Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545

ATTENTION: Chief, Public Proceedings Staff

Dear Sir:

Acknowledged 2-28-74, ERS

With reference to the proposed amendments Parts 31, 32 and 35 of AEC regulations as published January 21, 1974, may I draw attention and request revision of Section 35.100, Group IV, Subscript 7 which states "For Group IV any licensee who possesses and uses radiopharmaceuticals for therapy shall assure that patients containing more than 8 millicuries of Iodine 131 for the treatment of thyroid carcinoma or patients containing more than 23 millicuries of Gold 198 shall be hospitalized."

While this specifically refers to the treatment of thyroid carcinoma, there are cases of thyrotoxicosis or hyper-thyroidism which necessitate a calculated measured initial dose of radioactive Iodine 131 that is greater than 8 millicuries. It has not been our experience that a dosage greater than 10 millicuries has been required as the initial dose. It is therefore suggested that this regulation be changed to read "more than 10 millicuries of Iodine 131". As the regulation is now stated, it would seem that even though we are treating a benign condition as an out-patient, should the dosage be greater than 8 millicuries, we would have to hospitalize.

Respectively,

A. Paul Compton, M.D.

APC:mt

CLIFF RATLIFF, JR., M.D., P.A.
WESTVIEW MALL
PROFESSIONAL SUITE 5772
BALTIMORE, MARYLAND 21228
744-8822

DOCKET NUMBER
PROPOSED RULE PR-31,32,35
(39 FR 2384)
Medical Uses

Practice Limited To
Internal Medicine
Nuclear Medicine

February 25, 1974

Acknowledged 2-28-74, ers

DOCKETED
USAEC
FEB 28 1974
Office of the Secretary
Public Proceedings
Branch

Mr. Gordon M. Grant
Acting Secretary of the Commission
United States Atomic Energy Commission
Germantown, Maryland 20767

Dear Mr. Grant,

I am writing this letter to protest 35.14 (b) Section 7, Page 2385 of the Federal Register which will require hospitalization of patients treated for thyroid cancer until the body burden is 8 millicuries or less of I-131 instead of 30 millicuries as previously required.

This, in my opinion, would create a hardship on people who are treated for Ca of the thyroid. It also would create a hardship for the hospitals involved. I would like to see this paragraph deleted. If this cannot be done, at least it should be discussed by the Medical Advisory Board of the Atomic Energy Commission, which I understand has not been done.

Sincerely yours,

Cliff Ratliff, Jr., M.D., P.A.

CR/jrb

AMERICAN COLLEGE OF RADIOLOGY: 20 NORTH WACKER DRIVE CHICAGO, ILLINOIS 60606 (312) 236-496
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DOCKET NUMBER Medical Uses
PROPOSED RULE PR-31,32,35
(39FR2384)

February 21, 1974

Secretary
U. S. Atomic Energy Commission
Washington, D. C.

ATTENTION: Chief, Public Proceedings Staff

Dear Sir:

Reference is made to the January 21 publication of proposed amendments to 10 CFR Parts 31, 32 and 35, dealing with group licensing for certain medical uses of radioisotopes. The following comment is submitted by the undersigned as Chairman of the Commission on Nuclear Medicine of the American College of Radiology and can be taken to represent the considered opinion of that Commission on behalf of the 9000 members of the College.

Members of the College are among the experts who were allowed to review some of this material in an earlier draft form. In general, they are pleased with the intentions of the review and are encouraged by the willingness of the AEC to take them into its confidence in the draft process.

There is one proposal to be found in paragraph 35.14 (b) (7) as stated on page 2386 of the Federal Register for January 21. This has reference to a proposed requirement that any patient who contains in the course of a procedure more than 8 millicuries of iodine 131 or more than 23 millicuries of gold 198 be hospitalized for the duration of his treatment.

In the opinion of members of the ACR Commission, this is an unnecessarily strict recommendation and would be more practical if the amounts requiring hospitalization were fixed at 30 millicuries of each agent. It should be pointed out that a treatment for hyperthyroidism can involve as much as 8 millicuries of iodine in a patient without producing any circumstance which would warrant that patient's isolation in a hospital.

It seemed to the members of the Commission that, in making these recommendations, they were exercising valid professional judgment concerning the safety of the patient, of his acquaintances and family and of others who might come into contact with him. Furthermore, with the current concerns and federal initiatives to hold down the cost of medical care, such a requirement as is now proposed would contribute significantly to an unnecessarily high expense for patients undergoing this kind of treatment without any benefit resulting therefrom.

ACKNOWLEDGED

Thank you for your consideration of our comments.

Sincerely,

James L. Quinn III

James L. Quinn, III, M.D.
Chairman, Commission on Nuclear Medicine

cc: J. Richard Crout, M.D., Food and Drug Administration
Robert E. Wise, M.D.
Robert D. Moseley, Jr., M.D.
Jack K. Goodrich, M.D.

DOCKET NUMBER Medical Uses
PROPOSED RULE PR-31, 32, 35
(34 FR 2384)

DRS. MCCONNELL, FULLER & RESTREPO
A PROFESSIONAL ASSOCIATION

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LOCKE MEDICAL BUILDING, SUITE 208
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NUCLEAR MEDICINE
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RADIATION THERAPY
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ROBERTO RESTREPO, M. D.
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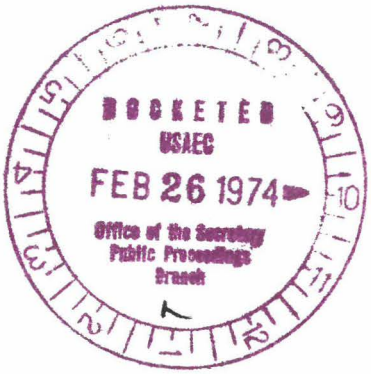
February 18, 1974



Mr. Gordon M. Grant,
Acting Secretary
United States Atomic
Energy Commission
Germantown, Maryland 20545

Dear Mr. Grant:

It is my understanding that the Federal Register for January 21, 1974, contains a Special Amendment 35.14, Section B (b) Item 7, dealing with the total body burden which a patient may have without hospitalization when being treated with radioiodine (131I) for carcinoma of the thyroid.

Present Regulations require hospitalization for a total body burden of 30 millicuries or more of radioiodine (131I) when this radionuclide is used in the treatment of a variety of diseases. It is pure lunacy to single out cancer patients for this kind of discretionary action. Radioiodine is used in the treatment of several other disease processes and in many instances more than eight millicuries is the initial amount given.

Requiring hospitalization for patients with hyperthyroidism, chronic cardiopathy, and patients with carcinoma of the thyroid in whom less than 30 millicuries would be the total body burden will essentially quadruple the cost of medical care for these patients. It seems paradoxical that in these days when we are attempting to decrease the cost of medical care such a Federal Regulation would be promulgated which would materially increase it.

I would hope that you would seriously consider striking this amendment from the Regulations.

Sincerely yours,

Robert W McConnell, MD

Robert W. McConnell, M.D.

RWM/cb

ACKNOWLEDGED

DOCKET NUMBER
PROPOSED RULE PR-31,32,35 (39 FR 2384)
Medical uses

THE STATE OF WYOMING

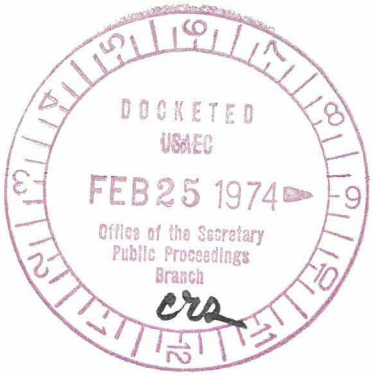
Department of Health and Social Services

Division of Health and Medical Services

STATE OFFICE BUILDING CHEYENNE, WYOMING 82001

February 19, 1974

Acknowledged 2-25-74, ers



Secretary
Atomic Energy Commission
Washington, D. C. 20545

Attention: Chief, Public Proceedings Staff

Dear Sir:

Re: Release T-26 (January 21, 1974)

During our field evaluation of the radiology sections of hospitals, we encounter several situations with respect to the use of radio-pharmaceuticals.

We agree that the expanded class system will enable the increased use of the procedures by making such increase simpler under license. Our applications, even in the largest hospital, would be considered minor as to hazard level in other states. However, we have limited disposal capability in some cases and I believe that very low flow rates of sanitary systems should be considered in these cases.

We see licenses authorizing an individual to use isotopes at a hospital. We believe that this is the only feasible way to initiate the use at a hospital or in a community. Such a license often forces the responsibility of handling the material on the hospital staff in some cases without the procedures being firmly established and documented in advance. This is contrary to the basic concept of hazard recognition and control under license.

Because of such problems, it would be best for a hospital to be licensed and the practicioner be listed as an authorized user. In some ways, this would insure more direct responsibility lines within the hospital. But cost recovery would have to be considered and the break even point would probably be a higher level of procedure use than most of our small hospitals could support.

Therefore, we would ask that the commission firm up the assumption of responsibility for isotope control in public facilities such as a hospital by an individual licensee, considering the impact on the facility of other possible licensees also.

Qualifications of persons responsible for storage of material and wastes, for dose preparation, for control of exposure to associated personnel and procedures for clean up of spills, etc., should be specific license conditions.

We trust that the foregoing will lead you to consider problems peculiar to the state where, however, the individual need is no less than elsewhere and special procedures may permit safe applications of radio-pharmaceuticals.

Sincerely yours,

Raymond A. Shader

Raymond A. Shader
Radiological Health Specialist

RS/kdr

PROPOSED RULE PR-31, 32 + 35 (39 FR 2384)
Medical Uses

BROOKHAVEN NATIONAL LABORATORY
ASSOCIATED UNIVERSITIES, INC., UPTON, L.I., N.Y. 11973

MEDICAL DEPARTMENT

TELEPHONE: (516) 345- 3590

February 19, 1974

Secretary of the Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545
Attn: Chief, Public Proceedings Staff

Acknowledged 2-22-74, OR

Dear Sir:

I am writing in regard to proposed amendments to 10CFR, parts 31, 32 and 35 as published in the Federal Register for January 21, 1974.

In paragraph 35.100, Schedule A, groups of medical uses of byproduct materials are classified in five categories. The separation of uses in group I and II appears arbitrary and obsolete with regard to current use for most materials listed. It is difficult, and indeed without purpose to separate measurement of uptake, dilution and excretion (i.e. function tests) from imaging procedures. Most modern usage combines both function and imaging. The localization of a radiopharmaceutical in an organ or space is directly related to function and any separation is artificial.

The listing of established procedures includes placental localization with pertechnetate and the use of technetium-99m macroaggegated human serum albumin for lung imaging while excluding technetium-99m human serum albumin for blood pool imaging. Placental localization is, in effect blood pool imaging and is preferably performed with the labeled albumin rather than pertechnetate so as to further reduce fetal irradiation. Since the labeled albumin is necessary to the use of macroaggregated albumin I would suggest it be included on the well established list, particularly for blood pool (placental) imaging.

Furthermore, in paragraph 35.14, part 7 it states that patients containing more than 8 millicuries of iodine-131 (previously 30 millicuries) for thyroid carcinoma must be hospitalized. Firstly, why the diagnosis of thyroid carcinoma must be specified is unclear. Secondly, this rule places an undue hardship on patients who must pay over $100.00 per day for hospitalization. A few simple rules for behavior on the part of the patient would avoid any undue radiation exposure to other individuals. The negligible risks do not appear to be balanced with the very high costs to the individuals involved.

Sincerely,

Harold L. Atkins

Harold L. Atkins, M.D.

HLA/jab

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Office of the Secretary
Public Proceedings
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ers

Duke University Medical Center
DURHAM, NORTH CAROLINA
27710

Box 3223

DEPARTMENT OF RADIOLOGY
DIVISION OF NUCLEAR MEDICINE

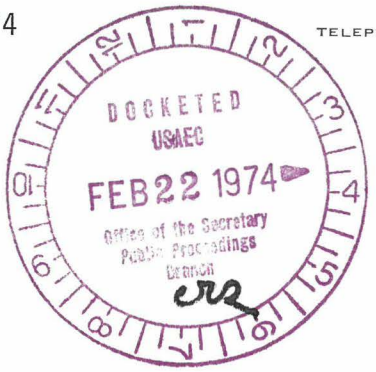
TELEPHONE 919—684-2466

DOCKET NUMBER
PROPOSED RULE PR-31,32+35
Medical Uses
(39 FR 2384)

February 14, 1974

Acknowledged

2-22-74 ers



Mr. Gordon M. Grant, Acting Secretary
U.S. Atomic Energy Commission
Germantown, Maryland

re: Proposed Rule Changes

Dear Mr. Grant:

I am writing in response to the proposed rule changes with respect to uses of radioisotopes which appeared in the Federal Register, January 21, 1974. My comments are in regard to the specific Amendment 35.14, Section B(b), Item 7 which reads as follows: "For group lV, any licensee who possesses and uses radiopharmaceuticals for therapy shall assure that patients containing more than eight millicuries of iodine-131 for treatment of thyroid carcinoma or patients containing more than twenty-three millicuries of gold-198 shall be hospitalized."

As Director of the Division of Nuclear Medicine, Department of Radiology, Duke Medical Center including Nuclear Medicine Service of the Durham VA Hospital and drawing on more than fifteen years experience limited to the practice of Nuclear Medicine I must protest the unnecessary restrictions which will be placed on the management of thyroid carcinoma patients as a result of the eight millicurie iodine-131 regulation cited above. The present limit of thirty millicuries is sufficiently restrictive to assure protection of family members and others in the general population who might find themselves in the immediate social company of a treatment patient. This restriction of thirty millicuries has resulted in additional financial hardship to patients with thyroid cancer by requiring their restriction to the private room of a hospital well beyond the needs which would be dictated by their medical status in the vast majority of cases. Should the proposed rule changes be imposed with the limit of eight millicuries then the unfortunate patients will have the added hardship of as much as four added days hospital stay as opposed to the present experience of three to four days of hospitalization. As you may know, the present average hospital day cost is $100. The proposed rule-making is quite likely to cost the individual patient treated for thyroid cancer to have a basic hospital bill in excess of $1,000 for the sole purpose of therapy administration.

The author of this ill-advised portion of the proposed rule has generated a most discriminatory article in that the limit is applied to cancer patients only. The eight millicurie level which is cited however is one which is often applied to patients in the treatment of thyrotoxicosis or in thyroid ablation for cardiac disease. Hospitalization of these patients would add a significant burden to the already expanded hospital census and would in the strictest sense represent an unnecessary hospitalization legislated by the Atomic Energy Commission's rule-making. If indeed the eight millicuries of iodine-131 represents a radiation hazard to the general population it certainly should not be applied to the relatively small number of thyroid cancer patients but the considerably larger population of hyperthyroid patients. This clearly is absurd.

In summary this aspect of the proposed rule-making to which I limit this discussion is discriminatory, ill-founded, and if adopted will represent an undue financial hardship on a small number of unfortunate patients who have experienced and still face extreme financial hardship as a result of their disease. It is ironic that patients are caught in the pincers movement of a bureacracy on the one hand excercising all possible means to reduce hospital costs and reduce hospital patient admissions while on the other hand another bureacracy is attempting legislation which would indeed require unnecessary hospital admissions as well as extended hospital stays. It is difficult for me to conceive of a government of the people, by the people and for the people tolerating such inconsistencies.

I respectfully urge the Commission to withdraw this aspect of the proposed rule-making for lack of justification in the face of compelling reasons to the contrary.

Sincerely,

Jack K. Goodrich, Director
Division of Nuclear Medicine

G. W. BOLES, M.D.
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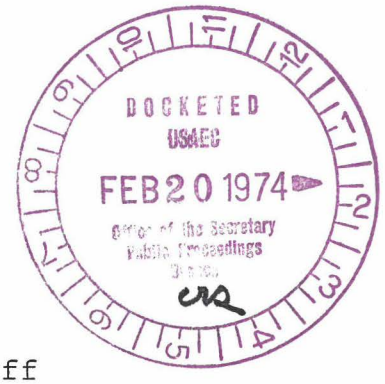
DIPLOMATES
AMERICAN BOARD
OF RADIOLOGY

0817

February 8, 1974

DOCKET NUMBER
PROPOSED RULE PR-31,32+35
Medical Uses
(39 FR 2384)



U. S. Atomic Energy Commission
Isotope Branch
Division of Materials Licensing
Washington, D. C. 20545

ATTENTION: Chief, Public Proceedings Staff

Gentlemen: Acknowledged 2-20-74, ers

This letter is in response to the publication released Monday, January 21, 1974 discussing the amendments to Atomic Energy Commission regulations which are presently under consideration. These amendments would span the group licensing of medical uses of radioisotopes, adding three more groups of uses to the present coverage, and adding more diagnostic uses to the first two groups.

It is our opinion that the group licensing method will greatly simplify the licensing procedures, without diminishing in the least the quality of the regulation of usage. We feel that the proposed changes would constitute a logical extension of the present method and should be instituted. The clerical work involved in Commission activities would doubtless be greatly simplified by eliminating redundant license applications for similar usages.

Therefore, we wish to indicate our hearty approval of the proposed amendments and certainly hope that they may be adopted.

Very truly yours,

COPIES SENT TO
REGULATORY OPERATIONS

H. J. Kearns, M.D.
H. J. Kearns, M.D.
Chairman, Isotope Committee

Glen D. Hallum, M.D.

G. W. Boles, M.D.

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Ronald I. Cramer, M.D.

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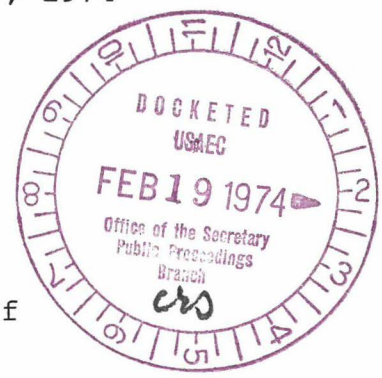
DOCKET NUMBER
PROPOSED RULE PR-31,32,35 (39 FR 2384)
Medical Uses

February 13, 1974

Acknowledged 2-19-74, crs



AIR MAIL

Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D. C. 20545

Attention: Chief, Public Proceedings Staff

Gentlemen:

Enclosed is a letter submitted in March of 1973. Since the suggestions made at that time also pertain to the "Notice of Proposed Rulemaking" published in the Federal Register January 21, 1974, pages 2384-2389, I have enclosed a copy of this letter.

It is particularly essential that Co^{57} be added to Section 31.11 since this is the only means by which vitamin B_{12}, employed in serum assays, can be suitably labeled. In addition, it is necessary to include Co^{57}-labeled B_{12} in Schedule A of Part 35.100 because of the decreased radiation dose to patients which I documented in the letter of March 26.

I would very much appreciate your careful consideration of these recommendations.

Very truly yours,

Mary Sue McCall
Executive Vice President

MSM:kg

FILE

NUCLEAR MEDICAL
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March 26, 1973

AIR MAIL

Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D. C. 20545

Attention Chief, Public Proceedings Staff

Gentlemen:

I have noted certain proposed changes in 10 CFR, Part 35 as published in the Federal Register, Vol. 38, No. 46, pages 6399-6401.

I would like to suggest additional changes in Part 35 as follows:

1. Most cyanocobalamin absorption studies are now performed with Co^{57} which delivers approximately 50 percent of the critical organ dose of Co^{58} and about 4 percent of the dose delivered by Co^{60}. (See Page 867, Principles of Nuclear Medicine, ed. H. N. Wagner Jr., W. B. Saunders Co., 1968 and Diagnostic Nuclear Medicine, ed. E. R. Powsner and D. E. Raeside, Grune & Stratton Inc., 1971, Page 463.)

   Therefore, Co^{57} Vitamin B_{12} certainly should be added to Parts 35.31 and 35.100. Because of the exceptionally high counting efficiency of this 122 KeV gamma, no increase in the dose of 0.5 μc is required.

2. Since it has been demonstrated that chromic chloride ($CrCl_3$) labeled serum albumin in vivo, this chemical form of Cr^{51} should also be added to Part 35.100, (a)(6). (Note listing on Page 868 of the above reference by Wagner.)

3. Although numerous users are rather broadly licensed under Part 35.31 for in vivo use, such users find themselves uniquely not licensed for in vitro use of the same isotopes.

We, therefore, strongly recommend that I^{131} and I^{125} for in vitro studies and Co^{57} labeled B_{12} for serum B_{12} assays be added to Part 35.31 and 35.100. In 35.100, it may be appropriate to add a separate Group III to include such isotopes coming into very widespread use in the isotopic assay field.

We recognize that the preceding recommendation (3) may more appropriately find correction elsewhere. However, since the title of Part 35 is to be changed from "Human Uses of Byproduct Material" to "Medical Uses of Radioisotopes (Byproduct Material)", it may not be inappropriate to include in vitro tests in such general licenses. Surely it follows that if a user qualifies to use isotopes accepted for routine in vivo procedures, such users should automatically qualify for in vitro usage of the same isotopes.

One simple solution may in fact be to add a section to Part 35 which states that one generally licensed under Parts 35.31 and 35.100 would automatically be licensed under the General License outlined in Part 31.11. With the expanding use of I^{125}, Co^{57}, and H^3, for numerous isotopic assays, it appears inevitable that Part 31.11 will require amendment to include I^{125} in any form and include Co^{57} and H^3 in any form. Packaging and possession limits could remain the same.

We would very much appreciate your consideration of the above suggestions.

Sincerely yours,

M. S. McCall
Executive Vice President

MSM/bj

Enclosures: (1) Principles of Nuclear Medicine
Ed. H. N. Wagner Jr.,
W. B. Saunders Co., 1968
Pages 867 and 868

(2) Diagnostic Nuclear Medicine
Ed. E. R. Powsner and D. E. Raeside
Grune & Stratton, Inc., 1971
Page 463 and 464

AVERAGE DOSES TO SELECTED ORGANS FOR VARIOUS AGES IN RADS/MICROCURIE ADMINISTERED FOR DIAGNOSTIC TESTS EMPLOYING RADIOACTIVE ISOTOPES*

ORGAN	RADIONUCLIDE	ROUTE OF ADMINISTRATION	DOSE					
			NEWBORN RADS/MICROCURIE	1 YR. RADS/MICROCURIE	5 YR. RADS/MICROCURIE	10 YR. RADS/MICROCURIE	15 YR. RADS/MICROCURIE	STANDARD MAN RADS/MICROCURIE
Liver	$Na_2H^{32}PO_4$	Intravenous	0.55	0.17	0.10	0.06	0.04	0.03
	Colloidal ^{198}Au	Intravenous	0.49	0.20	0.12	0.08	0.05	0.04
	^{57}Cobalt-labeled vitamin B_{12}	Oral	1.5	0.68	0.41	0.28	0.21	0.16
	^{58}Cobalt-labeled vitamin B_{12}	Oral	2.3	1.2	0.76	0.54	0.42	0.33
	^{60}Cobalt-labeled vitamin B_{12}	Oral	30.0	15.0	10.0	6.9	5.3	4.2
Spleen	$Na_2H^{32}PO_4$	Intravenous	0.55	0.17	0.10	0.06	0.04	0.03
	Colloid ^{198}Au	Intravenous	0.49	0.20	0.12	0.08	0.05	0.04
	$Na_2{}^{51}Cr_2O_4$ "altered red cell"	Intravenous	0.49	0.16	0.10	0.05	0.04	0.04
Bone and marrow	$Na_2H^{32}PO_4$	Intravenous	0.55	0.17	0.10	0.06	0.04	0.03
Thyroid	$Na^{131}I$	Oral	32.0	10.0	4.3	3.1	1.7	1.3
	$Na^{125}I$	Oral	19.0	6.1	2.6	1.8	1.0	0.82
	$Na^{132}I$	Oral	1.2	0.40	0.17	0.12	0.07	0.05
Kidney	Chlormerodrin	Intravenous	0.66	0.22	0.14	0.09	0.07	0.06
	Hippuran ^{131}I	Intravenous	0.01	0.004	0.003	0.002	0.001	0.001
	Hippuran ^{125}I	Intravenous	0.002	0.0006	0.0004	0.0002	0.0002	0.0002

* From Seltzer, R. A., Kereiakes, J. G., and Saenger, E. L.: Radiation Exposure from Radioisotopes in Pediatrics. *New England J. Med.* 271:84, 1964. Reproduced with permission of The New England Journal of Medicine.

Principles of Nuclear Medicine
Ed. H. N. Wagner Jr.,
W. B. Saunders Co., 1968

AVERAGE WHOLE-BODY DOSES FOR VARIOUS AGES IN MILLIRADS/MICROCURIE ADMINISTERED FOR DIAGNOSTIC TESTS EMPLOYING RADIOACTIVE ISOTOPES*

RADIONUCLIDE	ROUTE OF ADMINISTRATION	PURPOSE OF PROCEDURE	DOSE					
			NEWBORN	1 YR.	5 YR.	10 YR.	15 YR.	STANDARD MAN
			MILLIRADS/ MICROCURIE	MILLIRADS/ MICROCURIE	MILLIRADS/ MICROCURIE	MILLIRADS/ MICROCURIE	MILLIRADS/ MICROCURIE	MILLIRADS/ MICROCURIE
$^{55}Fe_2Cl_6$	Oral	Iron absorption	12.0	3.4	2.0	1.2	0.75	0.59
$^{59}Fe_2Cl_6$	Oral		40.0	15.0	9.1	5.9	3.9	3.3
$^{55}Fe_2Cl_6$	Intravenous	Plasma iron transport	120.0	34.0	20.0	12.0	7.5	5.9
$^{59}Fe_2Cl_6$	Intravenous	Degree and site of erythropoiesis	290.0	110.0	65.0	42.0	27.0	23.0
$Na_2{}^{51}CrO_4$	Intravenous	Red-cell volume, survival, gastrointestinal blood loss, and splenic scan	4.5	1.6	0.98	0.63	0.41	0.34
$^{51}CrCl_3$	Intravenous	Plasma volume, gastrointestinal protein loss	2.3	0.80	0 40	0.31	0.20	0.17
^{57}Cobalt-labeled vitamin B_{12}			54.0	22.0	14.0	9.1	6.1	5.3
^{58}Cobalt-labeled vitamin B_{12}		Vitamin B_{12} absorption	210.0	85.0	54.0	35.0	24.0	21.0
^{60}Cobalt-labeled vitamin B_{12}			2400.0	1000.0	630.0	410.0	270.0	240.0
$Na_2H^{32}PO_4$	Intravenous	Tumor localization	170.0	48.0	29.0	17.0	11.0	8.4
Colloidal ^{198}Au	Intravenous	Liver blood flow, scan	5.4	2.2	1.4	0.92	0.62	0.54
Chlormerodrin	Intravenous	Kidney scan, brain scan	2.1	0.84	0.53	0.36	0.23	0.20
$Na^{131}I$	Oral		10.0	2.0	1.3	0.81	0.53	0.45
$Na^{126}I$	Oral	Thyroid function, scan	9.4	1.6	1.0	0.67	0.44	0.39
$Na^{132}I$	Oral		1.1	0.44	0.27	0.17	0.11	0.09
$R^{131}ISA$	Intravenous	Plasma volume, cardiac output, gastrointestinal protein loss, and brain scan	28.0	8.9	5.4	3.4	2.1	1.7
Oleic acid ^{131}I or Triolein ^{131}I	Oral or intravenous	Lipid absorption, blood clearance	10.0	3.3	2.0	1.2	0.78	0.65
PVP ^{131}I	Intravenous	Gastrointestinal protein loss, brain scan	18.0	5.8	3.5	2.2	1.4	1.1
Rose Bengal ^{131}I	Intravenous	Liver blood flow, scan, function	3.7	1.5	0.92	0.61	0.40	0.36
Hippuran ^{131}I	Intravenous	Kidney function	0.33	0.13	0.08	0.06	0.04	0.03
Hippuran ^{126}I	Intravenous		0.09	0.04	0.02	0.02	0.01	0.01

* From Seltzer, R. A., Kereiakes, J. G., and Saenger, E. L.: Radiation Exposure from Isotopes in Pediatrics. *New England J. Med.* 271:84, 1964. Reproduced with permission of The New England Journal of Medicine.

Principles of Nuclear Medicine
Ed. H. N. Wagner Jr.,
W. B. Saunders Co., 1968

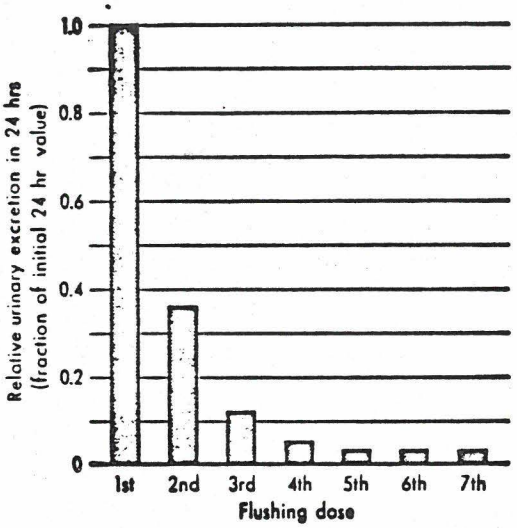


Fig. 10–6. Relative effectiveness of each of the daily flushing injections of nonradioactive cyanocobalamin (1 to 4 mg) following a single oral dose of labeled cyanocobalamin (0.5 to 2 μg). The first of the flushing doses is given within a few hours of the oral. Data are from both normal subjects (Doscherholmen and Hagen, 1962; Ellenbogen et al., 1955; Miller et al., 1957) and pernicious anemia patients who also received oral intrinsic factor (Ellenbogen et al., 1955).

of saturation achieved by the single flushing dose make the test results relatively insensitive to the interval between oral and flushing doses. Flushing doses may be given immediately after the oral dose or as long as 8 h later (see below). Convenience and custom have made the 2 h flushing dose the most popular. Plasma activity may be measured at 8 h whether or not the flushing dose was given at 2 h. Some experimental data [Baker and Mollin, 1955; Callender and Evans, 1955(*a*)] suggest a small but definite decrease in absorption of oral B_{12} as measured by excretion of unabsorbed vitamin in stools when the parenteral flushing dose is given 2 h after the oral dose. Despite this effect on absorption, the flushing dose does not appear to reduce the activity present in the plasma. As has been pointed out, plasma activity is reported to be increased by the flushing dose (Doscherholmen and Hagen, 1958; Doscherholmen, 1962). Nevertheless, parenteral cyanocobalamin in large amounts definitely decreases absorption if given before the oral dose (see below).

Although the measurement of plasma vitamin B_{12} concentration is not strictly a measurement of intestinal absorption, it is sometimes used as such. The traditional method has been the microbiologic assay; a newer method, competitive binding radioassay, is outlined in Chapter 13. In this method, labeled cyanocobalamin is added to an unknown amount of natural vitamin B_{12} extracted from the test plasma. The mixture is allowed to saturate a limited quantity of intrinsic factor. Vitamin not bound by the intrinsic factor is removed by dialysis or by adsorption onto protein-coated charcoal. The latter binds vitamin B_{12} strongly but not as strongly as does intrinsic factor. The labeled and the natural vitamin compete for the limited number of binding sites on the intrinsic factor. The concentration of natural vitamin in the test plasma can be calculated by measurement of the radioactivity bound to the intrinsic factor and by comparison with appropriate standards. For details refer to the bibliography (Barakat and Ekins, 1963; Beal, 1964; Gottlieb et al., 1965; Lau et al., 1965; Raven et al., 1966; Rothenberg, 1963).

d. Radiation Dose. Several radioisotopes of cobalt have been used for labeling the cyanocobalamin. Cobalt 60 was the first one available. It had the disadvantage of a 5 year half-life, two energetic photons per decay, and energetic beta radiation, all of which contributed to the radiation dose to the liver. Other isotopes used have included ^{56}Co, ^{57}Co, and ^{58}Co. The best is generally accepted to be ^{57}Co. The

Diagnostic Nuclear Medicine
Ed. E. R. Pe[illegible]sn and D. E. Raeside
Grune & Stratton, Inc., 1971

half-life of 270 days is perhaps longer than might be desired, but this is offset by the absence of beta radiation and by the low energy of the photons, 0.122 and 0.136 MeV (Fig. 5–1). The combination results in a comparatively low radiation dose and a high counting efficiency in the sodium iodide crystal scintillation detector.

The radiation dose to the liver from 0.5 μCi of ^{57}Co cyanocobalamin is 0.02 rads. For this calculation, it is assumed that the normal liver accumulates about 25 per cent of the oral dose when no parenteral flushing dose is given (Fig. 10–4), that the flushing dose washes out about one third of the absorbed cyanocobalamin, and that the flushing also reduces the amount of vitamin deposited in the liver (Doscherholmen and Hagen, 1962). If the reduction in liver radioactivity is directly proportional to the reduction in body activity, the liver will retain about 17 per cent of the oral dose. A second flushing dose should further reduce the amount deposited in the liver. The mean value of 520 days used here for the biologic half-life was calculated from published data for both normal and pernicious anemia subjects (Bozian et al., 1963).

2. Procedures for Measuring the Intestinal Absorption of Vitamin B_{12}

a. Advance Preparation.

(1) Prepare ^{57}Co counting standards.
(2) Prepare collection bottles and tubes.
(3) Prepare patient.

(1) *Prepare ^{57}Co counting standards.* Prepare urine or plasma standards or both as appropriate.

(a) *Urine standard.* Select a clean specimen bottle of the kind to be used for counting the urine specimens. If the radioactive cyanocobalamin has been purchased in solution, pipet one oral dose into a partially filled 100 ml volumetric flask, fill to volume, mix, and transfer 10 ml to the specimen bottle. Add enough distilled water to make 1 liter. (This liter now contains 10 per cent of the oral dose.) If cyanocobalamin has been purchased in capsule form, dissolve one capsule in about 30 ml of hot distilled water in a 100 ml volumetric flask. When the capsule is completely dissolved and when the flask has cooled to room temperature, fill to volume, mix, and transfer 10 ml to the specimen bottle as above. In either case, save the remainder for the plasma standard, below.

(b) *Plasma standard.* If a urine standard has been prepared, pipet 5 ml of the dilution remaining in the flask to a clean 50 ml volumetric flask, fill to volume, mix, and pipet 4 ml into a clean counting tube. This standard contains 0.1 per cent of the oral dose per milliliter.

If no urine standard has been prepared, proceed as follows: Starting with radioactive cyanocobalamin purchased in solution, pipet one oral dose into a partially filled 1000 ml volumetric flask, fill to volume, mix, and transfer 4 ml to a clean counting tube. The concentration of this solution is 0.1 per cent of the dose per milliliter. If the cyanocobalamin has been purchased as capsules, dissolve one capsule in about 30 ml of hot distilled water in a 1000 ml volumetric flask. When the capsule is completely dissolved and when the flask has cooled to room temperature, fill to volume, mix, and transfer 4 ml to the counting tube as above.

(2) *Prepare collection bottles and tubes.* Collection bottles must be free of any trace of radioactivity. New, 2 liter plastic jugs with handles are excellent. No jug should be reused unless it has been counted, to be certain it is free of radioactive material.

DOCKET NUMBER
PROPOSED RULE PR-31,32,35 (39 FR 2384)
Medical Uses

PROVIDENCE HOSPITAL
16001 W. NINE MILE RD. • SOUTHFIELD, MICHIGAN 48075 • PHONE 353-3000

Community
Service:
A Commitment

February 11, 1974

Acknowledged 2-19-74, cpo

DOCKETED
USAEC
FEB 19 1974
Office of the Secretary
Public Proceedings
Branch
ers

Secretary of the Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545
ATTENTION: Chief, Public Proceedings Staff

REF: AEC Proposed Rules: Dated January 21, 1974.

Dear Sir:

In the Federal Register, Vol. 39, No.14-Mon. January 21, 1974, Section 35.14 (B) (7), says that patients containing more than 8 mci I-131 or 23 mci Au-198 shall be hospitalized.

These are unreasonable values, and the wording of (7) should be stricken or changed. NCRP Report 37 "Precautions in the Management of Patients Who Have Received Therapeutic Amounts of Radionuclides" suggests that no person under 45 years old shall be permitted to receive a dose in excess of .5 rem, (persons over 45 may receive up to 5 rem in certain conditions).

From the guideline of 500 mrem, a value of 8 mci I-131, or 23 mci Au-198 was calculated as that activity which would give 500 mrem to another person. That calculation conseals the following condition:

(1) There is no absorbtion by the person with the isotope.

(2) The isotope has an infinite biological half life, i.e. none is excreted.

(3) A person is constantly one meter away from the person with the activity for the entire decay of the isotope (not just one half life).

In real life, these assumptions turn a reasonable NCRP recommendation into a ridiculous regulation, if the 8 mci and 23 mci quantities are blindly followed.

If implemented, it means that the nursing and hospital staff receives needless radiation.

If implemented, it means that elderly patients will spend an additional week sitting in a hospital room (cost: 7 days time $100.00/day equals $700.00).

If implemented, it means that someone else will be denied a hospital room.

For these reacons, I strongly urge the AEC to remove 35.14 (B) (7) from the proposed amendment.

Yours truly,

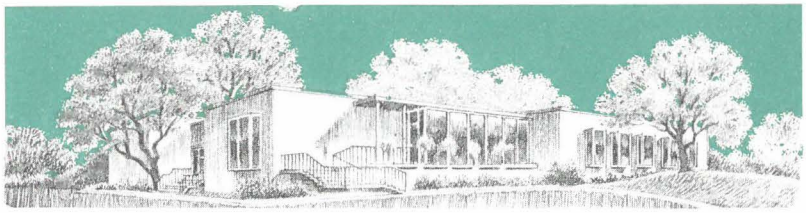
Ronald A. Rocchio

Ronald A. Rocchio, M.Sc.
Great Lakes Assoc. Medical Physicist

RAR/mg

cc: Dr. Wil B. Nelp
President, Society of Nuclear Medicine
Radioisotope Lab RC-70
University Hospital
Seattle, Washington 98195

TEXAS
PHARMACEUTICAL
ASSOCIATION



1624 U. S. HIGHWAY 183 EAST, AUSTIN, TEXAS, 78751

DOCKET NUMBER
PROPOSED RULE PR-31, 32, 35 (39 FR 2384)
Medical Uses

February 12, 1974

U.S. Atomic Energy Commission
Washington, D.C. 20545

Attn: Chief, Public Proceedings Staff

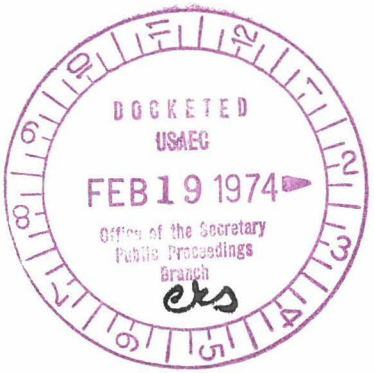
Gentlemen:

After review by our staff and practicing radiopharmacists of the proposed rule-making appearing in the Monday, January 21, 1974 issue of the Federal Register (Volume 39, Number 14), and we would like to offer the following comments for your consideration in preparing the final regulations:

Section 35.14 (b) (2), to be changed to read: "...reagent kits which are approved by the Commission or by an Agreement State upon recommendation by the FDA for use by persons licensed pursuant to this Section 35.14 and Group 3 of Schedule A, Section 35.1000, or equivalent Agreement State regulations."

Inclusion of such wording would insure, we feel, the involvement of the FDA, and aid in clarifying the precise areas of responsibility.

We appreciate your consideration of the above suggestion.



Sincerely,

Paul F. Davis

Paul F. Davis, R.Ph.
Director of Public Affairs

PFD/cw

Acknowledged 2-19-74, ces

MAILING ADDRESS: P. O. BOX 4487, AUSTIN, TEXAS 78765 • 512 / 836-8350

DOCKET NUMBER
PROPOSED RULE PR-31, 32,35 (39 FR 2384)
Medical Uses

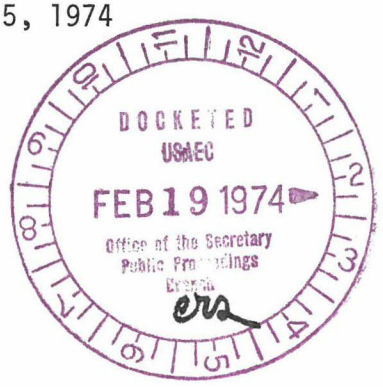
Duke University Medical Center

DURHAM, NORTH CAROLINA
27710

February 15, 1974

DEPARTMENT OF RADIOLOGY
DIVISION OF NUCLEAR MEDICINE

TELEPHONE 919—684-2466



Secretary of The Commission
U. S. Atomic Energy Commission
Washington, D. C. 20545

Attention: Chief, Public Proceedings Staff

Dear Sir:

I write in comment on rulemaking proposed by the Atomic Energy Commission, amendments to Section 35.14 10 #CFR, Part 35 as published in the Federal Register, Volume 39 No. 14, Monday, January 21, 1974. I write in opposition to a provision of this proposed rulemaking contained in paragraph (b), subparagraph (7) of Section 35.14 that requires the hospitalization of patients containing more than 8 millicuries of iodine-131 for the treatment of thyroid carcinoma.

The present requirements of the Atomic Energy Commission are that patients containing more than 30 millicuries of iodine-131 must be hospitalized. In effect, the Commission proposes to reduce this level a factor of 4 (approximately) but offers no justification for such a step. This kind of proposal essentially places the medical community in the position of having to show cause why it should not be done. I believe, on the other hand, that the Commission should be required to show a cause why it should be done.

This unjustified proposal by one branch of the Federal Government will increase the cost of medical care to a population of patients whose financial resources already are strained by their illnesses. By requiring extra days of hospitalization, at a time other branches of the Federal Government are placing considerable pressure on deliverers of health care to reduce costs to the patients, the Commission is in direct conflict with the Cost of Living Council. The proposed rulemaking would require that the patient be hospitalized for sufficient additional time that his body activity can drop from 30 millicuries to 8 millicuries, a factor of nearly 4. The mean effective half-time of iodine-131 in patients with some functioning portions of thyroid glands is about 2.5 days (the range is from about 2 to 3 days among many patients)(1). A reduction of a factor of 4 requires 2 half-times. Therefore, the average patient would have to be hospitalized 5 additional days, with some patients having to remain 6 or 7 days. With current costs of hospitalization, about $100 per day of stay, the Commission, in effect, is proposing that from $400-$700 be added to the cost of medical care for patients who, in many cases, are already in financial trouble. These facts are readily evident in any practical analysis of how the proposed rulemaking would be operative. To offset this compelling disadvantage, the Commission offers not one word of justification nor did it see fit to obtain the approval of its own Medical Advisory Committee.

Acknowledged 2-19-74, ers

I respectfully request that the Commission rescind its proposed rulemaking in the aforementioned subparagraph and retain the present level of 30 millicuries of iodine-131 as the threshold of patient body burden above which hospitalization is required.

Ref. (1) Saenger, E. L. et al, Experiences with I^{131} In The Management of Carcinoma of The Thyroid, Radiology 83: 892-901, November 1964.

Sincerely yours,

C. Craig Harris

C. Craig Harris
Associate Professor of Radiology

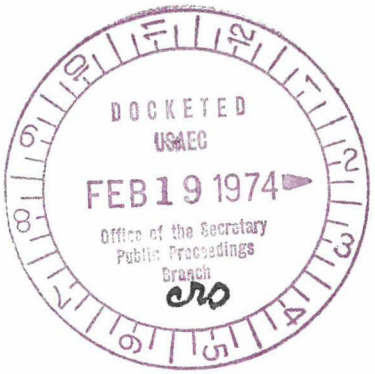
CCH:cmb

VETERANS ADMINISTRATION
HOSPITAL
1400 VETERANS OF FOREIGN WARS PARKWAY
WEST ROXBURY, MASS. 02132

February 13, 1974

IN REPLY REFER TO: 690-172

DOCKET NUMBER
PROPOSED RULE PR-31,32,35 (39 FR 2384)
Medical Uses



Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D. C. 20545

Attention: Chief, Public Proceedings Staff

Dear Sir/Madam,

Your proposed Amendments dated January 21, 1974 to parts 31, 32 and 35 of AEC regulations to expand the group licensing of medical uses of radioisotopes will simplify the procedure for users in applying for licensing.

We endorse these proposed amendments.

Sincerely,

Donald E Tow

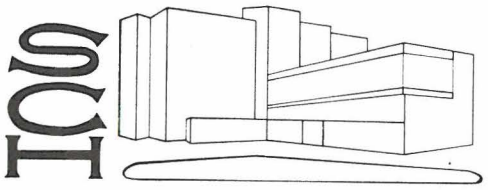
Donald E. Tow, M. D.
Chief, Nuclear Medicine Service

Acknowledged 2-19-74, ers

Show veteran's full name, VA file number, and social security number on all correspondence.

SUBU..AN COMMUNITY HOSPITAL
Warrensville Heights, Ohio 44122 / (216) 991-1700
An Ohio Not For Profit Corporation

DOCKET NUMBER
PROPOSED RULE PR-31,32,35 (39 FR 2384)
Medical Uses



February 11,1974

Secretary of Commission
U.S. Atomic Energy Commission,
Washington, D.C. 20545

Attention: Chief, Public
Proceedings Staff

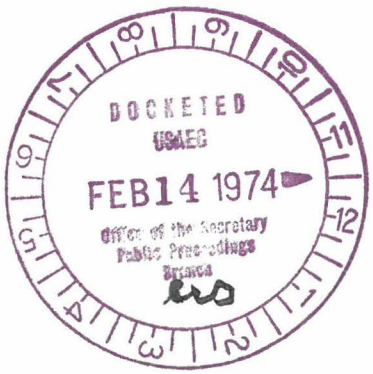
Acknowledged 2-14-74, ers

Dear Sir:

I am writing in regards to a recent document released by the Atomic Energy Commission with regards to proposals to expanded Group Licensing for certain medical uses of Radioisotopes.

As head of a department authorized by initial licensing dating back some ten years and numerous additional amendments, permitting the use of radioisotopes for medical diagnosis and treatment, I strongly concur with the proposals which would obviate the necessity of taking the necessary steps to have a licensed amended with the appearance of a new and accepted Radioisotope for diagnosis or treatment. I think the group licensing concept as proposed would certainly simplify the procedure not only for the licensee and the A.E.C. but even for the supplier, avoiding the delay involved in procuring amendments for original license.

Looking forward to an early acceptance of the proposals stated in this latest bulletin, I remain



Very truly yours;

Howard A. Steiner, M.D.
Chief, Department of Radiology
and Nuclear Medicine.

HAS;ep

DOCKET NUMBER
PROPOSED RULE PR-31,32,35 (39 FR 2384)
Medical Uses

KUAKINI HOSPITAL AND HOME
347 NORTH KUAKINI STREET / HONOLULU, HAWAII 96817
TELEPHONE 536-2236

February 8, 1974

Acknowledged 2-12-74, cas

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FEB 12 1974
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Public Proceedings
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Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D. C. 20545

Attention: Chief, Public Proceedings Staff.

Dear Sir:

I would like to express my unqualified support for the proposed amendments concerning medical uses of radioisotopes. I would urge prompt enactment of these amendments.

I also feel that the specialty of Nuclear Medicine, and our patients, would benefit from more stringent regulations regarding qualifications of physicians and allied personnel. There remain too many personnel who do not have the appropriate training or experience in this rapidly moving field, particularly with regard to radiation safety and techniques for reducing patient exposure. I would urge consideration of these factors in the licensing of individual laboratories; this could do more to improve safety and quality control than any of the regulations regarding specific radiopharmaceuticals.

Sincerely,

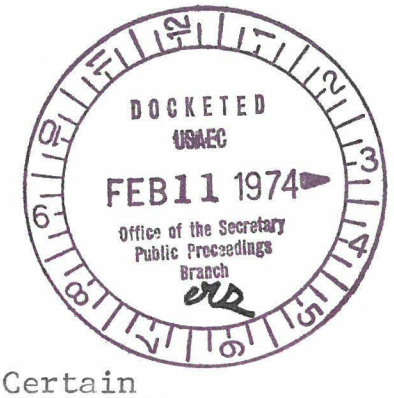
Richard Wasnich, M.D.
Director of Nuclear Medicine

DOCKET NUMBER
PROPOSED RULE PR-31,32+35 (39 FR 2384)
Medical uses

WARREN RADIOLOGY ASSOCIATES, INC.
NORTHWEST SAVINGS BUILDING
DANIEL G. LAREAU, M. D. P. O. BOX 295 KARL J. FRITZ, JR., M. D.
WARREN, PENNSYLVANIA 16365

February 6, 1974

Acknowledged 2-11-74, CR



Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D.C. 20545

Attention: Chief, Public Proceedings Staff

RE: AEC Proposal to Expand Group Licensing for Certain Medical Uses of RAdioisotopes, released Jan 21, 1974

I. Previous regulations required hospitalization of patients containing more than 30 millicuries of Iodine 131 regardless of diagnosis; but your new group licensing concept, proposed to simplify licensing procedure on Page 2385-2 Paragraph 7, requires hospitalization of patients containing more than 8 millicuries of I-131 for treatment of thyroid carcinoma.

It is recommended that this be changed to the original regulation of 30 millicuries for the following reasons:

1. Thyroid carcinoma is no more catching than hyperthyroidism for which you have no similar restriction.

2. Unnecessary hospitalization will result from this regulation.

3. Physicians treating these conditions with I-131 are quite aware of the hazards and are capable of controlling them without this blanket regulation which could result in greater exposure of personnel in loosely policed small community hospitals than if the patient (frequently living alone) were allowed to return home.

II. While I am at it, I would like to register another personal objection to the format of CFRs. Would you consider separating these many pages of small print information into categories of isotopes (a) "frequently used", (b)"rarely used", and (c) "for investigation, research, and educational use only". This would save readers considerable time wading through so much print to read the areas that concern them. It would be further helpful if items representing change were written in italics; surely not all the small-typed five pages of this recent communication represents change.

I realize you have a difficult job and that you want to be all inclusive, but the above suggested changes would result in more recipients reading your material; I do not believe it is your intention to hide changes like the above in the camouflage of multiple pages of not very exciting prose.

Sincerely,

D. Lareau M.D.

Daniel G. Lareau, M.D., FACP

DGL/s

cc: Milton A. Friedlander, M.D.
Chairman on Nuclear Radiology
Penna Radiological Society
Polyclinic Hospital
Harrisburg, Penna 17105

C. Jules Rominger, M.D., FACR
Mercy Catholic Medical Center
54th and Cedar Avenues
Philadelphia, Penna 18201

DOCKET NUMBER
PROPOSED RULE PR-31,32&35 (39 FR 2384)
Medical Uses

SURGERY
Hampton St. Clair, M.D.
Edward J. Flynn, Jr., M.D.
R. W. Neilson, Jr., M.D.
James P. Thomas, M.D.
Riaz A. Rana, M.D.

NEUROSURGERY
Wm. F. Hillier, Jr., M.D.
E. Lyle Gage, Jr., M.D.

DEPARTMENT OF PATHOLOGY
David F. Bell, Jr., M.D.
John J. Bryan, M.D.
Ilmia S. Bano, M.D.

OBSTETRICS AND GYNECOLOGY
E. W. McCauley, M.D.
Charles S. Flynn, M.D.
Frederick T. Edmunds, M.D.
M. S. Hajjar, M.D.
T. Keith Edwards, M.D.

RADIOISOTOPES
C. D. Pruett, M.D.
R. O. Rogers, Jr., M.D.

BLUEFIELD SANITARIUM
BLUEFIELD SANITARIUM CLINIC
BLUEFIELD, W. VA. 24701
Phone: 325-6176

INTERNAL MEDICINE
J. R. Shanklin, M.D.
Karl E. Weier, M.D.
H. F. Warden, Jr., M.D.
C. D. Pruett, M.D.
R. O. Rogers, Jr., M.D.

UROLOGY
T. B. Baer, M.D.
Steve J. Misak, M.D.

ROENTGENOLOGY
S. G. Davidson, M.D.
George C. King, M.D.
Brennan Purkall, Jr., M.D.

EYE, EAR, NOSE, and THROAT
F. D. White, M.D.

ANESTHESIOLOGY
David H. Gatherum, M.D.

PEDIATRICS
H. Grady McRae, Jr., M.D.
Edward M. Spencer, M.D.

Acknowledged 2-11-74, es

February 8, 1974

Chief, Public Proceedings Staff
Secretary of the Commission
of the United States Atomic Energy Commission
Washington, D. C. 20545

Dear Sir:

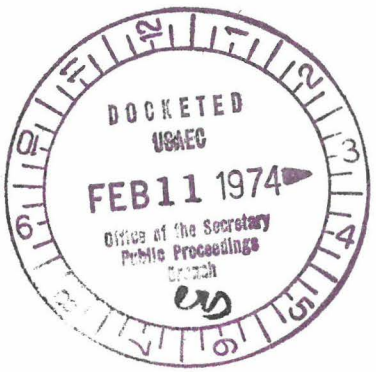
I concur wholeheartedly with the group licensing concept proposed by the Atomic Energy Commission. I have always thought that those of us that did not possess and qualify for a general license have been discriminated against, but it seems prudent to me that once a man's qualifications and equipment that he possess is on record with the Atomic Energy Commission that it is superfluous to go through the laborsome procedure of getting amendments to use new kits and generators which have been approved by the AEC. I would also like to suggest that when a new procedure or kit, and so forth is approved by the AEC that the AEC notify each individual licensee that this procedure or kit falls within the scope of the particular individual's license. I think that this proposed change in licensing procedure is an excellent one.

I would also like to state that since my license was issued in 1957 that all AEC personnel with whom I have delt have been extremely courteous, efficient, and helpful.

Sincerely yours,

Charles D. Pruett, M. D.

CDP:bsm



DOCKET NUMBER
PROPOSED RULE PR-31, 32 & 35 (39 FR 2384)
Medical Uses

JERSEY SHORE MEDICAL CENTER
FITKIN HOSPITAL
1945 Corlies Avenue / Neptune / New Jersey 07753
TELEPHONE / AREA CODE 201 / 775-5500

Acknowledged 2-11-74, ers

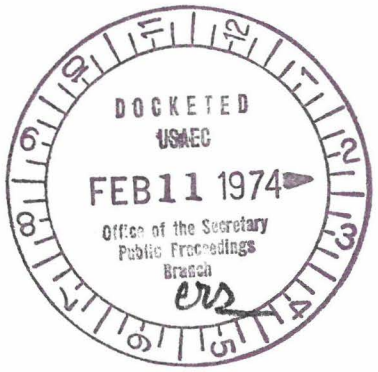
February 7, 1974

Secretary
United States Atomic Energy Commission
Washington, D.C. 20545

Attention: Chief Public Proceedings Staff

Dear Sir,

I support without restriction the proposed rules (2384-1) amending 10CFR parts 31, 32 and 35 of the AEC Regulations as published.



Sincerely,

R.C. Spagnoli, M.D.

R.C. SPAGNOLI, M.D.
Director, Department of Radiology

RCS/jn

JERSEY SHORE MEDICAL CENTER-FITKIN HOSPITAL
1945 CORLIES AVENUE
NEPTUNE, NEW JERSEY 07753

DOCKET NUMBER
PROPOSED RULE PR-31, 32 + 35 (39 FR 2384)
Medical Uses

JERSEY SHORE MEDICAL CENTER
FITKIN HOSPITAL
1945 Corlies Avenue / Neptune / New Jersey 07753
TELEPHONE /. AREA CODE 201 / 775-5500

Aeknowledged 2-11-74, ERB

February 7, 1974

Secretary of the Commission
U.S. Atomic Energy Commission
Washington, D.C. 20545

Attention: Chief, Public Proceedings Staff

Dear Sir or Madam:

As an AEC licensee for medical uses of radioisotopes I would like to express my approval concerning the proposed amendments to Parts 31, 32 and 35 of the AEC regulations being published in the Federal Register of January 21, 1974. I feel that implementation of these proposals would be beneficial and simplify the cumbersome present situation.

Yours truly,

Thomas Witomski, M.D.

aem/TW

DOCKETED
USAEC
FEB 11 1974
Office of the Secretary
Public Proceedings
Branch
ERB

Thomas Witomski, M.D.
JERSEY SHORE MEDICAL CENTER-FITKIN HOSPITAL
1945 Corlies Avenue
Neptune, New Jersey 07753

DOCKETED
USAEC
FEB 11 1974
Office of the Secretary
Public Proceedings
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DOCKET NUMBER
PROPOSED RULE PR 31,32 & 35 (39 FR 2384)
Medical Uses

Duke University Medical Center
DURHAM, NORTH CAROLINA
27710

February 5, 1974

DEPARTMENT OF RADIOLOGY
DIVISION OF NUCLEAR MEDICINE

TELEPHONE 919—684-2466

Mr. Gordon M. Grant
Acting Secretary
U. S. Atomic Energy Commission
Germantown, Maryland

Re: Proposed Rules Changes

Acknowledged 2-11-74 ers

Dear Mr. Grant:

I am writing in response to the proposed rules changes regarding uses of radioisotopes which appeared in the Federal Register, January 21, 1974. My comments are in regard to the amendment 35.14, Section (b), Item #7 which reads as follows: "For Group IV, any licensee who possesses and uses radiopharmaceuticals for therapy shall assure that patients containing more than 8 millicuries of iodine-131 for treatment of thyroid carcinoma or patients containing more than 23 millicuries of gold-198 shall be hospitalized."

As a practicing nuclear medicine physician with more than twenty years' experience in the field, I must protest the truly unnecessary restrictions placed on the management of thyroid carcinoma patients imposed by the 8 millicuries iodine-131 restriction noted above. The present limit of 30 millicuries is restrictive enough and has resulted in additional financial hardship to patients with thyroid cancer. To lower this limit to 8 millicuries will add a minimum of 2 and possibly 3 days to the presently required 3 to 4 days of hospitalization of thyroid cancer patients receiving I-131 therapy. At present average hospital day costs of $100.00, the added burden of $300.00 to $400.00 is truly excessive.

Patients with cancer of any type incur large hospital expenses from the initial diagnostic and therapeutic procedures. To add additional expense to such a patient should be avoided where possible and particularly where it is unnecessary.

The 8 millicuries I-131 limit actually seems discriminatory since it applies only to thyroid cancer patients. If such a limit truly has merit, it should also be applied to the larger number of hyperthyroid patients who receive more than 8 millicuries I-131 for treatment. Hospitalization of these patients would truly overload the already expanded hospital census due to the large number of patients receiving I-131 therapy for hyperthyroidism. If 8 millicuries I-131 truly represents a radiation hazard to the general population, it certainly should not be applied only to the relatively small number of thyroid cancer patients, but also to the infinitely larger group of hyperthyroid patients. Personally, I do not believe this is possible.

In summary, I believe the 8 millicuries I-131 amendment to current regulations is discriminatory, unnecessary and, if adopted, will represent an undue hardship on a small number of already financially depleted patients.

Sincerely,

Joseph B. Workman

Joseph B. Workman, M. D.
Associate Professor of Radiology

JBW:cmb

Joseph B. Workman, M. D. - Box 3223 - DNM
Duke University Medical Center
DURHAM, NORTH CAROLINA
27710

DOCKET NUMBER
PROPOSED RULE PR-31,32,35 (39 FR 2384)
Medical Uses

VETERANS ADMINISTRATION
HOSPITAL
ALEXANDRIA, LOUISIANA 71301

February 5, 1974

IN REPLY
REFER TO:

Secretary of the Commission
U. S. Atomic Energy Commission
Attention: Chief, Public Proceedings Staff
Washington, D. C. 20545

SUBJ: Proposed Amendments to Parts 31, 32, and 35 of the AEC Regulations Published in the Federal Register on January 21, 1974

1. The undersigned is greatly in favor of the proposed amendments since they will enable us to obtain isotopes more easily and for a greater variety of tests.

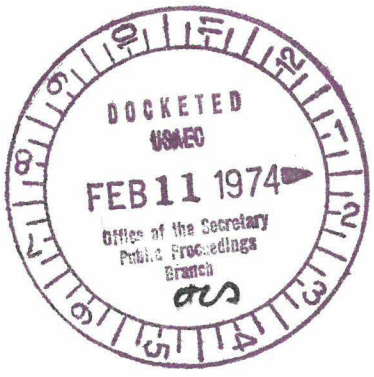
2. We are a dean's committee hospital but have been unable to obtain a broad license. Therefore, it has been very difficult for us to obtain amendments, especially for the different reagent kits. Thus, we have had to limit the scope of our work.

3. In the recent hotline conference with area chiefs of nuclear medicine, they all felt as the undersigned.

Sincerely yours,

William H. Kastl MD

WILLIAM H. KASTL, M. D.
Chief, Nuclear Medicine Service



Acknowledged 2-11-74, ors

Show veteran's full name, VA file number, and social security number on all correspondence.

DOCKET NUMBER
PROPOSED RULE PR-31,32+35 (39 FR 2384)
Medical uses

LAKEWOOD HOSPITAL
LAKEWOOD, OHIO
COMMUNITY MEDICAL CENTER

14519 DETROIT AVENUE LAKEWOOD, OHIO 44107 PHONE (216) 521-4200

Aeknowledged 2-11-74 crs

February 6, 1974

Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D. C.

Attention: Chief, Public Proceedings Staff

Dear Sir:

The proposed amendments to Parts 31, 32 and 35 of AEC regulations expanding the group licensing of medical uses of radioisotopes is a much needed change. It would be a great aid to the clinical practice of Nuclead Medicine in the community hospitals.

I heartily support this proposal.

Truly yours,

William J. Fayen, M.D.
Director
Nuclear Medicine

WJF:mlf

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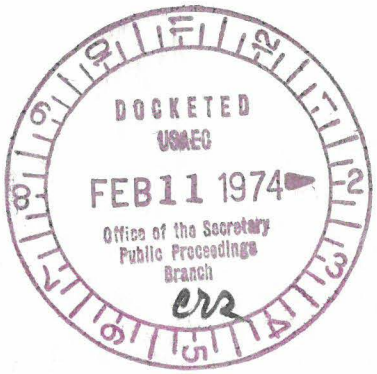
USAEC
FEB 11 1974
Office of the Secretary
Public Proceedings
Branch



DOCKET NUMBER
PROPOSED RULE PR-31,32 + 35 (39 FR 2384)
Medical uses

February 6, 1974

U. S. Atomic Energy Commision
Washington, D. C. 20545

Acknowledged 2-11-74 crz

Attention: Chief, Public Proceedings Staff.

Dear Sir:

We are most in favor of the new proposed amendments to parts 31, 32 and 35 of AEC regulation according to their letter of January 21, 1974. I feel that this would greatly facilitate the use of necessary radiopharmaceuticals and markedly deminish the costs acquired in trying to necessitate paper work for such. I highly recommend adoption of such amendments.

For further information please feel free to contact me.

Sincerely,

Harold C. Papson M.D.

HCP/mn
c

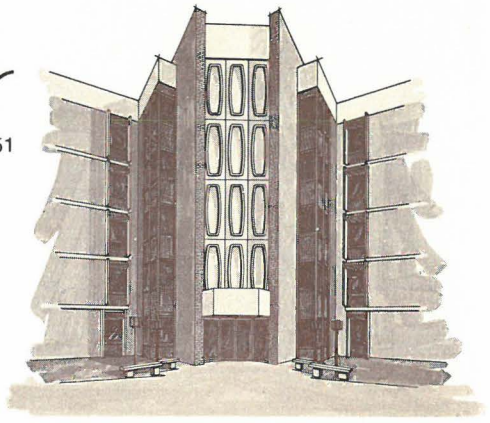
ST. JOSEPH HOSPITAL
Sisters of Charity
MOUNT CLEMENS, MICHIGAN 48043

Wesley Medical Center

550 North Hillside / Wichita, Kansas 67214 / (316) 685-2151

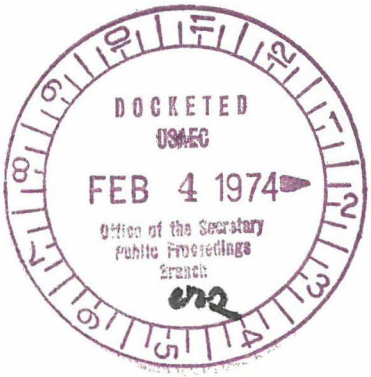
DEPARTMENT OF LABORATORY MEDICINE

BERT E. STOFER, M.D., DIRECTOR EMERITUS
LEO P. CAWLEY, M.D., DIRECTOR
TED STREET, ADMINISTRATIVE ASSISTANT
JESSE H. MARYMONT, M.D.
TOM HIRATZKA, M.D.
GEORGE E. FRITZ, M.D.
H. H. MARSH, M.D.
DWIGHT K. OXLEY, M.D.
CAROL SLEEPER, M.D.
DAVID L. PALMER, M.D.



DOCKET NUMBER
PROPOSED RULE PR-31,32,35 (38 FR 2384)
Medical Uses

January 31, 1974



Secretary of the Commission
U. S. Atomic Energy Commission
Washington, D. C. 20545

Attention: Chief, Public Proceedings Staff

Dear Sir:

With regard to the Notice of Proposed Rulemaking, "Group Licensing for Certain Medical Uses" (10CFR Parts 31, 32 and 35), published in the Federal Register Vol. 39, No. 14, Monday, January 21, 1974, pp. 2384ff, the following questions and comments are offered.

1. In the amended paragraph (a) of 35.14 (page 2385), reference is made to ".... an application for a specific license..." (emphasis MINE). It is correct to conclude that the provisions of 35.14, including the filing of a Registration Certificate, 35.14(b)(4), will apply only to holders of specific licenses and not to institutions operating under a broad institutional license?

2. A new registration process is described in the proposed 35.14 (b)(4), page 2385, which requires approval from the AEC prior to the use of investigational radiopharmaceuticals. Will holders of specific licenses issued by Agreement States proceed with this through the AEC or through the regulatory office of their Agreement State?

3. I suggest that Cobalt 57 as labelled cyanocobalamin for intestinal absorption studies be added to the list in paragraph (a), 35.100,(Group I). Cobalt-57 is widely used for this purpose; the physical half-life, and therefore the radiation dose received by the patient, are much more favorable than the equivalent properties of Cobalt-60 which is on the approved list.

Sincerely,

Dwight K. Oxley

Dwight K. Oxley, M.D.
Chief, Nuclear Medicine

cc: Dr. Leo P. Cawley
Dr. David Palmer
Mr. Robert J. O'Brien
Mr. Gerald Allen

DKO:ld