Principles of Radiopharmacology

Volume III

Editor

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CRC PRESS, INC.
Boca Raton, Florida 33431

Library of Congress Cataloging in Publication Data

Main entry under title:

Principles of radiopharmacology

Bibliography: p.
Includes index.
1. Radioisotopes in pharmacology. I. Colombetti, Lelio G. II. Title: Radiopharmacology. [DNLM: 1. Nuclear medicine. 2. Radioisotopes—Diagnostic use. 3. Radioisotopes—Therapeutic use. WN440 P957]
RM858.P74 615'.19 78-27853
ISBN 0-8493-5465- (v. 1)

International Standard Book Number 0-8493-5465-X (Volume I)
International Standard Book Number 0-8493-5466-8 (Volume II)
International Standard Book Number 0-8493-5467-6 (Volume III)

Library of Congress Card Number 78-27853
Printed in the United States

PREFACE

In less than two decades radiotracers and their applications to medicine have emerged from a position as a minor branch of chemistry to that of an independent discipline. The best proof of this thesis are the many teaching programs in radiopharmacy which demonstrate practical utility of radiotracers in medicine. Radiotracers have been applied to solve a wide variety of diagnostic problems. For example, the behavior of specific radiotracers changes from normal in disease states facilitating diagnosis; when localization or metabolism of the radiotracer occurs in specific organs in a predictable manner; when the uptake and concentration data yield information about the state of metabolism in an organ or part of an organ, etc.

There is an area in the medical application of radiotracers that has been neglected up to now. This area involves the study of the mechanisms by which the radiotracers are transported in a biological system, the mechanisms of localization of radiotracers in the cell, and the metabolic pathways of radiotracers. These aspects of radiotracer biochemistry are especially important if we want to know how to create more specifically labeled compounds. The significance of these in vivo radiotracer properties created the necessity for a course in which these aspects were taught. And from this course, which we called from the very beginning a "course in Radiopharmacology", because radiotracers act in a biological system in a similar manner to drugs — even if a pharmacological effect is not noticeable or desired — a symposium was organized and held in Innsbruck, Austria in May 1978. The widespread interest in the subject is evident from the list of sponsors: The Loyola University Stritch School of Medicine, the Society of Nuclear Medicine (U.S.A.), and its counterpart in Europe, the American College of Nuclear Physicians, local European societies of nuclear medicine, etc. Also, the large number of participants — 388 scientists representing 37 countries from all continents — in a symposium of such a specific concern is a recognition of the significance of this subject.

This book is an outgrowth of the symposium and it is intended to be used by scientists and clinical personnel involved in the further evolution of radiotracer research. Hopefully, it will serve as a reference book for all scientists working in the development of new radiotracers. It is also intended to serve as a textbook in the teaching of radiopharmacology to science and medical students. This publication is the first to present a comprehensive and integrated summary of the perspective of all the disciplines of the basic sciences that are fundamental to the understanding of the biological behavior of radiotracers.

The book is divided into five major areas:

1. Basic radiopharmacology techniques
2. Radiotracer design
3. Basic radiotracer and receptor properties
4. Biological transport of radiotracers
5. Mechanisms of localization of radiotracers

The subjects comprising these five general areas are basic to the aim of the book: to help prepare the scientists that will develop the radiotracers of the future.

The editor acknowledges most gratefully the contributions of the authors, extending to all of them our deep appreciation for their patience for the delays occasioned by the necessity of reviewing several times each manuscript. Every attempt has been made to make the texts as complete as possible, incorporating new and bold ideas which we hope will help the development of new radiotracers.

Several scientists made important contributions to this publication by contributing

to the success of the symposium from which this book evolved. I am referring to the members of all the committees involved in the preparation of the symposium and especially to Dr. W. Earl Barnes who spent countless hours in helping to organize the symposium, to Dr. Richard Reba, chairman of the scientific committee, to Dr. Howard Glenn who also helped in the organization of the symposium; the inspiration and support received from Dr. Alexander Karczmar, Chairman of the Department of Pharmacology at Loyola University School of Medicine; to Dr. Steven Pinsky, Director of the Division of Nuclear Medicine at Michael Reese Hospital and Drs. John J. Coupal, Garimella Rayudu, and so many others, whose names are not mentioned here but who are well remembered. To all of them my sincere thanks and appreciation.

Lastly, I would like to thank the large group of scientists from all over the world who joined us in Innsbruck and who encouraged and inspired us during this time. I hope that all of them will be at hand when the next event comes to be.

Lelio G. Colombetti

FOREWORD

There was only one international symposium devoted to radiopharmaceutical drug research and development in the decade from 1965 through 1974. However, during and since this interval, there has been a veritable explosion of presented and published material concerning the design, preparation, and verification of new labeled drugs. Improvements in instrumentation, data analysis, and increased clinical awareness of the importance of biochemical processes in the diagnosis and clinical management of disease have served to stimulate the developing field of radiopharmacology. This provocation resulted in the First International Symposium on Radiopharmacology. The general goals of the meeting are notable: (1) to make diagnoses more specific; (2) to improve the quantification of serial physiological and biochemical changes in vivo; (3) to improve radiolabeled drugs in order to reduce absorbed radiation dose to patients; and (4) to compile in one publication the fundamental principles of an emerging discipline, radiopharmacology.

Although in the past, the search for special labeled drugs has been based on the concept of the "magic bullet", the facts are that many of the labeled drugs currently used were uncovered fortuitously. Most past discoveries were the result of empirical methods, or chance alone. As emphasized by Dr. Henry Wagner, an understanding of regional function, i.e., organ function, cellular function, membrane function, and intracellular function will be more useful to the development of new labeled drugs than the idea of a magic bullet or any special attraction of an abnormal focus. Concepts of disease more than 100 years old, such as Virchow's idea that disease was due to abnormal cellular function and Bernard's idea that disease was due to some derangement in internal milieu (a physiochemical or internal physiology change), long believed to be true, can now be studied, refined, and exploited fully in clinical investigations and patient care.

Since one of the greatest frustrations to the advancement of nuclear medicine is the absence of convenient gamma-emitting radionuclides of carbon, hydrogen, oxygen, and nitrogen, an immense effort has been expended toward identifying biologically important molecules that can be linked to a radiolabel in a biologically inert portion of the molecule so that the biologic activity of the parent molecule remains unperturbed.

In order to use a rational approach to new drug development, it is apparent that one must understand the biological disposition, the biochemistry, and the immunology of proposed compounds. Likewise, drug metabolism and knowledge of the mechanisms of localization, including the pharmacokinetics of the compound of interest, will all lead to an understanding of the structure-activity and drug-receptor relationships so that molecular manipulation will lead to specific analogs or derivatives. An appreciation of the usefulness of these tenets of pharmacology to the development of more specific radiotracers were the specific goals of this symposium. As emphasized by many, it is now clear that progress in the development of new radiotracers will require that radiopharmacy evolve to become radiopharmacology.

We are now beginning to "see" cellular structure and function by noninvasive nuclear recording techniques. Internal physiology and internal cellular biochemistry can be followed by measurement of changes in time and distribution. An understanding of radiopharmacology will give critical importance to further advances in the development of new radiotracers and, therefore, nuclear medicine itself.

The First International Symposium on Radiopharmacology brought together diverse individuals from different countries, having different languages, different cultures, and, therefore, different problems and working to solve different medical illnesses. The common bond was science and the application of the scientific method to uncover

and understand the basic means which could be used to solve different problems. This work is being integrated into what is becoming a new scientific discipline, one directed toward the investigation of *kinetics* and *actions* of drugs, and based primarily on biokinetics. *PRINCIPLES OF RADIOPHARMACOLOGY* fills a timely need for a comprehensive, up-to-date text in this new discipline, one that will be used as a text by students and a reference by nuclear medicine physician specialists, residents, radiopharmacists, and scientists working in the preparation and uses of radiotracers in biology and medicine. The editor, Dr. Lelio G. Colombetti, has devoted a considerable effort during the last seven years to the development of university program in radiopharmacology, and he has been able to bring together a distinguished group of scientists for the preparation of the book. It is important to recognize radiopharmacology as a necessary tool for the development of the new radiotracers that will satisfy medical needs. If we are to advance from serendipitous and random discovery of new radiotracers to an approach that includes a rational basis for progression, then the principles and techniques discussed in the book must be learned and refined.

Richard C. Reba, M.D.

THE EDITOR

Lelio G. Colombetti, Sc.D., is Professor of Pharmacology at Loyola University Stritch School of Medicine in Maywood, Ill. and a member of the Nuclear Medicine Division Staff at Michael Reese Hospital and Medical Center in Chicago, Ill.

Dr. Colombetti graduated from the Litoral University in his native Argentina with a Doctor in Sciences degree (summa cum laude), and obtained two fellowships for postgraduate studies from the Georgetown University in Washington, D.C., and from the M. I. T. in Cambridge, Mass. He has published more than 150 scientific papers and is the author of several book chapters. He has presented over 300 lectures both at meetings held in the U.S. and abroad. Recently he organized the First International Symposium on Radiopharmacology, which took place in Innsbruck, Austria in May 1978 with an outstanding success, and is presently organizing a second international symposium on the same subject.

Dr. Colombetti is a member of various scientific societies, including the Society of Nuclear Medicine (U.S.) and the Gesellschaft fur Nuklearmedizin (Europe), and is an honorary member of the Mexican Society of Nuclear Medicine. He is also a member of the Society of Experimental Medicine and Biology, the Coblenz Society, and the Sigma Xi. He is a member of the Editorial board of Nuklearmedizin journal.

A SHORT HISTORY MADE SHORTER

. . . and great changes, indeed, are taking place for us, because the field of radiotracer application in medicine is taking a sharp turn in its march toward a greater future. Today we believe that static imaging will, in great part, be replaced by dynamic studies in which not only the anatomical integrity of an organ can be studied, but also the physiological response of the cells. And to do this job we need, in many cases, to develop the appropriate radiotracer.

More than three decades ago, Hamilton stated that "the discovery of artificial radioactivity and the development of the cyclotron, have given the biologist the most useful tools since the discovery of the microscope". Soon after von Hevesy introduced the radiotracer concept into chemistry and later into biology, it was proved that the amount of radiotracer needed to study a process was so small that it could not disturb the system under investigation. This peculiar characteristic allows the use of radiotracers to study the function of cells.

After the Joliots invented the artificial production of radionuclides in 1934 and Lawrence invented the cyclotron, a large number of artificially produced radiotracers became available and their applications in the biological and medical sciences increased manifold in a short period of time.

It is interesting to note that radiotracers were first used for therapeutic purposes. It took more than fifteen years before a tracer was used for the first time in diagnosis, and, incidently, the first uses were in dynamic studies.

A written history of the uses of radiotracers in their most important application, medicine, could start with the work done by Wickman and Desgrais in Paris in 1911. These investigators by subcutaneous administration of radium attempted to cure lesions of lupus. Later, radium was used by many investigators for the treatment of a variety of diseases, with negative results in most cases. Other radionuclides — when they became available — were also used, such as radiobismuth which was used by Lomholt in an attempt to cure syphilis.

To the best of our knowledge, the first human application of a radiotracer for diagnostic purposes was the use in the mid-twenties of ^{226}Ra by Yens, Blumgart and Weiss to study the blood circulation time in the human. Several years later von Hevesy used ^{3}H to determine the water content of the human body.

Soon after the Joliots discovered the production of radionuclides by artificial means in the early forties, and Fermi produced the first man-made radioiodine by using a radium-berylium source, other radionuclides were introduced rapidly. ^{131}I was produced by the Berkeley and Massachussetts groups in their cyclotrons as early as 1938. Chiewitz and Hevesy used in 1935 the newly produced ^{32}P to study phosphorous metabolism in the bones. ^{32}P was used later by John Lawrence to treat leukemia. By this time cyclotrons were built in other universities and scientists started using the newly found radionuclides. The discovery of ^{14}C at Oak Ridge in 1946 opened a floodgate of metabolic studies and in just a few years many investigations were performed to study the pathway of naturally occurring biochemicals and drugs. Reactor radionuclides produced by the neutroactivation of stable nuclides became available in the forties. This development led to the production of a number of radionuclides with special value for medical applications.

The discovery of the ^{99}Mo-^{99m}Tc generator and the work done by Harper and associates introduced a new concept in the preparation of radiotracers. Today, most radiotracers used in human studies are based on molecules labeled with ^{99m}Tc. Very recently other radionuclides such as ^{67}Ga and ^{201}Tl have been introduced and proved to be very valuable as diagnostic tools. These radionuclides have gained in popularity during the last few years, but we strongly believe that they will be replaced in the near future by

labeled molecules with specific localizations.

Until recently, most of the radiotracers developed for medical applications were based on labeling known drugs or on empirical approaches. Soon, the need for radiotracers outstripped the number of available agents. In order to develop new radiotracers, scientists working in this field applied known concepts of biochemistry and physiology. But their efforts were not sufficient to satisfy the needs.

More recently different approaches have been suggested, approaches that involve a variety of scientific disciplines, such as biochemistry, biophysics, physiology and pharmacology. The creation of biological models to study the mechanism of transport and localization, and metabolic pathways is helping researchers to solve the problems encountered with the development of radiotracers with specific localization. No need is greater than that of a better understanding of what happens to radiotracers once they are administered and the changes they suffer in a biological system, which, in turn, influence their disposition by the body.

As it was once said, "it is very difficult to make predictions . . . especially about the future . . . " anyhow we dare to predict today that with the passing of time there will be an increasing need for radiotracers suitable for measuring dynamic processes in the assessment of organ function. Also, assessment of organ perfusion and fate of radiometabolites will comprise a large portion of radiotracer use in medicine and biology. So we can say with confidence that a chapter in the history of radiotracers has been closed and that a new chapter is being opened . . . "for all those who dare to work for the future".

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