

Therapy in Nuclear Medicine

Editor

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

Professor and Chairman
Department of Nuclear Medicine
University of Connecticut Health Center
Farmington, Connecticut



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

© 1978 by Grune & Stratton, Inc.

All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the publisher.

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

THERAPY IN NUCLEAR MEDICINE

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.

Richard P. Spencer

List of Contributors

Mohammed A. Antar, M.D., Ph.D., University of Connecticut Health Center,
Farmington, Connecticut

Irving M. Ariel, M.D., Pack Medical Group, New York, New York

Harold L. Atkins, M.D., Brookhaven National Laboratory, Upton, New York

Philip A. Bardfeld, M.D., Montefiore Hospital, New York, New York

Stephen P. Bartok, M.D., Food and Drug Administration, Rockville, Maryland

William H. Beierwaltes, M.D., University Hospital, Ann Arbor, Michigan

Robert E. Belliveau, M.D., Salem Hospital, Salem, Massachusetts

Rodney E. Bigler, Ph.D., Memorial Sloan-Kettering Cancer Center, New York,
New York

R. J. Blanchard, M.D., University of Manitoba, Winnipeg, Manitoba, Canada

William D. Bloomer, M.D., Harvard Medical School, Boston, Massachusetts

Gordon L. Brownell, Ph.D., Massachusetts General Hospital, Boston,
Massachusetts

Gerald A. Bruno, Ph.D., Squibb Institute for Medical Research, New Brunswick,
New Jersey

H. Donald Burns, Ph.D., Johns Hopkins Medical Institutions, Baltimore, Maryland

Gerard N. Burrow, M.D., Toronto General Hospital, Toronto, Ontario, Canada

Tuhin K. Chaudhuri, M.D., University of Texas, San Antonio, Texas

Rashid A. Fawwaz, M.D., Ph.D., Columbia University, College of Physicians and
Surgeons, New York, New York

Arnold M. Friedman, Ph.D., Argonne National Laboratory, Argonne, Illinois

- Edgar D. Grady, M.D., Georgia Institute of Technology, Atlanta, Georgia
- Joel I. Hamburger, M.D., Northland Thyroid Laboratory, Southfield, Michigan
- Thomas P. Haynie, M.D., M. D. Anderson Hospital, Houston, Texas
- Tapan Hazra, M.D., Medical College of Virginia, Richmond, Virginia
- Fazle Hosain, Ph.D., University of Connecticut Health Center, Farmington, Connecticut
- Ervin Kaplan, M.D., Veterans Administration Hospital, Hines, Illinois
- Klaus Mayer, M.D., Memorial Sloan-Kettering Cancer Center, New York, New York
- I. Ross McDougall, Ph.D., Stanford University Medical Center, Stanford, California
- Robert E. O'Mara, M.D., Strong Memorial Hospital, Rochester, New York
- Savita Puri, M.D., University of Connecticut Health Center, Farmington, Connecticut
- Leonard Rosenthal, M.D., Montreal General Hospital, Montreal, Quebec, Canada
- Richard P. Spencer, M.D., Ph.D., University of Connecticut Health Center, Farmington, Connecticut
- Larry A. Spitznagle, Ph.D., University of Connecticut Health Center, Farmington, Connecticut
- Henry N. Wagner, Jr., M.D., Johns Hopkins Medical Institutions, Baltimore, Maryland
- Niel Wald, M.D., Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania
- Joseph T. Witek, M.D., St. Elizabeth's Hospital, Brighton, Massachusetts

Contents

Preface
List of Contributors

Section I. BACKGROUND

1. Nuclear Medicine and Therapy: A Reorientation to Specificity and Beta Ray Generators 3
Richard P. Spencer
2. Relationship of External Radiation Doses to Internal Dosimetry 17
Rodney E. Bigler
3. Selection of Radionuclides for Therapy 33
Fazle Hosain, Parvathi Hosain
4. Chromosomal Alterations After Therapeutic Use of Radionuclides 45
Niel Wald, Carol Rump Sherer
5. Effects of Therapy on Major Organ Function and Imaging 53
Mohamed A. Antar, Richard P. Spencer

Section II. THYROID

6. Treatment of Hyperthyroidism: Use of ^{131}I and ^{125}I 85
Harold L. Atkins
7. Radioiodide in the Therapy for Thyroid Carcinoma 101
William H. Beierwaltes
8. Role of Lithium in Radioiodide Therapy 113
Gerard N. Burrow, Stephen W. Spaulding
9. Attempts to Reduce Whole-Body Radiation 121
Richard P. Spencer
10. Avoiding Inadvertent Fetal Radiation Resulting from ^{131}I Therapy for Hyperthyroidism 129
Sheldon S. Stoffer, Joel I. Hamburger

11.	Radioastatine: Possible Uses of a Heavy Halogen <i>Arnold M. Friedman</i>	139
Section III. USES IN NONMALIGNANT DISEASES		
12.	Use of Radiocolloids for Intra-Articular Therapy for Synovitis <i>Leonard Rosenthal</i>	147
13.	Therapeutic Implications of Adrenal Scanning Agents <i>William H. Beierwaltes</i>	155
14.	Radionuclide Irradiation of the Choroid Plexus and Central Nervous System <i>Philip A. Bardfeld</i>	167
Section IV. SYSTEMIC THERAPY		
15.	5-(¹²⁵ I)-Iododeoxyuridine in Experimental Tumor Therapy <i>William D. Bloomer, S. James Adelstein</i>	177
16.	Sulfur-35 Therapy for Chondrosarcoma and Chordoma <i>Klaus Mayer, K. S. Pentlow, R. C. Marcove, H. Q. Woodward, A. G. Huvos, B. Chin, J. S. Laughlin</i>	185
17.	Systematically Administered Compounds for Lymphatic Ablation <i>Rashid A. Fawwaz</i>	193
18.	Boron Neutron Capture Therapy <i>Gordon L. Brownell, Robert G. Zamenhof, Brian W. Murray, Glyn R. Wellum</i>	205
19.	Role of ³² P in Polycythemia Vera and Leukemia <i>Tuhin K. Chaudhuri</i>	223
20.	Historical Development of ³² P in Bone Therapy <i>Ervin Kaplan</i>	237
21.	Androgen-Parathormone Primed Phosphorus 32 for Intractable Pain in Carcinoma of the Prostate <i>Thomas P. Haynie, Douglas E. Johnson</i>	251
22.	New ³² P Compounds in Therapy for Bone Lesions <i>Robert E. O'Mara</i>	257
23.	Intralesional Therapy <i>Savita Puri, Richard P. Spencer</i>	261
24.	Therapeutic Implications of Radiolabeled Vesicles <i>I. Ross McDougall, June K. Dunnick, Joseph P. Kriss</i>	267
25.	Use of ³ H- and ¹⁴ C-Labeled Compounds in the Therapy for Specific Metabolic Pathways <i>Larry A. Spitznagle</i>	275

26.	Relationship Between the Development of Radioactive and Nonradioactive Pharmaceuticals <i>H. Donald Burns</i>	283
27.	Possible Therapeutic Use of Radiolabeled Antibodies: A Review <i>Robert E. Belliveau, Joseph T. Witek</i>	295
Section V. "LIMITED ACCESS" USE OF RADIONUCLIDES		
28.	Uses of Beta Emitters for Intracavitary Therapy <i>Tapan A. Hazra, Robert Howells</i>	307
29.	Lymphography and the Endolymphatic Administration of Radioactive Isotopes for the Treatment of Certain Cancers <i>Irving M. Ariel</i>	313
30.	Adjuvant Therapy for Colon Cancer by Internal Radiation to the Liver <i>Edgar D. Grady</i>	351
31.	Treatment of Metastatic Cancer to the Liver from Primary Colon and Rectal Cancer by the Intra-Arterial Administration of Chemotherapy and Radioactive Isotopes <i>Irving M. Ariel</i>	357
32.	Precautions in the Use of ^{90}Y Microspheres <i>R. J. Blanchard</i>	367
33.	A Discussion of the Presentations	371
34.	Therapeutic Implications of Nuclear Medicine: Significance and Problems <i>Moderator: Henry N. Wagner, Jr.</i> <i>Panelists: Gerald A. Bruno, Stephen P. Bartok, Irving M. Ariel, Ervin Kaplan, Edgar D. Grady</i>	387
	Index	399

SECTION I

Background

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.

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 ¹⁹⁷Pt 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 ¹²³I, ¹⁸F, or ⁷⁷Br for imaging. For therapeutic applications, radionuclides which deposited much energy locally would be employed. These include ¹²⁵I (Auger electrons), ¹³¹I (beta particles in addition to the gamma rays; ⁸²Br and ⁸³Br are also in this class), and the pure beta emitters ³H, ¹⁴C, and ³⁵S. 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.

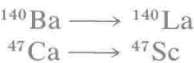
Table 1-4
Comparison of Views on Beta and Gamma Rays

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	
<i>cis</i> -diamminedichloroplatinum	^{193m} Pt	4.4 days x-rays	¹⁹⁷ Pt 0.75 days	670 kev β— plus gamma
	^{195m} Pt	4.1 days x-rays		
Purine and pyrimidine analogues	¹²³ I	13 hr	¹²⁵ I 57 days	E.C.
			¹³¹ I 8.1 days	600 kev β— plus gamma
	¹⁸ F	1.7 hr positron	³ H 12.5 years	18.6 kev β—
			¹⁴ C 5,700 years	156 kev β—
			³⁵ S 88 days	167 kev β—
	⁷⁷ Br	2.4 days positron	⁸² Br 1.5 days	444 kev β— many gammas
			⁸³ Br 2.4 hr	930 kev β— 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 ³²P (with its energetic beta particle), ³³P has a slightly longer physical half-life, but a less energetic beta particle. However, ⁸⁹Sr has also been used in the therapy of lesions in bone.⁷ Moreover, ⁹¹Sr 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.



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