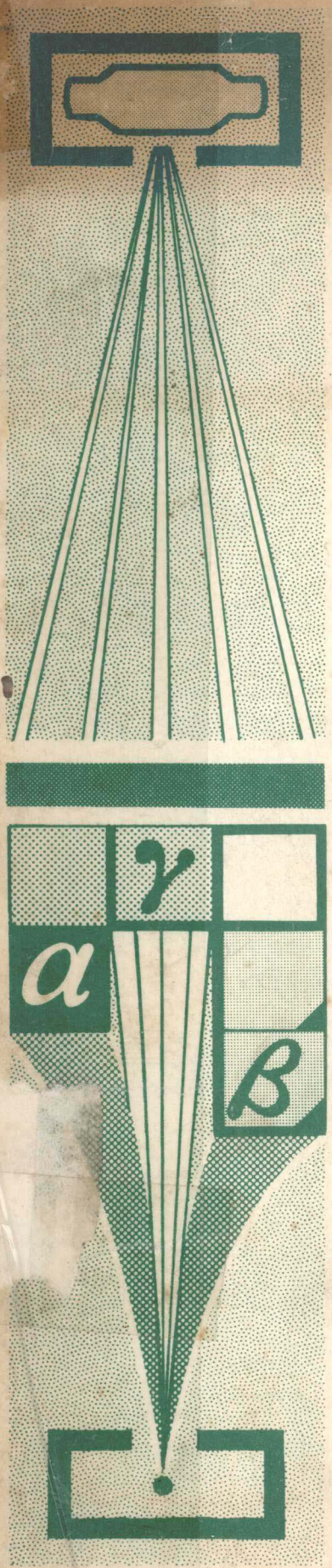

RADIOPHARMACEUTICAL DOSIMETRY SYMPOSIUM

Proceedings of Conference
held at Oak Ridge, Tenn.,
April 26-29, 1976

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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Edited and compiled by:

Roger J. Cloutier
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June 1976

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FOREWORD

The Bureau of Radiological Health conducts a national program to limit man's exposure to ionizing and nonionizing radiations. To this end, the Bureau (1) develops criteria and recommends standards for safe limits of radiation exposure, (2) develops methods and techniques for controlling radiation exposure, (3) plans and conducts research to determine health effects of radiation exposure, (4) provides technical assistance to agencies responsible for radiological health control programs, and (5) conducts an electronic product radiation control program to protect the public health and safety.

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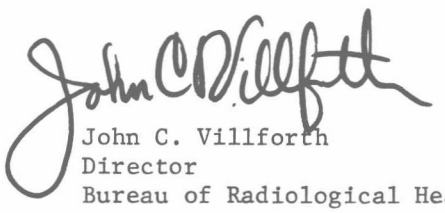

John C. Villforth
Director
Bureau of Radiological Health

PREFACE

Seven years ago Oak Ridge Associated Universities organized and conducted a symposium on *Medical Radionuclides: Radiation Dose and Effects*. In many ways this symposium, *Radiopharmaceutical Dosimetry*, is its sequel. It is not surprising that much progress and many changes have occurred during the intervening years. Radiopharmaceuticals unthought of just a few years ago are now routinely used and dosimetric techniques, once crude, are becoming increasingly sophisticated.

In organizing this symposium, the planning committee carefully selected speakers so that all phases of dosimetry would be included. Well-known scientists from the United States and several foreign countries agreed to present current views on radiopharmaceutical selection, biological distribution and retention, and the physics and mathematics of dose calculation.

Like the previous proceedings, we anticipate that this volume will serve as a foundation upon which further progress in radiopharmaceutical dosimetry can be built. Time will tell how successful we have been.

Symposium Planning Committee

Roger J. Cloutier, Chairman
Peter Paras
John W. Poston
Walter S. Snyder
Vincent J. Sodd
Evelyn E. Watson

Peter Paras
Director
Division of Radioactive Materials and
Nuclear Medicine
Bureau of Radiological Health

ABSTRACT

The major objective of this conference is to present the most up-to-date concepts of internal dosimetry techniques. Dosimetry experts will be invited to present various facets of the problem, exchange points of view, and define major disagreements that may exist. We expect the conference to generate fruitful pathways for resolving some of the continuing questions on dosimetry and obtaining the biological information needed to improve radiation dose estimates. An important goal is to provide a reference volume that will serve as a resource for nuclear medicine practitioners and clinical investigators.

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Alan S. Kirschner, Philadelphia College of Pharmacy and Science and Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, *and* *Rodney D. Ice,* College of Pharmacy, The University of Michigan, Ann Arbor, Michigan

INTRODUCTORY REMARKS

Philip L. Johnson, Executive Director
Oak Ridge Associated Universities, Inc.
Oak Ridge, Tennessee

Welcome to Oak Ridge and to the Radiopharmaceutical Dosimetry Symposium. It is my pleasure to open this symposium and welcome you to Oak Ridge Associated Universities, noting that this is the seventh in a series of Oak Ridge symposia in the area of medical radionuclides. Proceedings from these conferences have received a good deal of attention nationwide and worldwide and so we are indeed pleased to be able to welcome you and entertain the idea that your comments, questions, and deliberations will be objective, constructive, and enthusuastic. The major objective of this symposium is to present the most up-to-date concepts of internal dosimetry techniques. Dosimetry experts not only from the United States are attending but we are pleased to have participants and colleagues from England, from Germany, from Belgium, and from the Netherlands. Over 40 papers will be presented; we hope many different points of view will be presented, and we hope that those points of view will endeavor to clarify our present state of knowledge. We expect you will challenge those points which appear to you to be controversial, because therein lies part of the ingredients of the scientific process. The proceedings of course will be published in due course and widely circulated.

Sometimes we need to ask ourselves just what is the role of science in the society in which we live? The question is often asked, and I hope you recognize that the answer is important because so much of science has come to depend on the taxpayer's dollar. Perhaps the role of science over many decades and many centuries has been rather much the same in the sense that scientists dedicate themselves to the pursuit of knowledge, and that knowledge has helped lead us to our present civilization, both our advantages and our dilemmas. So also has the role of science contributed to the applications of technology. To those two points I think it is significant to add a third. I will refer to it as an ethic. We as a society face, worldwide, very complex problems. Some of them emanate from the very technology which, as scientists, we have contributed to, some emanate from growth, some emanate from aspirations and expectations which the communications technology has helped spread. Nevertheless, a process for coping with complex problems is called the scientific method, and that objective method is certainly preferable to many others we occasionally see in practice.

The point that ought to concern us is that society now expects, indeed demands, a form of accountability from science, and it isn't always clear how we can deliver on that expectation. Perhaps it is worth reminding ourselves that in the preindustrial society, man progressed by his ability to cope with nature. He was a farmer, a gatherer, and concentrated into cities as a result of the technologies which built cities, permitted mining and concentration of resources in cities, and then had to cope with the wastes of those concentrations and still does. The industrial society was built by technology, and it came to cherish things. We now question in our debates whether we cherish too

many things. We come to recognize that the aspirations of individuals and what is good for individuals is not necessarily good for communities.

There are those in our scholarly ranks who suggest that we are well on the road to a postindustrial society and one might well ask what is the critical parameter to a postindustrial society. It has been suggested that the critical parameter for survival in a postindustrial society is information. What kind of information? Well, so many of us are deluged with an information explosion that we hardly know how to process it and make use of what we know, or think we know. This, it seems to me, brings to gatherings of this kind rather important questions, because scientists are trained and have motivation to speak of what they know, and they are often tempted not to speak of the gap in knowledge or the frontier of what we don't know, although that is often the more critical piece of information. Therein lies part of this issue of accountability. It seems to me that scientists and science must insist on the integrity of its practices and the integrity of its practitioners. It has been very tempting during the decade of the 1960's when science was growing rapidly to speak out on some subject which went well beyond our own knowledge. Sometimes we communicated with the public, the essence of a discipline or the process by which scientists analyze problems; however, too many of us have seen our colleagues speak in areas of their incompetence. How is the public to accept science and the funding of science when scientists disagree on the facts? This is a question we read about every day in the newspapers and it ought to concern us because part of the issue underlying the accountability of science has to do with whether scientists are responsible for creating technology or utilizing it. This was the same issue which was around this part of the world when the TVA dams were built, and it most certainly was an urgent question when the atomic bomb was built. That responsibility is one which should concern the biomedical community, but, as Alvin Weinberg has written, many of these issues are trans-science problems. The scientific community cannot hold the whole albatross. Rather, science must better communicate what it accomplishes, how it helps society, and what alternatives are available to society if it chooses to utilize the scientific products.

I should like to acknowledge the sponsors of this symposium which helped make this conference possible. They include not only Oak Ridge Associated Universities (ORAU), but the Oak Ridge National Laboratory, the United States Energy Research and Development Administration, the National Cancer Institute, both the Bureau of Radiological Health and the Bureau of Drugs of the Food and Drug Administration, and the Health Physics Society.

This conference is convening in the new building of the American Museum of Atomic Energy, a museum which has operated in this community for some 25 years. In fact, ORAU energy educational programs reached about 3 million people nationwide in 1975. Like this symposium, it has the goal of providing useful information to as many people as possible.

DECISION-MAKING CONSIDERATIONS IN THE CHOICE OF RADIOACTIVE DIAGNOSTIC AND THERAPEUTIC AGENTS

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ABSTRACT

There are no ideal radioactive diagnostic or therapeutic agents. There is only the best compromise at a given time between the agent's physical, chemical, and biological characteristics, its compatibility with available instrumentation needed for its use, and the ability to assure quality and availability. This paper elaborates on the parameters affecting such compromise.

INTRODUCTION

Radiations from decay of naturally occurring radionuclides were used as encapsulated sources in therapy soon after the turn of the century. Artificially produced radioactive elements first were produced by Joliot and Curie (1) in 1934 by bombardment of boron and aluminum with alpha particles arising from natural decay of polonium-210 [$^{10}B(\alpha,n)^{13}N$] and [$^{27}Al(\alpha,n)^{30}P$]. But, it was not until the mid and late 1930's when charged-particle accelerators were used in the production of radionuclides that significant quantities of a large number of radioactive species of elements became available for general medical applications. Beginning in 1934, a wide variety of radionuclides were produced by means of charged-particle accelerators and their potential applications in medical diagnosis and in therapy were explored. In general, such investigations were limited to those having access to accelerator products, and the use of radionuclides was of a limited investigational character. Following World War II, the Congress of the United States created the U.S. Atomic Energy Commission and charged it with the mission of developing peaceful uses for the process and byproducts of nuclear fission. Subsequently, the efforts of the AEC largely were related to the development of nuclear reactor technology for power production. A byproduct of this technology was the widespread availability of certain radionuclides generated as products of nuclear fission and others generated from bombardment of nuclei of stable elements by neutrons released during fission.

During the decades of the 1930's and 1940's, radiation detection devices largely were based on the phenomenon of gas ionization (i.e., ionization chambers, gas proportional counters and Geiger-Müller counters). At the time, such gas ionization-based detectors were not utilized extensively in devices for graphic display of the in vivo distribution of radionuclides. Medical uses of radionuclides during this era largely were related to quantitation of volume-space distributions of labeled body constituents and evaluation of metabolic or cellular kinetics which could be deduced from data gathered by externally placed collimated probes and by in vitro assay of activity in serial blood, urine, breath, or tissue samples. Consequently, radioisotopes whose medical

use required detection of emitted radiation on body surfaces following their internal administration had to emit radiations which could be readily detected using gas ionization devices.

After development of scintillation detectors by Broser and Kallmann in Germany in 1947 (2), Cassen et al in 1951 (3) invented the rectilinear scanner, and Anger in 1958 (4) invented the single-crystal scintillation camera. These devices generated two-dimensional spatial displays (images) of the in vivo distributions of γ-radionuclides. Their introduction ushered in the present stage of nuclear medicine characterized by rapidly expanding clinical use of radionuclide imaging in the evaluation of the pathophysiology of local tissue disease processes. All of these latter devices utilize collimators fabricated from lead or tungsten in conjunction with thallium-activated sodium iodide scintillation detectors [NaI(Tl)]. The characteristics of these devices are such that the higher the gamma-ray energy detected, the better the energy resolution within the scintillation detector; and, therefore, the better the spatial resolution of the detector. Conversely, the higher the detected gamma-ray energy, the lower the detection efficiency within the scintillation crystal. The characteristics of mechanical collimators are such that collimator transmission efficiency and inherent resolution increase with decrease in energy of the gamma-ray emission. In the choice of γ-radionuclides for use within the total gamma-ray imaging system, consisting of both the mechanical collimator and the NaI(Tl) scintillation detector, compromises are made with regard to the energy of the gamma-ray emission, which simultaneously satisfies the restrictions set by all components of the detection systems. Moreover, the radionuclides to be used not only must possess the desirable characteristics outlined in the subsequent section, but they also must be generally available. Since the time of introduction of the above-mentioned γ-ray imaging devices the only large-scale source of radionuclides available at the time were produced in a nuclear reactor, the choice of potential radionuclides for use with the new γ-ray imaging devices were severely limited. During the early part of the 1950's and 1960's, ^{131}I was the principal radionuclide used in nuclear medicine. Reactor produced, it was available and inexpensive, and its 8-day physical $T\frac{1}{2}$ was sufficiently long so as to impose limited distribution logistics problems, a not inconsequential issue when the geographical densities of active nuclear medicine laboratories was too low to support a specialized rapid distribution network. During its halcyon days, ^{131}I was the "universal label"; and it was bound to plasma proteins, fats, and various other metabolites in addition to agents excreted by the kidney (e.g., ^{131}I-orthoiodohippurate) and the liver (e.g., ^{131}I-rose bengal). It became apparent that although ^{131}I satisfied the principal radionuclidic needs of the then embryonic discipline of nuclear medicine, other agents needed development in order to serve the evolving requirements of the field. For reasons more fully elaborated in subsequent sections, searches were instituted for short-lived radionuclides emitting a minimum of non-penetrating radiation and a penetrating gamma-ray emission compatible with the then existing radiation detection devices. Such radionuclides were preferably capable of production on a nuclear reactor (and therefore lending themselves to commercial availability) and compatible with distribution through existing transportation channels without incurring inordinate expense. Despite the severity of these restrictions, a few solutions were found. These were principally embodied in the ^{99}Mo-^{99m}Tc and the ^{113}Sn-^{113m} in generator systems. The relatively long-lived parent radionuclide in each of these instances could be produced in a reactor and the secondary generator system could be transported without undue haste, while the short-lived no-carrier-added (NCA) daughter could be separated from the parent at the site of usage. While both of these generator systems initially were afforded similar attention, it was the ^{99}Mo-^{99m}Tc system which emerged predominant; and by 1972, approximately half of all clinical nuclear-medical studies performed in the United States utilized ^{99m}Tc.

By the beginning of the present decade (1970's), the geographical density of institutions practicing nuclear medicine had increased sufficiently to justify establishment of specialized distribution networks capable of reliable daily delivery of short-lived radionuclides to nuclear-medical laboratories. Concurrently, the size and growth rate of the discipline justified development of facilities capable of producing large quantities of short-lived, neutron-deficient, accelerator-produced radionuclides. As a consequence, nuclear medicine no longer was bound by the severe restrictions in availability of suitable radionuclides such as that which characterized its early development. One can anticipate that the development of radionuclide imaging devices which favor the use of radionuclides emitting low-energy photons (e.g., solid-state detector systems or wire chambers filled with gas or liquid) or the emergence of high-resolution, high-count-rate capability positron annihilation radiation imaging devices will be met by early availability of suitable radionuclides to match the detection requirements of the evolving instrumentation as well as fulfilling the requirements of the biological systems to be studied.

DESIRABLE CHARACTERISTICS OF RADIOACTIVE DIAGNOSTIC AGENTS

Optimum Radionuclidic Characteristics Relative to Available Detection Devices and Intended Use

An optimum radionuclide for in vivo diagnostic use is one which results in the lowest possible absorbed radiation dose in the tissues of the patient while affording the greatest possible diagnostic information. The absorbed radiation dose can be minimized by utilization of a radionuclide with a mean decay time (physical $T_{\frac{1}{2}}/0.693$) comparable to the duration of the time following administration in which the study is performed (5, 6), as well as emissions having minimal abundance of non-penetrating components (i.e., α, $\beta-$, $\beta+$, conversion or Auger electrons, low-energy gamma-rays or X-rays), and maximum abundance of penetrating emissions (gamma-rays or high-energy X-rays) the energy of which is matched to the detection device in a manner which optimizes detection efficiency and spatial resolution. When single-headed detector devices are employed, these latter characteristics are best fulfilled by use of radionuclides decaying by electron capture or isomeric transition. When coincidence detectors for annihilation radiation are employed, the use of pure positron-emitting radionuclides is desirable. In addition to compatibility with available detection devices, it is necessary to choose radionuclides whose penetrating radiations intended for detection are compatible with the in vivo function they are to serve. Radionuclides intended for study of tissues or organs situated deep within the body are best chosen for gamma-ray emissions of energy greater than those which are chosen for study of structures close to the body surface so as to minimize the effects of attenuation and scatter during passage through tissue in the flight to the surface of the body. For example, other factors being equal, a radionuclide which is intended for evaluation of bone would optimally have a higher energy gamma-ray emission than a radionuclide intended for evaluation of the thyroid gland.

Except for special applications where penetrating emissions of different energies are individually utilized, it is desirable for a radionuclide to have monoenergetic penetrating emissions. This is so largely because for single-headed devices a particular combination of collimator and detector are matched optimally to detect and to estimate original photons of a given energy. Even when a detector device is capable of concurrent detection of several photopeaks, emission of photons of multiple energies is generally undesirable. This is so since the "lower energy" photons are inefficiently collimated by the "higher energy" collimator. If a collimator mated to the "lower energy" photon is used, then a significant number of the "higher energy" photons may penetrate the septa of the collimator without undergoing scatter or absorption.