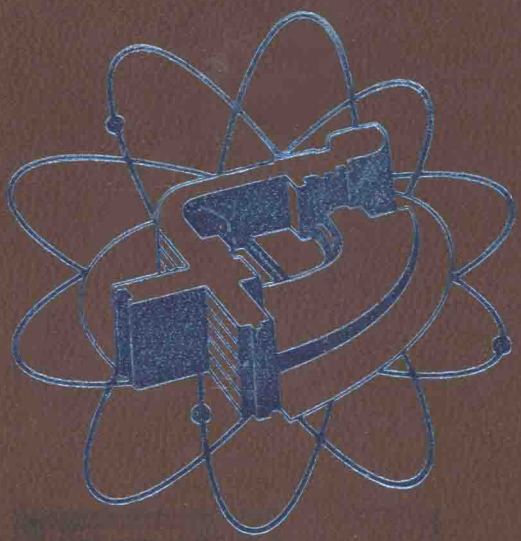
THERAPY IN NUCLEAR MEDICINE

Richard P. Spencer, M.D., Ph.D.
Editor



Therapy in Nuclear Medicine

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Grune & Stratton
A Subsidiary of Harcourt Brace Jovanovich, Publishers
New York San Francisco London

Library of Congress Cataloging in Publication Data
Main entry under title:

Therapy in nuclear medicine.

Based on a symposium held Mar. 17–19, 1977, Hartford.
Includes bibliographical references and index.
1. Radioisotopes—Therapeutic use—Congresses.
I. Spencer, Richard P. [DNLM: 1. Radioisotopes—Therapeutic use—Congresses. 2. Nuclear medicine—Congresses. WN450 T398 1977]
RM858.T38 615'.8424
ISBN 0-8089-1070-1 78-7384

Grune & Stratton, Inc.
111 Fifth Avenue
New York, New York 10003

Distributed in the United Kingdom by
Academic Press, Inc. (London) Ltd.
24/28 Oval Road, London NW1

Library of Congress Catalog Number 78-7384
International Standard Book Number 0-8089-1070-1
Printed in the United States of America

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Front cover: The University of Connecticut Health Center, the host for the symposium on *Therapy in Nuclear Medicine,* is depicted inside an atom.

Preface

The excellent and rapid advances in diagnostic aspects of nuclear medicine have perhaps made us lose sight of steady progress in the therapeutic use of radionuclides. In an effort to bring together the past history of such therapeutic applications, their present use, and emerging areas which have clinical implications, a symposium was held in Hartford, Connecticut (March 17–19, 1977).

By means of formal presentations, questions and answers, a round table discussion, and individual interactions, the extent of present information was probed. It became clear that this meeting, and its resultant publication, marked but an early step in exploring the clinical radiation biology of therapeutic radionuclides. The enthusiasm generated at the meeting suggested that others might follow. We are appreciative of the commercial support that aided in funding the symposium, and of the assistance of the sponsoring organizations: University of Connecticut Health Center, Hartford County Medical Association, American College of Nuclear Medicine, Society of Nuclear Medicine, and the Connecticut Division of the American Cancer Society.

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SECTION I

Background

Richard P. Spencer

1
Nuclear Medicine and Therapy: A Reorientation to Specificity and Beta Ray Generators

The field we refer to as nuclear medicine has come full circle. It began with a combination of diagnostic studies and therapeutic applications. Indeed ^{32}P and ^{131}I were the mainstays of the discipline for many years and they found employment in several therapeutic schemes. As the imaging applications of short-lived radionuclides were recognized and developed, nuclear medicine became primarily a diagnostic specialty. Yet we can ask a fundamental question: how have we benefited the patient if we establish the diagnosis of an incurable disorder? We view this volume as recognition of the immediacy of that question, and of the potential role of radioactive pharmaceuticals in the therapy for certain human diseases. The full circle has been traversed for we again notice that radioactive materials have a role to play in both diagnosis and therapy. We are at an early stage in understanding the microdosimetry of the therapeutic agents employed, and progress is needed in this fundamental area as well as in clinical applications.

The development of diagnostic radiopharmaceuticals was spurred both by their clinical usefulness and by the appreciation that there was no host reaction routinely expected. In other words, they were diagnostic agents, and were not given in pharmaceutical amounts or to elicit a pharmaceutical effect. By way of contrast, when we utilize radionuclides (R*) in therapy, we must reorient our thinking. The entire reason for using these materials is to elicit a therapeutic response; more particularly, we are relying on a response to radiation. There are thus the considerations shown in Table 1-1.

The list is by no means all inclusive, but it does illustrate the wide variety of considerations. We can perhaps make this concrete by mapping out some basic concepts in the therapeutic application of radionuclides (Table 1-2). As knowledge of these basic topics increases, we may be able to better design and utilize radiopharmaceuticals for therapeutic purposes.

Supported by U.S. Public Health Service Grant CA 17802 from the National Cancer Institute.

Table 1-1
Considerations in the Response to Radiation by a Radionuclide

1. Time course of R* deposition in the lesion.
2. Radiation to the lesion by R*.
3. Release of R* from the lesion.
4. Whole-body irradiation by R*.
5. Radiobiology of events within the lesion.
6. Abscopal effects (possibly by release of antigenic and other components).
7. Objective and subjective patient response.

CHOICE OF RADIONUCLIDES FOR THERAPY

There are two basic considerations in the selection of a radionuclide for a specific therapeutic purpose:

1. Chemical or physical properties required for localization in the lesion.
2. Type of radiation, and time course of irradiation (a combination of physical decay and biological turnover).

Five types of radionuclides useful in therapy can be identified (Table 1-3). In addition to pure beta ray emitters, we can also utilize beta ray emitting radionuclides which additionally give off positrons or gamma rays (both of which will somewhat contribute to the radiation dose in the region, and which can also be imaged, thus allowing a check on the uniformity of distribution). We presently have access to gamma ray emitters with conversion or Auger electrons. Additionally, alpha ray emitters and radionuclides which undergo fission might be used in therapy. The list is thus extensive and more choices are available than ^{131}I, ^{32}P, and ^{148}Au which have been the standbys in the past.

In a way this requires a reorientation of our thinking. Certain parallels with diagnostic nuclear medicine are apparent—for example, a high target to nontarget ratio. However, a marked reversal of viewpoints also occurs. Consider, for example, the use of radioiodide (^{131}I). When a scanner was passed over the neck, gamma rays were utilized and the presence of beta rays was deplored. When ^{131}I

Table 1-2
Some Basic Aspects of the Biological Effects of Radionuclide Delivery of Radiation*

1. "Added" effects of chemical interaction and irradiation. Example: enhanced tumoricidal effect of ^{125}I-iododeoxyuridine over iododexoyuridine.
2. "Radiation sensitizers." Example: adriamycin as an inhibitor of postirradiation proliferation.
3. Time-dose effects.
   a. Destruction of "repair mechanisms."
   b. Differential sensitivity, and recovery, of normal and malignant tissues.
   c. Role of anoxia.

*These effects are currently under investigation.

Table 1-3
Five Types of Radionuclides Potentially of Use in Therapy

1. Pure beta ray emitters
2. Beta ray emitters also having gamma and/or positron emissions
3. Gamma ray emitters with Auger or conversion electrons
4. Alpha ray emitters (administered, or produced internally)
5. Radionuclides which undergo fission

was employed in therapy, the beta rays were the essential contributors and the gamma rays had but a minor role to play. It was the same radioiodide. Only the perspective and intended use had changed. A comparison of views on beta and gamma rays from therapeutic and diagnostic viewpoints, is given in Table 1-4.

We can carry this to the next logical step by examining two groups of known antitumor chemicals (Table 1-5). The compound *cis*-diamminedichloroplatinum (II) has been synthesized with ^{193m}Pt or ^{195m}Pt for imaging.[1,2] If the radiolabeled compound were to be used in therapy, then ^{197}Pt might be the radionuclide of choice (this substance emits a 670-kev beta ray as well as a gamma emission). Similarly, purine and pyrimidine analogues can be labeled with ^{123}I, ^{18}F, or ^{77}Br for imaging. For therapeutic applications, radionuclides which deposited much energy locally would be employed. These include ^{125}I (Auger electrons), ^{131}I (beta particles in addition to the gamma rays; ^{82}Br and ^{83}Br are also in this class), and the pure beta emitters ^{3}H, ^{14}C, and ^{35}S. The choice of radionuclide is largely dictated by its intended purpose—diagnosis or therapy. The next extension is to ask if various radionuclides can be incorporated *into* an aliphatic chain or aromatic ring in order to gain the needed specificity of the molecule (Table 1-6). There are several apparent choices here (and the list will likely grow with time). Some of these are monoseleno and diseleno compounds,[3] mono- and diarseno chemicals,[4] rings carrying a positively charged iodine,[5] and those carrying both phosphorus and iodine in the ring.[6] Indeed, if a molecule were cleaved in vivo, it might be possible to deliver two or more labeled atoms into the tissue, so that each (or the selected portion) would carry a therapeutic radionuclide.

Table 1-4
Comparison of Views on Beta and Gamma Rays

Therapy	Diagnosis
Beta rays are useful since they deliver ionizing radiation to the limited area that is to be treated.	Beta rays can not be visualized externally and only increase tissue radiation exposure.
Gamma rays are of little therapeutic value (except those of very low energy) since they distribute the radiation exposure over a wide area.	Gamma rays are of primary importance in imaging (except those of low energy, which do not penetrate the tissue).
There may be a role for longer lived radionuclides if the radiation has to be delivered over a period of time.	Short-lived radionuclides are preferred since they do not have to be present after the initial images are obtained.

Table 1-5
Imaging and Therapeutic Radionuclides Which Might Be Employed in the Antitumor Agent *cis*-Diamminedichloroplatinum and in Purine and Pyrimidine Analogues

	Imaging			Therapy		
cis-diamminedichloroplatinum	^{193m}Pt	4.4 days	x-rays	^{197}Pt	0.75 days	670 kev $\beta-$ plus gamma
	^{195m}Pt	4.1 days	x-rays			
Purine and pyrimidine analogues	^{123}I	13 hr	159 kev gamma	^{125}I	57 days	E.C.
				^{131}I	8.1 days	600 kev $\beta-$ plus gamma
	^{18}F	1.7 hr	positron	^{3}H	12.5 years	18.6 kev $\beta-$
				^{14}C	5,700 years	156 kev $\beta-$
				^{35}S	88 days	167 kev $\beta-$
	^{77}Br	2.4 days	positron	^{82}Br	1.5 days	444 kev $\beta-$ many gammas
				^{83}Br	2.4 hr	930 kev $\beta-$ 1% gamma

In some instances we have a plethora of radionuclides which might do the task for us. Consider the therapy of lesions in bone (Table 1-7). In addition to ^{32}P (with its energetic beta particle), ^{33}P has a slightly longer physical half-life, but a less energetic beta particle. However, ^{89}Sr has also been used in the therapy of lesions in bone.[7] Moreover, ^{91}Sr has an even more energetic beta emission and also gives off gamma rays. There are, in addition, two radionuclide pairs that might be used in therapy as "internal" or "in situ" or "in vivo" radionuclide generators. That is, the parent localizes in bone and emits a beta particle. The daughter radionuclide produced is also a beta particle emitter.

$$^{140}\text{Ba} \longrightarrow {}^{140}\text{La}$$
$$^{47}\text{Ca} \longrightarrow {}^{47}\text{Sc}$$

The use of such internal radionuclide generators still awaits biological exploration.

Table 1-6
Noncarbon Atoms that Can Be Inserted into Aliphatic or Aromatic Molecules and Radiolabeled

Grouping	Example
—C—Se—C—	Selenomethionine
—C—Se—Se—C—	Diselenodibutyric acid
—C—As—	Arsonoacetic acid
—C—As=As—C—	Diarsono compounds
—C—I^+—C—	Diphenyleneiodonium
—P—I—	Iodophosphorus ring compounds